

## Anhang 4-H

# Separate Darstellung zu den Linear mixed effects model-Analysen

*Alpelisib (Piqray®)*

Novartis Pharma GmbH

## **Modul 4 A Anhang 4-H**

*Alpelisib in Kombination mit Fulvestrant zur Behandlung von postmenopausalen Frauen und Männern mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom mit PIK3CA-Mutation bei Fortschreiten der Erkrankung nach endokriner Therapie als Monotherapie (siehe Abschnitt 5.1)*

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#### **4.8 Patientenberichtete Endpunkte: Linear mixed effects model-Analysen – 2. Datenschnitt**

##### **4.8.1 Patientenberichtete Endpunkte: Linear mixed effects model-Analysen zur Gesamtpopulation – 2. Datenschnitt**

###### **4.8.1.1 Krankheitssymptomatik EORTC QLQ-C30 – 2. Datenschnitt**

Tabelle 4H-1: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Fatigue“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	9,753	2,296	7,458
	SEM	2,542	2,591	2,256
	95%-KI	( 4,8;14,8)	( -2,8; 7,4)	( 3,0;11,9)
Woche 16	n	124	107	
	LS-Mean	7,177	4,229	2,948
	SEM	2,605	2,718	2,426
	95%-KI	( 2,1;12,3)	( -1,1; 9,6)	( -1,8; 7,7)
Woche 24	n	105	81	
	LS-Mean	7,017	4,607	2,409
	SEM	2,670	2,849	2,626
	95%-KI	( 1,8;12,3)	( -1,0;10,2)	( -2,7; 7,6)
Woche 32	n	86	73	
	LS-Mean	7,041	3,240	3,801
	SEM	2,771	2,907	2,762
	95%-KI	( 1,6;12,5)	( -2,5; 9,0)	( -1,6; 9,2)
Woche 40	n	75	62	
	LS-Mean	5,414	2,856	2,557
	SEM	2,831	2,997	2,908
	95%-KI	( -0,1;11,0)	( -3,0; 8,7)	( -3,1; 8,3)
Woche 48	n	69	51	
	LS-Mean	8,082	4,147	3,935
	SEM	2,870	3,108	3,061
	95%-KI	( 2,4;13,7)	( -2,0;10,2)	( -2,1; 9,9)
Woche 56	n	59	45	
	LS-Mean	6,523	3,938	2,585
	SEM	2,948	3,188	3,217
	95%-KI	( 0,7;12,3)	( -2,3;10,2)	( -3,7; 8,9)
Woche 64	n	47	42	
	LS-Mean	7,913	5,720	2,193
	SEM	3,079	3,236	3,385
	95%-KI	( 1,9;14,0)	( -0,6;12,1)	( -4,4; 8,8)
Woche 72	n	48	35	
	LS-Mean	6,990	4,233	2,756
	SEM	3,068	3,370	3,503
	95%-KI	( 1,0;13,0)	( -2,4;10,8)	( -4,1; 9,6)
Woche 84	n	40	33	
	LS-Mean	10,818	3,994	6,824
	SEM	3,199	3,417	3,655
	95%-KI	( 4,5;17,1)	( -2,7;10,7)	( -0,3;14,0)
Woche 96	n	35	24	
	LS-Mean	9,896	3,130	6,767
	SEM	3,295	3,711	4,014
	95%-KI	( 3,4;16,4)	( -4,2;10,4)	( -1,1;14,6)
Woche 108	n	26	21	
	LS-Mean	5,389	11,403	-6,014
	SEM	3,565	3,856	4,361
	95%-KI	( -1,6;12,4)	( 3,8;19,0)	(-14,6; 2,5)
Woche 120	n	28	16	
	LS-Mean	8,753	0,050	8,702
	SEM	3,489	4,195	4,609
	95%-KI	( 1,9;15,6)	( -8,2; 8,3)	( -0,3;17,7)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes

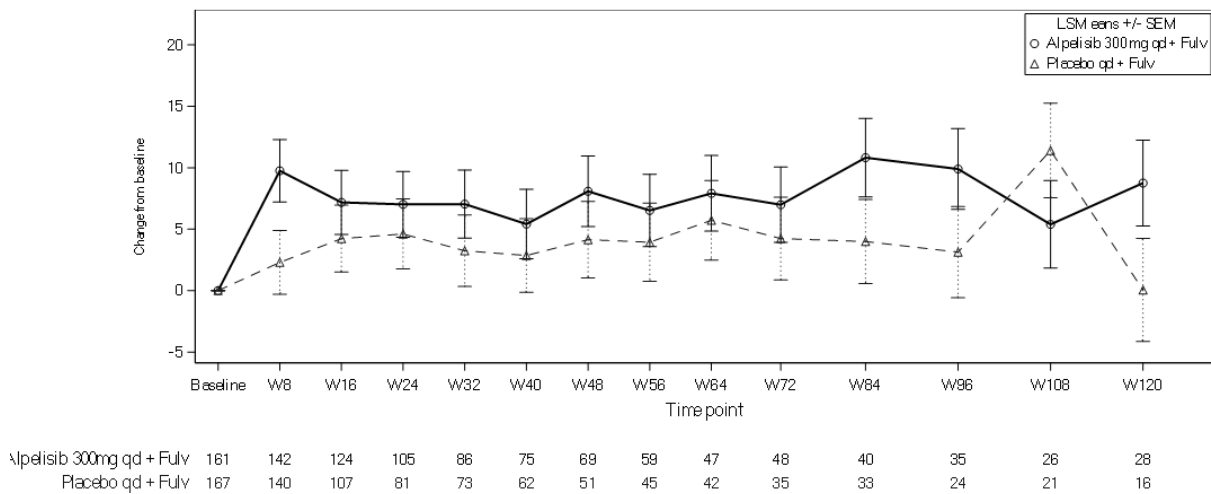
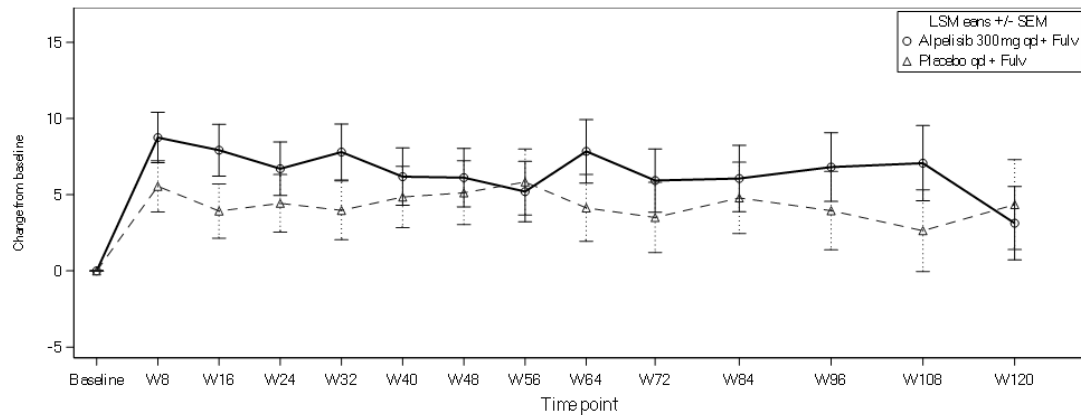


Abbildung 4H-1: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Fatigue – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-2: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Übelkeit/Erbrechen“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	8,751	5,555	3,197
	SEM	1,655	1,683	1,498
	95%-KI	( 5,5;12,0)	( 2,2; 8,9)	( 0,3; 6,1)
Woche 16	n	124	107	
	LS-Mean	7,923	3,931	3,993
	SEM	1,704	1,783	1,631
	95%-KI	( 4,6;11,3)	( 0,4; 7,4)	( 0,8; 7,2)
Woche 24	n	105	81	
	LS-Mean	6,707	4,435	2,272
	SEM	1,756	1,886	1,787
	95%-KI	( 3,3;10,2)	( 0,7; 8,1)	( -1,2; 5,8)
Woche 32	n	86	73	
	LS-Mean	7,800	3,974	3,826
	SEM	1,837	1,934	1,893
	95%-KI	( 4,2;11,4)	( 0,2; 7,8)	( 0,1; 7,5)
Woche 40	n	75	62	
	LS-Mean	6,185	4,850	1,335
	SEM	1,886	2,006	2,008
	95%-KI	( 2,5; 9,9)	( 0,9; 8,8)	( -2,6; 5,3)
Woche 48	n	69	51	
	LS-Mean	6,122	5,127	0,995
	SEM	1,917	2,096	2,126
	95%-KI	( 2,4; 9,9)	( 1,0; 9,2)	( -3,2; 5,2)
Woche 56	n	59	45	
	LS-Mean	5,208	5,834	-0,625
	SEM	1,980	2,159	2,247
	95%-KI	( 1,3; 9,1)	( 1,6;10,1)	( -5,0; 3,8)
Woche 64	n	47	42	
	LS-Mean	7,847	4,135	3,712
	SEM	2,084	2,197	2,377
	95%-KI	( 3,8;11,9)	( -0,2; 8,4)	( -1,0; 8,4)
Woche 72	n	48	35	
	LS-Mean	5,931	3,506	2,425
	SEM	2,075	2,305	2,468
	95%-KI	( 1,9;10,0)	( -1,0; 8,0)	( -2,4; 7,3)
Woche 84	n	40	33	
	LS-Mean	6,065	4,790	1,275
	SEM	2,181	2,342	2,584
	95%-KI	( 1,8;10,3)	( 0,2; 9,4)	( -3,8; 6,3)
Woche 96	n	35	24	
	LS-Mean	6,814	3,953	2,860
	SEM	2,256	2,572	2,858
	95%-KI	( 2,4;11,2)	( -1,1; 9,0)	( -2,7; 8,5)
Woche 108	n	26	21	
	LS-Mean	7,070	2,638	4,432
	SEM	2,469	2,685	3,120
	95%-KI	( 2,2;11,9)	( -2,6; 7,9)	( -1,7;10,6)
Woche 120	n	28	16	
	LS-Mean	3,129	4,350	-1,220
	SEM	2,408	2,947	3,308
	95%-KI	( -1,6; 7,9)	( -1,4;10,1)	( -7,7; 5,3)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



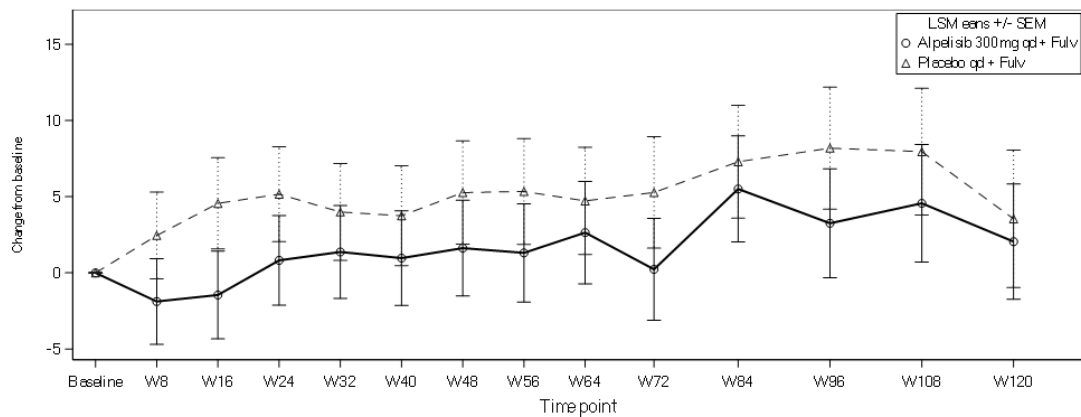
Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

Abbildung 4H-2: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Übelkeit/Erbrechen – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-3: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schmerzen“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-1,883	2,450	-4,333
	SEM	2,815	2,854	2,455
	95%-KI	(-7,4; 3,7)	(-3,2; 8,1)	(-9,2; 0,5)
Woche 16	n	124	107	
	LS-Mean	-1,454	4,562	-6,017
	SEM	2,880	2,990	2,641
	95%-KI	(-7,1; 4,2)	(-1,3; 10,4)	(-11,2; -0,8)
Woche 24	n	105	81	
	LS-Mean	0,819	5,163	-4,343
	SEM	2,946	3,123	2,849
	95%-KI	(-5,0; 6,6)	(-1,0; 11,3)	(-9,9; 1,2)
Woche 32	n	86	73	
	LS-Mean	1,369	3,993	-2,624
	SEM	3,047	3,183	2,990
	95%-KI	(-4,6; 7,4)	(-2,3; 10,2)	(-8,5; 3,2)
Woche 40	n	75	62	
	LS-Mean	0,968	3,749	-2,781
	SEM	3,109	3,275	3,143
	95%-KI	(-5,1; 7,1)	(-2,7; 10,2)	(-8,9; 3,4)
Woche 48	n	69	51	
	LS-Mean	1,624	5,267	-3,643
	SEM	3,148	3,389	3,299
	95%-KI	(-4,6; 7,8)	(-1,4; 11,9)	(-10,1; 2,8)
Woche 56	n	59	45	
	LS-Mean	1,309	5,340	-4,031
	SEM	3,228	3,471	3,461
	95%-KI	(-5,0; 7,6)	(-1,5; 12,2)	(-10,8; 2,8)
Woche 64	n	47	42	
	LS-Mean	2,643	4,725	-2,082
	SEM	3,362	3,520	3,636
	95%-KI	(-4,0; 9,2)	(-2,2; 11,6)	(-9,2; 5,1)
Woche 72	n	48	35	
	LS-Mean	0,228	5,276	-5,048
	SEM	3,350	3,659	3,760
	95%-KI	(-6,3; 6,8)	(-1,9; 12,5)	(-12,4; 2,3)
Woche 84	n	40	33	
	LS-Mean	5,506	7,295	-1,789
	SEM	3,484	3,707	3,916
	95%-KI	(-1,3; 12,3)	(0,0; 14,6)	(-9,5; 5,9)
Woche 96	n	35	24	
	LS-Mean	3,253	8,185	-4,931
	SEM	3,581	4,010	4,291
	95%-KI	(-3,8; 10,3)	(0,3; 16,1)	(-13,3; 3,5)
Woche 108	n	26	21	
	LS-Mean	4,565	7,958	-3,393
	SEM	3,860	4,158	4,652
	95%-KI	(-3,0; 12,1)	(-0,2; 16,1)	(-12,5; 5,7)
Woche 120	n	28	16	
	LS-Mean	2,050	3,544	-1,494
	SEM	3,781	4,509	4,913
	95%-KI	(-5,4; 9,5)	(-5,3; 12,4)	(-11,1; 8,1)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

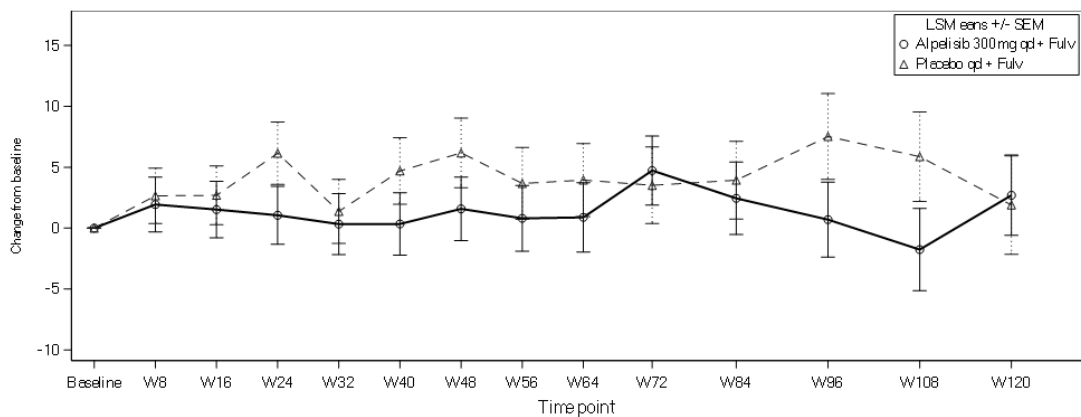
Abbildung 4H-3: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schmerzen – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel



Tabelle 4H-4: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Dyspnoe“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	1,937	2,651	-0,714
	SEM	2,243	2,277	2,039
	95%-KI	(-2,5; 6,3)	(-1,8; 7,1)	(-4,7; 3,3)
Woche 16	n	124	107	
	LS-Mean	1,521	2,690	-1,169
	SEM	2,311	2,419	2,225
	95%-KI	(-3,0; 6,1)	(-2,1; 7,4)	(-5,5; 3,2)
Woche 24	n	105	81	
	LS-Mean	1,054	6,149	-5,096
	SEM	2,383	2,563	2,441
	95%-KI	(-3,6; 5,7)	( 1,1;11,2)	(-9,9;-0,3)
Woche 32	n	86	73	
	LS-Mean	0,328	1,371	-1,043
	SEM	2,498	2,630	2,588
	95%-KI	(-4,6; 5,2)	(-3,8; 6,5)	(-6,1; 4,0)
Woche 40	n	75	62	
	LS-Mean	0,339	4,692	-4,353
	SEM	2,566	2,732	2,748
	95%-KI	(-4,7; 5,4)	(-0,7;10,1)	(-9,7; 1,0)
Woche 48	n	69	51	
	LS-Mean	1,581	6,180	-4,599
	SEM	2,610	2,857	2,912
	95%-KI	(-3,5; 6,7)	( 0,6;11,8)	(-10,3; 1,1)
Woche 56	n	59	45	
	LS-Mean	0,802	3,666	-2,864
	SEM	2,698	2,946	3,081
	95%-KI	(-4,5; 6,1)	(-2,1; 9,4)	(-8,9; 3,2)
Woche 64	n	47	42	
	LS-Mean	0,882	3,945	-3,062
	SEM	2,844	2,999	3,261
	95%-KI	(-4,7; 6,5)	(-1,9; 9,8)	(-9,5; 3,3)
Woche 72	n	48	35	
	LS-Mean	4,730	3,515	1,215
	SEM	2,831	3,149	3,388
	95%-KI	(-0,8;10,3)	(-2,7; 9,7)	(-5,4; 7,9)
Woche 84	n	40	33	
	LS-Mean	2,445	3,933	-1,488
	SEM	2,980	3,201	3,549
	95%-KI	(-3,4; 8,3)	(-2,3;10,2)	(-8,4; 5,5)
Woche 96	n	35	24	
	LS-Mean	0,696	7,524	-6,827
	SEM	3,084	3,522	3,929
	95%-KI	(-5,4; 6,7)	( 0,6;14,4)	(-14,5; 0,9)
Woche 108	n	26	21	
	LS-Mean	-1,764	5,868	-7,632
	SEM	3,382	3,679	4,294
	95%-KI	(-8,4; 4,9)	(-1,3;13,1)	(-16,1; 0,8)
Woche 120	n	28	16	
	LS-Mean	2,693	1,896	0,797
	SEM	3,296	4,044	4,554
	95%-KI	(-3,8; 9,2)	(-6,0; 9,8)	(-8,1; 9,7)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



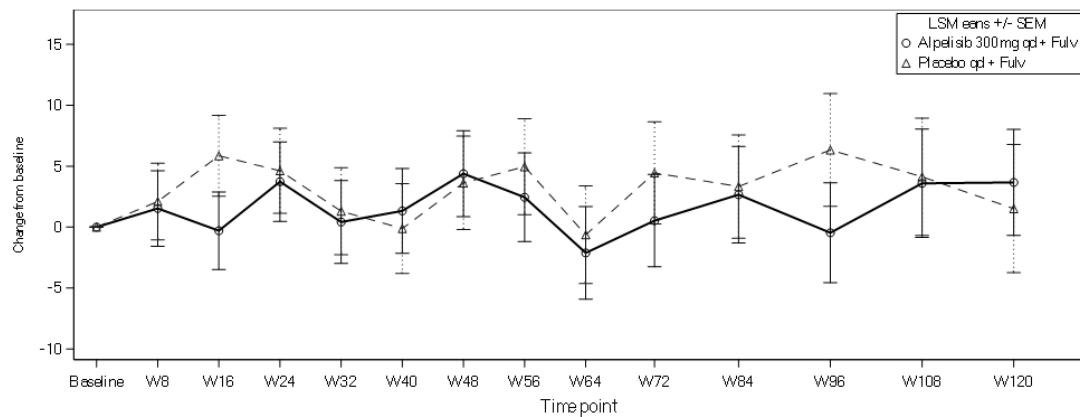
Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	28	28
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

Abbildung 4H-4: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Dyspnoe – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-5: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schlaflosigkeit“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	1,529	2,100	-0,571
	SEM	3,101	3,150	2,768
	95%-KI	(-4,6; 7,6)	(-4,1; 8,3)	(-6,0; 4,9)
Woche 16	n	124	107	
	LS-Mean	-0,298	5,856	-6,154
	SEM	3,184	3,321	2,995
	95%-KI	(-6,6; 6,0)	(-0,7; 12,4)	(-12,0; -0,3)
Woche 24	n	105	81	
	LS-Mean	3,729	4,620	-0,891
	SEM	3,269	3,492	3,255
	95%-KI	(-2,7; 10,2)	(-2,2; 11,5)	(-7,3; 5,5)
Woche 32	n	86	73	
	LS-Mean	0,415	1,303	-0,888
	SEM	3,402	3,570	3,432
	95%-KI	(-6,3; 7,1)	(-5,7; 8,3)	(-7,6; 5,8)
Woche 40	n	75	62	
	LS-Mean	1,329	-0,119	1,448
	SEM	3,482	3,690	3,626
	95%-KI	(-5,5; 8,2)	(-7,4; 7,1)	(-5,7; 8,6)
Woche 48	n	69	51	
	LS-Mean	4,384	3,624	0,761
	SEM	3,533	3,837	3,824
	95%-KI	(-2,6; 11,3)	(-3,9; 11,2)	(-6,7; 8,3)
Woche 56	n	59	45	
	LS-Mean	2,449	4,963	-2,514
	SEM	3,637	3,942	4,027
	95%-KI	(-4,7; 9,6)	(-2,8; 12,7)	(-10,4; 5,4)
Woche 64	n	47	42	
	LS-Mean	-2,117	-0,631	-1,486
	SEM	3,809	4,005	4,247
	95%-KI	(-9,6; 5,4)	(-8,5; 7,2)	(-9,8; 6,8)
Woche 72	n	48	35	
	LS-Mean	0,528	4,448	-3,920
	SEM	3,794	4,182	4,401
	95%-KI	(-6,9; 8,0)	(-3,8; 12,7)	(-12,6; 4,7)
Woche 84	n	40	33	
	LS-Mean	2,662	3,329	-0,667
	SEM	3,968	4,244	4,597
	95%-KI	(-5,1; 10,4)	(-5,0; 11,7)	(-9,7; 8,3)
Woche 96	n	35	24	
	LS-Mean	-0,468	6,331	-6,799
	SEM	4,093	4,629	5,062
	95%-KI	(-8,5; 7,6)	(-2,8; 15,4)	(-16,7; 3,1)
Woche 108	n	26	21	
	LS-Mean	3,591	4,131	-0,539
	SEM	4,447	4,817	5,508
	95%-KI	(-5,1; 12,3)	(-5,3; 13,6)	(-11,3; 10,3)
Woche 120	n	28	16	
	LS-Mean	3,666	1,514	2,152
	SEM	4,346	5,259	5,829
	95%-KI	(-4,9; 12,2)	(-8,8; 11,8)	(-9,3; 13,6)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



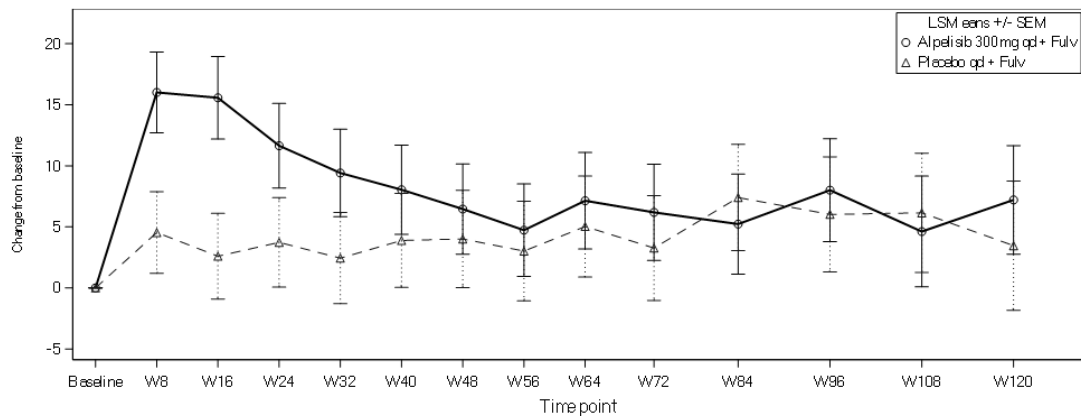
Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

Abbildung 4H-5: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schlaflosigkeit – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-6: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Appetitverlust“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	16,010	4,533	11,477
	SEM	3,304	3,347	2,895
	95%-KI	( 9,5;22,5)	( -2,0;11,1)	( 5,8;17,2)
Woche 16	n	124	107	
	LS-Mean	15,572	2,595	12,978
	SEM	3,381	3,508	3,112
	95%-KI	( 8,9;22,2)	( -4,3; 9,5)	( 6,9;19,1)
Woche 24	n	105	81	
	LS-Mean	11,643	3,728	7,915
	SEM	3,458	3,665	3,354
	95%-KI	( 4,8;18,4)	( -3,5;10,9)	( 1,3;14,5)
Woche 32	n	86	73	
	LS-Mean	9,412	2,436	6,975
	SEM	3,578	3,736	3,520
	95%-KI	( 2,4;16,4)	( -4,9; 9,8)	( 0,1;13,9)
Woche 40	n	75	62	
	LS-Mean	8,040	3,883	4,157
	SEM	3,651	3,844	3,699
	95%-KI	( 0,9;15,2)	( -3,7;11,4)	( -3,1;11,4)
Woche 48	n	69	51	
	LS-Mean	6,457	4,007	2,449
	SEM	3,697	3,979	3,884
	95%-KI	( -0,8;13,7)	( -3,8;11,8)	( -5,2;10,1)
Woche 56	n	59	45	
	LS-Mean	4,726	3,015	1,711
	SEM	3,792	4,075	4,074
	95%-KI	( -2,7;12,2)	( -5,0;11,0)	( -6,3; 9,7)
Woche 64	n	47	42	
	LS-Mean	7,137	5,025	2,112
	SEM	3,949	4,133	4,279
	95%-KI	( -0,6;14,9)	( -3,1;13,1)	( -6,3;10,5)
Woche 72	n	48	35	
	LS-Mean	6,185	3,265	2,920
	SEM	3,935	4,296	4,424
	95%-KI	( -1,5;13,9)	( -5,2;11,7)	( -5,8;11,6)
Woche 84	n	40	33	
	LS-Mean	5,226	7,396	-2,171
	SEM	4,094	4,353	4,610
	95%-KI	( -2,8;13,3)	( -1,1;15,9)	(-11,2; 6,9)
Woche 96	n	35	24	
	LS-Mean	8,002	6,020	1,983
	SEM	4,209	4,710	5,049
	95%-KI	( -0,3;16,3)	( -3,2;15,3)	( -7,9;11,9)
Woche 108	n	26	21	
	LS-Mean	4,615	6,148	-1,533
	SEM	4,536	4,886	5,475
	95%-KI	( -4,3;13,5)	( -3,4;15,7)	(-12,3; 9,2)
Woche 120	n	28	16	
	LS-Mean	7,206	3,461	3,745
	SEM	4,443	5,299	5,781
	95%-KI	( -1,5;15,9)	( -6,9;13,9)	( -7,6;15,1)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



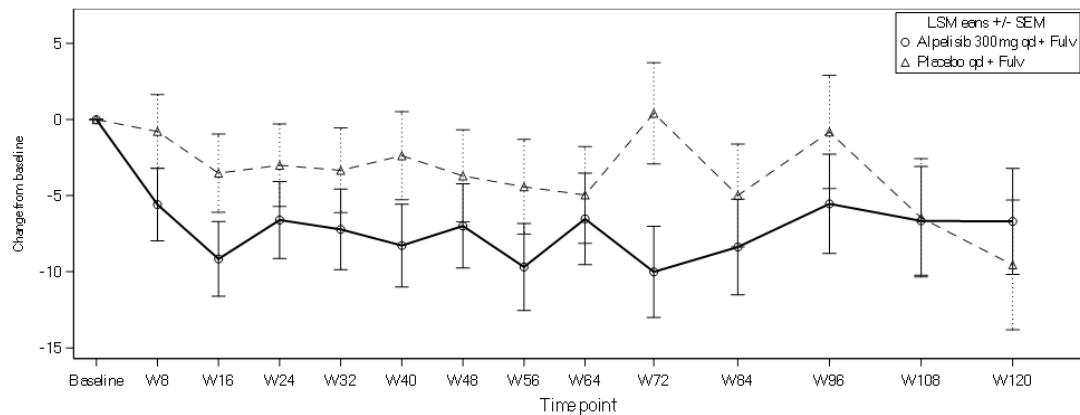
Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

Abbildung 4H-6: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Appetitverlust – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-7: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Obstipation“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-5,584	-0,784	-4,800
	SEM	2,380	2,417	2,159
	95%-KI	(-10,3;-0,9)	(-5,5; 4,0)	(-9,0;-0,6)
Woche 16	n	124	107	
	LS-Mean	-9,157	-3,523	-5,633
	SEM	2,452	2,566	2,355
	95%-KI	(-14,0;-4,3)	(-8,6; 1,5)	(-10,3;-1,0)
Woche 24	n	105	81	
	LS-Mean	-6,601	-3,003	-3,598
	SEM	2,527	2,716	2,580
	95%-KI	(-11,6;-1,6)	(-8,3; 2,3)	(-8,7; 1,5)
Woche 32	n	86	73	
	LS-Mean	-7,217	-3,337	-3,880
	SEM	2,647	2,785	2,735
	95%-KI	(-12,4;-2,0)	(-8,8; 2,1)	(-9,2; 1,5)
Woche 40	n	75	62	
	LS-Mean	-8,278	-2,372	-5,907
	SEM	2,718	2,892	2,902
	95%-KI	(-13,6;-2,9)	(-8,0; 3,3)	(-11,6;-0,2)
Woche 48	n	69	51	
	LS-Mean	-6,992	-3,704	-3,288
	SEM	2,764	3,022	3,074
	95%-KI	(-12,4;-1,6)	(-9,6; 2,2)	(-9,3; 2,7)
Woche 56	n	59	45	
	LS-Mean	-9,687	-4,419	-5,268
	SEM	2,856	3,115	3,250
	95%-KI	(-15,3;-4,1)	(-10,5; 1,7)	(-11,6; 1,1)
Woche 64	n	47	42	
	LS-Mean	-6,525	-4,956	-1,570
	SEM	3,009	3,171	3,440
	95%-KI	(-12,4;-0,6)	(-11,2; 1,3)	(-8,3; 5,2)
Woche 72	n	48	35	
	LS-Mean	-10,01	0,414	-10,42
	SEM	2,995	3,328	3,572
	95%-KI	(-15,9;-4,1)	(-6,1; 6,9)	(-17,4;-3,4)
Woche 84	n	40	33	
	LS-Mean	-8,376	-4,985	-3,391
	SEM	3,149	3,382	3,741
	95%-KI	(-14,6;-2,2)	(-11,6; 1,7)	(-10,7; 3,9)
Woche 96	n	35	24	
	LS-Mean	-5,540	-0,814	-4,725
	SEM	3,259	3,719	4,140
	95%-KI	(-11,9; 0,9)	(-8,1; 6,5)	(-12,8; 3,4)
Woche 108	n	26	21	
	LS-Mean	-6,657	-6,455	-0,202
	SEM	3,570	3,882	4,522
	95%-KI	(-13,7; 0,3)	(-14,1; 1,2)	(-9,1; 8,7)
Woche 120	n	28	16	
	LS-Mean	-6,693	-9,553	2,860
	SEM	3,481	4,265	4,796
	95%-KI	(-13,5; 0,1)	(-17,9;-1,2)	(-6,5; 12,3)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



Alpelisib 300mg qd + Fulv	161	142	124	105	88	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

Abbildung 4H-7: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Obstipation – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel



Tabelle 4H-8: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Diarrhoe“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	14,049	2,325	11,724
	SEM	2,585	2,625	2,364
	95%-KI	( 9,0;19,1)	( -2,8; 7,5)	( 7,1;16,4)
Woche 16	n	124	107	
	LS-Mean	13,883	3,280	10,603
	SEM	2,667	2,793	2,586
	95%-KI	( 8,6;19,1)	( -2,2; 8,8)	( 5,5;15,7)
Woche 24	n	105	81	
	LS-Mean	15,090	1,121	13,969
	SEM	2,753	2,965	2,841
	95%-KI	( 9,7;20,5)	( -4,7; 6,9)	( 8,4;19,5)
Woche 32	n	86	73	
	LS-Mean	13,882	-0,259	14,141
	SEM	2,891	3,044	3,016
	95%-KI	( 8,2;19,6)	( -6,2; 5,7)	( 8,2;20,1)
Woche 40	n	75	62	
	LS-Mean	14,711	1,443	13,269
	SEM	2,971	3,166	3,205
	95%-KI	( 8,9;20,5)	( -4,8; 7,7)	( 7,0;19,6)
Woche 48	n	69	51	
	LS-Mean	12,718	1,918	10,800
	SEM	3,023	3,315	3,399
	95%-KI	( 6,8;18,7)	( -4,6; 8,4)	( 4,1;17,5)
Woche 56	n	59	45	
	LS-Mean	14,393	0,232	14,161
	SEM	3,128	3,421	3,598
	95%-KI	( 8,3;20,5)	( -6,5; 6,9)	( 7,1;21,2)
Woche 64	n	47	42	
	LS-Mean	13,256	-0,118	13,374
	SEM	3,303	3,485	3,812
	95%-KI	( 6,8;19,7)	( -7,0; 6,7)	( 5,9;20,9)
Woche 72	n	48	35	
	LS-Mean	11,094	2,239	8,855
	SEM	3,287	3,663	3,962
	95%-KI	( 4,6;17,5)	( -4,9; 9,4)	( 1,1;16,6)
Woche 84	n	40	33	
	LS-Mean	15,565	1,589	13,976
	SEM	3,464	3,725	4,153
	95%-KI	( 8,8;22,4)	( -5,7; 8,9)	( 5,8;22,1)
Woche 96	n	35	24	
	LS-Mean	18,101	-3,545	21,646
	SEM	3,588	4,108	4,604
	95%-KI	( 11,1;25,1)	(-11,6; 4,5)	( 12,6;30,7)
Woche 108	n	26	21	
	LS-Mean	9,473	-1,251	10,723
	SEM	3,943	4,294	5,035
	95%-KI	( 1,7;17,2)	( -9,7; 7,2)	( 0,8;20,6)
Woche 120	n	28	16	
	LS-Mean	10,275	0,612	9,664
	SEM	3,841	4,727	5,343
	95%-KI	( 2,7;17,8)	( -8,7; 9,9)	( -0,8;20,1)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes

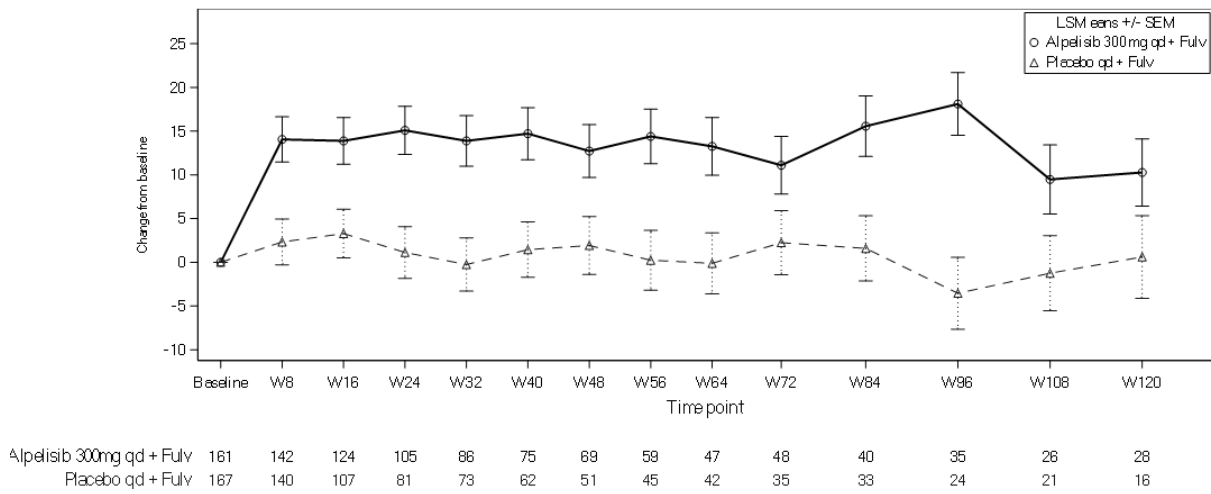


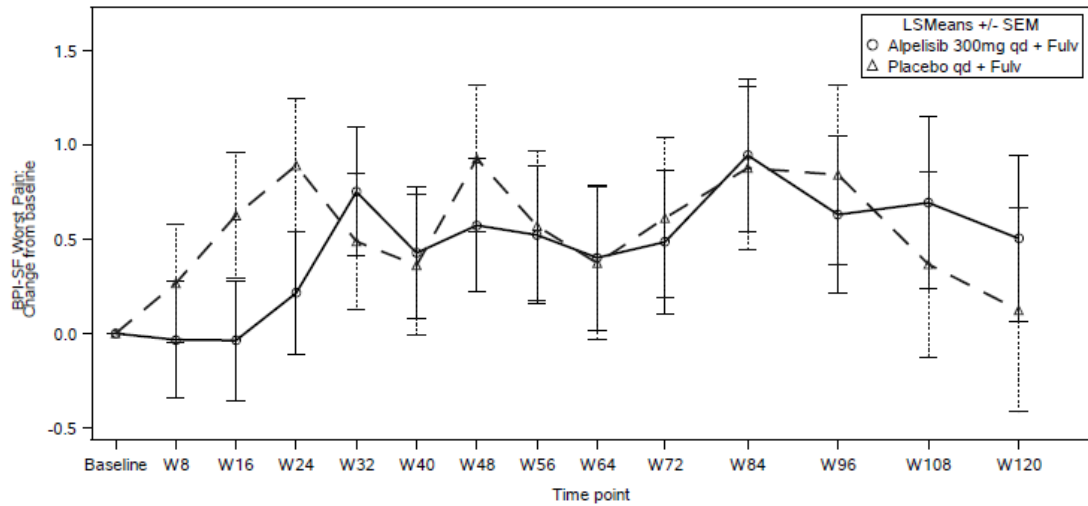
Abbildung 4H-8: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Diarrhoe – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

**4.8.1.2 Krankheitssymptomatik: BPI-SF – 2. Datenschnitt**

Tabelle 4H-9: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Stärkster Schmerz“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	137	
	LS-Mean	-0,033	0,266	-0,300
	SEM	0,308	0,314	0,279
	95%-KI	( -0,6; 0,6)	( -0,4; 0,9)	( -0,8; 0,2)
Woche 16	n	124	105	
	LS-Mean	-0,037	0,626	-0,663
	SEM	0,317	0,332	0,303
	95%-KI	( -0,7; 0,6)	( -0,0; 1,3)	( -1,3; -0,1)
Woche 24	n	105	80	
	LS-Mean	0,214	0,891	-0,677
	SEM	0,326	0,351	0,331
	95%-KI	( -0,4; 0,9)	( 0,2; 1,6)	( -1,3; -0,0)
Woche 32	n	86	72	
	LS-Mean	0,751	0,488	0,263
	SEM	0,341	0,359	0,350
	95%-KI	( 0,1; 1,4)	( -0,2; 1,2)	( -0,4; 1,0)
Woche 40	n	75	61	
	LS-Mean	0,427	0,362	0,065
	SEM	0,350	0,373	0,371
	95%-KI	( -0,3; 1,1)	( -0,4; 1,1)	( -0,7; 0,8)
Woche 48	n	69	50	
	LS-Mean	0,573	0,926	-0,353
	SEM	0,355	0,389	0,393
	95%-KI	( -0,1; 1,3)	( 0,2; 1,7)	( -1,1; 0,4)
Woche 56	n	59	45	
	LS-Mean	0,522	0,570	-0,048
	SEM	0,366	0,399	0,413
	95%-KI	( -0,2; 1,2)	( -0,2; 1,4)	( -0,9; 0,8)
Woche 64	n	47	42	
	LS-Mean	0,401	0,373	0,029
	SEM	0,385	0,406	0,436
	95%-KI	( -0,4; 1,2)	( -0,4; 1,2)	( -0,8; 0,9)
Woche 72	n	48	35	
	LS-Mean	0,485	0,612	-0,127
	SEM	0,383	0,425	0,452
	95%-KI	( -0,3; 1,2)	( -0,2; 1,4)	( -1,0; 0,8)
Woche 84	n	40	33	
	LS-Mean	0,945	0,878	0,067
	SEM	0,402	0,432	0,473
	95%-KI	( 0,2; 1,7)	( 0,0; 1,7)	( -0,9; 1,0)
Woche 96	n	35	24	
	LS-Mean	0,630	0,842	-0,211
	SEM	0,416	0,473	0,523
	95%-KI	( -0,2; 1,4)	( -0,1; 1,8)	( -1,2; 0,8)
Woche 108	n	26	21	
	LS-Mean	0,693	0,367	0,326
	SEM	0,454	0,493	0,570
	95%-KI	( -0,2; 1,6)	( -0,6; 1,3)	( -0,8; 1,4)
Woche 120	n	28	16	
	LS-Mean	0,504	0,124	0,380
	SEM	0,443	0,540	0,604
	95%-KI	( -0,4; 1,4)	( -0,9; 1,2)	( -0,8; 1,6)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up 7,6 Monate im Alpelisib-Arm und 3,7 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum. **Abkürzungen:** LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	164	137	105	80	72	61	50	45	42	35	33	24	21	16

- The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as derived from the repeated measurement model.

- The mixed effect model includes terms for treatment, stratification factors, baseline value, time and time \* treatment interaction.

This analysis only includes assessments up to the time point where there are at least 10 patients on each of the treatment groups

Abbildung 4H-9: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (BPI-SF): Stärkster Schmerz – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-10: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Schweregrad-Index“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	137	
	LS-Mean	0,072	0,255	-0,183
	SEM	0,244	0,248	0,217
	95%-KI	(-0,4; 0,6)	(-0,2; 0,7)	(-0,6; 0,2)
Woche 16	n	124	105	
	LS-Mean	0,075	0,543	-0,469
	SEM	0,250	0,261	0,235
	95%-KI	(-0,4; 0,6)	(0,0; 1,1)	(-0,9; -0,0)
Woche 24	n	105	80	
	LS-Mean	0,287	0,725	-0,438
	SEM	0,257	0,274	0,255
	95%-KI	(-0,2; 0,8)	(0,2; 1,3)	(-0,9; 0,1)
Woche 32	n	86	72	
	LS-Mean	0,538	0,493	0,045
	SEM	0,267	0,280	0,268
	95%-KI	(0,0; 1,1)	(-0,1; 1,0)	(-0,5; 0,6)
Woche 40	n	75	61	
	LS-Mean	0,352	0,442	-0,090
	SEM	0,273	0,290	0,283
	95%-KI	(-0,2; 0,9)	(-0,1; 1,0)	(-0,6; 0,5)
Woche 48	n	69	50	
	LS-Mean	0,659	0,701	-0,042
	SEM	0,277	0,301	0,299
	95%-KI	(0,1; 1,2)	(0,1; 1,3)	(-0,6; 0,5)
Woche 56	n	59	45	
	LS-Mean	0,553	0,557	-0,003
	SEM	0,285	0,308	0,313
	95%-KI	(-0,0; 1,1)	(-0,0; 1,2)	(-0,6; 0,6)
Woche 64	n	47	42	
	LS-Mean	0,381	0,396	-0,015
	SEM	0,298	0,313	0,330
	95%-KI	(-0,2; 1,0)	(-0,2; 1,0)	(-0,7; 0,6)
Woche 72	n	48	35	
	LS-Mean	0,558	0,525	0,034
	SEM	0,297	0,327	0,342
	95%-KI	(-0,0; 1,1)	(-0,1; 1,2)	(-0,6; 0,7)
Woche 84	n	40	33	
	LS-Mean	0,765	0,874	-0,108
	SEM	0,310	0,331	0,357
	95%-KI	(0,2; 1,4)	(0,2; 1,5)	(-0,8; 0,6)
Woche 96	n	35	24	
	LS-Mean	0,714	0,709	0,006
	SEM	0,319	0,361	0,393
	95%-KI	(0,1; 1,3)	(0,0; 1,4)	(-0,8; 0,8)
Woche 108	n	26	21	
	LS-Mean	0,692	0,344	0,348
	SEM	0,347	0,375	0,427
	95%-KI	(0,0; 1,4)	(-0,4; 1,1)	(-0,5; 1,2)
Woche 120	n	28	16	
	LS-Mean	0,551	0,350	0,201
	SEM	0,339	0,409	0,452
	95%-KI	(-0,1; 1,2)	(-0,5; 1,2)	(-0,7; 1,1)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up 7,6 Monate im Alpelisib-Arm und 3,7 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes

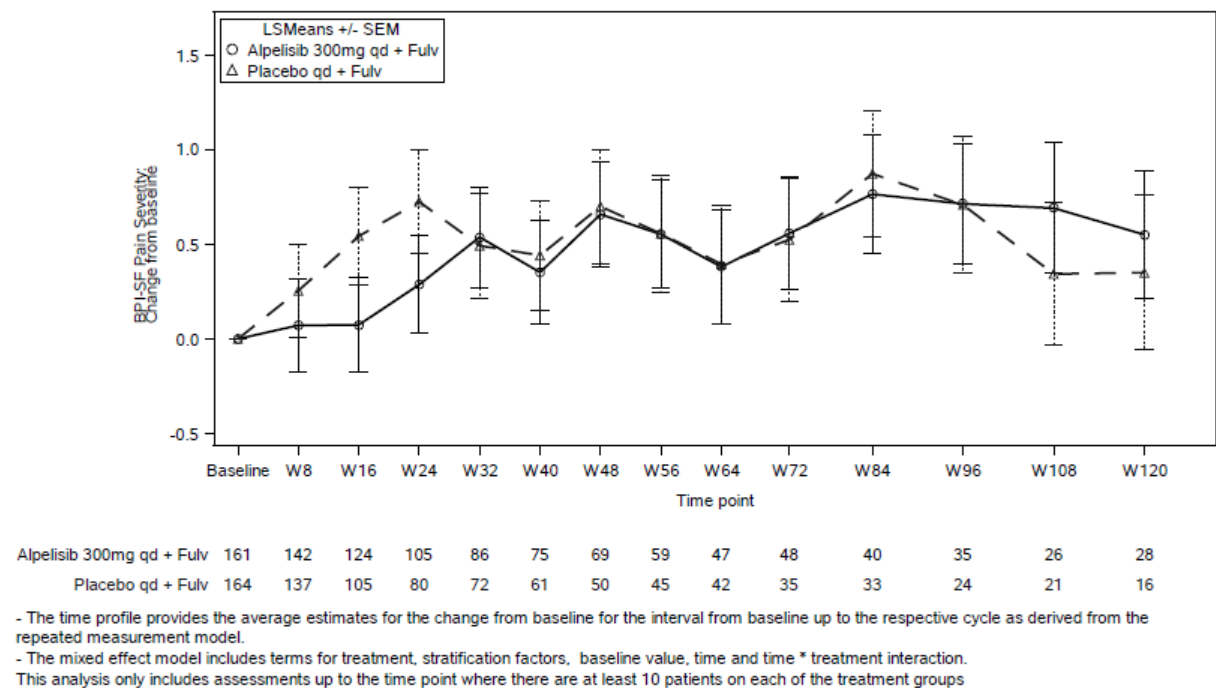
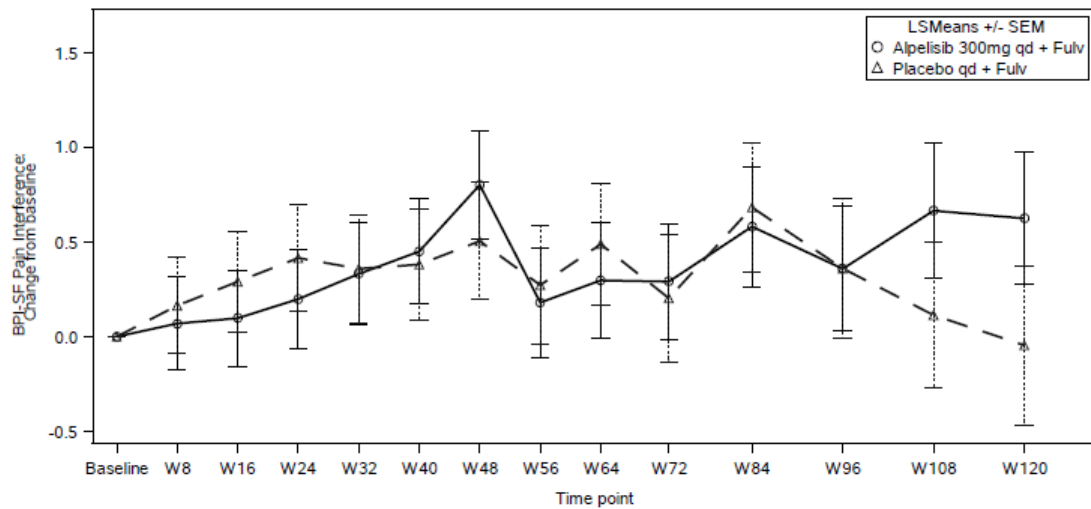


Abbildung 4H-10: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Schweregrad-Index – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-11: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Interferenz-Index“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	137	
	LS-Mean	0,070	0,164	-0,095
	SEM	0,248	0,252	0,222
	95%-KI	(-0,4; 0,6)	(-0,3; 0,7)	(-0,5; 0,3)
Woche 16	n	124	105	
	LS-Mean	0,098	0,291	-0,193
	SEM	0,254	0,266	0,240
	95%-KI	(-0,4; 0,6)	(-0,2; 0,8)	(-0,7; 0,3)
Woche 24	n	105	79	
	LS-Mean	0,199	0,416	-0,217
	SEM	0,261	0,281	0,262
	95%-KI	(-0,3; 0,7)	(-0,1; 1,0)	(-0,7; 0,3)
Woche 32	n	86	72	
	LS-Mean	0,332	0,359	-0,028
	SEM	0,272	0,286	0,276
	95%-KI	(-0,2; 0,9)	(-0,2; 0,9)	(-0,6; 0,5)
Woche 40	n	75	61	
	LS-Mean	0,450	0,381	0,069
	SEM	0,279	0,296	0,291
	95%-KI	(-0,1; 1,0)	(-0,2; 1,0)	(-0,5; 0,6)
Woche 48	n	69	50	
	LS-Mean	0,802	0,505	0,297
	SEM	0,283	0,309	0,308
	95%-KI	( 0,2; 1,4)	(-0,1; 1,1)	(-0,3; 0,9)
Woche 56	n	59	45	
	LS-Mean	0,180	0,273	-0,092
	SEM	0,291	0,316	0,323
	95%-KI	(-0,4; 0,8)	(-0,3; 0,9)	(-0,7; 0,5)
Woche 64	n	47	42	
	LS-Mean	0,298	0,489	-0,191
	SEM	0,305	0,321	0,341
	95%-KI	(-0,3; 0,9)	(-0,1; 1,1)	(-0,9; 0,5)
Woche 72	n	48	35	
	LS-Mean	0,291	0,204	0,087
	SEM	0,304	0,335	0,353
	95%-KI	(-0,3; 0,9)	(-0,5; 0,9)	(-0,6; 0,8)
Woche 84	n	40	33	
	LS-Mean	0,582	0,683	-0,102
	SEM	0,318	0,340	0,369
	95%-KI	(-0,0; 1,2)	( 0,0; 1,4)	(-0,8; 0,6)
Woche 96	n	35	24	
	LS-Mean	0,359	0,360	-0,002
	SEM	0,328	0,371	0,406
	95%-KI	(-0,3; 1,0)	(-0,4; 1,1)	(-0,8; 0,8)
Woche 108	n	26	21	
	LS-Mean	0,666	0,114	0,552
	SEM	0,356	0,386	0,442
	95%-KI	(-0,0; 1,4)	(-0,6; 0,9)	(-0,3; 1,4)
Woche 120	n	28	16	
	LS-Mean	0,625	-0,045	0,670
	SEM	0,348	0,422	0,468
	95%-KI	(-0,1; 1,3)	(-0,9; 0,8)	(-0,2; 1,6)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up 7,6 Monate im Alpelisib-Arm und 3,7 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	164	137	105	79	72	61	50	45	42	35	33	24	21	16

- The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as derived from the repeated measurement model.

- The mixed effect model includes terms for treatment, stratification factors, baseline value, time and time \* treatment interaction. This analysis only includes assessments up to the time point where there are at least 10 patients on each of the treatment groups

Abbildung 4H-11: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Interferenz-Index – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel



**4.8.1.3 Gesundheitszustand: EQ-5D-VAS – 2. Datenschnitt**

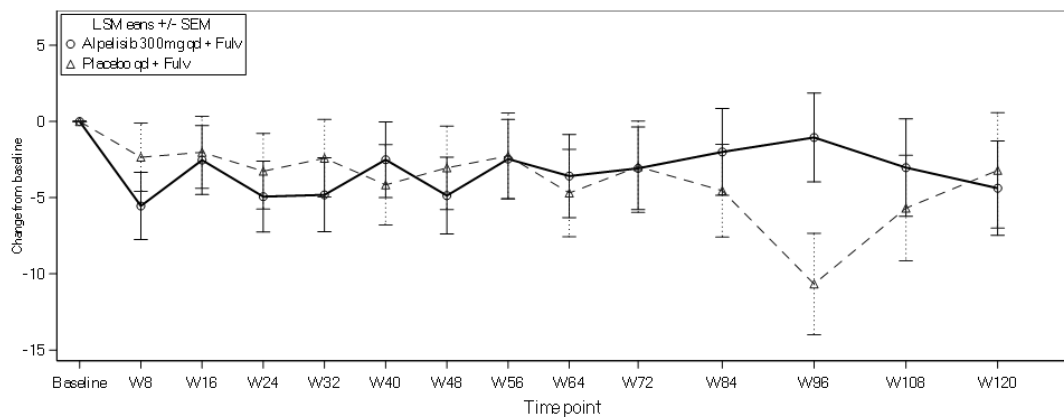
Tabelle 4H-12: Ergebnisse für den Endpunkt „Gesundheitszustand (EQ-5D VAS)“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	141	
	LS-Mean	-5,546	-2,348	-3,198
	SEM	2,205	2,238	1,968
	95%-KI	(-9,9; -1,2)	(-6,7; 2,0)	(-7,1; 0,7)
Woche 16	n	125	107	
	LS-Mean	-2,536	-2,023	-0,513
	SEM	2,263	2,365	2,135
	95%-KI	(-7,0; 1,9)	(-6,7; 2,6)	(-4,7; 3,7)
Woche 24	n	105	82	
	LS-Mean	-4,933	-3,267	-1,667
	SEM	2,328	2,485	2,324
	95%-KI	(-9,5; -0,4)	(-8,1; 1,6)	(-6,2; 2,9)
Woche 32	n	86	73	
	LS-Mean	-4,817	-2,411	-2,406
	SEM	2,427	2,547	2,460
	95%-KI	(-9,6; -0,1)	(-7,4; 2,6)	(-7,2; 2,4)
Woche 40	n	75	62	
	LS-Mean	-2,510	-4,160	1,650
	SEM	2,486	2,636	2,601
	95%-KI	(-7,4; 2,4)	(-9,3; 1,0)	(-3,5; 6,8)
Woche 48	n	69	51	
	LS-Mean	-4,864	-3,044	-1,820
	SEM	2,524	2,744	2,746
	95%-KI	(-9,8; 0,1)	(-8,4; 2,3)	(-7,2; 3,6)
Woche 56	n	59	45	
	LS-Mean	-2,464	-2,264	-0,200
	SEM	2,600	2,822	2,895
	95%-KI	(-7,6; 2,6)	(-7,8; 3,3)	(-5,9; 5,5)
Woche 64	n	47	42	
	LS-Mean	-3,584	-4,694	1,110
	SEM	2,727	2,868	3,056
	95%-KI	(-8,9; 1,8)	(-10,3; 0,9)	(-4,9; 7,1)
Woche 72	n	48	35	
	LS-Mean	-3,076	-2,972	-0,104
	SEM	2,716	2,999	3,169
	95%-KI	(-8,4; 2,3)	(-8,9; 2,9)	(-6,3; 6,1)
Woche 84	n	40	33	
	LS-Mean	-2,000	-4,541	2,542
	SEM	2,844	3,045	3,313
	95%-KI	(-7,6; 3,6)	(-10,5; 1,4)	(-4,0; 9,0)
Woche 96	n	36	24	
	LS-Mean	-1,052	-10,67	9,615
	SEM	2,915	3,328	3,636
	95%-KI	(-6,8; 4,7)	(-17,2; -4,1)	(2,5; 16,7)
Woche 108	n	26	21	
	LS-Mean	-3,028	-5,689	2,661
	SEM	3,197	3,466	3,981
	95%-KI	(-9,3; 3,2)	(-12,5; 1,1)	(-5,1; 10,5)
Woche 120	n	29	16	
	LS-Mean	-4,380	-3,209	-1,171
	SEM	3,092	3,790	4,193
	95%-KI	(-10,4; 1,7)	(-10,6; 4,2)	(-9,4; 7,1)

\* 2. Datenschnitt (30.09.2019); medianer Follow-up: 6,2 Monate im Alpelisib-Arm und 3,6 Monate im Placebo-Arm.

<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.

Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



Alpelisib 300mg qd + Fulv	161	142	125	105	86	75	69	59	47	48	40	36	26	29
Placebo qd + Fulv	167	141	107	82	73	62	51	45	42	35	33	24	21	16

Abbildung 4H-12: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Gesundheitszustand (EQ-5D VAS) – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

#### 4.8.1.4 Gesundheitsbezogenen Lebensqualität: EORTC QLQ-C30 – 2. Datenschnitt

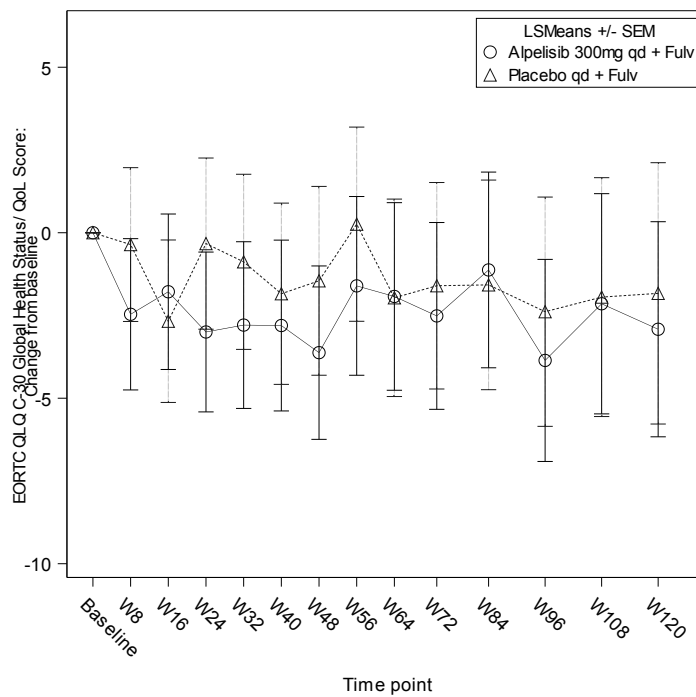
Tabelle 4H-13: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30: Allgemeiner Gesundheitszustand/Lebensqualität)“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analyse\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-2,464	-0,358	-2,107
	SEM	2,285	2,324	2,047
	95%-KI	(-7,0; 2,0)	(-4,9; 4,2)	(-6,1; 1,9)
Woche 16	n	124	107	
	LS-Mean	-1,783	-2,674	0,890
	SEM	2,349	2,455	2,222
	95%-KI	(-6,4; 2,8)	(-7,5; 2,1)	(-3,5; 5,3)
Woche 24	n	105	81	
	LS-Mean	-2,999	-0,329	-2,670
	SEM	2,415	2,586	2,422
	95%-KI	(-7,7; 1,7)	(-5,4; 4,8)	(-7,4; 2,1)
Woche 32	n	86	73	
	LS-Mean	-2,790	-0,879	-1,911
	SEM	2,518	2,646	2,559
	95%-KI	(-7,7; 2,2)	(-6,1; 4,3)	(-6,9; 3,1)
Woche 40	n	75	62	
	LS-Mean	-2,804	-1,844	-0,960
	SEM	2,580	2,738	2,707
	95%-KI	(-7,9; 2,3)	(-7,2; 3,5)	(-6,3; 4,4)
Woche 48	n	69	51	
	LS-Mean	-3,623	-1,453	-2,170
	SEM	2,620	2,852	2,859
	95%-KI	(-8,8; 1,5)	(-7,1; 4,1)	(-7,8; 3,4)
Woche 56	n	59	45	
	LS-Mean	-1,606	0,258	-1,864
	SEM	2,700	2,934	3,016
	95%-KI	(-6,9; 3,7)	(-5,5; 6,0)	(-7,8; 4,1)
Woche 64	n	47	42	
	LS-Mean	-1,926	-1,966	0,041
	SEM	2,834	2,983	3,184
	95%-KI	(-7,5; 3,6)	(-7,8; 3,9)	(-6,2; 6,3)
Woche 72	n	48	35	
	LS-Mean	-2,514	-1,602	-0,912
	SEM	2,822	3,119	3,302
	95%-KI	(-8,1; 3,0)	(-7,7; 4,5)	(-7,4; 5,6)
Woche 84	n	40	33	
	LS-Mean	-1,124	-1,576	0,451
	SEM	2,956	3,167	3,453
	95%-KI	(-6,9; 4,7)	(-7,8; 4,6)	(-6,3; 7,2)
Woche 96	n	35	24	
	LS-Mean	-3,858	-2,386	-1,472
	SEM	3,053	3,464	3,809
	95%-KI	(-9,8; 2,1)	(-9,2; 4,4)	(-8,9; 6,0)
Woche 108	n	26	21	
	LS-Mean	-2,147	-1,945	-0,201
	SEM	3,327	3,609	4,151
	95%-KI	(-8,7; 4,4)	(-9,0; 5,1)	(-8,3; 7,9)
Woche 120	n	28	16	
	LS-Mean	-2,917	-1,832	-1,085
	SEM	3,249	3,948	4,396
	95%-KI	(-9,3; 3,5)	(-9,6; 5,9)	(-9,7; 7,5)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,6 Monate im Alpelisib-Arm und 3,7 Monate im Placebo-Arm.

<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.

Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	59	47	48	40	35	26	28
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

- The time profile provides the average estimates for the change from baseline for the interval from baseline up to the respective cycle as derived from the repeated measurement model.  
 - The mixed effect model includes terms for treatment, stratification factors, baseline value, time and time \* treatment interaction.

This analysis only includes assessments up to the time point where there are at least 10 patients on each of the treatment groups

Abbildung 4H-13: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Allgemeiner Gesundheitszustand/Lebensqualität – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-14: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Körperliche Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-2,881	-2,117	-0,764
	SEM	2,068	2,099	1,779
	95%-KI	(-6,9; 1,2)	(-6,2; 2,0)	(-4,3; 2,7)
Woche 16	n	124	107	
	LS-Mean	-2,488	-2,608	0,120
	SEM	2,109	2,185	1,899
	95%-KI	(-6,6; 1,7)	(-6,9; 1,7)	(-3,6; 3,9)
Woche 24	n	105	81	
	LS-Mean	-3,497	-4,343	0,845
	SEM	2,150	2,269	2,031
	95%-KI	(-7,7; 0,7)	(-8,8; 0,1)	(-3,1; 4,8)
Woche 32	n	86	73	
	LS-Mean	-2,045	-4,054	2,010
	SEM	2,213	2,306	2,122
	95%-KI	(-6,4; 2,3)	(-8,6; 0,5)	(-2,2; 6,2)
Woche 40	n	75	62	
	LS-Mean	-0,880	-4,729	3,849
	SEM	2,252	2,363	2,219
	95%-KI	(-5,3; 3,5)	(-9,4; -0,1)	(-0,5; 8,2)
Woche 48	n	69	51	
	LS-Mean	-4,042	-5,118	1,076
	SEM	2,276	2,435	2,320
	95%-KI	(-8,5; 0,4)	(-9,9; -0,3)	(-3,5; 5,6)
Woche 56	n	59	45	
	LS-Mean	-2,194	-3,832	1,637
	SEM	2,326	2,486	2,424
	95%-KI	(-6,8; 2,4)	(-8,7; 1,1)	(-3,1; 6,4)
Woche 64	n	47	42	
	LS-Mean	-3,211	-3,030	-0,180
	SEM	2,410	2,517	2,536
	95%-KI	(-7,9; 1,5)	(-8,0; 1,9)	(-5,2; 4,8)
Woche 72	n	48	35	
	LS-Mean	-2,751	-3,114	0,363
	SEM	2,403	2,604	2,616
	95%-KI	(-7,5; 2,0)	(-8,2; 2,0)	(-4,8; 5,5)
Woche 84	n	40	33	
	LS-Mean	-4,102	-2,757	-1,345
	SEM	2,487	2,635	2,718
	95%-KI	(-9,0; 0,8)	(-7,9; 2,4)	(-6,7; 4,0)
Woche 96	n	35	24	
	LS-Mean	-3,172	-5,411	2,239
	SEM	2,549	2,828	2,961
	95%-KI	(-8,2; 1,8)	(-11,0; 0,1)	(-3,6; 8,0)
Woche 108	n	26	21	
	LS-Mean	-3,839	-6,374	2,535
	SEM	2,725	2,923	3,198
	95%-KI	(-9,2; 1,5)	(-12,1; -0,6)	(-3,7; 8,8)
Woche 120	n	28	16	
	LS-Mean	-3,832	-1,867	-1,965
	SEM	2,676	3,148	3,369
	95%-KI	(-9,1; 1,4)	(-8,0; 4,3)	(-8,6; 4,6)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,6 Monate im Alpelisib-Arm und 3,7 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes

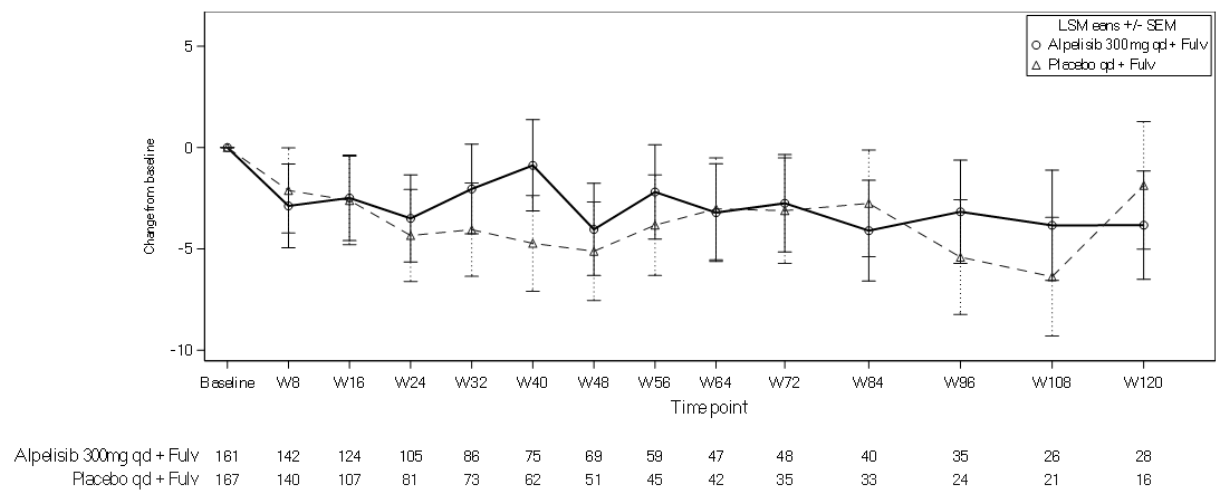
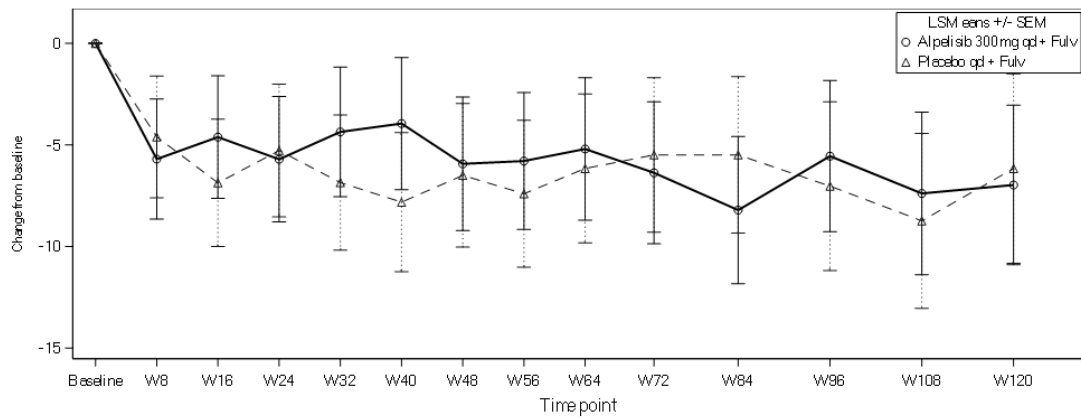


Abbildung 4H-14: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Körperliche Funktion – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-15: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Rollenfunktion“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-5,698	-4,604	-1,094
	SEM	2,957	2,999	2,569
	95%-KI	(-11,5; 0,1)	(-10,5; 1,3)	(-6,1; 4,0)
Woche 16	n	124	107	
	LS-Mean	-4,615	-6,868	2,252
	SEM	3,022	3,136	2,756
	95%-KI	(-10,6; 1,3)	(-13,0; -0,7)	(-3,2; 7,7)
Woche 24	n	105	81	
	LS-Mean	-5,707	-5,278	-0,429
	SEM	3,088	3,269	2,964
	95%-KI	(-11,8; 0,4)	(-11,7; 1,1)	(-6,2; 5,4)
Woche 32	n	86	73	
	LS-Mean	-4,360	-6,856	2,496
	SEM	3,190	3,329	3,106
	95%-KI	(-10,6; 1,9)	(-13,4; -0,3)	(-3,6; 8,6)
Woche 40	n	75	62	
	LS-Mean	-3,948	-7,818	3,870
	SEM	3,251	3,421	3,260
	95%-KI	(-10,3; 2,4)	(-14,5; -1,1)	(-2,5; 10,3)
Woche 48	n	69	51	
	LS-Mean	-5,932	-6,501	0,568
	SEM	3,290	3,535	3,418
	95%-KI	(-12,4; 0,5)	(-13,4; 0,4)	(-6,1; 7,3)
Woche 56	n	59	45	
	LS-Mean	-5,793	-7,404	1,611
	SEM	3,370	3,617	3,581
	95%-KI	(-12,4; 0,8)	(-14,5; -0,3)	(-5,4; 8,6)
Woche 64	n	47	42	
	LS-Mean	-5,201	-6,161	0,960
	SEM	3,503	3,666	3,757
	95%-KI	(-12,1; 1,7)	(-13,4; 1,0)	(-6,4; 8,3)
Woche 72	n	48	35	
	LS-Mean	-6,374	-5,493	-0,881
	SEM	3,492	3,805	3,881
	95%-KI	(-13,2; 0,5)	(-13,0; 2,0)	(-8,5; 6,7)
Woche 84	n	40	33	
	LS-Mean	-8,212	-5,493	-2,719
	SEM	3,626	3,853	4,040
	95%-KI	(-15,3; -1,1)	(-13,1; 2,1)	(-10,6; 5,2)
Woche 96	n	35	24	
	LS-Mean	-5,554	-7,029	1,475
	SEM	3,724	4,157	4,418
	95%-KI	(-12,9; 1,8)	(-15,2; 1,1)	(-7,2; 10,1)
Woche 108	n	26	21	
	LS-Mean	-7,390	-8,738	1,348
	SEM	4,002	4,306	4,784
	95%-KI	(-15,2; 0,5)	(-17,2; -0,3)	(-8,0; 10,7)
Woche 120	n	28	16	
	LS-Mean	-6,973	-6,165	-0,809
	SEM	3,924	4,660	5,048
	95%-KI	(-14,7; 0,7)	(-15,3; 3,0)	(-10,7; 9,1)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes



Alpelisib 300mg qd + Fulv	161	142	124	105	86	75	69	58	47	48	40	35	26	26
Placebo qd + Fulv	167	140	107	81	73	62	51	45	42	35	33	24	21	16

Abbildung 4H-15: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Rollenfunktion – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel



Tabelle 4H-16: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Emotionale Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-0,672	-0,137	-0,535
	SEM	2,374	2,417	2,085
	95%-KI	(-5,3; 4,0)	(-4,9; 4,6)	(-4,6; 3,6)
Woche 16	n	124	107	
	LS-Mean	-0,956	-3,104	2,147
	SEM	2,430	2,530	2,239
	95%-KI	(-5,7; 3,8)	(-8,1; 1,9)	(-2,2; 6,5)
Woche 24	n	105	81	
	LS-Mean	-3,862	0,130	-3,992
	SEM	2,486	2,645	2,418
	95%-KI	(-8,7; 1,0)	(-5,1; 5,3)	(-8,7; 0,8)
Woche 32	n	86	73	
	LS-Mean	0,878	-3,250	4,128
	SEM	2,575	2,697	2,539
	95%-KI	(-4,2; 5,9)	(-8,5; 2,0)	(-0,9; 9,1)
Woche 40	n	75	62	
	LS-Mean	-0,734	-2,648	1,913
	SEM	2,628	2,776	2,670
	95%-KI	(-5,9; 4,4)	(-8,1; 2,8)	(-3,3; 7,2)
Woche 48	n	69	51	
	LS-Mean	-4,487	-2,121	-2,366
	SEM	2,662	2,874	2,806
	95%-KI	(-9,7; 0,7)	(-7,8; 3,5)	(-7,9; 3,1)
Woche 56	n	59	45	
	LS-Mean	-0,247	-0,845	0,598
	SEM	2,731	2,945	2,945
	95%-KI	(-5,6; 5,1)	(-6,6; 4,9)	(-5,2; 6,4)
Woche 64	n	47	42	
	LS-Mean	-1,434	-3,619	2,185
	SEM	2,846	2,987	3,095
	95%-KI	(-7,0; 4,2)	(-9,5; 2,2)	(-3,9; 8,3)
Woche 72	n	48	35	
	LS-Mean	-1,772	-3,497	1,725
	SEM	2,836	3,106	3,201
	95%-KI	(-7,3; 3,8)	(-9,6; 2,6)	(-4,6; 8,0)
Woche 84	n	40	33	
	LS-Mean	-1,459	-3,953	2,494
	SEM	2,952	3,148	3,335
	95%-KI	(-7,3; 4,3)	(-10,1; 2,2)	(-4,0; 9,0)
Woche 96	n	35	24	
	LS-Mean	-0,715	-4,381	3,666
	SEM	3,036	3,408	3,656
	95%-KI	(-6,7; 5,2)	(-11,1; 2,3)	(-3,5; 10,8)
Woche 108	n	26	21	
	LS-Mean	2,674	-2,891	5,564
	SEM	3,276	3,536	3,967
	95%-KI	(-3,8; 9,1)	(-9,8; 4,0)	(-2,2; 13,3)
Woche 120	n	28	16	
	LS-Mean	-1,473	-0,964	-0,509
	SEM	3,208	3,838	4,190
	95%-KI	(-7,8; 4,8)	(-8,5; 6,6)	(-8,7; 7,7)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes

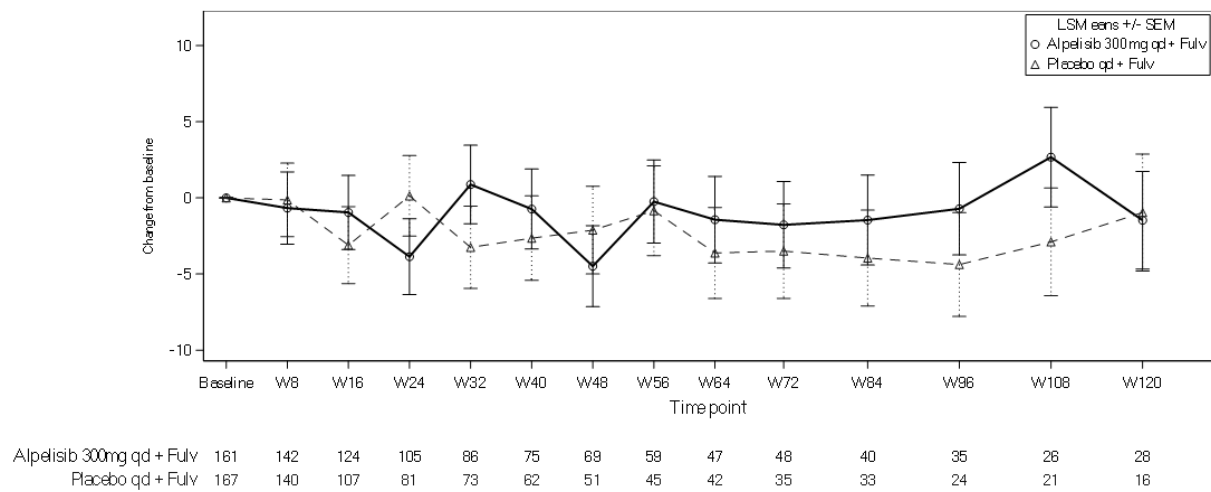


Abbildung 4H-16: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Emotionale Funktion – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-17: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Kognitive Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-2,851	-2,267	-0,584
	SEM	2,096	2,124	1,837
	95%-KI	(-7,0; 1,3)	(-6,4; 1,9)	(-4,2; 3,0)
Woche 16	n	124	107	
	LS-Mean	-0,997	-4,756	3,759
	SEM	2,146	2,229	1,977
	95%-KI	(-5,2; 3,2)	(-9,1; -0,4)	(-0,1; 7,6)
Woche 24	n	105	81	
	LS-Mean	-3,300	-4,646	1,346
	SEM	2,197	2,331	2,136
	95%-KI	(-7,6; 1,0)	(-9,2; -0,1)	(-2,8; 5,5)
Woche 32	n	86	73	
	LS-Mean	-2,756	-2,308	-0,448
	SEM	2,275	2,377	2,244
	95%-KI	(-7,2; 1,7)	(-7,0; 2,4)	(-4,9; 4,0)
Woche 40	n	75	62	
	LS-Mean	-0,323	-1,656	1,334
	SEM	2,322	2,448	2,361
	95%-KI	(-4,9; 4,2)	(-6,5; 3,2)	(-3,3; 6,0)
Woche 48	n	69	51	
	LS-Mean	-3,804	-4,779	0,975
	SEM	2,353	2,536	2,481
	95%-KI	(-8,4; 0,8)	(-9,8; 0,2)	(-3,9; 5,8)
Woche 56	n	59	45	
	LS-Mean	-3,509	-4,688	1,179
	SEM	2,414	2,599	2,605
	95%-KI	(-8,3; 1,2)	(-9,8; 0,4)	(-3,9; 6,3)
Woche 64	n	47	42	
	LS-Mean	-1,707	-4,112	2,406
	SEM	2,517	2,637	2,738
	95%-KI	(-6,6; 3,2)	(-9,3; 1,1)	(-3,0; 7,8)
Woche 72	n	48	35	
	LS-Mean	-4,221	-5,743	1,522
	SEM	2,508	2,743	2,832
	95%-KI	(-9,1; 0,7)	(-11,1; -0,4)	(-4,0; 7,1)
Woche 84	n	40	33	
	LS-Mean	-3,049	-3,909	0,861
	SEM	2,612	2,780	2,953
	95%-KI	(-8,2; 2,1)	(-9,4; 1,5)	(-4,9; 6,7)
Woche 96	n	35	24	
	LS-Mean	-1,441	-6,889	5,448
	SEM	2,687	3,012	3,238
	95%-KI	(-6,7; 3,8)	(-12,8; -1,0)	(-0,9; 11,8)
Woche 108	n	26	21	
	LS-Mean	-2,611	-5,686	3,075
	SEM	2,900	3,126	3,514
	95%-KI	(-8,3; 3,1)	(-11,8; 0,4)	(-3,8; 10,0)
Woche 120	n	28	16	
	LS-Mean	-2,549	-4,367	1,818
	SEM	2,839	3,395	3,712
	95%-KI	(-8,1; 3,0)	(-11,0; 2,3)	(-5,5; 9,1)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes

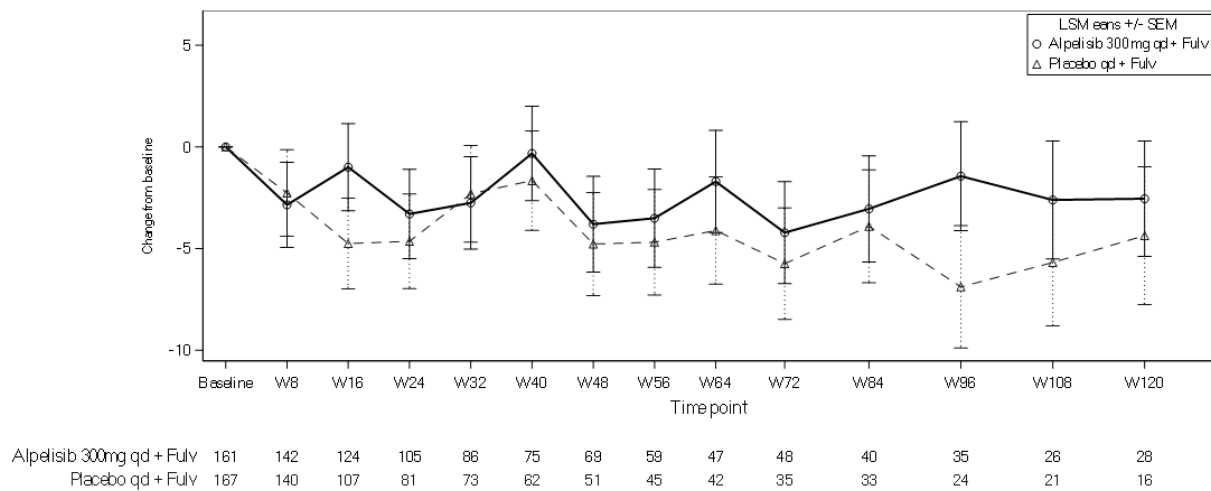


Abbildung 4H-17: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Kognitive Funktion – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

Tabelle 4H-18: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Soziale Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: „Linear mixed effects model“-Analysen\*

Zeitpunkt <sup>†</sup>	Parameter	Alpelisib + Fulvestrant (n=169)	Placebo + Fulvestrant (n=172)	Behandlungsdifferenz
Woche 8	n	142	140	
	LS-Mean	-6,194	1,468	-7,662
	SEM	2,555	2,597	2,249
	95%-KI	(-11,2; -1,2)	(-3,6; 6,6)	(-12,1; -3,2)
Woche 16	n	124	107	
	LS-Mean	-3,870	-0,068	-3,801
	SEM	2,618	2,727	2,425
	95%-KI	(-9,0; 1,3)	(-5,4; 5,3)	(-8,6; 1,0)
Woche 24	n	105	81	
	LS-Mean	-6,637	0,801	-7,438
	SEM	2,681	2,855	2,623
	95%-KI	(-11,9; -1,4)	(-4,8; 6,4)	(-12,6; -2,3)
Woche 32	n	86	73	
	LS-Mean	-4,046	-1,901	-2,145
	SEM	2,781	2,913	2,759
	95%-KI	(-9,5; 1,4)	(-7,6; 3,8)	(-7,6; 3,3)
Woche 40	n	75	62	
	LS-Mean	-2,930	-1,934	-0,996
	SEM	2,840	3,002	2,904
	95%-KI	(-8,5; 2,6)	(-7,8; 4,0)	(-6,7; 4,7)
Woche 48	n	69	51	
	LS-Mean	-4,444	-1,709	-2,735
	SEM	2,878	3,112	3,055
	95%-KI	(-10,1; 1,2)	(-7,8; 4,4)	(-8,7; 3,3)
Woche 56	n	59	45	
	LS-Mean	-4,296	-0,859	-3,437
	SEM	2,956	3,191	3,210
	95%-KI	(-10,1; 1,5)	(-7,1; 5,4)	(-9,7; 2,9)
Woche 64	n	47	42	
	LS-Mean	-5,095	-1,225	-3,870
	SEM	3,085	3,238	3,377
	95%-KI	(-11,2; 1,0)	(-7,6; 5,1)	(-10,5; 2,8)
Woche 72	n	48	35	
	LS-Mean	-5,155	0,756	-5,911
	SEM	3,074	3,371	3,494
	95%-KI	(-11,2; 0,9)	(-5,9; 7,4)	(-12,8; 0,9)
Woche 84	n	40	33	
	LS-Mean	-8,497	-2,354	-6,144
	SEM	3,203	3,417	3,644
	95%-KI	(-14,8; -2,2)	(-9,1; 4,4)	(-13,3; 1,0)
Woche 96	n	35	24	
	LS-Mean	-5,031	-5,548	0,517
	SEM	3,297	3,708	4,000
	95%-KI	(-11,5; 1,4)	(-12,8; 1,7)	(-7,3; 8,4)
Woche 108	n	26	21	
	LS-Mean	-4,905	-1,927	-2,978
	SEM	3,565	3,851	4,344
	95%-KI	(-11,9; 2,1)	(-9,5; 5,6)	(-11,5; 5,5)
Woche 120	n	28	16	
	LS-Mean	-5,555	-0,218	-5,336
	SEM	3,489	4,186	4,591
	95%-KI	(-12,4; 1,3)	(-8,4; 8,0)	(-14,3; 3,7)

\* 2. Datenschnitt 30.09.2019; medianer Follow-up: 7,9 Monate im Alpelisib-Arm und 3,8 Monate im Placebo-Arm.  
<sup>†</sup> Angaben basieren auf prädefinierten Zeitfenstern um den geplanten Tag herum.  
Abkürzungen: LMEM, Linear mixed effects model; LS-Mean, adjustierter Mittelwert nach der Methode der kleinsten Quadrate; SEM, Standardfehler des Mittelwertes

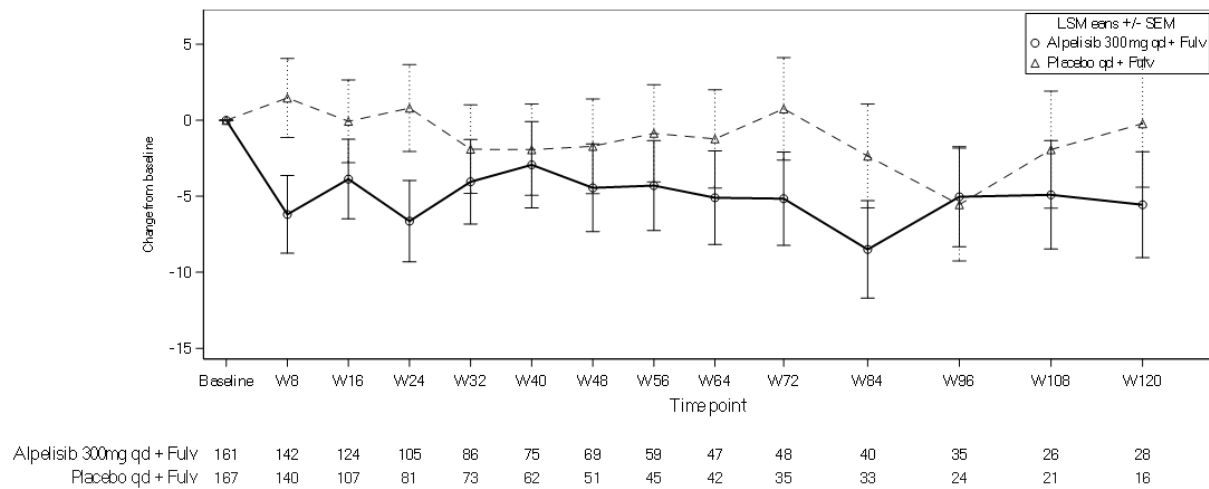


Abbildung 4H-18: Werte im Verlauf zu Änderungen gegenüber Baseline im mixed effect model für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Soziale Funktion – Veränderungen gegenüber Baseline im Verlauf“ aus RCT mit dem zu bewertenden Arzneimittel

## 4.8.2 Patientenberichtete Endpunkte: Interaktionstests zu Linear mixed effects model-Analysen – 2. Datenschnitt

### 4.8.2.1 Krankheitssymptomatik: EORTC QLQ-C30 – 2. Datenschnitt

Für die in Tabelle 4H-19 dargestellten Interaktionstests zum Linear mixed effects model gilt folgendes:

- In die Analysen werden jeweils nur Patientinnen eingeschlossen, für die Ausgangswerte und mindestens eine Post-Baseline-Untersuchung vorliegt.
- Die folgenden Faktoren und Kovariaten werden in das mixed effect model einbezogen: Therapie, Zeitpunkt des Besuchs (in Wochen gezählt ab dem Zeitpunkt der Randomisierung bis zum Zeitpunkt der jeweiligen Post-Baseline-Messung), Therapie nach Subgruppen-Interaktion, Ausgangswert.

Tabelle 4H-19: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30)“ aus RCT mit dem zu bewertenden Arzneimittel: Interaktionsterme für Subgruppenanalysen zu den „Linear mixed effects model“-Analysen

**Table 10.2-21**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.023
Presence of lung metastases (Yes/No)	<0.001
Presence of liver metastases (Yes/No)	0.171
Bone lesions only (Yes/No)	0.029
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.632
PTEN loss of expression (Yes/No)	0.213
Age (<65 Years/≥65 Years)	0.004
Age (<75 Years/≥75 Years)	0.453
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	0.041
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.072
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.096
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	<0.001
Progesterone receptor status (Positive/Negative)	0.544
Estr. & Progester. receptor status (Both positive/Positive negative)	0.458
Number of metastatic sites (<3/≥3)	0.017
Visceral disease (Yes/No)	0.046
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	0.005

**Table 10.2-22**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and Vomiting score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.069
Presence of lung metastases (Yes/No)	0.060
Presence of liver metastases (Yes/No)	0.891
Bone lesions only (Yes/No)	0.642
Prior CDK4/6 inhibitor (Prior use/No prior use)	<0.001
PTEN loss of expression (Yes/No)	0.271
Age (<65 Years/≥65 Years)	0.045
Age (<75 Years/≥75 Years)	0.324
Race (Asian/White/Other)	0.058
Region (Europe/North America/Asia/Latin America/Other)	0.174
ECOG performance status (0/1)	0.244
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.199
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.908
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	0.270
Estrogen receptor status (Positive/Negative)	0.154
Progesterone receptor status (Positive/Negative)	0.693
Estr. & Progester. receptor status (Both positive/Positive negative)	0.734
Number of metastatic sites (<3/≥3)	0.030
Visceral disease (Yes/No)	0.370
PIK3CA Mutation (E542K/E545X/H1047X)	0.920
PIK4CA Mutation by location (Exon 9/Exon 20)	0.639

**Table 10.2-23**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.406
Presence of lung metastases (Yes/No)	0.134
Presence of liver metastases (Yes/No)	0.258
Bone lesions only (Yes/No)	0.008
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.329
PTEN loss of expression (Yes/No)	0.915
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.080
Race (Asian/White/Other)	0.062
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.001
Line of adv. anti-cancer treatment (First line/Second line)	<0.001
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.260
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.545
Progesterone receptor status (Positive/Negative)	0.419
Estr. & Porgest. receptor status (Both positive/Positive negative)	0.429
Number of metastatic sites (<3/>=3)	0.240
Visceral disease (Yes/No)	0.579
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	<0.001

**Table 10.2-24**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.046
Presence of lung metastases (Yes/No)	0.006
Presence of liver metastases (Yes/No)	0.683
Bone lesions only (Yes/No)	0.061
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.904
PTEN loss of expression (Yes/No)	0.004
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.146
Race (Asian/White/Other)	0.002
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	0.047
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.003
Line of adv. anti-cancer treatment (First line/Second line)	0.177
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.001
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	0.014
Prior Tamoxifen use (Yes/No)	0.004
Estrogen receptor status (Positive/Negative)	0.946
Progesterone receptor status (Positive/Negative)	0.045
Estr. & Porgest. receptor status (Both positive/Positive negative)	0.046
Number of metastatic sites (<3/>=3)	0.348
Visceral disease (Yes/No)	0.018
PIK3CA Mutation (E542K/E545X/H1047X)	0.008
PIK4CA Mutation by location (Exon 9/Exon 20)	0.002



**Table 10.2-25**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.062
Presence of lung metastases (Yes/No)	0.095
Presence of liver metastases (Yes/No)	0.056
Bone lesions only (Yes/No)	0.123
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.552
PTEN loss of expression (Yes/No)	0.152
Age (<65 Years/>=65 Years)	0.003
Age (<75 Years/>=75 Years)	0.004
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	0.003
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.001
Line of adv. anti-cancer treatment (First line/Second line)	<0.001
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.322
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	0.265
Estrogen receptor status (Positive/Negative)	0.004
Progesterone receptor status (Positive/Negative)	0.505
Estr. & Progesterone receptor status (Both positive/Positive negative)	0.591
Number of metastatic sites (<3/>=3)	0.307
Visceral disease (Yes/No)	0.025
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	<0.001

**Table 10.2-26**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.792
Presence of lung metastases (Yes/No)	0.609
Presence of liver metastases (Yes/No)	0.978
Bone lesions only (Yes/No)	0.349
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.141
PTEN loss of expression (Yes/No)	0.038
Age (<65 Years/>=65 Years)	0.132
Age (<75 Years/>=75 Years)	0.002
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	0.311
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.629
Line of adv. anti-cancer treatment (First line/Second line)	0.212
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.588
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	0.201
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.024
Progesterone receptor status (Positive/Negative)	0.125
Estr. & Progesterone receptor status (Both positive/Positive negative)	0.159
Number of metastatic sites (<3/>=3)	<0.001
Visceral disease (Yes/No)	0.082
PIK3CA Mutation (E542K/E545X/H1047X)	0.027
PIK4CA Mutation by location (Exon 9/Exon 20)	0.008

**Table 10.2-27**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	Treatment-by-Subgroup Interaction p-value
Lung and/or Liver metastases (Present/Absent)	0.218
Presence of lung metastases (Yes/No)	0.216
Presence of liver metastases (Yes/No)	0.636
Bone lesions only (Yes/No)	0.053
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.075
PTEN loss of expression (Yes/No)	0.243
Age (<65 Years/>=65 Years)	0.035
Age (<75 Years/>=75 Years)	0.312
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	0.010
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	<0.001
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.033
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	0.036
Prior Tamoxifen use (Yes/No)	0.538
Estrogen receptor status (Positive/Negative)	0.554
Progesterone receptor status (Positive/Negative)	0.836
Estr. & Progester. receptor status (Both positive/Positive negative)	0.829
Number of metastatic sites (<3/>=3)	0.073
Visceral disease (Yes/No)	0.193
PIK3CA Mutation (E542K/E545X/H1047X)	0.206
PIK4CA Mutation by location (Exon 9/Exon 20)	0.158

**Table 10.2-28**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	Treatment-by-Subgroup Interaction p-value
Lung and/or Liver metastases (Present/Absent)	0.255
Presence of lung metastases (Yes/No)	0.005
Presence of liver metastases (Yes/No)	<0.001
Bone lesions only (Yes/No)	0.120
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.870
PTEN loss of expression (Yes/No)	0.043
Age (<65 Years/>=65 Years)	0.974
Age (<75 Years/>=75 Years)	0.648
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	0.320
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.007
Line of adv. anti-cancer treatment (First line/Second line)	0.014
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.048
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	0.210
Estrogen receptor status (Positive/Negative)	0.007
Progesterone receptor status (Positive/Negative)	0.114
Estr. & Progester. receptor status (Both positive/Positive negative)	0.126
Number of metastatic sites (<3/>=3)	0.529
Visceral disease (Yes/No)	0.992
PIK3CA Mutation (E542K/E545X/H1047X)	0.489
PIK4CA Mutation by location (Exon 9/Exon 20)	0.493

#### 4.8.2.2 Krankheitssymptomatik: BPI-SF – 2. Datenschnitt

Für die in Tabelle 4H-20 dargestellten Interaktionstests zum Linear mixed effects model gilt folgendes:

- In die Analysen werden jeweils nur Patientinnen eingeschlossen, für die Ausgangswerte und mindestens eine Post-Baseline-Untersuchung vorliegt.

- Die folgenden Faktoren und Kovariaten werden in das mixed effect model einbezogen: Therapie, Zeitpunkt des Besuchs (in Wochen gezählt ab dem Zeitpunkt der Randomisierung bis zum Zeitpunkt der jeweiligen Post-Baseline-Messung), Therapie nach Subgruppen-Interaktion, Ausgangswert.

Tabelle 4H-20: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF)“ aus RCT mit dem zu bewertenden Arzneimittel: Interaktionsterme für Subgruppenanalysen zu den „Linear mixed effects model“-Analysen

**Table 10.2-29**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.195
Presence of lung metastases (Yes/No)	0.188
Presence of liver metastases (Yes/No)	0.007
Bone lesions only (Yes/No)	0.066
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.017
PTEN loss of expression (Yes/No)	0.273
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.219
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.196
Line of adv. anti-cancer treatment (First line/Second line)	<0.001
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.315
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)ad/metastatic Tx/2L: PD post metastatic Tx only)	0.005
Prior Tamoxifen use (Yes/No)	0.301
Estrogen receptor status (Positive/Negative)	0.202
Progesterone receptor status (Positive/Negative)	0.010
Estr. & Porgest. receptor status (Both positive/Positive negative)	0.013
Number of metastatic sites (<3/>=3)	0.068
Visceral disease (Yes/No)	0.797
PIK3CA Mutation (E542K/E545X/H1047X)	0.009
PIK4CA Mutation by location (Exon 9/Exon 20)	0.002

**Table 10.2-30**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.043
Presence of lung metastases (Yes/No)	0.162
Presence of liver metastases (Yes/No)	0.107
Bone lesions only (Yes/No)	0.008
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.036
PTEN loss of expression (Yes/No)	0.762
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.876
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.006
Line of adv. anti-cancer treatment (First line/Second line)	<0.001
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.005
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)ad/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	0.094
Estrogen receptor status (Positive/Negative)	0.090
Progesterone receptor status (Positive/Negative)	0.122
Estr. & Porgest. receptor status (Both positive/Positive negative)	0.147
Number of metastatic sites (<3/>=3)	0.073
Visceral disease (Yes/No)	0.893
PIK3CA Mutation (E542K/E545X/H1047X)	0.030
PIK4CA Mutation by location (Exon 9/Exon 20)	0.010

**Table 10.2-31**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.126
Presence of lung metastases (Yes/No)	0.021
Presence of liver metastases (Yes/No)	0.031
Bone lesions only (Yes/No)	0.002
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.309
PTEN loss of expression (Yes/No)	0.047
Age (<65 Years/≥65 Years)	<0.001
Age (<75 Years/≥75 Years)	0.417
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	<0.001
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.001
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	0.056
Estrogen receptor status (Positive/Negative)	0.199
Progesterone receptor status (Positive/Negative)	0.628
Estr. & Progester. receptor status (Both positive/Positive negative)	0.654
Number of metastatic sites (<3/≥3)	0.006
Visceral disease (Yes/No)	0.778
PIK3CA Mutation (E542K/E545X/H1047X)	0.044
PIK4CA Mutation by location (Exon 9/Exon 20)	0.062

#### 4.8.2.3 Gesundheitszustand: EQ-5D-VAS – 2. Datenschnitt

Für die in Tabelle 4H-21 dargestellten Interaktionstests zum Linear mixed effects model gilt folgendes:

- In die Analysen werden jeweils nur Patientinnen eingeschlossen, für die Ausgangswerte und mindestens eine Post-Baseline-Untersuchung vorliegt.
- Die folgenden Faktoren und Kovariaten werden in das mixed effect model einbezogen: Therapie, Zeitpunkt des Besuchs (in Wochen gezählt ab dem Zeitpunkt der Randomisierung bis zum Zeitpunkt der jeweiligen Post-Baseline-Messung), Therapie nach Subgruppen-Interaktion, Ausgangswert.

Tabelle 4H-21: Ergebnisse für den Endpunkt „Gesundheitszustand (EQ-5D-VAS)“ aus RCT mit dem zu bewertenden Arzneimittel: Interaktionsterme für Subgruppenanalysen zu den „Linear mixed effects model“-Analysen

**Table 10.2-32**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.034
Presence of lung metastases (Yes/No)	0.010
Presence of liver metastases (Yes/No)	0.010
Bone lesions only (Yes/No)	0.070
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.025
PTEN loss of expression (Yes/No)	0.283
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.083
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.103
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.598
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.051
Progesterone receptor status (Positive/Negative)	<0.001
Estr. & Progesterone receptor status (Both positive/Positive negative)	<0.001
Number of metastatic sites (<3/>=3)	0.079
Visceral disease (Yes/No)	0.033
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	<0.001

#### 4.8.2.4 Gesundheitsbezogenen Lebensqualität: EORTC QLQ-C30 – 2. Datenschnitt

Für die in Tabelle 4H-22 dargestellten Interaktionstests zum Linear mixed effects model gilt folgendes:

- In die Analysen werden jeweils nur Patientinnen eingeschlossen, für die Ausgangswerte und mindestens eine Post-Baseline-Untersuchung vorliegt.
- Die folgenden Faktoren und Kovariaten werden in das mixed effect model einbezogen: Therapie, Zeitpunkt des Besuchs (in Wochen gezählt ab dem Zeitpunkt der Randomisierung bis zum Zeitpunkt der jeweiligen Post-Baseline-Messung), Therapie nach Subgruppen-Interaktion, Ausgangswert.

Tabelle 4H-22: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30)“ aus RCT mit dem zu bewertenden Arzneimittel: Interaktionsterme für Subgruppenanalysen zu den „Linear mixed effects model“-Analysen

**Table 10.2-15**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	Treatment-by-Subgroup Interaction p-value
Lung and/or Liver metastases (Present/Absent)	<0.001
Presence of lung metastases (Yes/No)	<0.001
Presence of liver metastases (Yes/No)	0.401
Bone lesions only (Yes/No)	0.039
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.997
PTEN loss of expression (Yes/No)	0.015
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.809
Race (Asian/White/Other)	0.002
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.213
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.075
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	0.001
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.092
Progesterone receptor status (Positive/Negative)	0.009
Estr. & Progester. receptor status (Both positive/Positive negative)	0.012
Number of metastatic sites (<3/>=3)	0.986
Visceral disease (Yes/No)	0.310
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	0.012

**Table 10.2-16**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	Treatment-by-Subgroup Interaction p-value
Lung and/or Liver metastases (Present/Absent)	0.065
Presence of lung metastases (Yes/No)	0.014
Presence of liver metastases (Yes/No)	0.971
Bone lesions only (Yes/No)	0.027
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.486
PTEN loss of expression (Yes/No)	<0.001
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.125
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.112
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.005
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.024
Progesterone receptor status (Positive/Negative)	0.072
Estr. & Progester. receptor status (Both positive/Positive negative)	0.054
Number of metastatic sites (<3/>=3)	0.090
Visceral disease (Yes/No)	0.672
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	<0.001

**Table 10.2-17**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale**  
**score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	<0.001
Presence of lung metastases (Yes/No)	<0.001
Presence of liver metastases (Yes/No)	0.243
Bone lesions only (Yes/No)	<0.001
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.506
PTEN loss of expression (Yes/No)	0.001
Age (<65 Years/>=65 Years)	<0.001
Age (<75 Years/>=75 Years)	0.103
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	0.064
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.016
Line of adv. anti-cancer treatment (First line/Second line)	0.012
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	<0.001
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	0.001
Prior Tamoxifen use (Yes/No)	0.028
Estrogen receptor status (Positive/Negative)	0.002
Progesterone receptor status (Positive/Negative)	0.039
Estr. & Progesterone receptor status (Both positive/Positive negative)	0.060
Number of metastatic sites (<3/>=3)	0.407
Visceral disease (Yes/No)	0.036
PIK3CA Mutation (E542K/E545X/H1047X)	0.058
PIK4CA Mutation by location (Exon 9/Exon 20)	0.246

**Table 10.2-18**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale**  
**score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	0.389
Presence of lung metastases (Yes/No)	0.264
Presence of liver metastases (Yes/No)	0.393
Bone lesions only (Yes/No)	0.029
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.253
PTEN loss of expression (Yes/No)	0.190
Age (<65 Years/>=65 Years)	0.064
Age (<75 Years/>=75 Years)	0.998
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	0.010
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.011
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.379
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	0.023
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.451
Progesterone receptor status (Positive/Negative)	0.272
Estr. & Progesterone receptor status (Both positive/Positive negative)	0.257
Number of metastatic sites (<3/>=3)	<0.001
Visceral disease (Yes/No)	0.712
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	<0.001



**Table 10.2-19**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	<0.001
Presence of lung metastases (Yes/No)	<0.001
Presence of liver metastases (Yes/No)	0.006
Bone lesions only (Yes/No)	<0.001
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.249
PTEN loss of expression (Yes/No)	0.189
Age (<65 Years/>=65 Years)	0.018
Age (<75 Years/>=75 Years)	0.178
Race (Asian/White/Other)	0.009
Region (Europe/North America/Asia/Latin America/Other)	0.004
ECOG performance status (0/1)	<0.001
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.033
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.121
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	<0.001
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.012
Progesterone receptor status (Positive/Negative)	0.950
Estr. & Progester. receptor status (Both positive/Positive negative)	0.984
Number of metastatic sites (<3/>=3)	0.011
Visceral disease (Yes/No)	0.008
PIK3CA Mutation (E542K/E545X/H1047X)	0.019
PIK4CA Mutation by location (Exon 9/Exon 20)	0.197

**Table 10.2-20**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score with an interaction test of treatment and subgroups**  
**(Full Analysis Set, PIK3CA mutant cohort)**

	<b>Treatment-by-Subgroup Interaction p-value</b>
Lung and/or Liver metastases (Present/Absent)	<0.001
Presence of lung metastases (Yes/No)	<0.001
Presence of liver metastases (Yes/No)	0.082
Bone lesions only (Yes/No)	0.009
Prior CDK4/6 inhibitor (Prior use/No prior use)	0.049
PTEN loss of expression (Yes/No)	<0.001
Age (<65 Years/>=65 Years)	0.010
Age (<75 Years/>=75 Years)	0.004
Race (Asian/White/Other)	<0.001
Region (Europe/North America/Asia/Latin America/Other)	<0.001
ECOG performance status (0/1)	0.607
Endocrine status (Primary resistant/Secondary resistant/Sensitive)	<0.001
Line of adv. anti-cancer treatment (First line/Second line)	0.002
Prior chemotherapy use (Adjuvant/Neoadjuvant/No Prior Use)	0.004
Endocr. Status & Line of Therapy (1L: endocrine sensitive/1L: endocrine resistant/2L: PD post(neo)adj/metastatic Tx/2L: PD post metastatic Tx only)	0.016
Prior Tamoxifen use (Yes/No)	<0.001
Estrogen receptor status (Positive/Negative)	0.799
Progesterone receptor status (Positive/Negative)	0.515
Estr. & Progester. receptor status (Both positive/Positive negative)	0.517
Number of metastatic sites (<3/>=3)	0.101
Visceral disease (Yes/No)	0.022
PIK3CA Mutation (E542K/E545X/H1047X)	<0.001
PIK4CA Mutation by location (Exon 9/Exon 20)	<0.001

### 4.8.3 Patientenberichtete Endpunkte: Linear mixed effects model-Subgruppenanalysen bei signifikantem Interaktionstest – 2. Datenschnitt

#### 4.8.3.1 Krankheitssymptomatik: EORTC QLQ-C30 – 2. Datenschnitt

Tabelle 4H-23: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Fatigue“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Week 8	Absent	n	77	73	
			LS Mean	9.054	1.087	7.967
			SEM	3.323	3.355	3.033
			95% CI	( 2.5,15.6)	( -5.5, 7.7)	( 2.0,13.9)
		Pr >  t			0.0090	
	Week 16		n	67	56	
			LS Mean	6.595	4.153	2.443
			SEM	3.381	3.554	3.281
			95% CI	( -0.1,13.3)	( -2.8,11.2)	( -4.0, 8.9)
		Pr >  t			0.4571	
	Week 24		n	61	46	
			LS Mean	5.537	2.323	3.215
			SEM	3.447	3.671	3.470
			95% CI	( -1.3,12.3)	( -4.9, 9.5)	( -3.6,10.0)
		Pr >  t			0.3547	
	Week 32		n	52	41	
		LS Mean	8.233	3.323	4.911	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	3.570	3.767	3.638
		95% CI	( 1.2,15.3)	( -4.1,10.7)	( -2.2,12.1)
		Pr >  t			0.1777
	Week 40	n	45	36	
		LS Mean	4.185	1.268	2.917
		SEM	3.655	3.878	3.817
		95% CI	( -3.0,11.4)	( -6.4, 8.9)	( -4.6,10.4)
		Pr >  t			0.4450
	Week 48	n	42	30	
		LS Mean	6.632	0.926	5.706
		SEM	3.701	4.020	4.005
		95% CI	( -0.6,13.9)	( -7.0, 8.8)	( -2.2,13.6)
		Pr >  t			0.1547
	Week 56	n	35	24	
		LS Mean	5.747	4.242	1.504
		SEM	3.824	4.224	4.323
		95% CI	( -1.8,13.3)	( -4.1,12.5)	( -7.0,10.0)
		Pr >  t			0.7279
	Week 64	n	25	25	
		LS Mean	6.673	1.066	5.606
		SEM	4.099	4.186	4.537
		95% CI	( -1.4,14.7)	( -7.2, 9.3)	( -3.3,14.5)
		Pr >  t			0.2170
	Week 72	n	27	20	
		LS Mean	6.487	4.091	2.396
		SEM	4.031	4.413	4.688
		95% CI	( -1.4,14.4)	( -4.6,12.8)	( -6.8,11.6)
		Pr >  t			0.6095
	Week 84	n	23	19	
		LS Mean	12.868	4.066	8.802
		SEM	4.195	4.472	4.872
		95% CI	( 4.6,21.1)	( -4.7,12.8)	( -0.8,18.4)
		Pr >  t			0.0712
	Week 96	n	20	13	
		LS Mean	9.423	1.018	8.405
		SEM	4.343	4.966	5.447
		95% CI	( 0.9,18.0)	( -8.7,10.8)	( -2.3,19.1)
		Pr >  t			0.1231
	Week 108	n	17	13	
		LS Mean	2.495	11.015	-8.520

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	4.535	4.967	5.601
		95% CI	( -6.4,11.4)	( 1.3,20.8)	(-19.5, 2.5)
		Pr >  t			0.1285
	Week 120	n	17	12	
		LS Mean	9.348	-0.592	9.941
		SEM	4.534	5.090	5.709
		95% CI	( 0.4,18.3)	(-10.6, 9.4)	( -1.3,21.1)
		Pr >  t			0.0820
	Week 132	n	13	6	
		LS Mean	7.276	8.423	-1.147
		SEM	4.897	6.454	7.196
		95% CI	( -2.3,16.9)	( -4.2,21.1)	(-15.3,13.0)
		Pr >  t			0.8734
	Week 144	n	11	4	
		LS Mean	11.779	0.916	10.863
		SEM	5.162	7.582	8.382
		95% CI	( 1.6,21.9)	(-14.0,15.8)	( -5.6,27.3)
		Pr >  t			0.1953
	Week 156	n	7	2	
		LS Mean	-0.273	-1.465	1.192
		SEM	6.034	10.22	11.27
		95% CI	(-12.1,11.6)	(-21.5,18.6)	(-20.9,23.3)
		Pr >  t			0.9158
	Week 168	n	3	1	
		LS Mean	3.650	-20.28	23.934
		SEM	8.489	14.08	16.02
		95% CI	(-13.0,20.3)	(-47.9, 7.4)	( -7.5,55.4)
		Pr >  t			0.1355
	Week 180	n	1	1	
		LS Mean	16.024	1.937	14.087
		SEM	14.05	14.08	19.54
		95% CI	(-11.6,43.6)	(-25.7,29.6)	(-24.3,52.4)
		Pr >  t			0.4712
	Week 192	n	1	1	
		LS Mean	4.914	-20.28	25.197
		SEM	14.05	14.08	19.54
		95% CI	(-22.7,32.5)	(-47.9, 7.4)	(-13.2,63.6)
		Pr >  t			0.1976
Present	Week 8	n	65	67	
		LS Mean	10.716	4.244	6.472

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 16	SEM	3.970	4.108	3.453
	95% CI	( 2.9,18.5)	( -3.9,12.3)	( -0.3,13.3)
	Pr >  t			0.0621
	n	57	51	
	LS Mean	7.893	4.763	3.130
Week 24	SEM	4.112	4.275	3.700
	95% CI	( -0.2,16.0)	( -3.7,13.2)	( -4.2,10.4)
	Pr >  t			0.3983
	n	44	35	
	LS Mean	9.013	8.051	0.962
Week 32	SEM	4.242	4.563	4.134
	95% CI	( 0.7,17.4)	( -0.9,17.0)	( -7.2, 9.1)
	Pr >  t			0.8161
	n	34	32	
	LS Mean	4.780	3.588	1.192
Week 40	SEM	4.430	4.631	4.383
	95% CI	( -3.9,13.5)	( -5.5,12.7)	( -7.4, 9.8)
	Pr >  t			0.7857
	n	30	26	
	LS Mean	7.004	5.386	1.618
Week 48	SEM	4.523	4.793	4.645
	95% CI	( -1.9,15.9)	( -4.0,14.8)	( -7.5,10.7)
	Pr >  t			0.7278
	n	27	21	
	LS Mean	10.079	9.052	1.027
Week 56	SEM	4.598	4.989	4.919
	95% CI	( 1.0,19.1)	( -0.8,18.9)	( -8.6,10.7)
	Pr >  t			0.8347
	n	24	21	
	LS Mean	7.535	4.342	3.192
Week 64	SEM	4.697	4.988	5.013
	95% CI	( -1.7,16.8)	( -5.5,14.2)	( -6.7,13.0)
	Pr >  t			0.5245
	n	22	17	
	LS Mean	9.346	12.934	-3.588
Week 72	SEM	4.775	5.207	5.302
	95% CI	( -0.0,18.7)	( 2.7,23.2)	( -14.0, 6.8)
	Pr >  t			0.4988
	n	21	15	
	LS Mean	7.446	4.757	2.690

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.822	5.351	5.485
		95% CI	(-2.0,16.9)	(-5.8,15.3)	(-8.1,13.5)
		Pr >  t			0.6241
	Week 84	n	17	14	
		LS Mean	7.924	4.411	3.513
		SEM	5.051	5.436	5.756
		95% CI	(-2.0,17.9)	(-6.3,15.1)	(-7.8,14.8)
		Pr >  t			0.5419
	Week 96	n	15	11	
		LS Mean	10.340	6.250	4.090
		SEM	5.181	5.775	6.203
		95% CI	(0.2,20.5)	(-5.1,17.6)	(-8.1,16.3)
		Pr >  t			0.5099
	Week 108	n	9	8	
		LS Mean	10.472	12.219	-1.748
		SEM	5.956	6.322	7.316
		95% CI	(-1.2,22.2)	(-0.2,24.6)	(-16.1,12.6)
		Pr >  t			0.8113
	Week 120	n	11	4	
		LS Mean	7.688	0.264	7.424
		SEM	5.618	7.997	8.593
		95% CI	(-3.3,18.7)	(-15.4,16.0)	(-9.4,24.3)
		Pr >  t			0.3879
	Week 132	n	7	2	
		LS Mean	15.572	-1.211	16.783
		SEM	6.441	10.53	11.42
		95% CI	(2.9,28.2)	(-21.9,19.5)	(-5.6,39.2)
		Pr >  t			0.1423
	Week 144	n	4	1	
		LS Mean	28.035	-0.046	28.081
		SEM	7.806	14.34	15.67
		95% CI	(12.7,43.4)	(-28.2,28.1)	(-2.7,58.9)
		Pr >  t			0.0736
	Week 156	n	3	1	
		LS Mean	9.984	-0.046	10.030
		SEM	8.799	14.34	16.16
		95% CI	(-7.3,27.3)	(-28.2,28.1)	(-21.7,41.8)
		Pr >  t			0.5350
	Week 168	n	1	1	
		LS Mean	17.676	-11.16	28.832

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	14.29	14.34	19.69
	95% CI	(-10.4,45.7)	(-39.3,17.0)	( -9.8,67.5)
	Pr >  t			0.1437

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	10.614	0.865	9.749		
			SEM	2.774	2.958	2.793		
			95% CI	( 5.2,16.1)	( -5.0, 6.7)	( 4.3,15.2)		
					Pr >  t			0.0005
		Week 16	n	86	68			
			LS Mean	7.413	4.692	2.721		
			SEM	2.846	3.086	2.989		
			95% CI	( 1.8,13.0)	( -1.4,10.8)	( -3.2, 8.6)		
					Pr >  t			0.3631
		Week 24	n	73	48			
			LS Mean	7.561	2.558	5.002		
			SEM	2.935	3.337	3.316		
			95% CI	( 1.8,13.3)	( -4.0, 9.1)	( -1.5,11.5)		
					Pr >  t			0.1319
		Week 32	n	60	43			
			LS Mean	6.876	2.496	4.380		
			SEM	3.081	3.434	3.497		
			95% CI	( 0.8,12.9)	( -4.3, 9.2)	( -2.5,11.2)		
					Pr >  t			0.2109
		Week 40	n	50	38			
			LS Mean	4.110	0.648	3.462		
			SEM	3.196	3.541	3.691		
			95% CI	( -2.2,10.4)	( -6.3, 7.6)	( -3.8,10.7)		
			Pr >  t			0.3485		
Week 48	n	48	31					
	LS Mean	7.683	1.771	5.912				
	SEM	3.225	3.716	3.886				
	95% CI	( 1.3,14.0)	( -5.5, 9.1)	( -1.7,13.5)				
			Pr >  t			0.1285		
Week 56	n	41	25					
	LS Mean	7.397	2.911	4.486				
	SEM	3.336	3.932	4.185				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 0.8,14.0)	( -4.8,10.6)	( -3.7,12.7)
		Pr >  t			0.2841
	Week 64	n	30	24	
		LS Mean	6.783	-0.541	7.324
		SEM	3.595	3.976	4.440
		95% CI	( -0.3,13.8)	( -8.3, 7.3)	( -1.4,16.0)
		Pr >  t			0.0993
	Week 72	n	32	19	
		LS Mean	7.735	2.347	5.388
		SEM	3.538	4.251	4.642
		95% CI	( 0.8,14.7)	( -6.0,10.7)	( -3.7,14.5)
		Pr >  t			0.2460
	Week 84	n	26	19	
		LS Mean	12.805	2.581	10.223
		SEM	3.755	4.252	4.798
		95% CI	( 5.4,20.2)	( -5.8,10.9)	( 0.8,19.6)
		Pr >  t			0.0334
	Week 96	n	23	14	
		LS Mean	8.459	-0.066	8.525
		SEM	3.879	4.681	5.280
		95% CI	( 0.8,16.1)	( -9.3, 9.1)	( -1.8,18.9)
		Pr >  t			0.1067
	Week 108	n	19	13	
		LS Mean	3.887	8.129	-4.242
		SEM	4.121	4.798	5.553
		95% CI	( -4.2,12.0)	( -1.3,17.5)	( -15.1, 6.7)
		Pr >  t			0.4450
	Week 120	n	19	11	
		LS Mean	10.266	-1.545	11.812
		SEM	4.109	5.085	5.802
		95% CI	( 2.2,18.3)	( -11.5, 8.4)	( 0.4,23.2)
		Pr >  t			0.0420
	Week 132	n	15	5	
		LS Mean	9.826	4.767	5.059
		SEM	4.447	6.903	7.634
		95% CI	( 1.1,18.6)	( -8.8,18.3)	( -9.9,20.0)
		Pr >  t			0.5077
	Week 144	n	12	3	
		LS Mean	12.790	0.343	12.447
		SEM	4.795	8.625	9.401

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 3.4,22.2)	(-16.6,17.3)	( -6.0,30.9)
		Pr >  t			0.1858
	Week 156	n	7	2	
		LS Mean	0.448	-2.494	2.942
		SEM	5.914	10.36	11.54
		95% CI	(-11.2,12.1)	(-22.8,17.8)	(-19.7,25.6)
		Pr >  t			0.7988
	Week 168	n	3	1	
		LS Mean	4.397	-21.24	25.640
		SEM	8.525	14.38	16.44
		95% CI	(-12.3,21.1)	(-49.5, 7.0)	( -6.6,57.9)
		Pr >  t			0.1192
	Week 180	n	1	1	
		LS Mean	16.764	0.977	15.787
		SEM	14.33	14.38	20.07
		95% CI	(-11.4,44.9)	(-27.2,29.2)	(-23.6,55.2)
		Pr >  t			0.4318
	Week 192	n	1	1	
		LS Mean	5.654	-21.24	26.897
		SEM	14.33	14.38	20.07
		95% CI	(-22.5,33.8)	(-49.5, 7.0)	(-12.5,66.3)
		Pr >  t			0.1806
Yes	Week 8	n	44	56	
		LS Mean	10.419	7.547	2.872
		SEM	6.287	5.990	3.958
		95% CI	( -2.0,22.8)	( -4.3,19.4)	( -4.9,10.7)
		Pr >  t			0.4691
	Week 16	n	38	39	
		LS Mean	9.053	6.347	2.706
		SEM	6.444	6.305	4.276
		95% CI	( -3.7,21.8)	( -6.1,18.8)	( -5.7,11.1)
		Pr >  t			0.5275
	Week 24	n	32	33	
		LS Mean	8.138	10.859	-2.721
		SEM	6.528	6.376	4.509
		95% CI	( -4.7,21.0)	( -1.7,23.4)	(-11.6, 6.2)
		Pr >  t			0.5467
	Week 32	n	26	30	
		LS Mean	9.683	7.679	2.004
		SEM	6.636	6.430	4.733

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-3.4,22.8)	(-5.0,20.4)	(-7.3,11.3)
	Pr >  t			0.6722
	n	25	24	
	LS Mean	10.266	9.548	0.718
	SEM	6.660	6.552	4.930
Week 48	95% CI	(-2.9,23.4)	(-3.4,22.5)	(-9.0,10.4)
	Pr >  t			0.8843
	n	21	20	
	LS Mean	11.170	11.176	-0.007
	SEM	6.757	6.669	5.212
Week 56	95% CI	(-2.2,24.5)	(-2.0,24.3)	(-10.3,10.2)
	Pr >  t			0.9990
	n	18	20	
	LS Mean	6.730	8.980	-2.250
	SEM	6.862	6.669	5.347
Week 64	95% CI	(-6.8,20.3)	(-4.2,22.1)	(-12.8, 8.3)
	Pr >  t			0.6742
	n	17	18	
	LS Mean	12.150	17.747	-5.597
	SEM	6.905	6.744	5.493
Week 72	95% CI	(-1.5,25.8)	( 4.5,31.0)	(-16.4, 5.2)
	Pr >  t			0.3088
	n	16	16	
	LS Mean	7.722	10.281	-2.560
	SEM	6.955	6.835	5.663
Week 84	95% CI	(-6.0,21.4)	(-3.2,23.7)	(-13.7, 8.6)
	Pr >  t			0.6515
	n	14	14	
	LS Mean	9.488	9.642	-0.154
	SEM	7.061	6.946	5.924
Week 96	95% CI	(-4.4,23.4)	(-4.0,23.3)	(-11.8,11.5)
	Pr >  t			0.9792
	n	12	10	
	LS Mean	14.992	11.179	3.813
	SEM	7.206	7.291	6.487
Week 108	95% CI	( 0.8,29.2)	(-3.2,25.5)	(-8.9,16.6)
	Pr >  t			0.5569
	n	7	8	
	LS Mean	11.948	19.945	-7.997
	SEM	7.875	7.580	7.515

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.5,27.4)	(-5.0,34.9)	(-22.8, 6.8)
		Pr >  t			0.2877
	Week 120	n	9	5	
		LS Mean	8.091	5.341	2.749
		SEM	7.541	8.380	8.004
		95% CI	(-6.7,22.9)	(-11.1,21.8)	(-13.0,18.5)
		Pr >  t			0.7313
	Week 132	n	5	3	
		LS Mean	14.239	12.341	1.898
		SEM	8.462	9.614	10.05
		95% CI	(-2.4,30.9)	(-6.5,31.2)	(-17.9,21.6)
		Pr >  t			0.8503
	Week 144	n	3	2	
		LS Mean	32.874	6.135	26.739
		SEM	9.683	10.98	12.30
		95% CI	(13.8,51.9)	(-15.4,27.7)	(2.6,50.9)
		Pr >  t			0.0302
	Week 156	n	3	1	
		LS Mean	11.556	5.032	6.525
		SEM	9.693	14.29	15.33
		95% CI	(-7.5,30.6)	(-23.0,33.1)	(-23.6,36.6)
		Pr >  t			0.6706
	Week 168	n	1	1	
		LS Mean	19.426	-6.078	25.505
		SEM	14.37	14.29	18.64
		95% CI	(-8.8,47.6)	(-34.1,22.0)	(-11.1,62.1)
		Pr >  t			0.1719

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	9.289	3.211	6.078		
			SEM	3.007	3.007	2.647		
			95% CI	( 3.4,15.2)	( -2.7, 9.1)	( 0.9,11.3)		
					Pr >  t			0.0222
				Week 16	n	92	83	
					LS Mean	7.242	3.405	3.837
					SEM	3.081	3.162	2.827
					95% CI	( 1.2,13.3)	( -2.8, 9.6)	( -1.7, 9.4)
					Pr >  t			0.1754
				Week 24	n	77	59	
					LS Mean	7.838	5.535	2.303
					SEM	3.144	3.339	3.086
					95% CI	( 1.7,14.0)	( -1.0,12.1)	( -3.8, 8.4)
					Pr >  t			0.4559
				Week 32	n	57	53	
					LS Mean	6.893	3.318	3.574
					SEM	3.313	3.395	3.291
					95% CI	( 0.4,13.4)	( -3.4,10.0)	( -2.9,10.0)
					Pr >  t			0.2779
				Week 40	n	50	44	
					LS Mean	5.939	2.663	3.276
					SEM	3.384	3.514	3.472
					95% CI	( -0.7,12.6)	( -4.2, 9.6)	( -3.5,10.1)
			Pr >  t			0.3456		
		Week 48	n	47	37			
			LS Mean	9.592	6.324	3.267		
			SEM	3.417	3.628	3.620		
			95% CI	( 2.9,16.3)	( -0.8,13.5)	( -3.8,10.4)		
			Pr >  t			0.3669		
		Week 56	n	40	32			
			LS Mean	8.995	4.261	4.734		
			SEM	3.514	3.734	3.816		

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	( 2.1,15.9)	( -3.1,11.6)	( -2.8,12.2)
		Pr >  t			0.2151
		n	32	27	
		LS Mean	8.695	6.987	1.708
		SEM	3.669	3.872	4.090
Week 72		95% CI	( 1.5,15.9)	( -0.6,14.6)	( -6.3, 9.7)
		Pr >  t			0.6764
		n	31	23	
		LS Mean	7.067	3.157	3.910
		SEM	3.695	4.018	4.250
Week 84		95% CI	( -0.2,14.3)	( -4.7,11.0)	( -4.4,12.2)
		Pr >  t			0.3578
		n	27	21	
		LS Mean	7.045	3.630	3.415
		SEM	3.810	4.108	4.430
Week 96		95% CI	( -0.4,14.5)	( -4.4,11.7)	( -5.3,12.1)
		Pr >  t			0.4409
		n	23	16	
		LS Mean	11.376	4.577	6.799
		SEM	3.949	4.414	4.834
Week 108		95% CI	( 3.6,19.1)	( -4.1,13.2)	( -2.7,16.3)
		Pr >  t			0.1599
		n	15	14	
		LS Mean	8.912	10.996	-2.083
		SEM	4.433	4.588	5.380
Week 120		95% CI	( 0.2,17.6)	( 2.0,20.0)	( -12.6, 8.5)
		Pr >  t			0.6986
		n	18	8	
		LS Mean	9.169	1.782	7.387
		SEM	4.210	5.509	6.032
Week 132		95% CI	( 0.9,17.4)	( -9.0,12.6)	( -4.4,19.2)
		Pr >  t			0.2210
		n	12	4	
		LS Mean	9.718	14.543	-4.825
		SEM	4.746	7.189	7.903
Week 144		95% CI	( 0.4,19.0)	( 0.4,28.6)	( -20.3,10.7)
		Pr >  t			0.5417
		n	8	3	
		LS Mean	21.154	-0.477	21.630
		SEM	5.430	8.130	9.166

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	( 10.5,31.8)	(-16.4,15.5)	( 3.6,39.6)
		Pr >  t			0.0185
	Week 156	n	5	1	
		LS Mean	4.396	-0.518	4.914
		SEM	6.517	13.41	14.51
		95% CI	( -8.4,17.2)	(-26.8,25.8)	(-23.6,33.4)
		Pr >  t			0.7349
	Week 168	n	2	1	
		LS Mean	17.881	-11.63	29.509
		SEM	9.693	13.41	16.19
		95% CI	( -1.1,36.9)	(-37.9,14.7)	( -2.3,61.3)
		Pr >  t			0.0686
	Week 180	n	1		
		LS Mean	18.831		
		SEM	13.37		
		95% CI	( -7.4,45.1)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	7.721		
		SEM	13.37		
		95% CI	(-18.5,34.0)		
		Pr >  t			
Yes	Week 8	n	38	30	
		LS Mean	10.412	-0.514	10.926
		SEM	4.931	5.308	4.608
		95% CI	( 0.6,20.2)	(-11.0,10.0)	( 1.8,20.0)
		Pr >  t			0.0186
	Week 16	n	32	24	
		LS Mean	6.170	7.593	-1.423
		SEM	5.044	5.497	5.014
		95% CI	( -3.8,16.2)	( -3.3,18.5)	(-11.3, 8.5)
		Pr >  t			0.7769
	Week 24	n	28	22	
		LS Mean	4.187	3.002	1.185
		SEM	5.232	5.587	5.233
		95% CI	( -6.2,14.5)	( -8.1,14.1)	( -9.1,11.5)
		Pr >  t			0.8210
	Week 32	n	29	20	
		LS Mean	6.594	3.808	2.786
		SEM	5.211	5.779	5.320

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-3.7,16.9)	(-7.6,15.2)	(-7.7,13.3)
	Pr >  t			0.6010
	n	25	18	
	LS Mean	3.888	4.100	-0.211
	SEM	5.333	5.886	5.569
Week 48	95% CI	(-6.7,14.4)	(-7.5,15.7)	(-11.2,10.7)
	Pr >  t			0.9698
	n	22	14	
	LS Mean	4.435	-0.854	5.289
	SEM	5.445	6.197	6.009
Week 56	95% CI	(-6.3,15.2)	(-13.1,11.4)	(-6.5,17.1)
	Pr >  t			0.3794
	n	19	13	
	LS Mean	1.009	3.811	-2.802
	SEM	5.590	6.303	6.261
Week 64	95% CI	(-10.0,12.0)	(-8.6,16.2)	(-15.1, 9.5)
	Pr >  t			0.6548
	n	15	15	
	LS Mean	5.822	3.741	2.081
	SEM	5.857	6.112	6.327
Week 72	95% CI	(-5.7,17.4)	(-8.3,15.8)	(-10.4,14.5)
	Pr >  t			0.7424
	n	17	12	
	LS Mean	6.193	6.447	-0.254
	SEM	5.711	6.419	6.489
Week 84	95% CI	(-5.1,17.5)	(-6.2,19.1)	(-13.0,12.5)
	Pr >  t			0.9688
	n	13	12	
	LS Mean	18.122	4.936	13.186
	SEM	6.106	6.420	6.801
Week 96	95% CI	( 6.1,30.2)	(-7.7,17.6)	(-0.2,26.6)
	Pr >  t			0.0532
	n	12	8	
	LS Mean	6.606	0.499	6.108
	SEM	6.224	7.123	7.567
Week 108	95% CI	(-5.7,18.9)	(-13.5,14.5)	(-8.8,21.0)
	Pr >  t			0.4200
	n	11	7	
	LS Mean	-0.136	12.706	-12.84
	SEM	6.365	7.402	7.942



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.7,12.4)	(-1.9,27.3)	(-28.5, 2.8)
		Pr >  t			0.1066
	Week 120	n	10	8	
		LS Mean	7.726	-2.066	9.792
		SEM	6.523	7.124	7.815
		95% CI	(-5.1,20.6)	(-16.1,12.0)	(-5.6,25.2)
		Pr >  t			0.2109
	Week 132	n	8	4	
		LS Mean	10.665	-1.838	12.503
		SEM	6.936	8.885	9.740
		95% CI	(-3.0,24.3)	(-19.3,15.6)	(-6.6,31.6)
		Pr >  t			0.1999
	Week 144	n	7	2	
		LS Mean	10.263	4.062	6.201
		SEM	7.223	11.62	12.45
		95% CI	(-3.9,24.5)	(-18.8,26.9)	(-18.3,30.7)
		Pr >  t			0.6188
	Week 156	n	5	2	
		LS Mean	0.771	-1.493	2.265
		SEM	8.061	11.62	12.96
		95% CI	(-15.1,16.6)	(-24.3,21.3)	(-23.2,27.7)
		Pr >  t			0.8613
	Week 168	n	2	1	
		LS Mean	-3.541	-20.38	16.842
		SEM	11.48	15.72	18.61
		95% CI	(-26.1,19.0)	(-51.3,10.5)	(-19.7,53.4)
		Pr >  t			0.3661
	Week 180	n		1	
		LS Mean		1.837	
		SEM		15.72	
		95% CI		(-29.0,32.7)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-20.38	
		SEM		15.72	
		95% CI		(-51.3,10.5)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69	
			LS Mean	9.069	3.952	5.117
			SEM	3.288	3.423	3.283
			95% CI	( 2.6,15.6)	( -2.8,10.7)	( -1.3,11.6)
		Pr >  t			0.1202	
		Week 16	n	70	52	
			LS Mean	5.731	4.901	0.830
			SEM	3.359	3.682	3.533
			95% CI	( -0.9,12.3)	( -2.3,12.1)	( -6.1, 7.8)
		Pr >  t			0.8144	
		Week 24	n	61	37	
			LS Mean	7.694	8.029	-0.335
			SEM	3.441	3.957	3.854
			95% CI	( 0.9,14.5)	( 0.2,15.8)	( -7.9, 7.2)
		Pr >  t			0.9308	
		Week 32	n	48	33	
			LS Mean	6.410	6.230	0.180
			SEM	3.607	4.050	4.074
			95% CI	( -0.7,13.5)	( -1.7,14.2)	( -7.8, 8.2)
		Pr >  t			0.9648	
		Week 40	n	42	31	
			LS Mean	3.871	3.610	0.261
			SEM	3.692	4.104	4.205
			95% CI	( -3.4,11.1)	( -4.5,11.7)	( -8.0, 8.5)
		Pr >  t			0.9506	
		Week 48	n	40	25	
			LS Mean	6.050	4.976	1.074
			SEM	3.726	4.293	4.419
			95% CI	( -1.3,13.4)	( -3.5,13.4)	( -7.6, 9.8)
		Pr >  t			0.8081	
		Week 56	n	35	20	
			LS Mean	4.443	6.277	-1.834
			SEM	3.819	4.527	4.726

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-3.1,12.0)	(-2.6,15.2)	(-11.1, 7.4)
	Pr >  t			0.6981
	n	29	18	
	LS Mean	6.041	6.433	-0.392
	SEM	3.965	4.652	4.963
Week 72	95% CI	(-1.8,13.8)	(-2.7,15.6)	(-10.1, 9.4)
	Pr >  t			0.9371
	n	28	18	
	LS Mean	7.859	5.039	2.820
	SEM	3.996	4.649	4.986
Week 84	95% CI	( 0.0,15.7)	(-4.1,14.2)	(-7.0,12.6)
	Pr >  t			0.5719
	n	27	17	
	LS Mean	9.278	6.774	2.503
	SEM	4.047	4.721	5.078
Week 96	95% CI	( 1.3,17.2)	(-2.5,16.0)	(-7.5,12.5)
	Pr >  t			0.6221
	n	23	14	
	LS Mean	10.707	4.975	5.733
	SEM	4.191	4.975	5.434
Week 108	95% CI	( 2.5,18.9)	(-4.8,14.7)	(-4.9,16.4)
	Pr >  t			0.2918
	n	19	12	
	LS Mean	2.823	10.413	-7.590
	SEM	4.410	5.205	5.802
Week 120	95% CI	(-5.8,11.5)	( 0.2,20.6)	(-19.0, 3.8)
	Pr >  t			0.1912
	n	18	8	
	LS Mean	10.790	3.177	7.613
	SEM	4.461	5.935	6.506
Week 132	95% CI	( 2.0,19.6)	(-8.5,14.8)	(-5.2,20.4)
	Pr >  t			0.2423
	n	11	4	
	LS Mean	4.665	-6.416	11.081
	SEM	5.180	7.705	8.563
Week 144	95% CI	(-5.5,14.8)	(-21.5, 8.7)	(-5.7,27.9)
	Pr >  t			0.1960
	n	11	4	
	LS Mean	12.773	0.433	12.339
	SEM	5.166	7.710	8.569

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 2.6,22.9)	(-14.7,15.6)	( -4.5,29.2)
		Pr >  t			0.1502
	Week 156	n	5	2	
		LS Mean	-3.815	-4.532	0.717
		SEM	6.917	10.36	11.93
		95% CI	(-17.4, 9.8)	(-24.9,15.8)	(-22.7,24.1)
		Pr >  t			0.9521
	Week 168	n	1	2	
		LS Mean	-26.80	-15.64	-11.16
		SEM	14.15	10.36	17.17
		95% CI	(-54.6, 1.0)	(-36.0, 4.7)	(-44.9,22.5)
		Pr >  t			0.5159
	Week 180	n		1	
		LS Mean		3.347	
		SEM		14.24	
		95% CI		(-24.6,31.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-18.87	
		SEM		14.24	
		95% CI		(-46.8, 9.1)	
		Pr >  t			
>= 65 Years	Week 8	n	63	71	
		LS Mean	11.148	0.990	10.158
		SEM	4.322	4.344	3.148
		95% CI	( 2.6,19.7)	( -7.6, 9.6)	( 4.0,16.4)
		Pr >  t			0.0014
	Week 16	n	54	55	
		LS Mean	9.495	3.805	5.690
		SEM	4.440	4.417	3.394
		95% CI	( 0.7,18.3)	( -4.9,12.5)	( -1.0,12.4)
		Pr >  t			0.0945
	Week 24	n	44	44	
		LS Mean	6.465	1.825	4.641
		SEM	4.541	4.517	3.676
		95% CI	( -2.5,15.4)	( -7.1,10.7)	( -2.6,11.9)
		Pr >  t			0.2074
	Week 32	n	38	40	
		LS Mean	8.224	0.850	7.373
		SEM	4.660	4.605	3.840

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.0,17.4)	(-8.2, 9.9)	(-0.2,14.9)
		Pr >  t			0.0555
	Week 40	n	33	31	
		LS Mean	7.660	2.534	5.127
		SEM	4.750	4.788	4.120
		95% CI	(-1.7,17.0)	(-6.9,12.0)	(-3.0,13.2)
		Pr >  t			0.2140
	Week 48	n	29	26	
		LS Mean	11.150	3.734	7.416
		SEM	4.832	4.916	4.362
		95% CI	( 1.6,20.7)	(-5.9,13.4)	(-1.2,16.0)
		Pr >  t			0.0896
	Week 56	n	24	25	
		LS Mean	9.802	2.188	7.615
		SEM	4.970	4.945	4.551
		95% CI	( 0.0,19.6)	(-7.5,11.9)	(-1.3,16.6)
		Pr >  t			0.0948
	Week 64	n	18	24	
		LS Mean	10.988	5.236	5.752
		SEM	5.226	4.978	4.864
		95% CI	( 0.7,21.3)	(-4.6,15.0)	(-3.8,15.3)
		Pr >  t			0.2374
	Week 72	n	20	17	
		LS Mean	5.973	3.872	2.101
		SEM	5.131	5.291	5.086
		95% CI	(-4.1,16.1)	(-6.5,14.3)	(-7.9,12.1)
		Pr >  t			0.6796
	Week 84	n	13	16	
		LS Mean	13.805	1.564	12.241
		SEM	5.584	5.354	5.609
		95% CI	( 2.8,24.8)	(-9.0,12.1)	( 1.2,23.3)
		Pr >  t			0.0294
	Week 96	n	12	10	
		LS Mean	8.250	1.815	6.434
		SEM	5.693	5.968	6.294
		95% CI	(-2.9,19.4)	(-9.9,13.5)	(-5.9,18.8)
		Pr >  t			0.3069
	Week 108	n	7	9	
		LS Mean	11.225	13.738	-2.513
		SEM	6.571	6.134	7.238

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-1.7,24.1)	(-1.7,25.8)	(-16.7,11.7)
		Pr >  t			0.7285
	Week 120	n	10	8	
		LS Mean	4.941	-2.647	7.588
		SEM	5.971	6.339	6.881
		95% CI	(-6.8,16.7)	(-15.1, 9.8)	(-5.9,21.1)
		Pr >  t			0.2705
	Week 132	n	9	4	
		LS Mean	17.683	19.735	-2.052
		SEM	6.121	7.916	8.466
		95% CI	(-5.7,29.7)	(-4.2,35.3)	(-18.7,14.6)
		Pr >  t			0.8085
	Week 144	n	4	1	
		LS Mean	25.450	7.844	17.606
		SEM	7.902	14.04	15.20
		95% CI	(-9.9,41.0)	(-19.7,35.4)	(-12.3,47.5)
		Pr >  t			0.2473
	Week 156	n	5	1	
		LS Mean	10.562	7.844	2.718
		SEM	7.318	14.04	14.91
		95% CI	(-3.8,24.9)	(-19.7,35.4)	(-26.6,32.0)
		Pr >  t			0.8554
	Week 168	n	3		
		LS Mean	20.619		
		SEM	8.804		
		95% CI	(-3.3,37.9)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	20.262		
		SEM	14.03		
		95% CI	(-7.3,47.8)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	9.152		
		SEM	14.03		
		95% CI	(-18.4,36.7)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	7.895	-6.748	14.643		
			SEM	5.029	4.818	4.350		
			95% CI	(-2.1,17.9)	(-16.3, 2.8)	( 6.0,23.2)		
					Pr >  t			0.0010
		Week 16	n	30	30			
			LS Mean	7.844	-5.037	12.881		
			SEM	5.065	5.036	4.547		
			95% CI	(-2.2,17.9)	(-15.0, 5.0)	( 3.9,21.9)		
					Pr >  t			0.0053
		Week 24	n	21	26			
			LS Mean	2.216	-3.652	5.868		
			SEM	5.311	5.120	4.935		
			95% CI	(-8.3,12.8)	(-13.8, 6.5)	(-3.9,15.6)		
					Pr >  t			0.2360
		Week 32	n	19	24			
			LS Mean	6.866	-4.013	10.879		
			SEM	5.391	5.181	5.098		
			95% CI	(-3.8,17.6)	(-14.3, 6.3)	( 0.8,20.9)		
					Pr >  t			0.0341
		Week 40	n	16	19			
			LS Mean	0.153	-4.902	5.054		
			SEM	5.541	5.426	5.465		
			95% CI	(-10.8,11.1)	(-15.6, 5.8)	(-5.7,15.8)		
					Pr >  t			0.3560
		Week 48	n	16	18			
			LS Mean	2.930	0.520	2.410		
			SEM	5.541	5.470	5.508		
95% CI	(-8.0,13.9)		(-10.3,11.3)	(-8.4,13.3)				
			Pr >  t			0.6621		
Week 56	n	12	14					
	LS Mean	1.495	-2.136	3.631				
	SEM	5.834	5.709	6.044				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.0,13.0)	(-8.3,15.5)
		Pr >  t		0.5484
	Week 64	n	12	11
		LS Mean	6.125	2.229
		SEM	5.834	5.989
		95% CI	(-5.4,17.7)	(-9.6,14.1)
		Pr >  t		(-8.5,16.3)
	Week 72	n	10	9
		LS Mean	0.146	-0.079
		SEM	6.057	6.251
		95% CI	(-11.8,12.1)	(-12.4,12.3)
		Pr >  t		(-13.1,13.5)
	Week 84	n	8	8
		LS Mean	7.416	0.913
		SEM	6.438	6.433
		95% CI	(-5.3,20.1)	(-11.8,13.6)
		Pr >  t		(-7.7,20.7)
	Week 96	n	6	6
		LS Mean	11.248	2.970
		SEM	6.943	6.950
		95% CI	(-2.4,24.9)	(-10.7,16.7)
		Pr >  t		(-7.7,24.2)
	Week 108	n	4	5
		LS Mean	8.188	11.872
		SEM	7.849	7.334
		95% CI	(-7.3,23.6)	(-2.6,26.3)
		Pr >  t		(-21.8,14.4)
	Week 120	n	4	4
		LS Mean	10.965	-2.078
		SEM	7.849	7.871
		95% CI	(-4.5,26.4)	(-17.6,13.4)
		Pr >  t		(-5.9,32.0)
	Week 132	n	3	2
		LS Mean	15.122	2.868
		SEM	8.653	10.07
		95% CI	(-1.9,32.1)	(-16.9,22.7)
		Pr >  t		(-11.5,36.0)
	Week 144	n	3	1
		LS Mean	22.532	3.000
		SEM	8.653	13.44
				19.532
				14.99

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 5.5,39.6)	(-23.4,29.4)	(-10.0,49.0)
		Pr >  t			0.1935
	Week 156	n	2	1	
		LS Mean	11.100	3.000	8.099
		SEM	10.06	13.44	15.85
		95% CI	( -8.7,30.9)	(-23.4,29.4)	(-23.1,39.3)
		Pr >  t			0.6096
	Week 168	n	1		
		LS Mean	20.950		
		SEM	13.42		
		95% CI	( -5.4,47.3)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	0.652	-1.311	1.963
		SEM	10.88	10.61	6.850
		95% CI	(-21.0,22.3)	(-22.4,19.7)	(-11.7,15.6)
		Pr >  t			0.7752
	Week 16	n	15	14	
		LS Mean	-2.813	-2.353	-0.460
		SEM	10.95	9.893	7.320
		95% CI	(-24.6,19.0)	(-22.0,17.3)	(-15.0,14.1)
		Pr >  t			0.9500
	Week 24	n	12	11	
		LS Mean	0.570	0.661	-0.092
		SEM	11.19	10.98	8.023
		95% CI	(-21.7,22.8)	(-21.1,22.4)	(-16.0,15.8)
		Pr >  t			0.9909
	Week 32	n	8	9	
		LS Mean	5.094	-4.039	9.133
		SEM	11.70	11.25	9.025
		95% CI	(-18.1,28.3)	(-26.3,18.3)	( -8.7,27.0)
		Pr >  t			0.3137
	Week 40	n	6	7	
		LS Mean	8.574	2.933	5.641
		SEM	12.20	11.61	10.04
		95% CI	(-15.6,32.8)	(-20.1,25.9)	(-14.2,25.5)
		Pr >  t			0.5754
	Week 48	n	4	6	
		LS Mean	4.223	-5.540	9.763
		SEM	13.10	11.87	11.40

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-21.7,30.2)	(-29.1,18.0)	(-12.8,32.3)
		Pr >  t			0.3932
	Week 56	n	4	6	
		LS Mean	3.868	-7.081	10.948
		SEM	13.09	11.90	11.41
		95% CI	(-22.1,29.8)	(-30.6,16.5)	(-11.6,33.5)
		Pr >  t			0.3391
	Week 64	n	4	4	
		LS Mean	-4.424	6.327	-10.75
		SEM	13.11	12.77	12.31
		95% CI	(-30.4,21.5)	(-18.9,31.6)	(-35.1,13.6)
		Pr >  t			0.3839
	Week 72	n	4	4	
		LS Mean	1.131	-4.783	5.914
		SEM	13.11	12.77	12.31
		95% CI	(-24.8,27.1)	(-30.1,20.5)	(-18.4,30.2)
		Pr >  t			0.6317
	Week 84	n	4	4	
		LS Mean	9.781	-4.783	14.564
		SEM	13.10	12.77	12.33
		95% CI	(-16.2,35.7)	(-30.1,20.5)	(-9.8,38.9)
		Pr >  t			0.2393
	Week 96	n	3	2	
		LS Mean	0.387	-5.940	6.327
		SEM	13.91	15.07	15.40
		95% CI	(-27.1,27.9)	(-35.7,23.8)	(-24.1,36.8)
		Pr >  t			0.6817
	Week 108	n	3	3	
		LS Mean	-3.316	-7.220	3.904
		SEM	13.91	13.60	13.98
		95% CI	(-30.8,24.2)	(-34.1,19.7)	(-23.7,31.5)
		Pr >  t			0.7805
	Week 120	n	2	1	
		LS Mean	-6.798	-23.95	17.155
		SEM	15.38	18.80	20.16
		95% CI	(-37.2,23.6)	(-61.1,13.2)	(-22.7,57.0)
		Pr >  t			0.3963
	Week 132	n	2	1	
		LS Mean	23.072	20.487	2.585
		SEM	15.36	18.80	20.16

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.3,53.4)	(-16.7,57.6)	(-37.3,42.5)
		Pr >  t			0.8982
	Week 156	n	1		
		LS Mean	-1.955		
		SEM	19.08		
		95% CI	(-39.7,35.8)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	9.155		
		SEM	19.08		
		95% CI	(-28.6,46.9)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	11.690	6.731	4.960
		SEM	3.060	3.235	2.895
		95% CI	( 5.7,17.7)	( 0.4,13.1)	(-0.7,10.7)
		Pr >  t			0.0875
	Week 16	n	79	61	
		LS Mean	8.602	9.471	-0.870
		SEM	3.165	3.480	3.186
		95% CI	( 2.4,14.8)	( 2.6,16.3)	(-7.1, 5.4)
		Pr >  t			0.7850
	Week 24	n	71	43	
		LS Mean	9.535	8.809	0.727
		SEM	3.228	3.700	3.479
		95% CI	( 3.2,15.9)	( 1.5,16.1)	(-6.1, 7.6)
		Pr >  t			0.8346
	Week 32	n	59	39	
		LS Mean	7.456	7.990	-0.534
		SEM	3.362	3.790	3.643
		95% CI	( 0.8,14.1)	( 0.5,15.4)	(-7.7, 6.6)
		Pr >  t			0.8836
	Week 40	n	52	35	
		LS Mean	6.856	6.420	0.436
		SEM	3.435	3.871	3.794
		95% CI	( 0.1,13.6)	(-1.2,14.0)	(-7.0, 7.9)
		Pr >  t			0.9086
	Week 48	n	48	26	
		LS Mean	10.983	7.046	3.937
		SEM	3.482	4.125	4.092

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 4.1,17.8)	( -1.1,15.1)	( -4.1,12.0)
		Pr >  t			0.3364
	Week 56	n	42	24	
		LS Mean	9.213	9.253	-0.041
		SEM	3.564	4.203	4.244
		95% CI	( 2.2,16.2)	( 1.0,17.5)	( -8.4, 8.3)
		Pr >  t			0.9924
	Week 64	n	30	26	
		LS Mean	10.063	9.027	1.035
		SEM	3.813	4.127	4.387
		95% CI	( 2.6,17.6)	( 0.9,17.1)	( -7.6, 9.6)
		Pr >  t			0.8135
	Week 72	n	34	21	
		LS Mean	10.030	8.603	1.427
		SEM	3.715	4.340	4.506
		95% CI	( 2.7,17.3)	( 0.1,17.1)	( -7.4,10.3)
		Pr >  t			0.7515
	Week 84	n	28	20	
		LS Mean	12.338	8.003	4.336
		SEM	3.881	4.392	4.687
		95% CI	( 4.7,20.0)	( -0.6,16.6)	( -4.9,13.5)
		Pr >  t			0.3552
	Week 96	n	26	15	
		LS Mean	11.162	5.203	5.959
		SEM	3.941	4.746	5.074
		95% CI	( 3.4,18.9)	( -4.1,14.5)	( -4.0,15.9)
		Pr >  t			0.2405
	Week 108	n	19	12	
		LS Mean	6.658	14.482	-7.824
		SEM	4.283	5.075	5.630
		95% CI	( -1.8,15.1)	( 4.5,24.4)	( -18.9, 3.2)
		Pr >  t			0.1649
	Week 120	n	22	10	
		LS Mean	10.545	3.984	6.560
		SEM	4.112	5.381	5.791
		95% CI	( 2.5,18.6)	( -6.6,14.5)	( -4.8,17.9)
		Pr >  t			0.2576
	Week 132	n	15	4	
		LS Mean	8.283	-4.084	12.367
		SEM	4.582	7.587	8.134

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.7,17.3)	(-19.0,10.8)	(-3.6,28.3)
		Pr >  t			0.1287
	Week 144	n	12	4	
		LS Mean	16.138	2.722	13.416
		SEM	4.903	7.591	8.332
		95% CI	( 6.5,25.8)	(-12.2,17.6)	(-2.9,29.8)
		Pr >  t			0.1077
	Week 156	n	7	2	
		LS Mean	1.575	-2.279	3.855
		SEM	5.955	10.24	11.32
		95% CI	(-10.1,13.3)	(-22.4,17.8)	(-18.4,26.1)
		Pr >  t			0.7334
	Week 168	n	2	2	
		LS Mean	-2.366	-13.39	11.024
		SEM	10.14	10.24	13.98
		95% CI	(-22.3,17.5)	(-33.5, 6.7)	(-16.4,38.5)
		Pr >  t			0.4306
	Week 180	n	1	1	
		LS Mean	18.017	5.571	12.446
		SEM	14.06	14.11	19.60
		95% CI	(-9.6,45.6)	(-22.1,33.3)	(-26.0,50.9)
		Pr >  t			0.5256
	Week 192	n	1	1	
		LS Mean	6.907	-16.65	23.556
		SEM	14.06	14.11	19.60
		95% CI	(-20.7,34.5)	(-44.3,11.0)	(-14.9,62.0)
		Pr >  t			0.2298

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Geographic Region 1 (L)	Asia	Week 8	n	30	35	
			LS Mean	5.350	-6.054	11.404
			SEM	4.985	4.747	4.345
			95% CI	(-4.6,15.3)	(-15.5, 3.4)	( 2.8,20.0)
			Pr >  t			0.0098
		Week 16	n	28	29	
			LS Mean	9.291	-4.188	13.480
			SEM	5.023	4.961	4.541
			95% CI	(-0.7,19.3)	(-14.0, 5.7)	( 4.5,22.5)
			Pr >  t			0.0035
		Week 24	n	21	25	
			LS Mean	1.899	-2.691	4.590
			SEM	5.211	5.045	4.855
			95% CI	(-8.5,12.3)	(-12.7, 7.3)	(-5.0,14.2)
			Pr >  t			0.3459
		Week 32	n	19	23	
			LS Mean	6.612	-3.501	10.114
			SEM	5.285	5.107	5.012
			95% CI	(-3.9,17.1)	(-13.6, 6.6)	( 0.2,20.0)
			Pr >  t			0.0451
		Week 40	n	16	18	
			LS Mean	-0.120	-3.863	3.743
			SEM	5.424	5.352	5.369
			95% CI	(-10.9,10.6)	(-14.5, 6.7)	(-6.8,14.3)
			Pr >  t			0.4865
		Week 48	n	16	17	
			LS Mean	2.657	1.896	0.761
			SEM	5.424	5.397	5.414
95% CI	(-8.1,13.4)		(-8.8,12.6)	(-9.9,11.4)		
	Pr >  t			0.8884		
Week 56	n	12	14			
	LS Mean	1.255	-1.271	2.526		
	SEM	5.696	5.572	5.866		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.0,12.5)	(-12.3, 9.8)	(-9.0,14.1)
	Pr >  t			0.6671
	n	12	11	
	LS Mean	5.885	3.121	2.764
	SEM	5.696	5.832	6.113
Week 72	95% CI	(-5.4,17.2)	(-8.4,14.6)	(-9.3,14.8)
	Pr >  t			0.6515
	n	10	8	
	LS Mean	-0.100	1.857	-1.958
	SEM	5.903	6.247	6.697
Week 84	95% CI	(-11.8,11.6)	(-10.5,14.2)	(-15.1,11.2)
	Pr >  t			0.7702
	n	8	8	
	LS Mean	7.188	1.857	5.330
	SEM	6.256	6.247	6.971
Week 96	95% CI	(-5.2,19.5)	(-10.5,14.2)	(-8.4,19.0)
	Pr >  t			0.4451
	n	6	6	
	LS Mean	11.038	3.931	7.107
	SEM	6.727	6.730	7.809
Week 108	95% CI	(-2.2,24.3)	(-9.3,17.2)	(-8.2,22.5)
	Pr >  t			0.3633
	n	4	5	
	LS Mean	7.986	12.820	-4.834
	SEM	7.574	7.088	8.830
Week 120	95% CI	(-6.9,22.9)	(-1.1,26.8)	(-22.2,12.5)
	Pr >  t			0.5844
	n	4	4	
	LS Mean	10.764	-1.127	11.891
	SEM	7.574	7.592	9.238
Week 132	95% CI	(-4.1,25.7)	(-16.1,13.8)	(-6.3,30.1)
	Pr >  t			0.1989
	n	3	2	
	LS Mean	14.916	3.818	11.098
	SEM	8.330	9.659	11.53
Week 144	95% CI	(-1.5,31.3)	(-15.2,22.8)	(-11.6,33.8)
	Pr >  t			0.3365
	n	3	1	
	LS Mean	22.326	3.981	18.345
	SEM	8.330	12.85	14.31

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Europe	Week 156	95% CI	( 5.9,38.7)	(-21.3,29.2)	( -9.8,46.5)
		Pr >  t			0.2006
		n	2	1	
	Week 168	LS Mean	10.902	3.981	6.922
		SEM	9.657	12.85	15.12
		95% CI	( -8.1,29.9)	(-21.3,29.2)	(-22.8,36.7)
	Week 8	Pr >  t			0.6473
		n	1		
		LS Mean	20.809		
	Week 16	SEM	12.83		
		95% CI	( -4.4,46.0)		
		Pr >  t			
	Week 24	n	66	68	
		LS Mean	8.589	0.017	8.572
		SEM	6.477	6.517	3.551
	Week 32	95% CI	( -4.2,21.4)	(-12.9,12.9)	( 1.6,15.6)
		Pr >  t			0.0164
		n	58	48	
	Week 40	LS Mean	2.602	4.137	-1.535
		SEM	6.519	6.608	3.889
		95% CI	(-10.3,15.5)	( -8.9,17.2)	( -9.2, 6.1)
	Week 48	Pr >  t			0.6932
		n	51	36	
		LS Mean	6.032	4.417	1.614
Week 8	SEM	6.564	6.734	4.215	
	95% CI	( -6.9,19.0)	( -8.9,17.7)	( -6.7, 9.9)	
	Pr >  t			0.7019	
Week 16	n	43	30		
	LS Mean	2.146	1.792	0.354	
	SEM	6.693	6.905	4.491	
Week 24	95% CI	(-11.1,15.4)	(-11.8,15.4)	( -8.5, 9.2)	
	Pr >  t			0.9372	
	n	37	25		
Week 32	LS Mean	2.794	0.240	2.553	
	SEM	6.763	7.015	4.766	
	95% CI	(-10.6,16.1)	(-13.6,14.1)	( -6.8,11.9)	
Week 40	Pr >  t			0.5923	
	n	33	21		
	LS Mean	6.791	0.356	6.435	
Week 48	SEM	6.818	7.146	5.032	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-6.7,20.2)	(-13.7,14.4)	(-3.4,16.3)
	Pr >  t			0.2015
	n	29	20	
	LS Mean	3.705	2.455	1.250
	SEM	6.886	7.186	5.186
Week 64	95% CI	(-9.9,17.3)	(-11.7,16.6)	(-8.9,11.4)
	Pr >  t			0.8096
	n	23	20	
	LS Mean	4.881	5.673	-0.792
	SEM	7.032	7.187	5.381
Week 72	95% CI	(-9.0,18.7)	(-8.5,19.8)	(-11.4, 9.8)
	Pr >  t			0.8831
	n	25	19	
	LS Mean	4.029	3.632	0.398
	SEM	6.980	7.228	5.364
Week 84	95% CI	(-9.7,17.8)	(-10.6,17.9)	(-10.1,10.9)
	Pr >  t			0.9409
	n	22	17	
	LS Mean	9.402	1.397	8.005
	SEM	7.065	7.325	5.605
Week 96	95% CI	(-4.5,23.3)	(-13.0,15.8)	(-3.0,19.0)
	Pr >  t			0.1536
	n	20	13	
	LS Mean	9.438	-3.257	12.695
	SEM	7.138	7.599	6.047
Week 108	95% CI	(-4.6,23.5)	(-18.2,11.7)	( 0.8,24.6)
	Pr >  t			0.0361
	n	15	11	
	LS Mean	1.917	6.895	-4.979
	SEM	7.401	7.804	6.596
Week 120	95% CI	(-12.7,16.5)	(-8.5,22.3)	(-17.9, 8.0)
	Pr >  t			0.4506
	n	16	8	
	LS Mean	2.561	1.829	0.731
	SEM	7.341	8.282	7.091
Week 132	95% CI	(-11.9,17.0)	(-14.5,18.1)	(-13.2,14.7)
	Pr >  t			0.9179
	n	12	3	
	LS Mean	3.477	-5.899	9.376
	SEM	7.644	10.73	10.07

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.6,18.5)	(-27.0,15.2)	(-10.4,29.1)
		Pr >  t			0.3522
	Week 144	n	7	4	
		LS Mean	15.461	-2.911	18.373
		SEM	8.467	9.829	9.804
		95% CI	(-1.2,32.1)	(-22.2,16.4)	(-0.9,37.6)
		Pr >  t			0.0613
	Week 156	n	5	2	
		LS Mean	-0.498	-7.958	7.460
		SEM	9.186	12.33	12.82
		95% CI	(-18.5,17.6)	(-32.2,16.3)	(-17.7,32.6)
		Pr >  t			0.5608
	Week 168	n	2	2	
		LS Mean	-8.013	-19.07	11.055
		SEM	12.29	12.33	15.20
		95% CI	(-32.1,16.1)	(-43.3, 5.1)	(-18.8,40.9)
		Pr >  t			0.4672
	Week 180	n		1	
		LS Mean		0.008	
		SEM		16.20	
		95% CI		(-31.8,31.8)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-22.21	
		SEM		16.20	
		95% CI		(-54.0, 9.6)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	0.033	0.709	-0.676
		SEM	5.286	5.461	7.722
		95% CI	(-10.6,10.6)	(-10.2,11.6)	(-16.2,14.8)
		Pr >  t			0.9305
	Week 16	n	13	12	
		LS Mean	-6.005	1.528	-7.534
		SEM	5.407	5.628	7.891
		95% CI	(-16.8, 4.8)	(-9.7,12.8)	(-23.3, 8.3)
		Pr >  t			0.3437
	Week 24	n	12	10	
		LS Mean	-0.384	1.794	-2.178
		SEM	5.539	5.956	8.210

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32		95% CI	(-11.5,10.7)	(-10.1,13.7)	(-18.6,14.2)
		Pr >  t			0.7916
		n	9	10	
		LS Mean	5.844	1.794	4.050
		SEM	6.086	5.956	8.582
Week 40		95% CI	(-6.3,18.0)	(-10.1,13.7)	(-13.1,21.2)
		Pr >  t			0.6384
		n	7	10	
		LS Mean	8.594	2.904	5.690
		SEM	6.632	5.956	9.007
Week 48		95% CI	(-4.6,21.8)	(-9.0,14.8)	(-12.2,23.6)
		Pr >  t			0.5293
		n	7	7	
		LS Mean	0.658	-0.504	1.162
		SEM	6.632	6.657	9.462
Week 56		95% CI	(-12.5,13.8)	(-13.7,12.7)	(-17.6,20.0)
		Pr >  t			0.9026
		n	6	7	
		LS Mean	0.898	1.606	-0.708
		SEM	7.010	6.659	9.746
Week 64		95% CI	(-13.0,14.8)	(-11.6,14.8)	(-20.0,18.6)
		Pr >  t			0.9422
		n	4	7	
		LS Mean	-2.769	1.314	-4.083
		SEM	8.117	6.637	10.54
Week 72		95% CI	(-18.8,13.3)	(-11.9,14.5)	(-25.0,16.8)
		Pr >  t			0.6991
		n	4	4	
		LS Mean	2.786	-1.073	3.860
		SEM	8.117	8.100	11.51
Week 84		95% CI	(-13.3,18.8)	(-17.1,15.0)	(-18.9,26.6)
		Pr >  t			0.7379
		n	4	5	
		LS Mean	0.743	5.320	-4.577
		SEM	8.110	7.465	11.09
Week 96		95% CI	(-15.3,16.8)	(-9.5,20.1)	(-26.5,17.4)
		Pr >  t			0.6804
		n	3	2	
		LS Mean	-9.301	9.420	-18.72
		SEM	9.089	10.73	14.11

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-27.3, 8.7)	(-11.8,30.6)	(-46.6, 9.2)
		Pr >  t			0.1865
		n	2	3	
	Week 120	LS Mean	-5.361	2.822	-8.183
		SEM	10.75	9.142	14.17
		95% CI	(-26.6,15.9)	(-15.2,20.9)	(-36.2,19.8)
	Week 132	Pr >  t			0.5646
		n	2	2	
		LS Mean	5.378	-21.52	26.900
	Week 8	SEM	10.75	10.75	15.23
		95% CI	(-15.9,26.6)	(-42.8,-0.3)	(-3.2,57.0)
		Pr >  t			0.0794
	Week 16	n	1	2	
		LS Mean	-1.100	0.698	-1.798
		SEM	14.64	10.75	18.20
	Week 24	95% CI	(-30.0,27.8)	(-20.5,21.9)	(-37.8,34.2)
		Pr >  t			0.9214
		n	16	19	
	Week 32	LS Mean	8.694	6.506	2.189
		SEM	5.292	5.096	6.343
		95% CI	(-2.0,19.4)	(-3.8,16.8)	(-10.6,15.0)
	Week 40	Pr >  t			0.7316
		n	12	14	
		LS Mean	12.070	8.171	3.899
Week 8	SEM	5.740	5.531	6.945	
	95% CI	( 0.5,23.6)	(-2.9,19.3)	(-10.0,17.8)	
	Pr >  t			0.5766	
Week 16	n	12	8		
	LS Mean	3.373	3.481	-0.108	
	SEM	5.729	6.522	7.715	
Week 24	95% CI	(-8.1,14.9)	(-9.5,16.4)	(-15.5,15.2)	
	Pr >  t			0.9889	
	n	9	7		
Week 32	LS Mean	7.056	6.148	0.907	
	SEM	6.180	6.762	8.217	
	95% CI	(-5.3,19.4)	(-7.3,19.6)	(-15.4,17.2)	
Week 40	Pr >  t			0.9123	
	n	9	7		
	LS Mean	1.580	9.324	-7.744	
		SEM	6.184	6.762	8.236

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-10.8,13.9)	(-4.1,22.7)	(-24.1, 8.6)
	Pr >  t			0.3495
	n	8	5	
	LS Mean	8.283	6.404	1.878
	SEM	6.372	7.437	8.931
Week 56	95% CI	(-4.4,21.0)	(-8.3,21.1)	(-15.8,19.6)
	Pr >  t			0.8338
	n	7	3	
	LS Mean	12.398	3.295	9.103
	SEM	6.591	8.777	10.22
Week 64	95% CI	(-0.7,25.5)	(-14.1,20.7)	(-11.1,29.3)
	Pr >  t			0.3747
	n	5	3	
	LS Mean	10.934	-7.819	18.753
	SEM	7.247	8.777	10.67
Week 72	95% CI	(-3.4,25.3)	(-25.2, 9.5)	(-2.3,39.8)
	Pr >  t			0.0810
	n	5	3	
	LS Mean	13.823	-4.709	18.532
	SEM	7.237	8.763	10.63
Week 84	95% CI	(-0.5,28.2)	(-22.0,12.6)	(-2.5,39.6)
	Pr >  t			0.0837
	n	2	2	
	LS Mean	7.909	-7.473	15.383
	SEM	10.01	10.17	13.67
Week 96	95% CI	(-11.9,27.7)	(-27.6,12.6)	(-11.7,42.4)
	Pr >  t			0.2625
	n	3	2	
	LS Mean	2.702	9.192	-6.489
	SEM	8.539	10.17	12.68
Week 108	95% CI	(-14.2,19.6)	(-10.9,29.3)	(-31.6,18.6)
	Pr >  t			0.6095
	n	1	2	
	LS Mean	14.974	20.302	-5.328
	SEM	13.28	10.17	16.22
Week 120	95% CI	(-11.3,41.2)	( 0.2,40.4)	(-37.4,26.8)
	Pr >  t			0.7431
	n	3	2	
	LS Mean	17.519	-1.918	19.437
	SEM	8.539	10.17	12.68

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 0.6,34.4)	(-22.0,18.2)	( -5.6,44.5)
		Pr >  t			0.1274
	Week 132	n	1	1	
		LS Mean	19.075	37.980	-18.90
		SEM	13.28	13.41	18.44
		95% CI	( -7.2,45.3)	( 11.5,64.5)	(-55.4,17.6)
		Pr >  t			0.3073
	Week 144	n	2		
		LS Mean	18.787		
		SEM	9.925		
		95% CI	( -0.8,38.4)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	-3.145		
		SEM	13.28		
		95% CI	(-29.4,23.1)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	19.075		
		SEM	13.28		
		95% CI	( -7.2,45.3)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	19.075		
		SEM	13.28		
		95% CI	( -7.2,45.3)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	7.965		
		SEM	13.28		
		95% CI	(-18.3,34.2)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	16.954	11.600	5.353
		SEM	4.743	7.422	8.028
		95% CI	( 7.3,26.6)	( -3.4,26.6)	(-10.9,21.6)
		Pr >  t			0.5087
	Week 16	n	13	4	
		LS Mean	13.737	-1.283	15.021
		SEM	5.083	8.434	8.893



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	( 3.5,24.0)	(-18.2,15.7)	( -2.9,32.9)
	Pr >  t			0.0977
	n	9	2	
	LS Mean	15.748	10.158	5.591
	SEM	5.685	10.73	11.35
Week 32	95% CI	( 4.3,27.2)	(-11.3,31.6)	(-17.1,28.2)
	Pr >  t			0.6240
	n	6	3	
	LS Mean	14.212	2.977	11.234
	SEM	6.562	9.246	10.46
Week 40	95% CI	( 1.1,27.3)	(-15.5,21.5)	( -9.7,32.1)
	Pr >  t			0.2871
	n	6	2	
	LS Mean	13.440	-4.938	18.378
	SEM	6.677	10.66	11.77
Week 48	95% CI	( 0.1,26.8)	(-26.2,16.3)	( -5.1,41.8)
	Pr >  t			0.1228
	n	5	1	
	LS Mean	15.694	-0.283	15.977
	SEM	7.073	14.11	15.22
Week 56	95% CI	( 1.6,29.8)	(-28.4,27.8)	(-14.3,46.3)
	Pr >  t			0.2970
	n	5	1	
	LS Mean	11.250	-0.283	11.533
	SEM	7.073	14.11	15.22
Week 64	95% CI	( -2.9,25.4)	(-28.4,27.8)	(-18.8,41.8)
	Pr >  t			0.4508
	n	3	1	
	LS Mean	14.680	-0.283	14.963
	SEM	8.438	14.11	15.90
Week 72	95% CI	( -2.1,31.5)	(-28.4,27.8)	(-16.7,46.6)
	Pr >  t			0.3496
	n	4	1	
	LS Mean	15.169	-0.283	15.452
	SEM	7.636	14.11	15.50
Week 84	95% CI	( -0.0,30.4)	(-28.4,27.8)	(-15.4,46.3)
	Pr >  t			0.3216
	n	4	1	
	LS Mean	17.946	-0.283	18.230
	SEM	7.636	14.11	15.50

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	( 2.7,33.2)	(-28.4,27.8)	(-12.6,49.1)
	Pr >  t			0.2429
	n	3	1	
	LS Mean	14.680	-0.283	14.963
	SEM	8.438	14.11	15.90
Week 108	95% CI	( -2.1,31.5)	(-28.4,27.8)	(-16.7,46.6)
	Pr >  t			0.3496
	n	4		
	LS Mean	9.614		
	SEM	7.636		
Week 120	95% CI	( -5.6,24.8)		
	Pr >  t			
	n	3		
	LS Mean	18.383		
	SEM	8.438		
Week 132	95% CI	( 1.6,35.2)		
	Pr >  t			
	n	3		
	LS Mean	25.793		
	SEM	8.438		
Week 144	95% CI	( 9.0,42.6)		
	Pr >  t			
	n	3		
	LS Mean	11.276		
	SEM	8.448		
Week 156	95% CI	( -5.5,28.1)		
	Pr >  t			
	n	2		
	LS Mean	5.271		
	SEM	9.810		
	95% CI	(-14.2,24.8)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	9.100	1.425	7.675	
		SEM	3.496	3.415	2.757	
		95% CI	( 2.2,16.0)	( -5.3, 8.1)	( 2.3,13.1)	
					Pr >  t	0.0056
	Week 16	n	88	71		
		LS Mean	6.325	3.212	3.113	
		SEM	3.558	3.629	2.940	
		95% CI	( -0.7,13.3)	( -3.9,10.4)	( -2.7, 8.9)	
					Pr >  t	0.2901
	Week 24	n	75	54		
		LS Mean	6.813	4.897	1.917	
		SEM	3.612	3.756	3.177	
		95% CI	( -0.3,13.9)	( -2.5,12.3)	( -4.3, 8.2)	
					Pr >  t	0.5465
	Week 32	n	62	52		
		LS Mean	7.949	1.836	6.113	
		SEM	3.706	3.777	3.296	
		95% CI	( 0.7,15.2)	( -5.6, 9.3)	( -0.4,12.6)	
					Pr >  t	0.0641
	Week 40	n	51	46		
		LS Mean	5.893	0.710	5.182	
		SEM	3.797	3.861	3.476	
		95% CI	( -1.6,13.4)	( -6.9, 8.3)	( -1.6,12.0)	
				Pr >  t	0.1365	
Week 48	n	50	37			
	LS Mean	9.324	2.799	6.524		
	SEM	3.807	3.993	3.633		
	95% CI	( 1.8,16.8)	( -5.0,10.6)	( -0.6,13.7)		
				Pr >  t	0.0729	
Week 56	n	43	33			
	LS Mean	7.500	2.637	4.863		
	SEM	3.888	4.073	3.805		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-0.1,15.1)	(-5.4,10.6)	(-2.6,12.3)
	Pr >  t			0.2015
	n	35	33	
	LS Mean	7.301	2.349	4.952
	SEM	4.012	4.073	3.934
Week 72	95% CI	(-0.6,15.2)	(-5.7,10.4)	(-2.8,12.7)
	Pr >  t			0.2084
	n	35	31	
	LS Mean	8.899	2.921	5.977
	SEM	4.012	4.117	3.981
Week 84	95% CI	( 1.0,16.8)	(-5.2,11.0)	(-1.8,13.8)
	Pr >  t			0.1335
	n	31	29	
	LS Mean	10.374	2.718	7.656
	SEM	4.105	4.167	4.116
Week 96	95% CI	( 2.3,18.4)	(-5.5,10.9)	(-0.4,15.7)
	Pr >  t			0.0632
	n	27	22	
	LS Mean	8.186	1.024	7.161
	SEM	4.201	4.406	4.459
Week 108	95% CI	(-0.1,16.4)	(-7.6, 9.7)	(-1.6,15.9)
	Pr >  t			0.1086
	n	19	20	
	LS Mean	5.339	10.469	-5.130
	SEM	4.540	4.501	4.858
Week 120	95% CI	(-3.6,14.3)	( 1.6,19.3)	(-14.7, 4.4)
	Pr >  t			0.2912
	n	20	15	
	LS Mean	10.139	-0.160	10.300
	SEM	4.471	4.830	5.116
Week 132	95% CI	( 1.4,18.9)	(-9.6, 9.3)	( 0.3,20.3)
	Pr >  t			0.0443
	n	15	7	
	LS Mean	12.945	2.047	10.898
	SEM	4.812	6.098	6.565
Week 144	95% CI	( 3.5,22.4)	(-9.9,14.0)	(-2.0,23.8)
	Pr >  t			0.0972
	n	10	5	
Week 144	LS Mean	21.248	-0.094	21.342
	SEM	5.383	6.902	7.720

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 10.7,31.8)	(-13.6,13.4)	( 6.2,36.5)
		Pr >  t			0.0058
	Week 156	n	6	3	
		LS Mean	0.823	-2.228	3.051
		SEM	6.432	8.470	9.791
		95% CI	(-11.8,13.4)	(-18.8,14.4)	(-16.2,22.3)
		Pr >  t			0.7554
	Week 168	n	3	2	
		LS Mean	3.247	-17.27	20.517
		SEM	8.460	10.10	12.50
		95% CI	(-13.4,19.8)	(-37.1, 2.5)	( -4.0,45.0)
		Pr >  t			0.1010
	Week 180	n	1	1	
		LS Mean	17.644	1.723	15.921
		SEM	13.86	13.86	19.15
		95% CI	( -9.6,44.8)	(-25.5,28.9)	(-21.7,53.5)
		Pr >  t			0.4060
	Week 192	n	1	1	
		LS Mean	6.534	-20.50	27.031
		SEM	13.86	13.86	19.15
		95% CI	(-20.7,33.7)	(-47.7, 6.7)	(-10.6,64.6)
		Pr >  t			0.1585
1	Week 8	n	43	50	
		LS Mean	9.655	1.690	7.965
		SEM	3.965	4.144	4.113
		95% CI	( 1.8,17.5)	( -6.5, 9.9)	( -0.2,16.1)
		Pr >  t			0.0544
	Week 16	n	35	35	
		LS Mean	7.847	3.766	4.081
		SEM	4.175	4.313	4.548
		95% CI	( -0.4,16.1)	( -4.8,12.3)	( -4.9,13.0)
		Pr >  t			0.3705
	Week 24	n	29	26	
		LS Mean	6.045	1.332	4.713
		SEM	4.367	4.669	4.972
		95% CI	( -2.6,14.7)	( -7.9,10.5)	( -5.1,14.5)
		Pr >  t			0.3440
	Week 32	n	23	21	
		LS Mean	2.945	3.861	-0.917
		SEM	4.653	4.946	5.372

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.2,12.1)	(-5.9,13.6)	(-11.5, 9.7)
		Pr >  t			0.8646
	Week 40	n	23	16	
		LS Mean	2.505	5.809	-3.304
		SEM	4.665	5.270	5.680
		95% CI	(-6.7,11.7)	(-4.6,16.2)	(-14.5, 7.9)
		Pr >  t			0.5612
	Week 48	n	18	14	
		LS Mean	3.268	4.742	-1.475
		SEM	4.932	5.459	6.087
		95% CI	(-6.4,13.0)	(-6.0,15.5)	(-13.4,10.5)
		Pr >  t			0.8087
	Week 56	n	15	12	
		LS Mean	0.754	4.405	-3.651
		SEM	5.176	5.691	6.501
		95% CI	(-9.4,10.9)	(-6.8,15.6)	(-16.4, 9.1)
		Pr >  t			0.5748
	Week 64	n	11	9	
		LS Mean	8.691	14.036	-5.346
		SEM	5.638	6.204	7.313
		95% CI	(-2.4,19.8)	( 1.8,26.2)	(-19.7, 9.0)
		Pr >  t			0.4652
	Week 72	n	12	4	
		LS Mean	-2.125	4.697	-6.822
		SEM	5.511	8.274	9.054
		95% CI	(-13.0, 8.7)	(-11.6,21.0)	(-24.6,11.0)
		Pr >  t			0.4516
	Week 84	n	8	4	
		LS Mean	12.500	4.697	7.803
		SEM	6.285	8.274	9.528
		95% CI	( 0.1,24.9)	(-11.6,21.0)	(-10.9,26.5)
		Pr >  t			0.4133
	Week 96	n	8	2	
		LS Mean	13.889	13.097	0.792
		SEM	6.285	11.01	11.98
		95% CI	( 1.5,26.2)	(-8.5,34.7)	(-22.8,24.3)
		Pr >  t			0.9473
	Week 108	n	6	1	
		LS Mean	2.837	6.210	-3.373
		SEM	6.949	15.04	16.03

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.8,16.5)	(-23.4,35.8)	(-34.9,28.2)
		Pr >  t			0.8335
	Week 120	n	8	1	
		LS Mean	3.522	-16.01	19.532
		SEM	6.301	15.04	15.76
		95% CI	(-8.9,15.9)	(-45.6,13.6)	(-11.5,50.5)
		Pr >  t			0.2161
	Week 132	n	5	1	
		LS Mean	0.889	28.430	-27.54
		SEM	7.430	15.04	16.25
		95% CI	(-13.7,15.5)	(-1.1,58.0)	(-59.5, 4.4)
		Pr >  t			0.0909
	Week 144	n	5		
		LS Mean	5.333		
		SEM	7.430		
		95% CI	(-9.3,19.9)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	3.998		
		SEM	8.091		
		95% CI	(-11.9,19.9)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	18.651		
		SEM	14.81		
		95% CI	(-10.5,47.8)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status (L) Primary resistant		Week 8	n	21	16		
			LS Mean	6.979	3.288	3.692	
			SEM	6.402	7.609	8.145	
			95% CI	(-6.0,19.9)	(-12.1,18.7)	(-12.7,20.0)	
				Pr >  t			0.6523
		Week 16	n	17	10		
			LS Mean	4.312	3.327	0.985	
			SEM	6.854	8.746	9.250	
			95% CI	(-9.5,18.1)	(-14.2,20.9)	(-17.5,19.5)	
				Pr >  t			0.9155
		Week 24	n	9	5		
			LS Mean	5.870	21.522	-15.65	
			SEM	7.936	10.63	11.96	
			95% CI	(-10.0,21.7)	( 0.4,42.6)	(-39.4, 8.1)	
				Pr >  t			0.1937
		Week 32	n	8	4		
			LS Mean	0.793	-3.014	3.807	
			SEM	8.210	11.34	12.79	
			95% CI	(-15.6,17.1)	(-25.5,19.5)	(-21.5,29.2)	
				Pr >  t			0.7666
		Week 40	n	5	4		
			LS Mean	-0.665	-3.014	2.350	
			SEM	9.435	11.34	13.73	
			95% CI	(-19.4,18.1)	(-25.5,19.5)	(-24.8,29.5)	
				Pr >  t			0.8644
		Week 48	n	5	3		
			LS Mean	10.445	10.877	-0.432	
			SEM	9.435	12.41	14.61	
95% CI	(-8.3,29.2)		(-13.7,35.5)	(-29.4,28.5)			
		Pr >  t			0.9765		
Week 56	n	4	3				
	LS Mean	17.409	7.173	10.235			
	SEM	10.15	12.41	15.12			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	95% CI	(-2.7,37.5)	(-17.4,31.8)	(-19.7,40.2)	
	Pr >  t			0.4999	
	n	4	3		
	LS Mean	6.296	-0.237	6.533	
	SEM	10.15	12.41	15.12	
Week 72	95% CI	(-13.8,26.4)	(-24.8,24.4)	(-23.4,36.5)	
	Pr >  t			0.6665	
	n	4	3		
	LS Mean	20.186	3.470	16.716	
	SEM	10.15	12.41	15.12	
Week 84	95% CI	( 0.1,40.3)	(-21.1,28.1)	(-13.2,46.7)	
	Pr >  t			0.2713	
	n	2	3		
	LS Mean	22.079	10.877	11.202	
	SEM	13.39	12.41	17.33	
Week 96	95% CI	(-4.4,48.6)	(-13.7,35.5)	(-23.1,45.5)	
	Pr >  t			0.5193	
	n	1	3		
	LS Mean	-5.680	14.580	-20.26	
	SEM	17.84	12.41	21.19	
Week 108	95% CI	(-41.1,29.7)	(-10.0,39.2)	(-62.3,21.8)	
	Pr >  t			0.3414	
	n		2		
	LS Mean		28.456		
	SEM		14.22		
Week 120	95% CI		( 0.3,56.6)		
	Pr >  t				
	n	1	1		
	LS Mean	5.430	9.134	-3.704	
	SEM	17.84	18.58	25.33	
Week 132	95% CI	(-30.0,40.8)	(-27.7,46.0)	(-54.0,46.6)	
	Pr >  t			0.8841	
	n		1		
	LS Mean		42.464		
	SEM		18.58		
Week 144	95% CI		( 5.6,79.3)		
	Pr >  t				
	n	1			
	LS Mean	16.540			
	SEM	17.84			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.9,51.9)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	11.878	4.928	6.949
		SEM	3.014	3.020	2.552
		95% CI	( 5.9,17.8)	( -1.0,10.9)	( 1.9,12.0)
		Pr >  t			0.0067
	Week 16	n	83	81	
		LS Mean	9.634	7.116	2.518
		SEM	3.092	3.155	2.762
		95% CI	( 3.6,15.7)	( 0.9,13.3)	( -2.9, 7.9)
		Pr >  t			0.3623
	Week 24	n	75	62	
		LS Mean	9.272	5.422	3.850
		SEM	3.149	3.302	2.956
		95% CI	( 3.1,15.5)	( -1.1,11.9)	( -2.0, 9.7)
		Pr >  t			0.1931
	Week 32	n	59	56	
		LS Mean	9.217	5.182	4.035
		SEM	3.305	3.352	3.134
		95% CI	( 2.7,15.7)	( -1.4,11.8)	( -2.1,10.2)
		Pr >  t			0.1983
	Week 40	n	52	48	
		LS Mean	8.659	4.955	3.704
		SEM	3.371	3.450	3.290
		95% CI	( 2.0,15.3)	( -1.8,11.7)	( -2.8,10.2)
		Pr >  t			0.2607
	Week 48	n	47	37	
		LS Mean	10.341	6.913	3.428
		SEM	3.427	3.614	3.517
		95% CI	( 3.6,17.1)	( -0.2,14.0)	( -3.5,10.3)
		Pr >  t			0.3300
	Week 56	n	41	31	
		LS Mean	7.503	6.726	0.777
		SEM	3.510	3.745	3.732
		95% CI	( 0.6,14.4)	( -0.6,14.1)	( -6.5, 8.1)
		Pr >  t			0.8352
	Week 64	n	32	28	
		LS Mean	9.044	8.667	0.377
		SEM	3.681	3.829	3.973

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72		95% CI	( 1.8,16.3)	( 1.1,16.2)	( -7.4, 8.2)
		Pr >  t			0.9243
		n	29	22	
		LS Mean	9.070	5.466	3.604
		SEM	3.762	4.051	4.259
Week 84		95% CI	( 1.7,16.5)	( -2.5,13.4)	( -4.8,12.0)
		Pr >  t			0.3977
		n	26	21	
		LS Mean	9.778	4.358	5.420
		SEM	3.852	4.098	4.383
Week 96		95% CI	( 2.2,17.3)	( -3.7,12.4)	( -3.2,14.0)
		Pr >  t			0.2165
		n	23	14	
		LS Mean	7.123	5.270	1.852
		SEM	3.966	4.584	4.932
Week 108		95% CI	( -0.7,14.9)	( -3.7,14.3)	( -7.8,11.5)
		Pr >  t			0.7073
		n	18	13	
		LS Mean	6.014	8.868	-2.854
		SEM	4.228	4.690	5.238
Week 120		95% CI	( -2.3,14.3)	( -0.3,18.1)	( -13.1, 7.4)
		Pr >  t			0.5859
		n	19	10	
		LS Mean	12.621	-0.623	13.244
		SEM	4.170	5.103	5.567
Week 132		95% CI	( 4.4,20.8)	( -10.6, 9.4)	( 2.3,24.2)
		Pr >  t			0.0175
		n	13	4	
		LS Mean	12.581	0.133	12.448
		SEM	4.646	7.224	7.832
Week 144		95% CI	( 3.5,21.7)	( -14.0,14.3)	( -2.9,27.8)
		Pr >  t			0.1123
		n	8	1	
		LS Mean	20.612	3.492	17.121
		SEM	5.475	13.52	14.15
Week 156		95% CI	( 9.9,31.4)	( -23.0,30.0)	( -10.7,44.9)
		Pr >  t			0.2267
		n	5	1	
		LS Mean	1.660	-7.618	9.278
		SEM	6.560	13.52	14.61

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-11.2,14.5)	(-34.1,18.9)	(-19.4,37.9)
		Pr >  t			0.5255
		n	3	1	
		LS Mean	4.387	-18.73	23.116
		SEM	8.128	13.52	15.38
	Week 180	95% CI	(-11.6,20.3)	(-45.3, 7.8)	(-7.1,53.3)
		Pr >  t			0.1331
		n	1	1	
		LS Mean	18.873	3.492	15.382
		SEM	13.46	13.52	18.75
	Week 192	95% CI	(-7.5,45.3)	(-23.0,30.0)	(-21.4,52.2)
		Pr >  t			0.4122
		n	1	1	
		LS Mean	7.763	-18.73	26.492
		SEM	13.46	13.52	18.75
	Week 8	95% CI	(-18.7,34.2)	(-45.3, 7.8)	(-10.3,63.3)
		Pr >  t			0.1580
		n	17	16	
		LS Mean	2.315	-9.481	11.796
		SEM	4.683	4.852	6.627
	Week 16	95% CI	(-7.0,11.6)	(-19.1, 0.2)	(-1.4,24.9)
		Pr >  t			0.0781
		n	18	14	
		LS Mean	-3.918	-10.75	6.835
		SEM	4.587	5.076	6.759
	Week 24	95% CI	(-13.0, 5.2)	(-20.8,-0.7)	(-6.6,20.2)
		Pr >  t			0.3143
		n	16	13	
LS Mean		-1.444	-7.046	5.602	
SEM		4.801	5.201	6.990	
Week 32	95% CI	(-11.0, 8.1)	(-17.4, 3.3)	(-8.2,19.5)	
	Pr >  t			0.4245	
	n	15	13		
	LS Mean	3.374	-4.234	7.608	
	SEM	4.889	5.214	7.073	
Week 40	95% CI	(-6.3,13.1)	(-14.6, 6.1)	(-6.4,21.6)	
	Pr >  t			0.2843	
	n	14	10		
	LS Mean	-4.945	-4.753	-0.192	
		SEM	5.023	5.674	7.502

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	95% CI	(-14.9, 5.0)	(-16.0, 6.5)	(-15.0,14.6)	
	Pr >  t			0.9796	
	n	14	11		
	LS Mean	-0.977	-9.650	8.674	
	SEM	5.023	5.510	7.376	
Week 56	95% CI	(-10.9, 9.0)	(-20.6, 1.3)	( -5.9,23.3)	
	Pr >  t			0.2418	
	n	11	11		
	LS Mean	0.622	-8.640	9.262	
	SEM	5.416	5.510	7.655	
Week 64	95% CI	(-10.1,11.3)	(-19.5, 2.3)	( -5.9,24.4)	
	Pr >  t			0.2283	
	n	8	11		
	LS Mean	2.904	-4.600	7.504	
	SEM	6.021	5.510	8.102	
Week 72	95% CI	( -9.0,14.8)	(-15.5, 6.3)	( -8.5,23.5)	
	Pr >  t			0.3557	
	n	11	10		
	LS Mean	-2.409	-3.608	1.199	
	SEM	5.416	5.681	7.779	
Week 84	95% CI	(-13.1, 8.3)	(-14.8, 7.6)	(-14.2,16.6)	
	Pr >  t			0.8777	
	n	9	9		
	LS Mean	12.272	-4.038	16.310	
	SEM	5.781	5.879	8.187	
Week 96	95% CI	( 0.9,23.7)	(-15.7, 7.6)	( 0.1,32.5)	
	Pr >  t			0.0480	
	n	8	7		
	LS Mean	20.007	-11.59	31.600	
	SEM	6.025	6.403	8.740	
Week 108	95% CI	( 8.1,31.9)	(-24.2, 1.0)	( 14.4,48.8)	
	Pr >  t			0.0004	
	n	7	6		
	LS Mean	3.517	5.867	-2.350	
	SEM	6.320	6.779	9.218	
Week 120	95% CI	( -8.9,16.0)	( -7.5,19.2)	(-20.5,15.8)	
	Pr >  t			0.7990	
	n	6	5		
	LS Mean	-2.442	-6.627	4.185	
	SEM	6.697	7.272	9.826	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132		95% CI	(-15.6,10.8)	(-21.0, 7.7)	(-15.2,23.5)
		Pr >  t			0.6706
		n	5	3	
		LS Mean	4.353	-3.725	8.078
		SEM	7.179	8.911	11.40
Week 144		95% CI	(-9.8,18.5)	(-21.3,13.8)	(-14.4,30.5)
		Pr >  t			0.4790
		n	5	4	
		LS Mean	8.799	-8.739	17.538
		SEM	7.179	7.925	10.64
Week 156		95% CI	(-5.3,22.9)	(-24.3, 6.9)	(-3.4,38.5)
		Pr >  t			0.1006
		n	4	2	
		LS Mean	2.751	-6.742	9.494
		SEM	7.840	10.61	13.16
Week 168		95% CI	(-12.7,18.2)	(-27.6,14.1)	(-16.4,35.4)
		Pr >  t			0.4712
		n	1	1	
		LS Mean	16.562	-22.14	38.697
		SEM	14.52	14.57	20.55
		95% CI	(-12.0,45.1)	(-50.8, 6.6)	(-1.8,79.2)
		Pr >  t			0.0608

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	4.793	0.419	4.374
		SEM	8.237	8.586	3.715
		95% CI	(-11.5,21.1)	(-16.6,17.4)	(-2.9,11.7)
		Pr >  t			0.2402
	Week 16	n	51	41	
		LS Mean	6.779	3.267	3.512
		SEM	8.257	8.684	4.020
		95% CI	(-9.6,23.1)	(-13.9,20.5)	(-4.4,11.4)
		Pr >  t			0.3831
	Week 24	n	38	33	
		LS Mean	3.609	5.900	-2.291
		SEM	8.315	8.767	4.395
		95% CI	(-12.8,20.1)	(-11.4,23.2)	(-10.9, 6.4)
		Pr >  t			0.6026
	Week 32	n	34	28	
		LS Mean	3.502	1.337	2.165
		SEM	8.464	8.825	4.593
		95% CI	(-13.2,20.2)	(-16.1,18.8)	(-6.9,11.2)
		Pr >  t			0.6377
	Week 40	n	26	23	
		LS Mean	1.452	-0.945	2.397
		SEM	8.586	8.918	4.977
		95% CI	(-15.5,18.4)	(-18.6,16.7)	(-7.4,12.2)
		Pr >  t			0.6303
	Week 48	n	24	17	
		LS Mean	6.496	1.714	4.782
		SEM	8.625	9.096	5.362
95% CI		(-10.6,23.5)	(-16.3,19.7)	(-5.8,15.3)	
	Pr >  t			0.3729	
Week 56	n	21	17		
	LS Mean	2.031	1.443	0.588	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	8.699	9.097	5.479
	95% CI	(-15.2,19.2)	(-16.5,19.4)	(-10.2,11.4)
	Pr >  t			0.9146
Week 64	n	15	15	
	LS Mean	4.580	2.719	1.861
	SEM	8.921	9.183	5.964
	95% CI	(-13.0,22.2)	(-15.4,20.9)	(-9.9,13.6)
	Pr >  t			0.7551
Week 72	n	16	15	
	LS Mean	2.763	0.940	1.823
	SEM	8.874	9.184	5.895
	95% CI	(-14.8,20.3)	(-17.2,19.1)	(-9.8,13.4)
	Pr >  t			0.7573
Week 84	n	14	13	
	LS Mean	5.191	-1.287	6.478
	SEM	8.975	9.294	6.215
	95% CI	(-12.5,22.9)	(-19.6,17.1)	(-5.7,18.7)
	Pr >  t			0.2977
Week 96	n	12	9	
	LS Mean	7.920	2.572	5.348
	SEM	9.110	9.665	6.934
	95% CI	(-10.1,25.9)	(-16.5,21.6)	(-8.3,19.0)
	Pr >  t			0.4408
Week 108	n	13	8	
	LS Mean	-0.114	6.410	-6.524
	SEM	9.039	9.809	7.046
	95% CI	(-18.0,17.7)	(-12.9,25.8)	(-20.4, 7.3)
	Pr >  t			0.3549
Week 120	n	11	6	
	LS Mean	7.780	-1.196	8.976
	SEM	9.193	10.23	7.800
	95% CI	(-10.4,25.9)	(-21.3,19.0)	(-6.3,24.3)
	Pr >  t			0.2503
Week 132	n	8	3	
	LS Mean	0.850	13.029	-12.18
	SEM	9.557	11.75	10.05
	95% CI	(-18.0,19.7)	(-10.1,36.1)	(-31.9, 7.6)
	Pr >  t			0.2261
Week 144	n	5	1	
	LS Mean	17.607	0.799	16.808

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	10.31	16.46	15.78
		95% CI	(-2.7,37.9)	(-31.5,33.1)	(-14.2,47.8)
		Pr >  t			0.2874
	Week 168	n	3	1	
		LS Mean	-3.392	-10.31	6.919
		SEM	11.53	16.46	16.61
	Week 180	95% CI	(-26.1,19.3)	(-42.6,22.0)	(-25.7,39.5)
		Pr >  t			0.6771
		n	2	1	
	Week 192	LS Mean	-8.681	-21.42	12.740
		SEM	12.88	16.46	17.57
		95% CI	(-34.0,16.6)	(-53.8,10.9)	(-21.8,47.3)
	Week 8	Pr >  t			0.4687
		n		1	
		LS Mean		0.799	
	Week 16	SEM		16.46	
		95% CI		(-31.5,33.1)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-21.42	
		SEM		16.46	
	Week 32	95% CI		(-53.8,10.9)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	2.315	-9.481	11.796	
	SEM	4.683	4.852	6.627	
	95% CI	(-7.0,11.6)	(-19.1, 0.2)	(-1.4,24.9)	
Week 16	Pr >  t			0.0781	
	n	18	14		
	LS Mean	-3.918	-10.75	6.835	
Week 24	SEM	4.587	5.076	6.759	
	95% CI	(-13.0, 5.2)	(-20.8,-0.7)	(-6.6,20.2)	
	Pr >  t			0.3143	
Week 32	n	16	13		
	LS Mean	-1.444	-7.046	5.602	
	SEM	4.801	5.201	6.990	
Week 8	95% CI	(-11.0, 8.1)	(-17.4, 3.3)	(-8.2,19.5)	
	Pr >  t			0.4245	
	n	15	13		
Week 16	LS Mean	3.374	-4.234	7.608	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	4.889	5.214	7.073
		95% CI	(-6.3,13.1)	(-14.6, 6.1)	(-6.4,21.6)
		Pr >  t			0.2843
	Week 40	n	14	10	
		LS Mean	-4.945	-4.753	-0.192
		SEM	5.023	5.674	7.502
		95% CI	(-14.9, 5.0)	(-16.0, 6.5)	(-15.0,14.6)
		Pr >  t			0.9796
	Week 48	n	14	11	
		LS Mean	-0.977	-9.650	8.674
		SEM	5.023	5.510	7.376
		95% CI	(-10.9, 9.0)	(-20.6, 1.3)	(-5.9,23.3)
		Pr >  t			0.2418
	Week 56	n	11	11	
		LS Mean	0.622	-8.640	9.262
		SEM	5.416	5.510	7.655
		95% CI	(-10.1,11.3)	(-19.5, 2.3)	(-5.9,24.4)
		Pr >  t			0.2283
	Week 64	n	8	11	
		LS Mean	2.904	-4.600	7.504
		SEM	6.021	5.510	8.102
		95% CI	(-9.0,14.8)	(-15.5, 6.3)	(-8.5,23.5)
		Pr >  t			0.3557
	Week 72	n	11	10	
		LS Mean	-2.409	-3.608	1.199
		SEM	5.416	5.681	7.779
		95% CI	(-13.1, 8.3)	(-14.8, 7.6)	(-14.2,16.6)
		Pr >  t			0.8777
	Week 84	n	9	9	
		LS Mean	12.272	-4.038	16.310
		SEM	5.781	5.879	8.187
		95% CI	( 0.9,23.7)	(-15.7, 7.6)	( 0.1,32.5)
		Pr >  t			0.0480
	Week 96	n	8	7	
		LS Mean	20.007	-11.59	31.600
		SEM	6.025	6.403	8.740
		95% CI	( 8.1,31.9)	(-24.2, 1.0)	( 14.4,48.8)
		Pr >  t			0.0004
	Week 108	n	7	6	
		LS Mean	3.517	5.867	-2.350

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	6.320	6.779	9.218
		95% CI	(-8.9,16.0)	(-7.5,19.2)	(-20.5,15.8)
		Pr >  t			0.7990
	Week 120	n	6	5	
		LS Mean	-2.442	-6.627	4.185
		SEM	6.697	7.272	9.826
		95% CI	(-15.6,10.8)	(-21.0, 7.7)	(-15.2,23.5)
		Pr >  t			0.6706
	Week 132	n	5	3	
		LS Mean	4.353	-3.725	8.078
		SEM	7.179	8.911	11.40
		95% CI	(-9.8,18.5)	(-21.3,13.8)	(-14.4,30.5)
		Pr >  t			0.4790
	Week 144	n	5	4	
		LS Mean	8.799	-8.739	17.538
		SEM	7.179	7.925	10.64
		95% CI	(-5.3,22.9)	(-24.3, 6.9)	(-3.4,38.5)
		Pr >  t			0.1006
	Week 156	n	4	2	
		LS Mean	2.751	-6.742	9.494
		SEM	7.840	10.61	13.16
		95% CI	(-12.7,18.2)	(-27.6,14.1)	(-16.4,35.4)
		Pr >  t			0.4712
	Week 168	n	1	1	
		LS Mean	16.562	-22.14	38.697
		SEM	14.52	14.57	20.55
		95% CI	(-12.0,45.1)	(-50.8, 6.6)	(-1.8,79.2)
		Pr >  t			0.0608
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	14.641	6.642	7.999
		SEM	5.960	5.653	6.760
		95% CI	( 2.6,26.7)	(-4.8,18.1)	(-5.6,21.6)
		Pr >  t			0.2427
	Week 16	n	15	17	
		LS Mean	14.388	7.405	6.983
		SEM	6.189	5.799	6.913
		95% CI	( 1.9,26.8)	(-4.3,19.1)	(-6.9,20.9)
		Pr >  t			0.3173
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	11.808	6.183	5.625
	SEM	6.255	6.195	7.346
	95% CI	(-0.8,24.4)	(-6.2,18.6)	(-9.1,20.3)
	Pr >  t			0.4467
	n	12	9	
Week 40	LS Mean	12.161	5.993	6.168
	SEM	6.443	6.461	7.671
	95% CI	(-0.8,25.1)	(-6.9,18.9)	(-9.1,21.5)
	Pr >  t			0.4240
	n	11	7	
Week 48	LS Mean	11.970	1.396	10.574
	SEM	6.551	6.874	8.049
	95% CI	(-1.1,25.1)	(-12.3,15.1)	(-5.4,26.6)
	Pr >  t			0.1925
	n	8	6	
Week 56	LS Mean	13.587	10.099	3.488
	SEM	6.900	7.120	8.556
	95% CI	(-0.2,27.4)	(-4.0,24.2)	(-13.5,20.5)
	Pr >  t			0.6844
	n	7	5	
Week 64	LS Mean	14.538	8.016	6.521
	SEM	7.074	7.429	8.971
	95% CI	( 0.4,28.6)	(-6.7,22.7)	(-11.2,24.3)
	Pr >  t			0.4687
	n	5	3	
Week 72	LS Mean	16.259	4.806	11.452
	SEM	7.592	8.541	10.28
	95% CI	( 1.2,31.3)	(-12.1,21.7)	(-8.9,31.8)
	Pr >  t			0.2671
	n	5	2	
Week 84	LS Mean	12.679	5.485	7.194
	SEM	7.628	9.772	11.34
	95% CI	(-2.5,27.8)	(-13.8,24.8)	(-15.2,29.6)
	Pr >  t			0.5269
	n	4	2	
Week 96	LS Mean	13.916	5.485	8.430
	SEM	8.004	9.772	11.62
	95% CI	(-1.9,29.8)	(-13.8,24.8)	(-14.5,31.4)
	Pr >  t			0.4690
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	9.014	-0.070	9.084
	SEM	8.014	9.772	11.62
	95% CI	(-6.9,24.9)	(-19.4,19.2)	(-13.9,32.0)
	Pr >  t			0.4354
Week 108	n	1	2	
	LS Mean	2.554	-8.405	10.959
	SEM	12.66	9.762	15.19
	95% CI	(-22.4,27.5)	(-27.7,10.9)	(-19.0,41.0)
	Pr >  t			0.4718
Week 120	n	5	1	
	LS Mean	19.347	-4.171	23.519
	SEM	7.628	12.63	13.88
	95% CI	( 4.2,34.5)	(-29.1,20.8)	( -3.9,50.9)
	Pr >  t			0.0921
Week 132	n	3	1	
	LS Mean	18.915	6.939	11.976
	SEM	8.667	12.63	14.49
	95% CI	( 1.8,36.1)	(-18.0,31.9)	(-16.6,40.6)
	Pr >  t			0.4097
Week 144	n	3		
	LS Mean	15.211		
	SEM	8.667		
	95% CI	(-1.9,32.4)		
	Pr >  t			
Week 156	n	3		
	LS Mean	4.101		
	SEM	8.667		
	95% CI	(-13.0,21.2)		
	Pr >  t			
Week 168	n	1		
	LS Mean	23.111		
	SEM	12.65		
	95% CI	(-1.9,48.1)		
	Pr >  t			
Week 180	n	1		
	LS Mean	23.111		
	SEM	12.65		
	95% CI	(-1.9,48.1)		
	Pr >  t			
Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	12.001		
		SEM	12.65		
		95% CI	(-13.0,37.0)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	10.277	-0.032	10.310
		SEM	3.723	3.726	4.082
		95% CI	( 2.9,17.6)	( -7.4, 7.3)	( 2.2,18.4)
		Pr >  t			0.0125
	Week 16	n	30	29	
		LS Mean	4.408	1.265	3.144
		SEM	3.876	4.086	4.525
		95% CI	( -3.3,12.1)	( -6.8, 9.3)	( -5.8,12.1)
		Pr >  t			0.4880
	Week 24	n	26	20	
		LS Mean	8.709	-0.937	9.647
		SEM	4.050	4.557	5.026
		95% CI	( 0.7,16.7)	( -9.9, 8.0)	( -0.3,19.5)
		Pr >  t			0.0561
	Week 32	n	18	20	
		LS Mean	2.663	-0.937	3.600
		SEM	4.480	4.557	5.371
		95% CI	( -6.2,11.5)	( -9.9, 8.1)	( -7.0,14.2)
		Pr >  t			0.5032
	Week 40	n	18	19	
		LS Mean	4.797	2.186	2.611
		SEM	4.479	4.617	5.421
		95% CI	( -4.0,13.6)	( -6.9,11.3)	( -8.1,13.3)
		Pr >  t			0.6304
	Week 48	n	16	14	
		LS Mean	8.096	4.804	3.292
		SEM	4.622	4.997	5.866
		95% CI	( -1.0,17.2)	( -5.0,14.6)	( -8.3,14.8)
		Pr >  t			0.5751
	Week 56	n	14	10	
		LS Mean	9.237	4.089	5.148
		SEM	4.799	5.520	6.460
		95% CI	( -0.2,18.7)	( -6.8,15.0)	( -7.6,17.9)
		Pr >  t			0.4260

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	6.844	3.905	2.939
		SEM	4.905	5.363	6.408
		95% CI	(-2.8,16.5)	(-6.7,14.5)	(-9.7,15.5)
		Pr >  t			0.6468
Week 72		n	10	6	
		LS Mean	6.618	2.577	4.040
		SEM	5.312	6.565	7.727
		95% CI	(-3.8,17.1)	(-10.3,15.5)	(-11.2,19.2)
		Pr >  t			0.6014
Week 84		n	8	7	
		LS Mean	9.066	3.257	5.810
		SEM	5.786	6.214	7.741
		95% CI	(-2.3,20.4)	(-9.0,15.5)	(-9.4,21.0)
		Pr >  t			0.4534
Week 96		n	6	5	
		LS Mean	-1.496	5.296	-6.793
		SEM	6.393	7.015	8.852
		95% CI	(-14.1,11.1)	(-8.5,19.1)	(-24.2,10.6)
		Pr >  t			0.4434
Week 108		n	2	4	
		LS Mean	8.919	16.089	-7.171
		SEM	10.12	7.651	12.19
		95% CI	(-11.0,28.8)	( 1.0,31.1)	(-31.2,16.8)
		Pr >  t			0.5569
Week 120		n	4	4	
		LS Mean	0.897	-6.133	7.030
		SEM	7.485	7.651	10.15
		95% CI	(-13.8,15.6)	(-21.2, 8.9)	(-12.9,27.0)
		Pr >  t			0.4891
Week 132		n	3	1	
		LS Mean	11.016	-22.13	33.145
		SEM	8.476	14.00	15.99
		95% CI	(-5.7,27.7)	(-49.7, 5.4)	( 1.7,64.6)
		Pr >  t			0.0390
Week 144		n	2		
		LS Mean	19.297		
		SEM	10.06		
		95% CI	(-0.5,39.1)		
		Pr >  t			



-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	10.770	0.349	10.421		
			SEM	3.582	3.582	2.925		
			95% CI	( 3.7,17.8)	( -6.7, 7.4)	( 4.7,16.2)		
					Pr >  t			0.0004
		Week 16	n	79	68			
			LS Mean	6.672	2.138	4.534		
			SEM	3.621	3.774	3.165		
			95% CI	( -0.5,13.8)	( -5.3, 9.6)	( -1.7,10.8)		
					Pr >  t			0.1526
		Week 24	n	64	55			
			LS Mean	7.080	2.311	4.770		
			SEM	3.735	3.926	3.421		
			95% CI	( -0.3,14.4)	( -5.4,10.0)	( -2.0,11.5)		
					Pr >  t			0.1638
		Week 32	n	49	53			
			LS Mean	5.535	0.064	5.471		
			SEM	3.918	3.950	3.608		
			95% CI	( -2.2,13.2)	( -7.7, 7.8)	( -1.6,12.6)		
					Pr >  t			0.1299
		Week 40	n	44	45			
			LS Mean	3.589	0.833	2.756		
			SEM	3.985	4.045	3.785		
			95% CI	( -4.2,11.4)	( -7.1, 8.8)	( -4.7,10.2)		
					Pr >  t			0.4668
		Week 48	n	41	36			
			LS Mean	7.700	2.233	5.467		
			SEM	4.030	4.196	3.990		
95% CI	( -0.2,15.6)		( -6.0,10.5)	( -2.4,13.3)				
			Pr >  t			0.1710		
Week 56	n	33	32					
	LS Mean	4.946	0.927	4.019				
	SEM	4.183	4.286	4.241				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.3,13.2)	(-7.5, 9.3)	(-4.3,12.3)
		Pr >  t			0.3436
	Week 64	n	27	31	
		LS Mean	8.824	3.411	5.412
		SEM	4.347	4.313	4.432
		95% CI	( 0.3,17.4)	(-5.1,11.9)	(-3.3,14.1)
		Pr >  t			0.2224
	Week 72	n	26	26	
		LS Mean	4.484	3.144	1.340
		SEM	4.381	4.465	4.612
		95% CI	(-4.1,13.1)	(-5.6,11.9)	(-7.7,10.4)
		Pr >  t			0.7714
	Week 84	n	22	23	
		LS Mean	13.696	0.201	13.495
		SEM	4.563	4.581	4.879
		95% CI	( 4.7,22.7)	(-8.8, 9.2)	( 3.9,23.1)
		Pr >  t			0.0058
	Week 96	n	18	18	
		LS Mean	13.173	1.288	11.885
		SEM	4.789	4.851	5.335
		95% CI	( 3.8,22.6)	(-8.2,10.8)	( 1.4,22.4)
		Pr >  t			0.0261
	Week 108	n	14	14	
		LS Mean	5.505	10.228	-4.722
		SEM	5.126	5.184	5.926
		95% CI	(-4.6,15.6)	( 0.1,20.4)	(-16.4, 6.9)
		Pr >  t			0.4257
	Week 120	n	12	12	
		LS Mean	1.942	-1.640	3.582
		SEM	5.357	5.418	6.326
		95% CI	(-8.6,12.5)	(-12.3, 9.0)	(-8.8,16.0)
		Pr >  t			0.5714
	Week 132	n	9	5	
		LS Mean	6.528	14.904	-8.376
		SEM	5.865	7.299	8.347
		95% CI	(-5.0,18.0)	( 0.6,29.2)	(-24.8, 8.0)
		Pr >  t			0.3159
	Week 144	n	7	4	
		LS Mean	7.139	-0.726	7.864
		SEM	6.396	7.979	9.303

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.4,19.7)	(-16.4,14.9)	(-10.4,26.1)
		Pr >  t			0.3981
	Week 156	n	4	2	
		LS Mean	5.557	1.662	3.895
		SEM	7.922	10.71	12.63
		95% CI	(-10.0,21.1)	(-19.4,22.7)	(-20.9,28.7)
		Pr >  t			0.7578
	Week 168	n	2	1	
		LS Mean	-2.892	-13.57	10.676
		SEM	10.66	14.73	17.68
		95% CI	(-23.8,18.0)	(-42.5,15.3)	(-24.0,45.4)
		Pr >  t			0.5461
Yes	Week 8	n	53	48	
		LS Mean	7.004	4.793	2.211
		SEM	3.569	3.775	3.557
		95% CI	(-0.1,14.1)	(-2.7,12.3)	(-4.8, 9.2)
		Pr >  t			0.5350
	Week 16	n	45	39	
		LS Mean	6.927	6.898	0.029
		SEM	3.730	3.938	3.794
		95% CI	(-0.4,14.3)	(-0.9,14.7)	(-7.4, 7.5)
		Pr >  t			0.9939
	Week 24	n	41	26	
		LS Mean	5.858	7.427	-1.569
		SEM	3.781	4.216	4.166
		95% CI	(-1.6,13.3)	(-0.9,15.7)	(-9.8, 6.6)
		Pr >  t			0.7067
	Week 32	n	37	20	
		LS Mean	8.108	8.435	-0.327
		SEM	3.867	4.478	4.461
		95% CI	( 0.5,15.7)	(-0.4,17.3)	(-9.1, 8.4)
		Pr >  t			0.9416
	Week 40	n	31	17	
		LS Mean	7.085	5.020	2.065
		SEM	3.983	4.677	4.726
		95% CI	(-0.8,14.9)	(-4.2,14.2)	(-7.2,11.4)
		Pr >  t			0.6623
	Week 48	n	28	15	
		LS Mean	7.562	6.063	1.499
		SEM	4.051	4.815	4.926

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-0.4,15.5)	(-3.4,15.5)	(-8.2,11.2)
		Pr >  t			0.7610
	Week 56	n	26	13	
		LS Mean	7.648	8.605	-0.957
		SEM	4.105	4.989	5.143
		95% CI	(-0.4,15.7)	(-1.2,18.4)	(-11.1, 9.1)
		Pr >  t			0.8524
	Week 64	n	20	11	
		LS Mean	5.737	8.654	-2.917
		SEM	4.322	5.209	5.529
		95% CI	(-2.8,14.2)	(-1.6,18.9)	(-13.8, 7.9)
		Pr >  t			0.5980
	Week 72	n	22	9	
		LS Mean	9.192	3.561	5.631
		SEM	4.241	5.511	5.755
		95% CI	( 0.8,17.5)	(-7.3,14.4)	(-5.7,16.9)
		Pr >  t			0.3283
	Week 84	n	18	10	
		LS Mean	6.483	10.279	-3.797
		SEM	4.432	5.351	5.740
		95% CI	(-2.2,15.2)	(-0.2,20.8)	(-15.1, 7.5)
		Pr >  t			0.5087
	Week 96	n	17	6	
		LS Mean	5.645	4.635	1.010
		SEM	4.477	6.258	6.637
		95% CI	(-3.2,14.5)	(-7.7,16.9)	(-12.0,14.0)
		Pr >  t			0.8791
	Week 108	n	12	7	
		LS Mean	4.202	12.054	-7.851
		SEM	4.902	5.954	6.643
		95% CI	(-5.4,13.8)	( 0.4,23.8)	(-20.9, 5.2)
		Pr >  t			0.2378
	Week 120	n	16	4	
		LS Mean	13.491	0.457	13.034
		SEM	4.548	7.233	7.603
		95% CI	( 4.5,22.4)	(-13.8,14.7)	(-1.9,28.0)
		Pr >  t			0.0870
	Week 132	n	11	3	
		LS Mean	12.846	-8.803	21.649
		SEM	5.021	8.085	8.676

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 3.0,22.7)	(-24.7, 7.1)	( 4.6,38.7)
		Pr >  t			0.0129
	Week 144	n	8	1	
		LS Mean	23.992	4.078	19.914
		SEM	5.502	13.02	13.60
		95% CI	( 13.2,34.8)	(-21.5,29.7)	( -6.8,46.6)
		Pr >  t			0.1436
	Week 156	n	6	1	
		LS Mean	0.958	-7.032	7.990
		SEM	6.086	13.02	13.83
		95% CI	(-11.0,12.9)	(-32.6,18.6)	(-19.2,35.2)
		Pr >  t			0.5638
	Week 168	n	2	1	
		LS Mean	17.400	-18.14	35.542
		SEM	9.436	13.02	15.60
		95% CI	( -1.1,35.9)	(-43.7, 7.4)	( 4.9,66.2)
		Pr >  t			0.0231
	Week 180	n	1	1	
		LS Mean	18.661	4.078	14.583
		SEM	12.90	13.02	17.90
		95% CI	( -6.7,44.0)	(-21.5,29.7)	(-20.6,49.8)
		Pr >  t			0.4157
	Week 192	n	1	1	
		LS Mean	7.551	-18.14	25.693
		SEM	12.90	13.02	17.90
		95% CI	(-17.8,32.9)	(-43.7, 7.4)	( -9.5,60.9)
		Pr >  t			0.1519

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Estrogen Receptor Status (L)	Negative	Week 8	n	2				
			LS Mean	-5.555				
			SEM	11.78				
			95% CI	(-56.3,45.1)				
				Week 16	n	2		
					LS Mean	-11.11		
					SEM	11.78		
					95% CI	(-61.8,39.6)		
				Week 24	n	1		
					LS Mean	-22.22		
					SEM	28.86		
					95% CI	( -146, 102)		
				Week 32	n	1		
					LS Mean	-22.22		
					SEM	28.86		
					95% CI	( -146, 102)		
				Week 40	n	1		
					LS Mean	-11.11		
					SEM	28.86		
					95% CI	( -135, 113)		
				Week 48	n	1		
					LS Mean	-0.000		
					SEM	28.86		
					95% CI	( -124, 124)		
		Week 56	n	1				
			LS Mean	-22.22				
			SEM	28.86				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI Pr >  t  n	( -146, 102) 1	
	Week 72	LS Mean SEM 95% CI Pr >  t  n	-22.22 28.86 ( -146, 102) 1	
	Week 84	LS Mean SEM 95% CI Pr >  t  n	-22.22 28.86 ( -146, 102) 1	
	Week 96	LS Mean SEM 95% CI Pr >  t  n	-22.22 28.86 ( -146, 102) 1	
Positive	Week 8	n LS Mean SEM 95% CI Pr >  t  n	140 9.861 2.539 ( 4.9,14.9)	140 2.185 2.583 ( -2.9, 7.3)
	Week 16	n LS Mean SEM 95% CI Pr >  t  n	122 7.301 2.606 ( 2.2,12.4)	107 4.050 2.715 ( -1.3, 9.4)
	Week 24	n LS Mean SEM 95% CI Pr >  t  n	104 7.195 2.672 ( 1.9,12.4)	81 4.380 2.851 ( -1.2,10.0)
	Week 32	n LS Mean SEM 95% CI Pr >  t  n	85 7.223 2.780 ( 1.8,12.7)	73 3.015 2.912 ( -2.7, 8.7)
	Week 40	n LS Mean SEM	74 5.638 2.845	62 3.011 2.948



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 0.1,11.2)	( -3.3, 8.5)	( -2.8, 8.8)
		Pr >  t			0.3072
	Week 48	n	68	51	
		LS Mean	8.198	3.916	4.282
		SEM	2.886	3.123	3.106
		95% CI	( 2.5,13.9)	( -2.2,10.0)	( -1.8,10.4)
		Pr >  t			0.1683
	Week 56	n	58	45	
		LS Mean	6.989	3.716	3.273
		SEM	2.971	3.206	3.271
		95% CI	( 1.2,12.8)	( -2.6,10.0)	( -3.1, 9.7)
		Pr >  t			0.3172
	Week 64	n	47	42	
		LS Mean	8.052	5.503	2.549
		SEM	3.098	3.256	3.436
		95% CI	( 2.0,14.1)	( -0.9,11.9)	( -4.2, 9.3)
		Pr >  t			0.4582
	Week 72	n	47	35	
		LS Mean	7.211	3.928	3.283
		SEM	3.100	3.396	3.570
		95% CI	( 1.1,13.3)	( -2.7,10.6)	( -3.7,10.3)
		Pr >  t			0.3579
	Week 84	n	39	33	
		LS Mean	11.207	3.770	7.437
		SEM	3.242	3.445	3.731
		95% CI	( 4.8,17.6)	( -3.0,10.5)	( 0.1,14.8)
		Pr >  t			0.0464
	Week 96	n	34	24	
		LS Mean	10.211	2.879	7.332
		SEM	3.347	3.751	4.105
		95% CI	( 3.6,16.8)	( -4.5,10.2)	( -0.7,15.4)
		Pr >  t			0.0743
	Week 108	n	26	21	
		LS Mean	5.559	11.178	-5.619
		SEM	3.603	3.901	4.442
		95% CI	( -1.5,12.6)	( 3.5,18.8)	(-14.3, 3.1)
		Pr >  t			0.2061
	Week 120	n	28	16	
		LS Mean	8.969	-0.251	9.220
		SEM	3.524	4.252	4.698

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 2.1,15.9)	( -8.6, 8.1)	( 0.0,18.4)
		Pr >  t			0.0499
	Week 132	n	20	8	
		LS Mean	10.504	6.204	4.300
		SEM	3.894	5.468	6.050
		95% CI	( 2.9,18.1)	( -4.5,16.9)	( -7.6,16.2)
		Pr >  t			0.4773
	Week 144	n	15	5	
		LS Mean	16.684	1.064	15.620
		SEM	4.270	6.645	7.349
		95% CI	( 8.3,25.1)	(-12.0,14.1)	( 1.2,30.0)
		Pr >  t			0.0337
	Week 156	n	10	3	
		LS Mean	3.198	-0.982	4.179
		SEM	4.961	8.321	9.240
		95% CI	( -6.5,12.9)	(-17.3,15.3)	(-13.9,22.3)
		Pr >  t			0.6511
	Week 168	n	4	2	
		LS Mean	7.744	-16.03	23.773
		SEM	7.270	10.03	12.04
		95% CI	( -6.5,22.0)	(-35.7, 3.6)	( 0.1,47.4)
		Pr >  t			0.0486
	Week 180	n	1	1	
		LS Mean	17.586	2.917	14.669
		SEM	13.93	13.94	19.49
		95% CI	( -9.7,44.9)	(-24.4,30.3)	(-23.6,52.9)
		Pr >  t			0.4518
	Week 192	n	1	1	
		LS Mean	6.476	-19.30	25.779
		SEM	13.93	13.94	19.49
		95% CI	(-20.8,33.8)	(-46.7, 8.0)	(-12.5,64.0)
		Pr >  t			0.1862

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	11.218	3.610	7.608
			SEM	2.781	2.895	2.685
			95% CI	( 5.7,16.7)	( -2.1, 9.3)	( 2.3,12.9)
		Pr >  t			0.0048	
		Week 16	n	90	75	
			LS Mean	8.172	5.765	2.407
			SEM	2.851	3.029	2.880
			95% CI	( 2.6,13.8)	( -0.2,11.7)	( -3.3, 8.1)
		Pr >  t			0.4037	
		Week 24	n	79	62	
			LS Mean	5.855	5.169	0.686
			SEM	2.918	3.150	3.050
			95% CI	( 0.1,11.6)	( -1.0,11.4)	( -5.3, 6.7)
		Pr >  t			0.8221	
		Week 32	n	70	56	
			LS Mean	6.768	5.166	1.601
			SEM	3.004	3.219	3.165
			95% CI	( 0.9,12.7)	( -1.2,11.5)	( -4.6, 7.8)
		Pr >  t			0.6132	
		Week 40	n	61	46	
			LS Mean	4.647	3.022	1.625
			SEM	3.074	3.347	3.349
			95% CI	( -1.4,10.7)	( -3.6, 9.6)	( -5.0, 8.2)
		Pr >  t			0.6277	
		Week 48	n	56	38	
			LS Mean	6.901	4.273	2.628
			SEM	3.119	3.480	3.524
95% CI	( 0.8,13.0)		( -2.6,11.1)	( -4.3, 9.5)		
Pr >  t			0.4560			
Week 56	n	49	33			
	LS Mean	7.657	3.912	3.745		
	SEM	3.195	3.588	3.701		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 1.4,13.9)	( -3.1,11.0)	( -3.5,11.0)
		Pr >  t			0.3118
	Week 64	n	37	29	
		LS Mean	8.777	4.597	4.180
		SEM	3.378	3.700	3.967
		95% CI	( 2.1,15.4)	( -2.7,11.9)	( -3.6,12.0)
		Pr >  t			0.2923
	Week 72	n	40	25	
		LS Mean	8.194	4.907	3.286
		SEM	3.325	3.837	4.050
		95% CI	( 1.7,14.7)	( -2.6,12.4)	( -4.7,11.2)
		Pr >  t			0.4173
	Week 84	n	32	23	
		LS Mean	11.823	5.040	6.783
		SEM	3.505	3.922	4.268
		95% CI	( 4.9,18.7)	( -2.7,12.7)	( -1.6,15.2)
		Pr >  t			0.1123
	Week 96	n	29	17	
		LS Mean	8.449	3.947	4.502
		SEM	3.583	4.271	4.656
		95% CI	( 1.4,15.5)	( -4.4,12.3)	( -4.6,13.6)
		Pr >  t			0.3338
	Week 108	n	22	15	
		LS Mean	4.981	10.834	-5.853
		SEM	3.863	4.439	5.015
		95% CI	( -2.6,12.6)	( 2.1,19.5)	(-15.7, 4.0)
		Pr >  t			0.2434
	Week 120	n	23	13	
		LS Mean	11.086	0.546	10.539
		SEM	3.810	4.649	5.168
		95% CI	( 3.6,18.6)	( -8.6, 9.7)	( 0.4,20.7)
		Pr >  t			0.0416
	Week 132	n	17	5	
		LS Mean	11.314	7.291	4.022
		SEM	4.164	6.631	7.200
		95% CI	( 3.1,19.5)	( -5.7,20.3)	(-10.1,18.1)
		Pr >  t			0.5765
	Week 144	n	14	3	
		LS Mean	16.754	2.959	13.795
		SEM	4.421	8.264	8.857

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 8.1,25.4)	(-13.3,19.2)	( -3.6,31.2)
		Pr >  t			0.1196
	Week 156	n	9	2	
		LS Mean	1.699	0.116	1.582
		SEM	5.180	9.915	10.75
		95% CI	( -8.5,11.9)	(-19.3,19.6)	(-19.5,22.7)
		Pr >  t			0.8831
	Week 168	n	4	1	
		LS Mean	7.884	-18.64	26.521
		SEM	7.206	13.74	15.20
		95% CI	( -6.3,22.0)	(-45.6, 8.3)	( -3.3,56.4)
		Pr >  t			0.0814
	Week 180	n	1	1	
		LS Mean	17.632	3.582	14.050
		SEM	13.69	13.74	19.15
		95% CI	( -9.2,44.5)	(-23.4,30.5)	(-23.5,51.6)
		Pr >  t			0.4632
	Week 192	n	1	1	
		LS Mean	6.522	-18.64	25.160
		SEM	13.69	13.74	19.15
		95% CI	(-20.3,33.4)	(-45.6, 8.3)	(-12.4,62.7)
		Pr >  t			0.1891
>= 3	Week 8	n	37	45	
		LS Mean	-0.968	-7.857	6.888
		SEM	7.539	7.441	4.319
		95% CI	(-15.9,13.9)	(-22.6, 6.8)	( -1.6,15.4)
		Pr >  t			0.1125
	Week 16	n	34	32	
		LS Mean	-2.334	-6.666	4.332
		SEM	7.745	7.783	4.684
		95% CI	(-17.6,13.0)	(-22.0, 8.7)	( -4.9,13.6)
		Pr >  t			0.3562
	Week 24	n	26	19	
		LS Mean	4.105	-3.670	7.775
		SEM	7.896	8.124	5.470
		95% CI	(-11.5,19.7)	(-19.7,12.4)	( -3.0,18.5)
		Pr >  t			0.1563
	Week 32	n	16	17	
		LS Mean	2.648	-9.514	12.162
		SEM	8.253	8.225	6.120

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-13.6,18.9)	(-25.7, 6.7)	( 0.1,24.2)
		Pr >  t			0.0478
		n	14	16	
		LS Mean	3.114	-4.538	7.652
		SEM	8.384	8.274	6.361
Week 48		95% CI	(-13.4,19.6)	(-20.9,11.8)	( -4.9,20.2)
		Pr >  t			0.2299
		n	13	13	
		LS Mean	7.500	-3.101	10.601
		SEM	8.451	8.472	6.704
Week 56		95% CI	( -9.2,24.2)	(-19.8,13.6)	( -2.6,23.8)
		Pr >  t			0.1147
		n	10	12	
		LS Mean	-4.686	-3.013	-1.673
		SEM	8.767	8.564	7.180
Week 64		95% CI	(-22.0,12.6)	(-19.9,13.9)	(-15.8,12.4)
		Pr >  t			0.8158
		n	10	13	
		LS Mean	-1.465	0.640	-2.105
		SEM	8.769	8.481	7.085
Week 72		95% CI	(-18.7,15.8)	(-16.1,17.4)	(-16.0,11.8)
		Pr >  t			0.7666
		n	8	10	
		LS Mean	-4.741	-5.020	0.280
		SEM	9.069	8.778	7.790
Week 84		95% CI	(-22.6,13.1)	(-22.3,12.3)	(-15.0,15.6)
		Pr >  t			0.9714
		n	8	10	
		LS Mean	1.046	-6.007	7.053
		SEM	9.075	8.771	7.791
Week 96		95% CI	(-16.8,18.9)	(-23.3,11.3)	( -8.3,22.4)
		Pr >  t			0.3659
		n	6	7	
		LS Mean	10.969	-6.388	17.357
		SEM	9.565	9.290	8.886
Week 108		95% CI	( -7.9,29.8)	(-24.7,11.9)	( -0.1,34.8)
		Pr >  t			0.0515
		n	4	6	
	LS Mean	2.178	5.476	-3.298	
	SEM	10.44	9.549	10.09	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.4,22.7)	(-13.3,24.3)	(-23.1,16.5)
		Pr >  t			0.7439
	Week 120	n	5	3	
		LS Mean	-7.170	-8.891	1.721
		SEM	9.922	11.25	11.25
		95% CI	(-26.7,12.4)	(-31.0,13.2)	(-20.4,23.8)
		Pr >  t			0.8784
	Week 132	n	3	3	
		LS Mean	-0.528	-3.022	2.494
		SEM	11.25	11.25	12.44
		95% CI	(-22.6,21.6)	(-25.1,19.1)	(-22.0,27.0)
		Pr >  t			0.8412
	Week 144	n	1	2	
		LS Mean	11.023	-9.324	20.347
		SEM	16.34	12.72	18.18
		95% CI	(-21.1,43.1)	(-34.3,15.7)	(-15.4,56.1)
		Pr >  t			0.2639
	Week 156	n	1	1	
		LS Mean	11.023	-10.24	21.259
		SEM	16.34	16.36	20.87
		95% CI	(-21.1,43.1)	(-42.4,21.9)	(-19.8,62.3)
		Pr >  t			0.3093
	Week 168	n		1	
		LS Mean		-21.35	
		SEM		16.36	
		95% CI		(-53.5,10.8)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Visceral Disease (L)	No	Week 8	n	69	60		
			LS Mean	4.868	-3.668	8.536	
			SEM	6.794	7.015	3.207	
			95% CI	(-8.6,18.3)	(-17.6,10.2)	( 2.2,14.8)	
					Pr >  t		0.0081
		Week 16	n	59	49		
			LS Mean	2.153	0.157	1.996	
			SEM	6.825	7.086	3.445	
			95% CI	(-11.4,15.7)	(-13.9,14.2)	(-4.8, 8.8)	
					Pr >  t		0.5627
		Week 24	n	54	41		
			LS Mean	-0.225	-2.559	2.333	
			SEM	6.844	7.152	3.633	
			95% CI	(-13.8,13.3)	(-16.7,11.6)	(-4.8, 9.5)	
					Pr >  t		0.5211
		Week 32	n	48	37		
			LS Mean	1.707	-1.033	2.740	
			SEM	6.871	7.191	3.779	
			95% CI	(-11.9,15.3)	(-15.3,13.2)	(-4.7,10.2)	
					Pr >  t		0.4687
		Week 40	n	43	33		
			LS Mean	-1.820	-3.380	1.560	
			SEM	6.902	7.240	3.933	
			95% CI	(-15.5,11.9)	(-17.7,11.0)	(-6.2, 9.3)	
					Pr >  t		0.6917
		Week 48	n	41	28		
			LS Mean	1.564	-3.563	5.128	
			SEM	6.918	7.315	4.101	
95% CI	(-12.1,15.3)		(-18.0,10.9)	(-2.9,13.2)			
			Pr >  t		0.2117		
Week 56	n	35	22				
	LS Mean	1.632	0.123	1.510			
	SEM	6.970	7.449	4.432			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.2,15.4)	(-14.6,14.9)	(-7.2,10.2)
		Pr >  t			0.7335
	Week 64	n	26	23	
		LS Mean	1.496	-4.322	5.819
		SEM	7.095	7.424	4.604
		95% CI	(-12.5,15.5)	(-19.0,10.4)	(-3.2,14.9)
		Pr >  t			0.2067
	Week 72	n	28	18	
		LS Mean	2.128	-0.553	2.681
		SEM	7.060	7.581	4.800
		95% CI	(-11.9,16.1)	(-15.5,14.4)	(-6.7,12.1)
		Pr >  t			0.5766
	Week 84	n	22	18	
		LS Mean	7.633	-0.305	7.938
		SEM	7.227	7.582	4.992
		95% CI	(-6.7,21.9)	(-15.3,14.7)	(-1.9,17.7)
		Pr >  t			0.1122
	Week 96	n	21	13	
		LS Mean	3.560	-3.594	7.154
		SEM	7.207	7.850	5.432
		95% CI	(-10.7,17.8)	(-19.1,11.9)	(-3.5,17.8)
		Pr >  t			0.1882
	Week 108	n	17	12	
		LS Mean	-2.643	7.348	-9.992
		SEM	7.402	7.929	5.733
		95% CI	(-17.3,12.0)	(-8.3,23.0)	(-21.2, 1.3)
		Pr >  t			0.0817
	Week 120	n	18	11	
		LS Mean	3.985	-5.253	9.239
		SEM	7.301	8.021	5.808
		95% CI	(-10.5,18.4)	(-21.1,10.6)	(-2.2,20.6)
		Pr >  t			0.1121
	Week 132	n	13	5	
		LS Mean	2.112	1.031	1.082
		SEM	7.628	9.220	7.647
		95% CI	(-13.0,17.2)	(-17.1,19.2)	(-13.9,16.1)
		Pr >  t			0.8875
	Week 144	n	12	3	
		LS Mean	7.033	-3.293	10.326
		SEM	7.628	10.51	9.229

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.0,22.1)	(-24.0,17.4)	(-7.8,28.4)
		Pr >  t			0.2635
	Week 156	n	7	2	
		LS Mean	-5.380	-6.181	0.801
		SEM	8.406	11.91	11.30
		95% CI	(-21.9,11.2)	(-29.6,17.2)	(-21.4,23.0)
		Pr >  t			0.9435
	Week 168	n	3	1	
		LS Mean	-1.485	-25.01	23.520
		SEM	10.32	15.37	16.06
		95% CI	(-21.8,18.8)	(-55.2, 5.2)	(-8.0,55.0)
		Pr >  t			0.1435
	Week 180	n	1	1	
		LS Mean	10.939	-2.785	13.724
		SEM	15.24	15.37	19.59
		95% CI	(-19.0,40.9)	(-33.0,27.4)	(-24.7,52.2)
		Pr >  t			0.4838
	Week 192	n	1	1	
		LS Mean	-0.171	-25.01	24.834
		SEM	15.24	15.37	19.59
		95% CI	(-30.1,29.7)	(-55.2, 5.2)	(-13.6,63.3)
		Pr >  t			0.2053
Yes	Week 8	n	73	80	
		LS Mean	12.170	6.180	5.989
		SEM	4.235	4.311	3.249
		95% CI	( 3.8,20.5)	(-2.3,14.7)	(-0.4,12.4)
		Pr >  t			0.0663
	Week 16	n	65	58	
		LS Mean	9.752	6.350	3.402
		SEM	4.345	4.486	3.489
		95% CI	( 1.2,18.3)	(-2.5,15.2)	(-3.5,10.3)
		Pr >  t			0.3302
	Week 24	n	51	40	
		LS Mean	11.904	9.907	1.997
		SEM	4.439	4.722	3.876
		95% CI	( 3.2,20.6)	( 0.6,19.2)	(-5.6, 9.6)
		Pr >  t			0.6066
	Week 32	n	38	36	
		LS Mean	9.742	5.499	4.243
		SEM	4.651	4.791	4.139

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	( 0.6,18.9)	( -3.9,14.9)	( -3.9,12.4)
		Pr >  t			0.3058
		n	32	29	
		LS Mean	10.793	7.190	3.604
		SEM	4.772	4.939	4.428
Week 48		95% CI	( 1.4,20.2)	( -2.5,16.9)	( -5.1,12.3)
		Pr >  t			0.4160
		n	28	23	
		LS Mean	12.611	10.342	2.269
		SEM	4.863	5.126	4.725
Week 56		95% CI	( 3.0,22.2)	( 0.3,20.4)	( -7.0,11.5)
		Pr >  t			0.6312
		n	24	23	
		LS Mean	8.697	6.034	2.664
		SEM	4.989	5.126	4.850
Week 64		95% CI	( -1.1,18.5)	( -4.0,16.1)	( -6.9,12.2)
		Pr >  t			0.5831
		n	21	19	
		LS Mean	12.165	14.886	-2.721
		SEM	5.110	5.297	5.147
Week 72		95% CI	( 2.1,22.2)	( 4.5,25.3)	( -12.8, 7.4)
		Pr >  t			0.5972
		n	20	17	
		LS Mean	9.097	7.048	2.049
		SEM	5.159	5.407	5.309
Week 84		95% CI	( -1.0,19.2)	( -3.6,17.7)	( -8.4,12.5)
		Pr >  t			0.6997
		n	18	15	
		LS Mean	11.094	6.258	4.835
		SEM	5.250	5.548	5.543
Week 96		95% CI	( 0.8,21.4)	( -4.6,17.2)	( -6.0,15.7)
		Pr >  t			0.3833
		n	14	11	
		LS Mean	14.198	8.232	5.966
		SEM	5.539	5.955	6.198
Week 108		95% CI	( 3.3,25.1)	( -3.5,19.9)	( -6.2,18.1)
		Pr >  t			0.3361
		n	9	9	
		LS Mean	13.301	13.142	0.159
		SEM	6.177	6.270	7.057

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.2,25.4)	( 0.8,25.5)	(-13.7,14.0)
		Pr >  t			0.9820
	Week 120	n	10	5	
		LS Mean	10.603	2.735	7.868
		SEM	6.027	7.492	8.048
		95% CI	( -1.2,22.4)	(-12.0,17.4)	( -7.9,23.7)
		Pr >  t			0.3286
	Week 132	n	7	3	
		LS Mean	18.401	9.813	8.589
		SEM	6.642	8.991	9.871
		95% CI	( 5.4,31.4)	( -7.8,27.5)	(-10.8,28.0)
		Pr >  t			0.3846
	Week 144	n	3	2	
		LS Mean	34.248	3.573	30.674
		SEM	8.921	10.58	12.81
		95% CI	( 16.7,51.8)	(-17.2,24.4)	( 5.5,55.8)
		Pr >  t			0.0169
	Week 156	n	3	1	
		LS Mean	12.857	2.500	10.357
		SEM	8.932	14.34	16.05
		95% CI	( -4.7,30.4)	(-25.6,30.6)	(-21.2,41.9)
		Pr >  t			0.5189
	Week 168	n	1	1	
		LS Mean	20.483	-8.610	29.093
		SEM	14.32	14.34	19.57
		95% CI	( -7.6,48.6)	(-36.8,19.5)	( -9.3,67.5)
		Pr >  t			0.1377

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-0.063	5.182	-5.245
			SEM	6.745	7.434	6.245
			95% CI	(-13.7,13.5)	(-9.8,20.2)	(-17.7, 7.3)
			Pr >  t			0.4045
		Week 16	n	14	17	
			LS Mean	-2.385	10.443	-12.83
			SEM	6.818	7.627	6.629
			95% CI	(-16.1,11.3)	(-4.9,25.8)	(-26.1, 0.4)
			Pr >  t			0.0571
		Week 24	n	14	11	
			LS Mean	3.170	2.715	0.454
			SEM	6.818	7.953	6.999
			95% CI	(-10.6,16.9)	(-13.3,18.7)	(-13.5,14.4)
			Pr >  t			0.9484
		Week 32	n	10	10	
			LS Mean	-1.539	3.591	-5.130
			SEM	7.317	8.053	7.357
			95% CI	(-16.2,13.1)	(-12.6,19.7)	(-19.7, 9.5)
			Pr >  t			0.4873
		Week 40	n	8	10	
			LS Mean	-6.421	1.462	-7.883
			SEM	7.546	8.052	7.578
			95% CI	(-21.5, 8.6)	(-14.7,17.6)	(-22.9, 7.1)
	Pr >  t			0.3006		
Week 48	n	7	11			
	LS Mean	-1.911	13.194	-15.11		
	SEM	7.690	7.977	7.662		
	95% CI	(-17.2,13.4)	(-2.8,29.2)	(-30.3, 0.1)		
	Pr >  t			0.0513		
Week 56	n	6	9			
	LS Mean	-0.143	7.257	-7.401		
	SEM	7.878	8.149	8.036		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.8,15.5)	(-9.1,23.6)	(-23.3, 8.5)
		Pr >  t			0.3589
	Week 64	n	5	8	
		LS Mean	-5.940	3.357	-9.297
		SEM	8.138	8.261	8.401
		95% CI	(-22.1,10.2)	(-13.2,19.9)	(-25.9, 7.3)
		Pr >  t			0.2704
	Week 72	n	7	7	
		LS Mean	4.071	4.828	-0.757
		SEM	7.679	8.405	8.107
		95% CI	(-11.2,19.4)	(-12.0,21.6)	(-16.8,15.3)
		Pr >  t			0.9257
	Week 84	n	7	7	
		LS Mean	-8.626	11.177	-19.80
		SEM	7.679	8.405	8.107
		95% CI	(-23.9, 6.7)	(-5.6,28.0)	(-35.8,-3.8)
		Pr >  t			0.0160
	Week 96	n	5	6	
		LS Mean	-5.382	4.251	-9.633
		SEM	8.136	8.588	8.719
		95% CI	(-21.6,10.8)	(-12.9,21.4)	(-26.9, 7.6)
		Pr >  t			0.2711
	Week 108	n	4	6	
		LS Mean	1.445	20.916	-19.47
		SEM	8.518	8.588	9.078
		95% CI	(-15.5,18.3)	( 3.8,38.1)	(-37.4,-1.5)
		Pr >  t			0.0335
	Week 120	n	4	4	
		LS Mean	8.210	7.948	0.262
		SEM	8.521	9.190	9.654
		95% CI	(-8.7,25.1)	(-10.3,26.2)	(-18.8,19.3)
		Pr >  t			0.9784
	Week 132	n	3	1	
		LS Mean	5.037	41.066	-36.03
		SEM	9.106	13.31	14.00
		95% CI	(-13.0,23.1)	( 14.8,67.3)	(-63.6,-8.4)
		Pr >  t			0.0108
	Week 144	n	1	1	
		LS Mean	74.343	-0.052	74.395
		SEM	12.86	13.35	16.72

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	( 49.0,99.7)	(-26.4,26.3)	( 41.4, 107)
		Pr >  t			<.0001
		n	35	37	
	Week 16	LS Mean	21.683	13.172	8.511
		SEM	8.824	9.302	3.994
		95% CI	( 4.3,39.1)	( -5.2,31.5)	( 0.6,16.4)
	Week 24	Pr >  t			0.0345
		n	34	30	
		LS Mean	18.882	15.129	3.754
	Week 32	SEM	9.106	9.385	4.171
		95% CI	( 0.9,36.9)	( -3.4,33.7)	( -4.5,12.0)
		Pr >  t			0.3693
	Week 40	n	32	23	
		LS Mean	21.425	18.169	3.256
		SEM	9.129	9.490	4.462
	Week 48	95% CI	( 3.4,39.4)	( -0.6,36.9)	( -5.5,12.0)
		Pr >  t			0.4663
		n	21	22	
	Week 56	LS Mean	20.855	14.727	6.128
		SEM	9.285	9.507	4.854
		95% CI	( 2.5,39.2)	( -4.0,33.5)	( -3.4,15.7)
	Week 64	Pr >  t			0.2079
		n	20	20	
		LS Mean	19.923	18.144	1.779
	Week 8	SEM	9.318	9.552	4.990
		95% CI	( 1.5,38.3)	( -0.7,37.0)	( -8.0,11.6)
		Pr >  t			0.7218
	Week 16	n	19	12	
		LS Mean	19.684	14.572	5.112
		SEM	9.334	9.860	5.607
	Week 24	95% CI	( 1.3,38.1)	( -4.9,34.0)	( -5.9,16.1)
		Pr >  t			0.3625
		n	16	8	
	Week 32	LS Mean	18.987	18.603	0.384
		SEM	9.430	10.24	6.375
		95% CI	( 0.4,37.6)	( -1.6,38.8)	(-12.2,12.9)
	Week 40	Pr >  t			0.9520
		n	12	11	
		LS Mean	19.911	18.407	1.505
	Week 48	SEM	9.627	9.941	6.187



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.9,38.9)	( -1.2,38.0)	(-10.7,13.7)
		Pr >  t			0.8080
	Week 72	n	13	7	
		LS Mean	20.080	20.345	-0.266
		SEM	9.574	10.40	6.816
		95% CI	( 1.2,39.0)	( -0.1,40.8)	(-13.7,13.1)
		Pr >  t			0.9689
	Week 84	n	12	6	
		LS Mean	24.952	18.106	6.846
		SEM	9.610	10.60	7.188
		95% CI	( 6.0,43.9)	( -2.8,39.0)	( -7.3,21.0)
		Pr >  t			0.3415
	Week 96	n	7	6	
		LS Mean	20.808	14.322	6.486
		SEM	10.14	10.60	7.870
		95% CI	( 0.8,40.8)	( -6.6,35.2)	( -9.0,22.0)
		Pr >  t			0.4104
	Week 108	n	5	3	
		LS Mean	18.432	15.005	3.427
		SEM	10.61	11.88	10.03
		95% CI	( -2.5,39.3)	( -8.4,38.4)	(-16.3,23.1)
		Pr >  t			0.7326
	Week 120	n	8	3	
		LS Mean	24.526	11.302	13.224
		SEM	10.02	11.88	9.374
		95% CI	( 4.8,44.3)	(-12.1,34.7)	( -5.2,31.7)
		Pr >  t			0.1591
	Week 132	n	2	1	
		LS Mean	41.556	19.394	22.161
		SEM	12.78	15.95	16.26
		95% CI	( 16.4,66.7)	(-12.0,50.8)	( -9.8,54.1)
		Pr >  t			0.1739
	Week 144	n	2		
		LS Mean	13.595		
		SEM	12.79		
		95% CI	(-11.6,38.8)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	13.595		
		SEM	12.79		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.6,38.8)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	9.816	2.251	7.564
		SEM	3.351	3.484	3.347
		95% CI	( 3.2,16.4)	( -4.6, 9.1)	( 1.0,14.1)
		Pr >  t			0.0245
	Week 16	n	70	52	
		LS Mean	7.983	2.058	5.925
		SEM	3.443	3.676	3.570
		95% CI	( 1.2,14.8)	( -5.2, 9.3)	( -1.1,12.9)
		Pr >  t			0.0979
	Week 24	n	54	40	
		LS Mean	4.540	2.569	1.971
		SEM	3.600	3.906	3.923
		95% CI	( -2.5,11.6)	( -5.1,10.3)	( -5.7, 9.7)
		Pr >  t			0.6157
	Week 32	n	50	36	
		LS Mean	6.237	2.127	4.110
		SEM	3.665	3.987	4.050
		95% CI	( -1.0,13.5)	( -5.7,10.0)	( -3.8,12.1)
		Pr >  t			0.3107
	Week 40	n	42	28	
		LS Mean	4.899	-0.096	4.995
		SEM	3.778	4.225	4.366
		95% CI	( -2.5,12.3)	( -8.4, 8.2)	( -3.6,13.6)
		Pr >  t			0.2530
	Week 48	n	38	24	
		LS Mean	9.066	-0.410	9.476
		SEM	3.849	4.378	4.577
		95% CI	( 1.5,16.6)	( -9.0, 8.2)	( 0.5,18.5)
		Pr >  t			0.0388
	Week 56	n	33	24	
		LS Mean	5.766	0.717	5.050
		SEM	3.958	4.380	4.674
		95% CI	( -2.0,13.5)	( -7.9, 9.3)	( -4.1,14.2)
		Pr >  t			0.2803
	Week 64	n	27	19	
		LS Mean	9.820	5.112	4.708
		SEM	4.131	4.645	5.065

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.7,17.9)	( -4.0,14.2)	( -5.2,14.7)
		Pr >  t			0.3530
	Week 72	n	26	17	
		LS Mean	5.350	1.786	3.563
		SEM	4.167	4.782	5.219
		95% CI	( -2.8,13.5)	( -7.6,11.2)	( -6.7,13.8)
		Pr >  t			0.4949
	Week 84	n	18	16	
		LS Mean	14.782	-3.040	17.823
		SEM	4.599	4.864	5.624
		95% CI	( 5.7,23.8)	(-12.6, 6.5)	( 6.8,28.9)
		Pr >  t			0.0016
	Week 96	n	20	10	
		LS Mean	12.327	0.831	11.496
		SEM	4.462	5.615	6.193
		95% CI	( 3.6,21.1)	(-10.2,11.9)	( -0.7,23.7)
		Pr >  t			0.0638
	Week 108	n	14	10	
		LS Mean	3.238	4.611	-1.374
		SEM	4.950	5.616	6.548
		95% CI	( -6.5,13.0)	( -6.4,15.6)	(-14.2,11.5)
		Pr >  t			0.8339
	Week 120	n	14	7	
		LS Mean	6.436	-2.856	9.292
		SEM	4.931	6.361	7.192
		95% CI	( -3.2,16.1)	(-15.3, 9.6)	( -4.8,23.4)
		Pr >  t			0.1967
	Week 132	n	12	5	
		LS Mean	6.751	2.333	4.418
		SEM	5.190	7.233	8.128
		95% CI	( -3.4,16.9)	(-11.9,16.5)	(-11.5,20.4)
		Pr >  t			0.5869
	Week 144	n	11	4	
		LS Mean	12.343	-0.450	12.793
		SEM	5.319	7.915	8.829
		95% CI	( 1.9,22.8)	(-16.0,15.1)	( -4.5,30.1)
		Pr >  t			0.1477
	Week 156	n	8	3	
		LS Mean	2.856	-3.596	6.453
		SEM	5.958	8.932	10.10

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.8,14.6)	(-21.1,13.9)	(-13.4,26.3)
		Pr >  t			0.5232
	Week 168	n	4	2	
		LS Mean	6.971	-18.65	25.619
		SEM	7.823	10.68	12.73
		95% CI	(-8.4,22.3)	(-39.6, 2.3)	( 0.6,50.6)
		Pr >  t			0.0445
	Week 180	n	1	1	
		LS Mean	16.733	0.348	16.385
		SEM	14.67	14.71	20.45
		95% CI	(-12.1,45.5)	(-28.5,29.2)	(-23.8,56.5)
		Pr >  t			0.4234
	Week 192	n	1	1	
		LS Mean	5.623	-21.87	27.495
		SEM	14.67	14.71	20.45
		95% CI	(-23.2,34.4)	(-50.7, 7.0)	(-12.7,67.7)
		Pr >  t			0.1793

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64	
			LS Mean	9.816	2.251	7.564
			SEM	3.351	3.484	3.347
			95% CI	( 3.2,16.4)	( -4.6, 9.1)	( 1.0,14.1)
		Pr >  t			0.0245	
		Week 16	n	70	52	
			LS Mean	7.983	2.058	5.925
			SEM	3.443	3.676	3.570
			95% CI	( 1.2,14.8)	( -5.2, 9.3)	( -1.1,12.9)
		Pr >  t			0.0979	
		Week 24	n	54	40	
			LS Mean	4.540	2.569	1.971
			SEM	3.600	3.906	3.923
			95% CI	( -2.5,11.6)	( -5.1,10.3)	( -5.7, 9.7)
		Pr >  t			0.6157	
		Week 32	n	50	36	
			LS Mean	6.237	2.127	4.110
			SEM	3.665	3.987	4.050
			95% CI	( -1.0,13.5)	( -5.7,10.0)	( -3.8,12.1)
		Pr >  t			0.3107	
		Week 40	n	42	28	
			LS Mean	4.899	-0.096	4.995
			SEM	3.778	4.225	4.366
			95% CI	( -2.5,12.3)	( -8.4, 8.2)	( -3.6,13.6)
		Pr >  t			0.2530	
		Week 48	n	38	24	
			LS Mean	9.066	-0.410	9.476
			SEM	3.849	4.378	4.577
			95% CI	( 1.5,16.6)	( -9.0, 8.2)	( 0.5,18.5)
		Pr >  t			0.0388	
		Week 56	n	33	24	
			LS Mean	5.766	0.717	5.050
			SEM	3.958	4.380	4.674

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-2.0,13.5)	(-7.9, 9.3)	(-4.1,14.2)
	Pr >  t			0.2803
	n	27	19	
	LS Mean	9.820	5.112	4.708
	SEM	4.131	4.645	5.065
Week 72	95% CI	( 1.7,17.9)	(-4.0,14.2)	(-5.2,14.7)
	Pr >  t			0.3530
	n	26	17	
	LS Mean	5.350	1.786	3.563
	SEM	4.167	4.782	5.219
Week 84	95% CI	(-2.8,13.5)	(-7.6,11.2)	(-6.7,13.8)
	Pr >  t			0.4949
	n	18	16	
	LS Mean	14.782	-3.040	17.823
	SEM	4.599	4.864	5.624
Week 96	95% CI	( 5.7,23.8)	(-12.6, 6.5)	( 6.8,28.9)
	Pr >  t			0.0016
	n	20	10	
	LS Mean	12.327	0.831	11.496
	SEM	4.462	5.615	6.193
Week 108	95% CI	( 3.6,21.1)	(-10.2,11.9)	(-0.7,23.7)
	Pr >  t			0.0638
	n	14	10	
	LS Mean	3.238	4.611	-1.374
	SEM	4.950	5.616	6.548
Week 120	95% CI	(-6.5,13.0)	(-6.4,15.6)	(-14.2,11.5)
	Pr >  t			0.8339
	n	14	7	
	LS Mean	6.436	-2.856	9.292
	SEM	4.931	6.361	7.192
Week 132	95% CI	(-3.2,16.1)	(-15.3, 9.6)	(-4.8,23.4)
	Pr >  t			0.1967
	n	12	5	
	LS Mean	6.751	2.333	4.418
	SEM	5.190	7.233	8.128
Week 144	95% CI	(-3.4,16.9)	(-11.9,16.5)	(-11.5,20.4)
	Pr >  t			0.5869
	n	11	4	
Week 144	LS Mean	12.343	-0.450	12.793
	SEM	5.319	7.915	8.829

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( -1.9,22.8)	(-16.0,15.1)	( -4.5,30.1)
		Pr >  t			0.1477
	Week 156	n	8	3	
		LS Mean	2.856	-3.596	6.453
		SEM	5.958	8.932	10.10
		95% CI	( -8.8,14.6)	(-21.1,13.9)	(-13.4,26.3)
		Pr >  t			0.5232
	Week 168	n	4	2	
		LS Mean	6.971	-18.65	25.619
		SEM	7.823	10.68	12.73
		95% CI	( -8.4,22.3)	(-39.6, 2.3)	( 0.6,50.6)
		Pr >  t			0.0445
	Week 180	n	1	1	
		LS Mean	16.733	0.348	16.385
		SEM	14.67	14.71	20.45
		95% CI	(-12.1,45.5)	(-28.5,29.2)	(-23.8,56.5)
		Pr >  t			0.4234
	Week 192	n	1	1	
		LS Mean	5.623	-21.87	27.495
		SEM	14.67	14.71	20.45
		95% CI	(-23.2,34.4)	(-50.7, 7.0)	(-12.7,67.7)
		Pr >  t			0.1793
Exon 9	Week 8	n	53	64	
		LS Mean	9.424	3.538	5.886
		SEM	4.976	5.370	3.409
		95% CI	( -0.4,19.3)	( -7.1,14.2)	( -0.8,12.6)
		Pr >  t			0.0856
	Week 16	n	48	48	
		LS Mean	6.063	6.325	-0.262
		SEM	5.085	5.470	3.629
		95% CI	( -4.0,16.1)	( -4.5,17.1)	( -7.4, 6.9)
		Pr >  t			0.9425
	Week 24	n	46	36	
		LS Mean	9.457	6.797	2.660
		SEM	5.101	5.594	3.847
		95% CI	( -0.6,19.5)	( -4.3,17.8)	( -4.9,10.2)
		Pr >  t			0.4898
	Week 32	n	31	33	
		LS Mean	7.559	4.462	3.096
		SEM	5.375	5.641	4.156

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.0,18.2)	(-6.7,15.6)	(-5.1,11.3)
		Pr >  t			0.4568
	Week 40	n	28	30	
		LS Mean	5.580	5.759	-0.179
		SEM	5.435	5.690	4.296
		95% CI	(-5.1,16.3)	(-5.5,17.0)	(-8.6, 8.3)
		Pr >  t			0.9668
	Week 48	n	26	23	
		LS Mean	6.552	8.530	-1.979
		SEM	5.474	5.846	4.557
		95% CI	(-4.2,17.3)	(-3.0,20.1)	(-10.9, 7.0)
		Pr >  t			0.6644
	Week 56	n	22	17	
		LS Mean	6.551	7.787	-1.236
		SEM	5.579	6.074	4.967
		95% CI	(-4.4,17.5)	(-4.2,19.8)	(-11.0, 8.5)
		Pr >  t			0.8036
	Week 64	n	17	19	
		LS Mean	5.465	6.264	-0.799
		SEM	5.777	5.986	5.085
		95% CI	(-5.9,16.8)	(-5.5,18.1)	(-10.8, 9.2)
		Pr >  t			0.8753
	Week 72	n	20	14	
		LS Mean	8.840	7.578	1.262
		SEM	5.653	6.251	5.259
		95% CI	(-2.3,20.0)	(-4.7,19.9)	(-9.1,11.6)
		Pr >  t			0.8105
	Week 84	n	19	13	
		LS Mean	7.272	9.736	-2.464
		SEM	5.684	6.325	5.385
		95% CI	(-3.9,18.5)	(-2.7,22.2)	(-13.0, 8.1)
		Pr >  t			0.6474
	Week 96	n	12	12	
		LS Mean	5.441	4.347	1.094
		SEM	6.118	6.412	5.934
		95% CI	(-6.6,17.5)	(-8.3,17.0)	(-10.6,12.7)
		Pr >  t			0.8537
	Week 108	n	9	9	
		LS Mean	7.035	15.742	-8.707
		SEM	6.483	6.764	6.666



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( -5.7,19.8)	( -2.4,29.1)	(-21.8, 4.4)
		Pr >  t			0.1920
	Week 120	n	12	7	
		LS Mean	12.938	5.366	7.572
		SEM	6.134	7.147	6.727
		95% CI	( 0.9,25.0)	( -8.7,19.4)	( -5.6,20.8)
		Pr >  t			0.2608
	Week 132	n	5	2	
		LS Mean	18.995	25.804	-6.809
		SEM	7.519	10.46	11.07
		95% CI	( 4.2,33.8)	( 5.3,46.3)	(-28.6,14.9)
		Pr >  t			0.5389
	Week 144	n	3	1	
		LS Mean	28.161	-0.331	28.491
		SEM	8.864	13.86	15.09
		95% CI	( 10.8,45.6)	(-27.6,26.9)	( -1.1,58.1)
		Pr >  t			0.0595
	Week 156	n	2		
		LS Mean	2.527		
		SEM	10.30		
		95% CI	(-17.7,22.8)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-24: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Übelkeit/Erbrechen“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and Vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	5.491	1.659	3.831		
			SEM	1.039	1.043	1.469		
			95% CI	( 3.4, 7.5)	( -0.4, 3.7)	( 0.9, 6.7)		
					Pr >  t			0.0094
		Week 16	n	118	104			
			LS Mean	4.124	0.041	4.083		
			SEM	1.095	1.162	1.595		
			95% CI	( 2.0, 6.3)	( -2.2, 2.3)	( 1.0, 7.2)		
					Pr >  t			0.0107
		Week 24	n	100	79			
			LS Mean	3.060	0.249	2.811		
			SEM	1.173	1.303	1.751		
			95% CI	( 0.8, 5.4)	( -2.3, 2.8)	( -0.6, 6.2)		
					Pr >  t			0.1087
		Week 32	n	84	72			
			LS Mean	4.352	-0.384	4.736		
			SEM	1.258	1.355	1.846		
			95% CI	( 1.9, 6.8)	( -3.0, 2.3)	( 1.1, 8.4)		
					Pr >  t			0.0104
		Week 40	n	73	62			
			LS Mean	2.724	0.814	1.910		
			SEM	1.331	1.437	1.957		
			95% CI	( 0.1, 5.3)	( -2.0, 3.6)	( -1.9, 5.7)		
			Pr >  t			0.3294		
Week 48	n	67	51					
	LS Mean	2.674	1.085	1.590				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	SEM	1.377	1.555	2.075
	95% CI	(-0.0, 5.4)	(-2.0, 4.1)	(-2.5, 5.7)
	Pr >  t			0.4439
	n	57	45	
	LS Mean	1.744	1.786	-0.042
Week 64	SEM	1.469	1.638	2.199
	95% CI	(-1.1, 4.6)	(-1.4, 5.0)	(-4.4, 4.3)
	Pr >  t			0.9849
	n	45	42	
	LS Mean	4.530	0.097	4.433
Week 72	SEM	1.617	1.686	2.335
	95% CI	( 1.4, 7.7)	(-3.2, 3.4)	(-0.1, 9.0)
	Pr >  t			0.0578
	n	46	35	
	LS Mean	2.160	-0.574	2.734
Week 84	SEM	1.604	1.819	2.424
	95% CI	(-1.0, 5.3)	(-4.1, 3.0)	(-2.0, 7.5)
	Pr >  t			0.2595
	n	40	33	
	LS Mean	2.550	0.753	1.797
Week 96	SEM	1.699	1.865	2.521
	95% CI	(-0.8, 5.9)	(-2.9, 4.4)	(-3.1, 6.7)
	Pr >  t			0.4760
	n	34	24	
	LS Mean	3.313	-0.078	3.390
Week 108	SEM	1.820	2.139	2.807
	95% CI	(-0.3, 6.9)	(-4.3, 4.1)	(-2.1, 8.9)
	Pr >  t			0.2274
	n	26	21	
	LS Mean	3.527	-1.396	4.923
Week 120	SEM	2.045	2.269	3.053
	95% CI	(-0.5, 7.5)	(-5.8, 3.1)	(-1.1, 10.9)
	Pr >  t			0.1071
	n	27	16	
	LS Mean	-0.515	0.352	-0.867
Week 132	SEM	2.013	2.565	3.259
	95% CI	(-4.5, 3.4)	(-4.7, 5.4)	(-7.3, 5.5)
	Pr >  t			0.7903
	n	20	8	
	LS Mean	-0.453	-1.293	0.840

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	2.297	3.535	4.214
	95% CI	(-5.0, 4.1)	(-8.2, 5.6)	(-7.4, 9.1)
	Pr >  t			0.8420
Week 144	n	14	5	
	LS Mean	1.015	-1.891	2.906
	SEM	2.704	4.430	5.188
	95% CI	(-4.3, 6.3)	(-10.6, 6.8)	(-7.3,13.1)
	Pr >  t			0.5755
Week 156	n	10	3	
	LS Mean	-0.466	-2.261	1.795
	SEM	3.164	5.673	6.495
	95% CI	(-6.7, 5.7)	(-13.4, 8.9)	(-10.9,14.5)
	Pr >  t			0.7822
Week 168	n	4	2	
	LS Mean	0.138	-3.251	3.390
	SEM	4.914	6.921	8.487
	95% CI	(-9.5, 9.8)	(-16.8,10.3)	(-13.3,20.0)
	Pr >  t			0.6897
Week 180	n	1	1	
	LS Mean	-1.210	-6.137	4.927
	SEM	9.736	9.737	13.77
	95% CI	(-20.3,17.9)	(-25.2,13.0)	(-22.1,31.9)
	Pr >  t			0.7205
Week 192	n	1	1	
	LS Mean	-1.210	-6.137	4.927
	SEM	9.736	9.737	13.77
	95% CI	(-20.3,17.9)	(-25.2,13.0)	(-22.1,31.9)
	Pr >  t			0.7205
Prior use	Week 8	n	8	6
	LS Mean	6.366	10.642	-4.276
	SEM	7.825	8.672	11.74
	95% CI	(-10.8,23.5)	(-8.1,29.4)	(-29.8,21.3)
	Pr >  t			0.7218
	Week 16	n	6	3
	LS Mean	14.395	15.174	-0.779
	SEM	8.256	10.50	13.33
	95% CI	(-3.3,32.1)	(-6.7,37.1)	(-28.9,27.3)
	Pr >  t			0.9541
	Week 24	n	5	2
	LS Mean	11.516	25.306	-13.79

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	8.537	11.28	14.11
	95% CI	(-6.6,29.7)	( 2.1,48.5)	(-43.1,15.5)
	Pr >  t			0.3395
Week 32	n	2	1	
	LS Mean	4.445	49.521	-45.08
	SEM	10.47	13.74	17.22
	95% CI	(-17.1,26.0)	( 21.4,77.7)	(-80.4,-9.8)
	Pr >  t			0.0142
Week 40	n	2		
	LS Mean	4.445		
	SEM	10.47		
	95% CI	(-17.1,26.0)		
	Pr >  t			
Week 48	n	2		
	LS Mean	4.445		
	SEM	10.47		
	95% CI	(-17.1,26.0)		
	Pr >  t			
Week 56	n	2		
	LS Mean	4.445		
	SEM	10.47		
	95% CI	(-17.1,26.0)		
	Pr >  t			
Week 64	n	2		
	LS Mean	4.445		
	SEM	10.47		
	95% CI	(-17.1,26.0)		
	Pr >  t			
Week 72	n	2		
	LS Mean	12.780		
	SEM	10.47		
	95% CI	(-8.8,34.3)		
	Pr >  t			
Week 96	n	1		
	LS Mean	7.193		
	SEM	12.70		
	95% CI	(-18.8,33.2)		
	Pr >  t			
Week 120	n	1		
	LS Mean	7.193		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	12.70	
		95% CI	(-18.8,33.2)	
		Pr >  t		
	Week 144	n	1	
		LS Mean	23.863	
		SEM	12.70	
		95% CI	(-2.2,49.9)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and Vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	9.889	7.082	2.807		
			SEM	2.205	2.304	2.227		
			95% CI	( 5.5,14.2)	( 2.5,11.6)	( -1.6, 7.2)		
					Pr >  t			0.2085
		Week 16	n	70	52			
			LS Mean	11.201	5.304	5.897		
			SEM	2.262	2.507	2.429		
			95% CI	( 6.7,15.7)	( 0.4,10.2)	( 1.1,10.7)		
					Pr >  t			0.0157
		Week 24	n	61	37			
			LS Mean	9.186	6.404	2.782		
			SEM	2.326	2.719	2.676		
			95% CI	( 4.6,13.8)	( 1.1,11.8)	( -2.5, 8.0)		
					Pr >  t			0.2991
		Week 32	n	48	33			
			LS Mean	9.959	4.663	5.295		
			SEM	2.457	2.792	2.845		
			95% CI	( 5.1,14.8)	( -0.8,10.2)	( -0.3,10.9)		
					Pr >  t			0.0633
		Week 40	n	42	31			
			LS Mean	6.657	7.253	-0.596		
			SEM	2.523	2.833	2.945		
			95% CI	( 1.7,11.6)	( 1.7,12.8)	( -6.4, 5.2)		
					Pr >  t			0.8397
		Week 48	n	40	25			
			LS Mean	7.576	4.995	2.581		
			SEM	2.550	2.979	3.106		
95% CI	( 2.6,12.6)		( -0.9,10.9)	( -3.5, 8.7)				
			Pr >  t			0.4063		
Week 56	n	35	20					
	LS Mean	6.804	8.631	-1.827				
	SEM	2.622	3.160	3.341				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.6,12.0)	( -8.4, 4.7)
		Pr >  t		0.5847
	Week 64	n	29	18
		LS Mean	7.450	5.459
		SEM	2.736	3.256
		95% CI	( 2.1,12.8)	( -0.9,11.9)
		Pr >  t		0.5721
	Week 72	n	28	18
		LS Mean	7.077	5.724
		SEM	2.760	3.253
		95% CI	( 1.7,12.5)	( -0.7,12.1)
		Pr >  t		0.7022
	Week 84	n	27	17
		LS Mean	8.004	6.418
		SEM	2.800	3.308
		95% CI	( 2.5,13.5)	( -0.1,12.9)
		Pr >  t		0.6603
	Week 96	n	23	14
		LS Mean	9.286	6.723
		SEM	2.912	3.503
		95% CI	( 3.6,15.0)	( -0.2,13.6)
		Pr >  t		0.5089
	Week 108	n	19	12
		LS Mean	9.272	4.642
		SEM	3.082	3.679
		95% CI	( 3.2,15.3)	( -2.6,11.9)
		Pr >  t		0.2653
	Week 120	n	18	8
		LS Mean	5.023	8.483
		SEM	3.120	4.231
		95% CI	( -1.1,11.2)	( 0.2,16.8)
		Pr >  t		0.4600
	Week 132	n	11	4
		LS Mean	5.755	3.436
		SEM	3.670	5.558
		95% CI	( -1.5,13.0)	( -7.5,14.3)
		Pr >  t		0.7090
	Week 144	n	11	4
		LS Mean	6.646	3.429
		SEM	3.659	5.562
				6.216



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.5,13.8)	(-7.5,14.3)	(-9.0,15.4)
		Pr >  t			0.6049
	Week 156	n	5	2	
		LS Mean	4.194	2.354	1.840
		SEM	4.977	7.533	8.704
		95% CI	(-5.6,14.0)	(-12.4,17.1)	(-15.2,18.9)
		Pr >  t			0.8326
	Week 168	n	1	2	
		LS Mean	-14.02	2.354	-16.38
		SEM	10.33	7.533	12.56
		95% CI	(-34.3, 6.3)	(-12.4,17.1)	(-41.0, 8.3)
		Pr >  t			0.1927
	Week 180	n		1	
		LS Mean		-0.551	
		SEM		10.40	
		95% CI		(-21.0,19.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.551	
		SEM		10.40	
		95% CI		(-21.0,19.9)	
		Pr >  t			
>= 65 Years	Week 8	n	63	71	
		LS Mean	7.970	5.135	2.835
		SEM	2.338	2.335	1.839
		95% CI	( 3.3,12.6)	( 0.5, 9.8)	(-0.8, 6.5)
		Pr >  t			0.1242
	Week 16	n	54	55	
		LS Mean	4.077	3.573	0.505
		SEM	2.428	2.394	2.016
		95% CI	(-0.7, 8.9)	(-1.2, 8.3)	(-3.5, 4.5)
		Pr >  t			0.8025
	Week 24	n	44	44	
		LS Mean	3.747	3.679	0.068
		SEM	2.509	2.474	2.226
		95% CI	(-1.2, 8.7)	(-1.2, 8.6)	(-4.3, 4.4)
		Pr >  t			0.9757
	Week 32	n	38	40	
		LS Mean	5.474	4.301	1.173
		SEM	2.609	2.552	2.352

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 0.3,10.6)	( -0.7, 9.3)	( -3.4, 5.8)
		Pr >  t			0.6184
	Week 40	n	33	31	
		LS Mean	5.971	3.465	2.506
		SEM	2.679	2.706	2.567
		95% CI	( 0.7,11.3)	( -1.9, 8.8)	( -2.5, 7.5)
		Pr >  t			0.3293
	Week 48	n	29	26	
		LS Mean	4.856	6.093	-1.237
		SEM	2.749	2.812	2.749
		95% CI	( -0.6,10.3)	( 0.6,11.6)	( -6.6, 4.2)
		Pr >  t			0.6528
	Week 56	n	24	25	
		LS Mean	3.724	4.256	-0.532
		SEM	2.865	2.836	2.891
		95% CI	( -1.9, 9.4)	( -1.3, 9.8)	( -6.2, 5.1)
		Pr >  t			0.8542
	Week 64	n	18	24	
		LS Mean	9.640	3.743	5.897
		SEM	3.074	2.863	3.125
		95% CI	( 3.6,15.7)	( -1.9, 9.4)	( -0.2,12.0)
		Pr >  t			0.0596
	Week 72	n	20	17	
		LS Mean	5.253	2.185	3.069
		SEM	2.995	3.123	3.290
		95% CI	( -0.6,11.1)	( -4.0, 8.3)	( -3.4, 9.5)
		Pr >  t			0.3513
	Week 84	n	13	16	
		LS Mean	4.015	4.203	-0.188
		SEM	3.367	3.174	3.677
		95% CI	( -2.6,10.6)	( -2.0,10.4)	( -7.4, 7.0)
		Pr >  t			0.9593
	Week 96	n	12	10	
		LS Mean	3.573	1.859	1.714
		SEM	3.452	3.665	4.178
		95% CI	( -3.2,10.4)	( -5.3, 9.1)	( -6.5, 9.9)
		Pr >  t			0.6817
	Week 108	n	7	9	
		LS Mean	3.963	1.723	2.240
		SEM	4.136	3.796	4.862

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.2,12.1)	(-5.7, 9.2)	(-7.3,11.8)
		Pr >  t			0.6452
	Week 120	n	10	8	
		LS Mean	1.041	1.516	-0.475
		SEM	3.665	3.956	4.602
		95% CI	(-6.2, 8.2)	(-6.3, 9.3)	(-9.5, 8.6)
		Pr >  t			0.9179
	Week 132	n	9	4	
		LS Mean	0.468	3.125	-2.657
		SEM	3.789	5.149	5.741
		95% CI	(-7.0, 7.9)	(-7.0,13.2)	(-13.9, 8.6)
		Pr >  t			0.6436
	Week 144	n	4	1	
		LS Mean	6.041	3.025	3.016
		SEM	5.140	9.575	10.50
		95% CI	(-4.1,16.1)	(-15.8,21.8)	(-17.6,23.6)
		Pr >  t			0.7739
	Week 156	n	5	1	
		LS Mean	2.143	3.025	-0.882
		SEM	4.702	9.575	10.29
		95% CI	(-7.1,11.4)	(-15.8,21.8)	(-21.1,19.3)
		Pr >  t			0.9317
	Week 168	n	3		
		LS Mean	8.472		
		SEM	5.807		
		95% CI	(-2.9,19.9)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	1.357		
		SEM	9.567		
		95% CI	(-17.4,20.1)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	1.357		
		SEM	9.567		
		95% CI	(-17.4,20.1)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and Vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	7.079	-0.199	7.278		
			SEM	2.136	2.050	2.041		
			95% CI	( 2.8,11.3)	( -4.3, 3.9)	( 3.3,11.3)		
					Pr >  t			0.0004
		Week 16	n	30	30			
			LS Mean	4.369	0.553	3.816		
			SEM	2.164	2.186	2.166		
			95% CI	( 0.1, 8.7)	( -3.8, 4.9)	( -0.4, 8.1)		
					Pr >  t			0.0791
		Week 24	n	21	26			
			LS Mean	0.551	1.463	-0.912		
			SEM	2.353	2.252	2.430		
			95% CI	( -4.1, 5.2)	( -3.0, 5.9)	( -5.7, 3.9)		
					Pr >  t			0.7078
		Week 32	n	19	24			
			LS Mean	0.908	2.517	-1.609		
			SEM	2.413	2.295	2.540		
			95% CI	( -3.9, 5.7)	( -2.0, 7.1)	( -6.6, 3.4)		
					Pr >  t			0.5270
		Week 40	n	16	19			
			LS Mean	1.093	0.253	0.840		
			SEM	2.526	2.481	2.787		
			95% CI	( -3.9, 6.1)	( -4.6, 5.1)	( -4.6, 6.3)		
					Pr >  t			0.7632
		Week 48	n	16	18			
			LS Mean	0.051	0.179	-0.127		
			SEM	2.526	2.517	2.819		
95% CI	( -4.9, 5.0)		( -4.8, 5.1)	( -5.7, 5.4)				
			Pr >  t			0.9640		
Week 56	n	12	14					
	LS Mean	2.204	2.613	-0.409				
	SEM	2.749	2.697	3.188				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.2, 7.6)	(-2.7, 7.9)	(-6.7, 5.9)
		Pr >  t			0.8979
	Week 64	n	12	11	
		LS Mean	4.981	1.971	3.010
		SEM	2.749	2.910	3.370
		95% CI	(-0.4, 10.4)	(-3.8, 7.7)	(-3.6, 9.6)
		Pr >  t			0.3724
	Week 72	n	10	9	
		LS Mean	4.417	-1.234	5.650
		SEM	2.915	3.119	3.690
		95% CI	(-1.3, 10.2)	(-7.4, 4.9)	(-1.6, 12.9)
		Pr >  t			0.1265
	Week 84	n	8	8	
		LS Mean	5.808	2.831	2.977
		SEM	3.202	3.247	3.985
		95% CI	(-0.5, 12.1)	(-3.6, 9.2)	(-4.9, 10.8)
		Pr >  t			0.4555
	Week 96	n	6	6	
		LS Mean	3.918	-1.991	5.909
		SEM	3.562	3.611	4.563
		95% CI	(-3.1, 10.9)	(-9.1, 5.1)	(-3.1, 14.9)
		Pr >  t			0.1961
	Week 108	n	4	5	
		LS Mean	5.037	-2.495	7.531
		SEM	4.189	3.880	5.263
		95% CI	(-3.2, 13.3)	(-10.1, 5.1)	(-2.8, 17.9)
		Pr >  t			0.1532
	Week 120	n	4	4	
		LS Mean	5.037	-3.202	8.239
		SEM	4.189	4.249	5.540
		95% CI	(-3.2, 13.3)	(-11.6, 5.2)	(-2.7, 19.1)
		Pr >  t			0.1378
	Week 132	n	3	2	
		LS Mean	6.498	-4.448	10.945
		SEM	4.730	5.677	7.050
		95% CI	(-2.8, 15.8)	(-15.6, 6.7)	(-2.9, 24.8)
		Pr >  t			0.1214
	Week 144	n	3	1	
		LS Mean	6.498	-0.269	6.767
		SEM	4.730	7.820	8.866

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-2.8,15.8)	(-15.6,15.1)	(-10.7,24.2)
		Pr >  t			0.4459
	Week 156	n	2	1	
		LS Mean	1.218	-0.269	1.487
		SEM	5.654	7.820	9.390
		95% CI	(-9.9,12.3)	(-15.6,15.1)	(-17.0,20.0)
		Pr >  t			0.8743
	Week 168	n	1		
		LS Mean	2.853		
		SEM	7.791		
		95% CI	(-12.5,18.2)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	1.736	8.037	-6.301
		SEM	9.534	9.098	5.849
		95% CI	(-17.7,21.2)	(-10.4,26.5)	(-18.2, 5.6)
		Pr >  t			0.2893
	Week 16	n	15	14	
		LS Mean	-1.908	0.198	-2.106
		SEM	9.577	8.709	6.167
		95% CI	(-21.4,17.6)	(-17.6,18.0)	(-14.6,10.4)
		Pr >  t			0.7346
	Week 24	n	12	11	
		LS Mean	-5.714	1.768	-7.482
		SEM	9.716	9.311	6.580
		95% CI	(-25.5,14.0)	(-17.0,20.6)	(-20.7, 5.8)
		Pr >  t			0.2612
	Week 32	n	8	9	
		LS Mean	1.780	0.716	1.065
		SEM	10.02	9.473	7.223
		95% CI	(-18.5,22.1)	(-18.4,19.8)	(-13.4,15.5)
		Pr >  t			0.8833
	Week 40	n	6	7	
		LS Mean	1.928	-0.722	2.651
		SEM	10.31	9.683	7.852
		95% CI	(-18.9,22.7)	(-20.2,18.8)	(-13.0,18.3)
		Pr >  t			0.7365
	Week 48	n	4	6	
		LS Mean	-5.978	3.462	-9.440
		SEM	10.81	9.840	8.669

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-27.7,15.7)	(-16.3,23.2)	(-26.6, 7.7)
		Pr >  t			0.2785
	Week 56	n	4	6	
		LS Mean	-4.271	3.951	-8.222
		SEM	10.81	9.852	8.678
		95% CI	(-26.0,17.4)	(-15.8,23.7)	(-25.4, 9.0)
		Pr >  t			0.3455
	Week 64	n	4	4	
		LS Mean	-2.179	5.498	-7.677
		SEM	10.82	10.36	9.258
		95% CI	(-23.9,19.5)	(-15.2,26.2)	(-26.0,10.6)
		Pr >  t			0.4086
	Week 72	n	4	4	
		LS Mean	-2.179	5.498	-7.677
		SEM	10.82	10.36	9.258
		95% CI	(-23.9,19.5)	(-15.2,26.2)	(-26.0,10.6)
		Pr >  t			0.4086
	Week 84	n	4	4	
		LS Mean	-5.978	5.498	-11.48
		SEM	10.81	10.36	9.257
		95% CI	(-27.7,15.7)	(-15.2,26.2)	(-29.8, 6.8)
		Pr >  t			0.2174
	Week 96	n	3	2	
		LS Mean	-6.669	2.754	-9.423
		SEM	11.28	11.73	11.23
		95% CI	(-29.2,15.9)	(-20.5,26.0)	(-31.6,12.8)
		Pr >  t			0.4030
	Week 108	n	3	3	
		LS Mean	-6.669	1.886	-8.556
		SEM	11.28	10.85	10.30
		95% CI	(-29.2,15.9)	(-19.7,23.5)	(-28.9,11.8)
		Pr >  t			0.4077
	Week 120	n	2	1	
		LS Mean	-7.694	2.570	-10.26
		SEM	12.15	14.04	14.35
		95% CI	(-31.9,16.5)	(-25.2,30.3)	(-38.7,18.1)
		Pr >  t			0.4758
	Week 132	n	2	1	
		LS Mean	-4.450	2.570	-7.020
		SEM	12.14	14.04	14.36



Subgroup	Time Window	Alpelisib 300mg qd + Fulv				Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	N=169	Placebo qd + Fulv N=172	95% CI	
	Week 156	95% CI Pr >  t  n LS Mean SEM 95% CI Pr >  t	(-28.6,19.7) 1 -4.280 14.42 (-32.8,24.3)	(-25.2,30.3)	(-35.4,21.4) 0.6257	
	Week 168	n LS Mean SEM 95% CI Pr >  t	1 -4.280 14.42 (-32.8,24.3)			
White	Week 8	n LS Mean SEM 95% CI Pr >  t	93 10.130 2.093 ( 6.0,14.3)	85 7.402 2.204 ( 3.1,11.7)	2.728 2.007 ( -1.2, 6.7) 0.1750	
	Week 16	n LS Mean SEM 95% CI Pr >  t	79 10.532 2.174 ( 6.3,14.8)	61 6.937 2.397 ( 2.2,11.7)	3.595 2.235 ( -0.8, 8.0) 0.1084	
	Week 24	n LS Mean SEM 95% CI Pr >  t	71 10.486 2.224 ( 6.1,14.9)	43 6.644 2.570 ( 1.6,11.7)	3.842 2.461 ( -1.0, 8.7) 0.1190	
	Week 32	n LS Mean SEM 95% CI Pr >  t	59 10.924 2.331 ( 6.3,15.5)	39 5.355 2.642 ( 0.2,10.5)	5.569 2.587 ( 0.5,10.6) 0.0317	
	Week 40	n LS Mean SEM 95% CI Pr >  t	52 8.596 2.387 ( 3.9,13.3)	35 8.886 2.707 ( 3.6,14.2)	-0.291 2.704 ( -5.6, 5.0) 0.9144	
	Week 48	n LS Mean SEM	48 9.750 2.424	26 8.994 2.906	0.756 2.933	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 5.0,14.5)	( 3.3,14.7)	( -5.0, 6.5)
		Pr >  t			0.7967
	Week 56	n	42	24	
		LS Mean	7.597	8.017	-0.420
		SEM	2.489	2.967	3.049
		95% CI	( 2.7,12.5)	( 2.2,13.8)	( -6.4, 5.6)
		Pr >  t			0.8905
	Week 64	n	30	26	
		LS Mean	10.217	6.058	4.160
		SEM	2.686	2.908	3.160
		95% CI	( 4.9,15.5)	( 0.3,11.8)	( -2.0,10.4)
		Pr >  t			0.1884
	Week 72	n	34	21	
		LS Mean	7.708	6.286	1.423
		SEM	2.608	3.075	3.250
		95% CI	( 2.6,12.8)	( 0.2,12.3)	( -5.0, 7.8)
		Pr >  t			0.6617
	Week 84	n	28	20	
		LS Mean	8.140	6.767	1.373
		SEM	2.740	3.115	3.391
		95% CI	( 2.8,13.5)	( 0.7,12.9)	( -5.3, 8.0)
		Pr >  t			0.6857
	Week 96	n	26	15	
		LS Mean	9.577	8.079	1.498
		SEM	2.786	3.390	3.685
		95% CI	( 4.1,15.0)	( 1.4,14.7)	( -5.7, 8.7)
		Pr >  t			0.6846
	Week 108	n	19	12	
		LS Mean	10.051	4.915	5.136
		SEM	3.053	3.644	4.108
		95% CI	( 4.1,16.0)	( -2.2,12.1)	( -2.9,13.2)
		Pr >  t			0.2115
	Week 120	n	22	10	
		LS Mean	4.717	9.635	-4.918
		SEM	2.919	3.880	4.230
		95% CI	( -1.0,10.4)	( 2.0,17.2)	(-13.2, 3.4)
		Pr >  t			0.2452
	Week 132	n	15	4	
		LS Mean	4.064	4.347	-0.283
		SEM	3.284	5.558	5.996

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-2.4,10.5)	(-6.6,15.3)	(-12.1,11.5)
		Pr >  t			0.9624
	Week 144	n	12	4	
		LS Mean	7.210	4.359	2.850
		SEM	3.531	5.561	6.145
		95% CI	( 0.3,14.1)	(-6.6,15.3)	(-9.2,14.9)
		Pr >  t			0.6429
	Week 156	n	7	2	
		LS Mean	5.073	3.269	1.804
		SEM	4.336	7.558	8.379
		95% CI	(-3.4,13.6)	(-11.6,18.1)	(-14.6,18.3)
		Pr >  t			0.8296
	Week 168	n	2	2	
		LS Mean	4.532	3.269	1.263
		SEM	7.492	7.558	10.37
		95% CI	(-10.2,19.2)	(-11.6,18.1)	(-19.1,21.6)
		Pr >  t			0.9031
	Week 180	n	1	1	
		LS Mean	4.669	0.426	4.243
		SEM	10.42	10.45	14.56
		95% CI	(-15.8,25.1)	(-20.1,20.9)	(-24.3,32.8)
		Pr >  t			0.7708
	Week 192	n	1	1	
		LS Mean	4.669	0.426	4.243
		SEM	10.42	10.45	14.56
		95% CI	(-15.8,25.1)	(-20.1,20.9)	(-24.3,32.8)
		Pr >  t			0.7708

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and Vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Endocrine Status (L) Primary resistant		Week 8	n	21	16	
			LS Mean	0.241	4.912	-4.671
			SEM	3.146	3.730	4.063
			95% CI	(-6.2, 6.7)	(-2.7,12.5)	(-12.9, 3.5)
		Pr >  t			0.2572	
		Week 16	n	17	10	
			LS Mean	1.346	-0.292	1.638
			SEM	3.387	4.216	4.511
			95% CI	(-5.5, 8.2)	(-8.8, 8.2)	(-7.4,10.7)
		Pr >  t			0.7181	
		Week 24	n	9	5	
			LS Mean	-2.104	4.581	-6.685
			SEM	3.881	5.099	5.761
			95% CI	(-9.9, 5.7)	(-5.6,14.7)	(-18.1, 4.8)
		Pr >  t			0.2488	
		Week 32	n	8	4	
			LS Mean	-5.059	2.287	-7.346
			SEM	4.001	5.476	6.202
			95% CI	(-13.1, 2.9)	(-8.6,13.2)	(-19.6, 5.0)
		Pr >  t			0.2389	
		Week 40	n	5	4	
			LS Mean	-2.732	-1.880	-0.852
			SEM	4.573	5.476	6.637
			95% CI	(-11.8, 6.4)	(-12.8, 9.0)	(-14.0,12.3)
		Pr >  t			0.8981	
		Week 48	n	5	3	
			LS Mean	-2.732	2.715	-5.447
			SEM	4.573	5.988	7.067
95% CI	(-11.8, 6.4)		(-9.2,14.6)	(-19.4, 8.6)		
Pr >  t			0.4425			
Week 56	n	4	3			
	LS Mean	-4.025	8.272	-12.30		
	SEM	4.907	5.988	7.305		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	95% CI	(-13.8, 5.7)	(-3.6,20.1)	(-26.8, 2.2)	
	Pr >  t			0.0951	
	n	4	3		
	LS Mean	-4.025	2.715	-6.740	
	SEM	4.907	5.988	7.305	
Week 72	95% CI	(-13.8, 5.7)	(-9.2,14.6)	(-21.2, 7.7)	
	Pr >  t			0.3582	
	n	4	3		
	LS Mean	0.143	2.715	-2.572	
	SEM	4.907	5.988	7.305	
Week 84	95% CI	(-9.6, 9.9)	(-9.2,14.6)	(-17.0,11.9)	
	Pr >  t			0.7254	
	n	2	3		
	LS Mean	5.198	-2.842	8.040	
	SEM	6.425	5.988	8.339	
Week 96	95% CI	(-7.5,17.9)	(-14.7, 9.0)	(-8.5,24.6)	
	Pr >  t			0.3372	
	n	1	3		
	LS Mean	-2.401	2.715	-5.116	
	SEM	8.528	5.988	10.16	
Week 108	95% CI	(-19.3,14.5)	(-9.2,14.6)	(-25.3,15.1)	
	Pr >  t			0.6157	
	n		2		
	LS Mean		6.675		
	SEM		6.832		
Week 120	95% CI		(-6.9,20.2)		
	Pr >  t				
	n	1	1		
	LS Mean	-2.401	-5.558	3.157	
	SEM	8.528	8.878	12.09	
Week 132	95% CI	(-19.3,14.5)	(-23.2,12.1)	(-20.9,27.2)	
	Pr >  t			0.7947	
	n		1		
	LS Mean		11.112		
	SEM		8.878		
Week 144	95% CI		(-6.5,28.7)		
	Pr >  t				
	n	1			
	LS Mean	14.269			
	SEM	8.528			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( -2.7,31.2)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	10.612	5.836	4.777
		SEM	2.183	2.170	1.863
		95% CI	( 6.3,14.9)	( 1.6,10.1)	( 1.1, 8.4)
		Pr >  t			0.0107
	Week 16	n	83	81	
		LS Mean	8.759	4.840	3.919
		SEM	2.247	2.286	2.043
		95% CI	( 4.3,13.2)	( 0.3, 9.3)	( -0.1, 7.9)
		Pr >  t			0.0557
	Week 24	n	75	62	
		LS Mean	8.524	5.185	3.339
		SEM	2.295	2.411	2.202
		95% CI	( 4.0,13.0)	( 0.4, 9.9)	( -1.0, 7.7)
		Pr >  t			0.1300
	Week 32	n	59	56	
		LS Mean	11.279	5.019	6.260
		SEM	2.430	2.454	2.352
		95% CI	( 6.5,16.1)	( 0.2, 9.8)	( 1.6,10.9)
		Pr >  t			0.0080
	Week 40	n	52	48	
		LS Mean	8.475	6.537	1.938
		SEM	2.484	2.539	2.484
		95% CI	( 3.6,13.4)	( 1.5,11.5)	( -2.9, 6.8)
		Pr >  t			0.4355
	Week 48	n	47	37	
		LS Mean	7.878	6.695	1.184
		SEM	2.531	2.679	2.673
		95% CI	( 2.9,12.9)	( 1.4,12.0)	( -4.1, 6.4)
		Pr >  t			0.6580
	Week 56	n	41	31	
		LS Mean	6.992	7.265	-0.273
		SEM	2.603	2.791	2.851
		95% CI	( 1.9,12.1)	( 1.8,12.7)	( -5.9, 5.3)
		Pr >  t			0.9237
	Week 64	n	32	28	
		LS Mean	10.144	4.785	5.359
		SEM	2.749	2.863	3.053

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	( 4.7,15.5)	( -0.8,10.4)	( -0.6,11.3)	
	Pr >  t			0.0795	
	n	29	22		
	LS Mean	7.566	4.362	3.204	
	SEM	2.817	3.051	3.288	
Week 84	95% CI	( 2.0,13.1)	( -1.6,10.4)	( -3.2, 9.7)	
	Pr >  t			0.3301	
	n	26	21		
	LS Mean	7.868	4.825	3.043	
	SEM	2.895	3.090	3.391	
Week 96	95% CI	( 2.2,13.6)	( -1.2,10.9)	( -3.6, 9.7)	
	Pr >  t			0.3697	
	n	23	14		
	LS Mean	9.635	5.274	4.360	
	SEM	2.992	3.498	3.841	
Week 108	95% CI	( 3.8,15.5)	( -1.6,12.1)	( -3.2,11.9)	
	Pr >  t			0.2566	
	n	18	13		
	LS Mean	10.526	2.564	7.962	
	SEM	3.211	3.586	4.090	
Week 120	95% CI	( 4.2,16.8)	( -4.5, 9.6)	( -0.1,16.0)	
	Pr >  t			0.0518	
	n	19	10		
	LS Mean	5.067	6.997	-1.930	
	SEM	3.162	3.929	4.358	
Week 132	95% CI	( -1.1,11.3)	( -0.7,14.7)	( -10.5, 6.6)	
	Pr >  t			0.6580	
	n	13	4		
	LS Mean	5.460	0.034	5.426	
	SEM	3.559	5.664	6.190	
Week 144	95% CI	( -1.5,12.4)	( -11.1,11.1)	( -6.7,17.6)	
	Pr >  t			0.3809	
	n	8	1		
	LS Mean	5.649	-2.151	7.800	
	SEM	4.244	10.74	11.26	
Week 156	95% CI	( -2.7,14.0)	( -23.2,18.9)	( -14.3,29.9)	
	Pr >  t			0.4887	
	n	5	1		
	LS Mean	5.386	-2.151	7.537	
	SEM	5.131	10.74	11.62	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-4.7,15.5)	(-23.2,18.9)	(-15.3,30.4)
		Pr >  t			0.5169
		n	3	1	
	Week 180	LS Mean	5.018	-2.151	7.168
		SEM	6.403	10.74	12.24
		95% CI	(-7.5,17.6)	(-23.2,18.9)	(-16.9,31.2)
	Week 180	Pr >  t			0.5583
		n	1	1	
		LS Mean	4.253	-2.151	6.404
	Week 192	SEM	10.69	10.74	14.94
		95% CI	(-16.7,25.2)	(-23.2,18.9)	(-22.9,35.7)
		Pr >  t			0.6683
	Week 192	n	1	1	
		LS Mean	4.253	-2.151	6.404
		SEM	10.69	10.74	14.94
	Week 8	95% CI	(-16.7,25.2)	(-23.2,18.9)	(-22.9,35.7)
		Pr >  t			0.6683
		n	17	16	
	Week 8	LS Mean	-0.676	3.680	-4.356
		SEM	1.819	1.890	2.608
		95% CI	(-4.3, 2.9)	(-0.0, 7.4)	(-9.5, 0.8)
	Week 16	Pr >  t			0.0965
		n	18	14	
		LS Mean	0.177	-2.217	2.394
Week 16	SEM	1.764	2.008	2.663	
	95% CI	(-3.3, 3.7)	(-6.2, 1.7)	(-2.9, 7.6)	
	Pr >  t			0.3698	
Week 24	n	16	13		
	LS Mean	-0.559	-3.494	2.935	
	SEM	1.877	2.080	2.788	
Week 24	95% CI	(-4.3, 3.1)	(-7.6, 0.6)	(-2.6, 8.4)	
	Pr >  t			0.2937	
	n	15	13		
Week 32	LS Mean	-2.210	-2.688	0.478	
	SEM	1.933	2.088	2.840	
	95% CI	(-6.0, 1.6)	(-6.8, 1.4)	(-5.1, 6.1)	
Week 32	Pr >  t			0.8665	
	n	14	10		
	LS Mean	-2.403	-3.554	1.150	
Week 40	SEM	2.005	2.343	3.078	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	95% CI	(-6.4, 1.5)	(-8.2, 1.1)	(-4.9, 7.2)	
	Pr >  t			0.7089	
	n	14	11		
	LS Mean	-0.023	-3.460	3.438	
	SEM	2.005	2.244	3.001	
Week 56	95% CI	(-4.0, 3.9)	(-7.9, 1.0)	(-2.5, 9.4)	
	Pr >  t			0.2532	
	n	11	11		
	LS Mean	-2.175	-3.460	1.285	
	SEM	2.238	2.244	3.165	
Week 64	95% CI	(-6.6, 2.2)	(-7.9, 1.0)	(-5.0, 7.5)	
	Pr >  t			0.6851	
	n	8	11		
	LS Mean	0.581	-1.945	2.526	
	SEM	2.593	2.244	3.428	
Week 72	95% CI	(-4.5, 5.7)	(-6.4, 2.5)	(-4.2, 9.3)	
	Pr >  t			0.4619	
	n	11	10		
	LS Mean	-2.175	-3.443	1.268	
	SEM	2.238	2.348	3.238	
Week 84	95% CI	(-6.6, 2.2)	(-8.1, 1.2)	(-5.1, 7.6)	
	Pr >  t			0.6957	
	n	9	9		
	LS Mean	-1.683	2.030	-3.713	
	SEM	2.455	2.466	3.478	
Week 96	95% CI	(-6.5, 3.2)	(-2.8, 6.9)	(-10.6, 3.1)	
	Pr >  t			0.2867	
	n	8	7		
	LS Mean	-1.665	-3.817	2.152	
	SEM	2.597	2.771	3.797	
Week 108	95% CI	(-6.8, 3.4)	(-9.3, 1.6)	(-5.3, 9.6)	
	Pr >  t			0.5714	
	n	7	6		
	LS Mean	-3.855	-3.920	0.066	
	SEM	2.764	2.985	4.067	
Week 120	95% CI	(-9.3, 1.6)	(-9.8, 2.0)	(-7.9, 8.1)	
	Pr >  t			0.9871	
	n	6	5		
	LS Mean	-4.192	-4.250	0.058	
	SEM	2.976	3.262	4.408	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132		95% CI	(-10.0, 1.7)	(-10.7, 2.2)	(-8.6, 8.7)
		Pr >  t			0.9894
		n	5	3	
		LS Mean	-4.604	-2.571	-2.033
		SEM	3.243	4.152	5.263
Week 144		95% CI	(-11.0, 1.8)	(-10.7, 5.6)	(-12.4, 8.3)
		Pr >  t			0.6996
		n	5	4	
		LS Mean	-1.270	-3.134	1.864
		SEM	3.243	3.617	4.851
Week 156		95% CI	(-7.7, 5.1)	(-10.3, 4.0)	(-7.7, 11.4)
		Pr >  t			0.7011
		n	4	2	
		LS Mean	-4.768	-2.548	-2.221
		SEM	3.605	5.053	6.207
Week 168		95% CI	(-11.9, 2.3)	(-12.5, 7.4)	(-14.4, 10.0)
		Pr >  t			0.7208
		n	1	1	
		LS Mean	-2.330	-2.426	0.096
		SEM	7.095	7.103	10.04
		95% CI	(-16.3, 11.6)	(-16.4, 11.6)	(-19.7, 19.9)
		Pr >  t			0.9924

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and Vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	3.743	-1.823	5.567
		SEM	6.151	6.358	2.692
		95% CI	(-8.5,16.0)	(-14.5,10.8)	( 0.3,10.9)
		Pr >  t			0.0402
	Week 16	n	51	41	
		LS Mean	3.095	-2.563	5.658
		SEM	6.166	6.436	2.916
		95% CI	(-9.2,15.4)	(-15.4,10.2)	(-0.1,11.4)
		Pr >  t			0.0537
	Week 24	n	38	33	
		LS Mean	-0.354	-1.068	0.714
		SEM	6.206	6.491	3.177
		95% CI	(-12.7,12.0)	(-14.0,11.8)	(-5.5, 7.0)
		Pr >  t			0.8223
	Week 32	n	34	28	
		LS Mean	1.752	-2.949	4.701
		SEM	6.305	6.537	3.331
		95% CI	(-10.8,14.3)	(-15.9,10.0)	(-1.9,11.3)
		Pr >  t			0.1592
	Week 40	n	26	23	
		LS Mean	2.649	-1.380	4.030
		SEM	6.389	6.603	3.605
		95% CI	(-10.0,15.3)	(-14.5,11.7)	(-3.1,11.1)
		Pr >  t			0.2644
	Week 48	n	24	17	
		LS Mean	2.215	-3.419	5.635
		SEM	6.416	6.727	3.874
95% CI		(-10.5,15.0)	(-16.8, 9.9)	(-2.0,13.2)	
	Pr >  t			0.1465	
Week 56	n	21	17		
	LS Mean	-0.405	-0.011	-0.394	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	6.466	6.727	3.958
		95% CI	(-13.2,12.4)	(-13.4,13.3)	(-8.2, 7.4)
		Pr >  t			0.9207
	Week 64	n	15	15	
		LS Mean	1.499	-2.852	4.351
		SEM	6.618	6.789	4.300
		95% CI	(-11.6,14.6)	(-16.3,10.6)	(-4.1,12.8)
		Pr >  t			0.3120
	Week 72	n	16	15	
		LS Mean	-0.301	-2.413	2.112
		SEM	6.585	6.789	4.251
		95% CI	(-13.4,12.8)	(-15.9,11.1)	(-6.2,10.5)
		Pr >  t			0.6195
	Week 84	n	14	13	
		LS Mean	-2.965	-4.213	1.248
		SEM	6.653	6.865	4.477
		95% CI	(-16.1,10.2)	(-17.8, 9.4)	(-7.5,10.0)
		Pr >  t			0.7805
	Week 96	n	12	9	
		LS Mean	7.703	-3.072	10.775
		SEM	6.746	7.116	4.980
		95% CI	(-5.7,21.1)	(-17.2,11.0)	( 1.0,20.6)
		Pr >  t			0.0309
	Week 108	n	13	8	
		LS Mean	5.517	-2.224	7.740
		SEM	6.698	7.214	5.058
		95% CI	(-7.8,18.8)	(-16.5,12.0)	(-2.2,17.7)
		Pr >  t			0.1265
	Week 120	n	11	6	
		LS Mean	-0.669	0.663	-1.332
		SEM	6.802	7.502	5.590
		95% CI	(-14.1,12.8)	(-14.2,15.5)	(-12.3, 9.6)
		Pr >  t			0.8117
	Week 132	n	8	3	
		LS Mean	-1.847	-1.878	0.032
		SEM	7.053	8.550	7.179
		95% CI	(-15.8,12.1)	(-18.7,15.0)	(-14.1,14.1)
		Pr >  t			0.9965
	Week 144	n	5	1	
		LS Mean	-0.946	-9.550	8.605

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	7.569	11.85	11.25
		95% CI	(-15.9,14.0)	(-32.8,13.7)	(-13.5,30.7)
		Pr >  t			0.4446
	Week 168	n	3	1	
		LS Mean	-1.735	-9.550	7.815
		SEM	8.413	11.85	11.83
	Week 180	95% CI	(-18.3,14.8)	(-32.8,13.7)	(-15.4,31.1)
		Pr >  t			0.5093
		n	2	1	
	Week 192	LS Mean	-10.56	-9.550	-1.005
		SEM	9.351	11.85	12.52
		95% CI	(-28.9, 7.8)	(-32.8,13.7)	(-25.6,23.6)
	Week 8	Pr >  t			0.9360
		n		1	
		LS Mean		-9.550	
	Week 16	SEM		11.85	
		95% CI		(-32.8,13.7)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-9.550	
		SEM		11.85	
	Week 32	95% CI		(-32.8,13.7)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	-0.676	3.680	-4.356	
	SEM	1.819	1.890	2.608	
	95% CI	(-4.3, 2.9)	(-0.0, 7.4)	(-9.5, 0.8)	
Week 16	Pr >  t			0.0965	
	n	18	14		
	LS Mean	0.177	-2.217	2.394	
Week 24	SEM	1.764	2.008	2.663	
	95% CI	(-3.3, 3.7)	(-6.2, 1.7)	(-2.9, 7.6)	
	Pr >  t			0.3698	
Week 32	n	16	13		
	LS Mean	-0.559	-3.494	2.935	
	SEM	1.877	2.080	2.788	
Week 8	95% CI	(-4.3, 3.1)	(-7.6, 0.6)	(-2.6, 8.4)	
	Pr >  t			0.2937	
	n	15	13		
Week 16	LS Mean	-2.210	-2.688	0.478	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	1.933	2.088	2.840
	95% CI	(-6.0, 1.6)	(-6.8, 1.4)	(-5.1, 6.1)
	Pr >  t			0.8665
Week 40	n	14	10	
	LS Mean	-2.403	-3.554	1.150
	SEM	2.005	2.343	3.078
	95% CI	(-6.4, 1.5)	(-8.2, 1.1)	(-4.9, 7.2)
	Pr >  t			0.7089
Week 48	n	14	11	
	LS Mean	-0.023	-3.460	3.438
	SEM	2.005	2.244	3.001
	95% CI	(-4.0, 3.9)	(-7.9, 1.0)	(-2.5, 9.4)
	Pr >  t			0.2532
Week 56	n	11	11	
	LS Mean	-2.175	-3.460	1.285
	SEM	2.238	2.244	3.165
	95% CI	(-6.6, 2.2)	(-7.9, 1.0)	(-5.0, 7.5)
	Pr >  t			0.6851
Week 64	n	8	11	
	LS Mean	0.581	-1.945	2.526
	SEM	2.593	2.244	3.428
	95% CI	(-4.5, 5.7)	(-6.4, 2.5)	(-4.2, 9.3)
	Pr >  t			0.4619
Week 72	n	11	10	
	LS Mean	-2.175	-3.443	1.268
	SEM	2.238	2.348	3.238
	95% CI	(-6.6, 2.2)	(-8.1, 1.2)	(-5.1, 7.6)
	Pr >  t			0.6957
Week 84	n	9	9	
	LS Mean	-1.683	2.030	-3.713
	SEM	2.455	2.466	3.478
	95% CI	(-6.5, 3.2)	(-2.8, 6.9)	(-10.6, 3.1)
	Pr >  t			0.2867
Week 96	n	8	7	
	LS Mean	-1.665	-3.817	2.152
	SEM	2.597	2.771	3.797
	95% CI	(-6.8, 3.4)	(-9.3, 1.6)	(-5.3, 9.6)
	Pr >  t			0.5714
Week 108	n	7	6	
	LS Mean	-3.855	-3.920	0.066

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	2.764	2.985	4.067
		95% CI	(-9.3, 1.6)	(-9.8, 2.0)	(-7.9, 8.1)
		Pr >  t			0.9871
	Week 120	n	6	5	
		LS Mean	-4.192	-4.250	0.058
		SEM	2.976	3.262	4.408
		95% CI	(-10.0, 1.7)	(-10.7, 2.2)	(-8.6, 8.7)
		Pr >  t			0.9894
	Week 132	n	5	3	
		LS Mean	-4.604	-2.571	-2.033
		SEM	3.243	4.152	5.263
		95% CI	(-11.0, 1.8)	(-10.7, 5.6)	(-12.4, 8.3)
		Pr >  t			0.6996
	Week 144	n	5	4	
		LS Mean	-1.270	-3.134	1.864
		SEM	3.243	3.617	4.851
		95% CI	(-7.7, 5.1)	(-10.3, 4.0)	(-7.7, 11.4)
		Pr >  t			0.7011
	Week 156	n	4	2	
		LS Mean	-4.768	-2.548	-2.221
		SEM	3.605	5.053	6.207
		95% CI	(-11.9, 2.3)	(-12.5, 7.4)	(-14.4, 10.0)
		Pr >  t			0.7208
	Week 168	n	1	1	
		LS Mean	-2.330	-2.426	0.096
		SEM	7.095	7.103	10.04
		95% CI	(-16.3, 11.6)	(-16.4, 11.6)	(-19.7, 19.9)
		Pr >  t			0.9924
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	7.129	9.675	-2.546
		SEM	5.080	4.665	5.618
		95% CI	(-3.1, 17.4)	(0.3, 19.1)	(-13.8, 8.7)
		Pr >  t			0.6523
	Week 16	n	15	17	
		LS Mean	7.561	6.901	0.660
		SEM	5.304	4.836	5.848
		95% CI	(-3.1, 18.2)	(-2.8, 16.6)	(-11.1, 12.4)
		Pr >  t			0.9105
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	6.448	10.258	-3.809
	SEM	5.369	5.215	6.258
	95% CI	(-4.3,17.2)	(-0.2,20.7)	(-16.3, 8.7)
	Pr >  t			0.5446
	n	12	9	
Week 40	LS Mean	2.199	10.231	-8.033
	SEM	5.547	5.481	6.579
	95% CI	(-8.9,13.3)	(-0.7,21.1)	(-21.1, 5.1)
	Pr >  t			0.2256
	n	11	7	
Week 48	LS Mean	2.907	8.341	-5.433
	SEM	5.651	5.887	6.952
	95% CI	(-8.4,14.2)	(-3.3,20.0)	(-19.2, 8.4)
	Pr >  t			0.4364
	n	8	6	
Week 56	LS Mean	4.851	8.267	-3.416
	SEM	5.980	6.126	7.425
	95% CI	(-7.1,16.8)	(-3.9,20.4)	(-18.1,11.3)
	Pr >  t			0.6464
	n	7	5	
Week 64	LS Mean	2.924	14.956	-12.03
	SEM	6.143	6.411	7.801
	95% CI	(-9.3,15.1)	( 2.3,27.7)	(-27.5, 3.4)
	Pr >  t			0.1255
	n	5	3	
Week 72	LS Mean	10.030	3.603	6.427
	SEM	6.633	7.482	9.053
	95% CI	(-3.1,23.2)	(-11.2,18.4)	(-11.5,24.3)
	Pr >  t			0.4788
	n	5	2	
Week 84	LS Mean	2.687	0.985	1.702
	SEM	6.664	8.629	10.04
	95% CI	(-10.5,15.9)	(-16.1,18.0)	(-18.1,21.5)
	Pr >  t			0.8656
	n	4	2	
Week 96	LS Mean	8.872	9.320	-0.447
	SEM	7.020	8.629	10.29
	95% CI	(-5.0,22.8)	(-7.7,26.4)	(-20.8,19.9)
	Pr >  t			0.9654
	n	4	2	



<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
	LS Mean	3.804	0.985	2.819
	SEM	7.030	8.629	10.30
	95% CI	(-10.1,17.7)	(-16.1,18.0)	(-17.5,23.1)
	Pr >  t			0.7846
Week 108	n	1	2	
	LS Mean	2.235	0.605	1.630
	SEM	11.34	8.588	13.58
	95% CI	(-20.1,24.6)	(-16.3,17.6)	(-25.2,28.4)
	Pr >  t			0.9046
Week 120	n	5	1	
	LS Mean	-0.647	-5.150	4.503
	SEM	6.664	11.27	12.39
	95% CI	(-13.9,12.6)	(-27.4,17.1)	(-20.0,29.0)
	Pr >  t			0.7167
Week 132	n	3	1	
	LS Mean	2.081	-5.150	7.231
	SEM	7.640	11.27	12.94
	95% CI	(-13.0,17.2)	(-27.4,17.1)	(-18.3,32.8)
	Pr >  t			0.5772
Week 144	n	3		
	LS Mean	2.081		
	SEM	7.640		
	95% CI	(-13.0,17.2)		
	Pr >  t			
Week 156	n	3		
	LS Mean	2.081		
	SEM	7.640		
	95% CI	(-13.0,17.2)		
	Pr >  t			
Week 168	n	1		
	LS Mean	18.445		
	SEM	11.33		
	95% CI	(-3.9,40.8)		
	Pr >  t			
Week 180	n	1		
	LS Mean	1.775		
	SEM	11.33		
	95% CI	(-20.6,24.1)		
	Pr >  t			
Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	1.775		
		SEM	11.33		
		95% CI	(-20.6,24.1)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	10.963	2.405	8.558
		SEM	2.047	2.043	2.438
		95% CI	( 6.9,15.0)	( -1.6, 6.4)	( 3.8,13.4)
		Pr >  t			0.0005
	Week 16	n	30	29	
		LS Mean	7.383	2.779	4.605
		SEM	2.180	2.329	2.780
		95% CI	( 3.1,11.7)	( -1.8, 7.4)	( -0.9,10.1)
		Pr >  t			0.0986
	Week 24	n	26	20	
		LS Mean	8.678	2.592	6.086
		SEM	2.321	2.710	3.161
		95% CI	( 4.1,13.2)	( -2.7, 7.9)	( -0.1,12.3)
		Pr >  t			0.0550
	Week 32	n	18	20	
		LS Mean	8.328	3.425	4.903
		SEM	2.695	2.710	3.436
		95% CI	( 3.0,13.6)	( -1.9, 8.8)	( -1.9,11.7)
		Pr >  t			0.1545
	Week 40	n	18	19	
		LS Mean	2.535	5.214	-2.679
		SEM	2.694	2.763	3.476
		95% CI	( -2.8, 7.8)	( -0.2,10.7)	( -9.5, 4.2)
		Pr >  t			0.4414
	Week 48	n	16	14	
		LS Mean	2.000	9.028	-7.028
		SEM	2.820	3.104	3.848
		95% CI	( -3.5, 7.5)	( 2.9,15.1)	( -14.6, 0.5)
		Pr >  t			0.0686
	Week 56	n	14	10	
		LS Mean	4.979	4.990	-0.012
		SEM	2.975	3.557	4.344
		95% CI	( -0.9,10.8)	( -2.0,12.0)	( -8.6, 8.5)
		Pr >  t			0.9979

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	7.574	3.306	4.268
		SEM	3.068	3.420	4.303
		95% CI	( 1.5,13.6)	( -3.4,10.0)	( -4.2,12.7)
		Pr >  t			0.3219
Week 72		n	10	6	
		LS Mean	11.240	1.229	10.012
		SEM	3.423	4.435	5.374
		95% CI	( 4.5,18.0)	( -7.5, 9.9)	( -0.6,20.6)
		Pr >  t			0.0633
Week 84		n	8	7	
		LS Mean	10.786	1.466	9.320
		SEM	3.847	4.144	5.386
		95% CI	( 3.2,18.4)	( -6.7, 9.6)	( -1.3,19.9)
		Pr >  t			0.0844
Week 96		n	6	5	
		LS Mean	1.208	7.970	-6.762
		SEM	4.341	4.809	6.284
		95% CI	( -7.3, 9.7)	( -1.5,17.4)	(-19.1, 5.6)
		Pr >  t			0.2826
Week 108		n	2	4	
		LS Mean	2.683	0.698	1.985
		SEM	7.331	5.324	8.892
		95% CI	(-11.7,17.1)	( -9.8,11.2)	(-15.5,19.5)
		Pr >  t			0.8235
Week 120		n	4	4	
		LS Mean	1.615	4.866	-3.251
		SEM	5.226	5.324	7.299
		95% CI	( -8.7,11.9)	( -5.6,15.3)	(-17.6,11.1)
		Pr >  t			0.6563
Week 132		n	3	1	
		LS Mean	1.563	0.859	0.704
		SEM	6.040	10.30	11.81
		95% CI	(-10.3,13.4)	(-19.4,21.1)	(-22.5,23.9)
		Pr >  t			0.9525
Week 144		n	2		
		LS Mean	10.221		
		SEM	7.265		
		95% CI	( -4.1,24.5)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and Vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	9.411	7.360	2.051
			SEM	1.743	1.805	1.701
			95% CI	( 6.0,12.8)	( 3.8,10.9)	( -1.3, 5.4)
			Pr >  t			0.2288
		Week 16	n	90	75	
			LS Mean	8.346	5.126	3.220
			SEM	1.793	1.905	1.843
			95% CI	( 4.8,11.9)	( 1.4, 8.9)	( -0.4, 6.8)
			Pr >  t			0.0812
		Week 24	n	79	62	
			LS Mean	7.039	5.372	1.667
			SEM	1.842	1.993	1.963
			95% CI	( 3.4,10.7)	( 1.5, 9.3)	( -2.2, 5.5)
			Pr >  t			0.3962
		Week 32	n	70	56	
			LS Mean	8.373	5.276	3.097
			SEM	1.904	2.045	2.046
			95% CI	( 4.6,12.1)	( 1.3, 9.3)	( -0.9, 7.1)
			Pr >  t			0.1307
		Week 40	n	61	46	
			LS Mean	7.092	6.130	0.962
			SEM	1.954	2.138	2.179
			95% CI	( 3.2,10.9)	( 1.9,10.3)	( -3.3, 5.2)
			Pr >  t			0.6589
		Week 48	n	56	38	
			LS Mean	7.155	4.665	2.489
			SEM	1.987	2.234	2.303
95% CI	( 3.2,11.1)		( 0.3, 9.1)	( -2.0, 7.0)		
Pr >  t				0.2800		
Week 56	n	49	33			
	LS Mean	6.522	7.409	-0.887		
	SEM	2.042	2.313	2.429		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 2.5,10.5)	( 2.9,12.0)	( -5.7, 3.9)
		Pr >  t			0.7149
	Week 64	n	37	29	
		LS Mean	9.789	5.655	4.134
		SEM	2.175	2.394	2.617
		95% CI	( 5.5,14.1)	( 1.0,10.4)	( -1.0, 9.3)
		Pr >  t			0.1145
	Week 72	n	40	25	
		LS Mean	6.052	5.327	0.725
		SEM	2.137	2.492	2.676
		95% CI	( 1.9,10.3)	( 0.4,10.2)	( -4.5, 6.0)
		Pr >  t			0.7866
	Week 84	n	32	23	
		LS Mean	6.410	6.530	-0.120
		SEM	2.267	2.553	2.828
		95% CI	( 2.0,10.9)	( 1.5,11.5)	( -5.7, 5.4)
		Pr >  t			0.9661
	Week 96	n	29	17	
		LS Mean	6.540	5.386	1.154
		SEM	2.323	2.801	3.100
		95% CI	( 2.0,11.1)	( -0.1,10.9)	( -4.9, 7.2)
		Pr >  t			0.7098
	Week 108	n	22	15	
		LS Mean	7.771	4.730	3.041
		SEM	2.523	2.920	3.350
		95% CI	( 2.8,12.7)	( -1.0,10.5)	( -3.5, 9.6)
		Pr >  t			0.3641
	Week 120	n	23	13	
		LS Mean	4.936	6.035	-1.099
		SEM	2.485	3.069	3.457
		95% CI	( 0.1, 9.8)	( 0.0,12.1)	( -7.9, 5.7)
		Pr >  t			0.7506
	Week 132	n	17	5	
		LS Mean	4.577	5.329	-0.751
		SEM	2.737	4.452	4.862
		95% CI	( -0.8, 9.9)	( -3.4,14.1)	( -10.3, 8.8)
		Pr >  t			0.8772
	Week 144	n	14	3	
		LS Mean	6.799	2.262	4.537
		SEM	2.918	5.580	6.002

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.1,12.5)	( -8.7,13.2)	( -7.2,16.3)
		Pr >  t			0.4499
	Week 156	n	9	2	
		LS Mean	4.031	1.998	2.033
		SEM	3.451	6.716	7.304
		95% CI	( -2.7,10.8)	(-11.2,15.2)	(-12.3,16.4)
		Pr >  t			0.7808
	Week 168	n	4	1	
		LS Mean	4.576	-1.101	5.677
		SEM	4.856	9.337	10.35
		95% CI	( -5.0,14.1)	(-19.4,17.2)	(-14.6,26.0)
		Pr >  t			0.5834
	Week 180	n	1	1	
		LS Mean	3.350	-1.101	4.452
		SEM	9.306	9.337	13.04
		95% CI	(-14.9,21.6)	(-19.4,17.2)	(-21.1,30.0)
		Pr >  t			0.7329
	Week 192	n	1	1	
		LS Mean	3.350	-1.101	4.452
		SEM	9.306	9.337	13.04
		95% CI	(-14.9,21.6)	(-19.4,17.2)	(-21.1,30.0)
		Pr >  t			0.7329
>= 3	Week 8	n	37	45	
		LS Mean	4.185	-1.727	5.913
		SEM	5.355	5.311	3.094
		95% CI	( -6.4,14.8)	(-12.2, 8.8)	( -0.2,12.0)
		Pr >  t			0.0577
	Week 16	n	34	32	
		LS Mean	3.840	-2.183	6.023
		SEM	5.547	5.605	3.408
		95% CI	( -7.1,14.8)	(-13.2, 8.9)	( -0.7,12.7)
		Pr >  t			0.0787
	Week 24	n	26	19	
		LS Mean	2.968	-0.748	3.717
		SEM	5.682	5.902	4.076
		95% CI	( -8.2,14.2)	(-12.4,10.9)	( -4.3,11.7)
		Pr >  t			0.3627
	Week 32	n	16	17	
		LS Mean	3.762	-2.394	6.156
		SEM	6.003	5.993	4.630

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-8.1,15.6)	(-14.2, 9.4)	(-3.0,15.3)
		Pr >  t			0.1846
		n	14	16	
		LS Mean	0.638	-1.362	2.000
		SEM	6.121	6.037	4.832
Week 48		95% CI	(-11.4,12.7)	(-13.3,10.5)	(-7.5,11.5)
		Pr >  t			0.6792
		n	13	13	
		LS Mean	0.091	4.009	-3.918
		SEM	6.183	6.212	5.121
Week 56		95% CI	(-12.1,12.3)	(-8.2,16.2)	(-14.0, 6.2)
		Pr >  t			0.4447
		n	10	12	
		LS Mean	-2.284	-1.039	-1.246
		SEM	6.455	6.293	5.523
Week 64		95% CI	(-15.0,10.4)	(-13.4,11.4)	(-12.1, 9.6)
		Pr >  t			0.8217
		n	10	13	
		LS Mean	-1.280	-2.407	1.127
		SEM	6.458	6.220	5.443
Week 72		95% CI	(-14.0,11.4)	(-14.7, 9.8)	(-9.6,11.8)
		Pr >  t			0.8362
		n	8	10	
		LS Mean	4.239	-3.960	8.199
		SEM	6.722	6.476	6.035
Week 84		95% CI	(-9.0,17.5)	(-16.7, 8.8)	(-3.7,20.1)
		Pr >  t			0.1751
		n	8	10	
		LS Mean	3.200	-2.346	5.546
		SEM	6.724	6.471	6.038
Week 96		95% CI	(-10.0,16.4)	(-15.1,10.4)	(-6.3,17.4)
		Pr >  t			0.3589
		n	6	7	
		LS Mean	7.017	-2.343	9.361
		SEM	7.151	6.925	6.952
Week 108		95% CI	(-7.1,21.1)	(-16.0,11.3)	(-4.3,23.0)
		Pr >  t			0.1790
		n	4	6	
		LS Mean	2.859	-5.360	8.219
		SEM	7.914	7.152	7.944



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.7,18.4)	(-19.4, 8.7)	( -7.4,23.8)
		Pr >  t			0.3016
	Week 120	n	5	3	
		LS Mean	-6.464	-2.922	-3.542
		SEM	7.464	8.611	8.898
		95% CI	(-21.1, 8.2)	(-19.9,14.0)	(-21.0,14.0)
		Pr >  t			0.6909
	Week 132	n	3	3	
		LS Mean	-5.357	-5.559	0.201
		SEM	8.603	8.612	9.878
		95% CI	(-22.3,11.6)	(-22.5,11.4)	(-19.2,19.6)
		Pr >  t			0.9837
	Week 144	n	1	2	
		LS Mean	-2.435	-2.472	0.037
		SEM	12.87	9.850	14.56
		95% CI	(-27.7,22.9)	(-21.8,16.9)	(-28.6,28.7)
		Pr >  t			0.9980
	Week 156	n	1	1	
		LS Mean	-2.435	-2.265	-0.169
		SEM	12.87	12.88	16.74
		95% CI	(-27.7,22.9)	(-27.6,23.1)	(-33.1,32.8)
		Pr >  t			0.9919
	Week 168	n		1	
		LS Mean		-2.265	
		SEM		12.88	
		95% CI		(-27.6,23.1)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-25: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schmerzen“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	-1.144	3.180	-4.325		
			SEM	3.165	3.157	2.758		
			95% CI	(-7.4, 5.1)	(-3.0, 9.4)	(-9.7, 1.1)		
					Pr >  t			0.1176
				Week 16	n	92	83	
					LS Mean	-1.274	2.964	-4.238
					SEM	3.246	3.331	2.968
					95% CI	(-7.7, 5.1)	(-3.6, 9.5)	(-10.1, 1.6)
					Pr >  t			0.1540
				Week 24	n	77	59	
					LS Mean	1.421	4.859	-3.437
					SEM	3.315	3.522	3.251
					95% CI	(-5.1, 7.9)	(-2.1, 11.8)	(-9.8, 2.9)
					Pr >  t			0.2908
				Week 32	n	57	53	
					LS Mean	0.265	2.643	-2.379
					SEM	3.498	3.585	3.474
					95% CI	(-6.6, 7.1)	(-4.4, 9.7)	(-9.2, 4.4)
					Pr >  t			0.4938
		Week 40	n	50	44			
			LS Mean	-1.246	3.795	-5.041		
			SEM	3.576	3.714	3.674		
			95% CI	(-8.3, 5.8)	(-3.5, 11.1)	(-12.3, 2.2)		
			Pr >  t			0.1704		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	n		47	37	
	LS Mean		1.308	7.219	-5.911
	SEM		3.612	3.839	3.834
	95% CI		(-5.8, 8.4)	(-0.3,14.8)	(-13.4, 1.6)
	Pr >  t				0.1235
Week 56	n		40	32	
	LS Mean		1.775	6.244	-4.469
	SEM		3.718	3.955	4.047
	95% CI		(-5.5, 9.1)	(-1.5,14.0)	(-12.4, 3.5)
	Pr >  t				0.2698
Week 64	n		32	27	
	LS Mean		1.632	5.570	-3.938
	SEM		3.886	4.105	4.345
	95% CI		(-6.0, 9.3)	(-2.5,13.6)	(-12.5, 4.6)
	Pr >  t				0.3650
Week 72	n		31	23	
	LS Mean		-0.780	4.772	-5.552
	SEM		3.915	4.264	4.520
	95% CI		(-8.5, 6.9)	(-3.6,13.1)	(-14.4, 3.3)
	Pr >  t				0.2196
Week 84	n		27	21	
	LS Mean		5.089	7.440	-2.351
	SEM		4.039	4.361	4.713
	95% CI		(-2.8,13.0)	(-1.1,16.0)	(-11.6, 6.9)
	Pr >  t				0.6181
Week 96	n		23	16	
	LS Mean		2.100	9.700	-7.601
	SEM		4.189	4.693	5.151
	95% CI		(-6.1,10.3)	( 0.5,18.9)	(-17.7, 2.5)
	Pr >  t				0.1404
Week 108	n		15	14	
	LS Mean		4.263	10.458	-6.195
	SEM		4.716	4.881	5.740
	95% CI		(-5.0,13.5)	( 0.9,20.0)	(-17.5, 5.1)
	Pr >  t				0.2807
Week 120	n		18	8	
	LS Mean		2.343	10.335	-7.992
	SEM		4.474	5.877	6.444
	95% CI		(-6.4,11.1)	(-1.2,21.9)	(-20.6, 4.7)
	Pr >  t				0.2152

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	n		12	4	
	LS Mean		-1.254	2.728	-3.982
	SEM		5.055	7.688	8.460
	95% CI		(-11.2, 8.7)	(-12.4,17.8)	(-20.6,12.6)
	Pr >  t				0.6379
Week 144	n		8	3	
	LS Mean		11.445	3.599	7.846
	SEM		5.794	8.703	9.821
	95% CI		( 0.1,22.8)	(-13.5,20.7)	(-11.4,27.1)
	Pr >  t				0.4246
Week 156	n		5	1	
	LS Mean		6.547	4.455	2.092
	SEM		6.968	14.38	15.57
	95% CI		( -7.1,20.2)	(-23.8,32.7)	(-28.5,32.6)
	Pr >  t				0.8931
Week 168	n		2	1	
	LS Mean		3.431	4.455	-1.024
	SEM		10.39	14.38	17.37
	95% CI		(-16.9,23.8)	(-23.8,32.7)	(-35.1,33.1)
	Pr >  t				0.9530
Week 180	n		1		
	LS Mean		-9.724		
	SEM		14.34		
	95% CI		(-37.9,18.4)		
	Pr >  t				
Week 192	n		1		
	LS Mean		23.606		
	SEM		14.34		
	95% CI		( -4.5,51.7)		
	Pr >  t				
Yes Week 8	n		38	30	
	LS Mean		-3.612	1.071	-4.683
	SEM		6.160	6.591	5.410
	95% CI		(-15.9, 8.6)	(-12.0,14.2)	(-15.4, 6.0)
	Pr >  t				0.3881
Week 16	n		32	24	
	LS Mean		-1.748	10.839	-12.59
	SEM		6.261	6.758	5.801
	95% CI		(-14.2,10.7)	( -2.6,24.2)	(-24.0,-1.1)
	Pr >  t				0.0314

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	n		28	22	
	LS Mean		-0.528	6.901	-7.429
	SEM		6.421	6.831	6.002
	95% CI		(-13.3,12.2)	(-6.6,20.5)	(-19.3, 4.4)
	Pr >  t				0.2173
Week 32	n		29	20	
	LS Mean		3.293	8.580	-5.287
	SEM		6.399	6.992	6.081
	95% CI		(-9.4,16.0)	(-5.3,22.4)	(-17.3, 6.7)
	Pr >  t				0.3857
Week 40	n		25	18	
	LS Mean		5.290	4.919	0.372
	SEM		6.503	7.085	6.305
	95% CI		(-7.6,18.2)	(-9.1,19.0)	(-12.1,12.8)
	Pr >  t				0.9530
Week 48	n		22	14	
	LS Mean		2.119	1.552	0.567
	SEM		6.602	7.346	6.700
	95% CI		(-11.0,15.2)	(-13.0,16.1)	(-12.6,13.8)
	Pr >  t				0.9326
Week 56	n		19	13	
	LS Mean		0.215	4.580	-4.365
	SEM		6.720	7.439	6.927
	95% CI		(-13.1,13.5)	(-10.1,19.3)	(-18.0, 9.3)
	Pr >  t				0.5292
Week 64	n		15	15	
	LS Mean		4.529	4.495	0.034
	SEM		6.944	7.277	6.986
	95% CI		(-9.2,18.3)	(-9.9,18.9)	(-13.7,13.8)
	Pr >  t				0.9961
Week 72	n		17	12	
	LS Mean		1.984	7.658	-5.674
	SEM		6.823	7.536	7.136
	95% CI		(-11.5,15.5)	(-7.2,22.6)	(-19.7, 8.4)
	Pr >  t				0.4272
Week 84	n		13	12	
	LS Mean		6.081	8.373	-2.292
	SEM		7.156	7.538	7.422
	95% CI		(-8.1,20.2)	(-6.5,23.3)	(-16.9,12.3)
	Pr >  t				0.7576

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	n		12	8	
	LS Mean		5.200	6.578	-1.378
	SEM		7.255	8.147	8.128
	95% CI		(-9.1,19.5)	(-9.5,22.6)	(-17.4,14.6)
	Pr >  t				0.8654
Week 108	n		11	7	
	LS Mean		4.952	4.504	0.448
	SEM		7.377	8.393	8.480
	95% CI		(-9.6,19.5)	(-12.0,21.1)	(-16.2,17.1)
	Pr >  t				0.9579
Week 120	n		10	8	
	LS Mean		1.532	-2.245	3.777
	SEM		7.514	8.148	8.362
	95% CI		(-13.3,16.4)	(-18.3,13.8)	(-12.7,20.2)
	Pr >  t				0.6518
Week 132	n		8	4	
	LS Mean		7.812	1.357	6.455
	SEM		7.873	9.725	10.18
	95% CI		(-7.7,23.3)	(-17.8,20.5)	(-13.5,26.5)
	Pr >  t				0.5263
Week 144	n		7	2	
	LS Mean		11.577	-0.670	12.246
	SEM		8.128	12.28	12.80
	95% CI		(-4.4,27.6)	(-24.8,23.5)	(-12.9,37.4)
	Pr >  t				0.3390
Week 156	n		5	2	
	LS Mean		-1.918	15.995	-17.91
	SEM		8.881	12.28	13.29
	95% CI		(-19.4,15.6)	(-8.1,40.1)	(-44.0, 8.2)
	Pr >  t				0.1782
Week 168	n		2	1	
	LS Mean		3.669	10.940	-7.271
	SEM		12.06	16.20	18.83
	95% CI		(-20.0,27.4)	(-20.9,42.8)	(-44.3,29.7)
	Pr >  t				0.6996
Week 180	n			1	
	LS Mean			10.940	
	SEM			16.20	
	95% CI			(-20.9,42.8)	
	Pr >  t				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 192	n	1	
		LS Mean	10.940	
		SEM	16.20	
		95% CI	(-20.9,42.8)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-2.796	2.360	-5.156		
			SEM	3.232	3.370	3.232		
			95% CI	(-9.2, 3.6)	(-4.3, 9.0)	(-11.5, 1.2)		
					Pr >  t			0.1116
		Week 16	n	70	52			
			LS Mean	-4.169	2.297	-6.467		
			SEM	3.309	3.641	3.509		
			95% CI	(-10.7, 2.3)	(-4.9, 9.5)	(-13.4, 0.4)		
					Pr >  t			0.0661
		Week 24	n	61	37			
			LS Mean	-0.246	5.793	-6.039		
			SEM	3.395	3.926	3.842		
			95% CI	(-6.9, 6.4)	(-1.9, 13.5)	(-13.6, 1.5)		
					Pr >  t			0.1167
		Week 32	n	48	33			
			LS Mean	-1.470	1.711	-3.181		
			SEM	3.565	4.022	4.067		
			95% CI	(-8.5, 5.5)	(-6.2, 9.6)	(-11.2, 4.8)		
					Pr >  t			0.4345
		Week 40	n	42	31			
			LS Mean	-1.887	4.088	-5.975		
			SEM	3.653	4.078	4.202		
			95% CI	(-9.1, 5.3)	(-3.9, 12.1)	(-14.2, 2.3)		
			Pr >  t			0.1556		
Week 48	n	40	25					
	LS Mean	1.333	5.638	-4.304				
	SEM	3.688	4.272	4.419				
	95% CI	(-5.9, 8.6)	(-2.8, 14.0)	(-13.0, 4.4)				
			Pr >  t			0.3304		
Week 56	n	35	20					
	LS Mean	1.697	-0.159	1.856				
	SEM	3.784	4.512	4.732				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.7, 9.1)	(-9.0, 8.7)	(-7.4, 11.1)
		Pr >  t			0.6950
	Week 64	n	29	18	
		LS Mean	2.347	7.141	-4.794
		SEM	3.934	4.642	4.977
		95% CI	(-5.4, 10.1)	(-2.0, 16.3)	(-14.6, 5.0)
		Pr >  t			0.3357
	Week 72	n	28	18	
		LS Mean	-1.996	3.887	-5.883
		SEM	3.966	4.639	5.001
		95% CI	(-9.8, 5.8)	(-5.2, 13.0)	(-15.7, 3.9)
		Pr >  t			0.2398
	Week 84	n	27	17	
		LS Mean	1.752	6.508	-4.756
		SEM	4.019	4.712	5.094
		95% CI	(-6.1, 9.6)	(-2.7, 15.8)	(-14.8, 5.2)
		Pr >  t			0.3508
	Week 96	n	23	14	
		LS Mean	3.012	10.446	-7.434
		SEM	4.167	4.972	5.456
		95% CI	(-5.2, 11.2)	( 0.7, 20.2)	(-18.1, 3.3)
		Pr >  t			0.1734
	Week 108	n	19	12	
		LS Mean	0.906	6.803	-5.898
		SEM	4.394	5.207	5.831
		95% CI	(-7.7, 9.5)	(-3.4, 17.0)	(-17.3, 5.5)
		Pr >  t			0.3121
	Week 120	n	18	8	
		LS Mean	-0.039	1.005	-1.044
		SEM	4.445	5.954	6.550
		95% CI	(-8.8, 8.7)	(-10.7, 12.7)	(-13.9, 11.8)
		Pr >  t			0.8734
	Week 132	n	11	4	
		LS Mean	-3.924	-2.442	-1.482
		SEM	5.183	7.757	8.639
		95% CI	(-14.1, 6.3)	(-17.7, 12.8)	(-18.4, 15.5)
		Pr >  t			0.8638
	Week 144	n	11	4	
		LS Mean	6.977	0.002	6.975
		SEM	5.169	7.762	8.645

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
>= 65 Years	Week 156	95% CI	(-3.2,17.1)	(-15.2,15.2)	(-10.0,23.9)
		Pr >  t			0.4200
		n	5	2	
	Week 168	LS Mean	-12.11	15.462	-27.57
		SEM	6.956	10.46	12.06
		95% CI	(-25.8, 1.5)	(-5.1,36.0)	(-51.2,-3.9)
	Week 180	Pr >  t			0.0225
		n	1	2	
		LS Mean	-12.61	7.127	-19.74
	Week 192	SEM	14.30	10.46	17.36
		95% CI	(-40.7,15.5)	(-13.4,27.7)	(-53.8,14.3)
		Pr >  t			0.2559
	Week 8	n		1	
		LS Mean		10.114	
		SEM		14.39	
	Week 16	95% CI		(-18.1,38.4)	
		Pr >  t			
		n		1	
	Week 24	LS Mean		10.114	
		SEM		14.39	
		95% CI		(-18.1,38.4)	
	Week 32	Pr >  t			
		n	63	71	
		LS Mean	-0.425	2.741	-3.166
Week 8	SEM	5.490	5.481	3.830	
	95% CI	(-11.3,10.4)	(-8.1,13.6)	(-10.7, 4.4)	
	Pr >  t			0.4091	
Week 16	n	54	55		
	LS Mean	2.427	6.818	-4.391	
	SEM	5.606	5.565	4.092	
Week 24	95% CI	(-8.6,13.5)	(-4.2,17.8)	(-12.4, 3.7)	
	Pr >  t			0.2841	
	n	44	44		
Week 32	LS Mean	2.481	4.701	-2.221	
	SEM	5.703	5.658	4.375	
	95% CI	(-8.8,13.7)	(-6.5,15.9)	(-10.8, 6.4)	
Week 8	Pr >  t			0.6121	
	n	38	40		
	LS Mean	5.205	5.954	-0.749	
Week 16	SEM	5.815	5.740	4.542	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.3,16.7)	(-5.4,17.3)	(-9.7, 8.2)
		Pr >  t			0.8691
	Week 40	n	33	31	
		LS Mean	4.987	3.381	1.607
		SEM	5.901	5.914	4.827
		95% CI	(-6.6,16.6)	(-8.3,15.0)	(-7.9,11.1)
		Pr >  t			0.7394
	Week 48	n	29	26	
		LS Mean	2.065	4.860	-2.795
		SEM	5.978	6.039	5.072
		95% CI	(-9.7,13.8)	(-7.0,16.8)	(-12.8, 7.2)
		Pr >  t			0.5818
	Week 56	n	24	25	
		LS Mean	0.648	9.781	-9.133
		SEM	6.112	6.066	5.261
		95% CI	(-11.4,12.7)	(-2.2,21.7)	(-19.5, 1.2)
		Pr >  t			0.0832
	Week 64	n	18	24	
		LS Mean	2.901	2.955	-0.054
		SEM	6.358	6.098	5.582
		95% CI	(-9.6,15.4)	(-9.1,15.0)	(-11.0,10.9)
		Pr >  t			0.9923
	Week 72	n	20	17	
		LS Mean	3.493	6.626	-3.133
		SEM	6.268	6.402	5.813
		95% CI	(-8.8,15.8)	(-6.0,19.2)	(-14.5, 8.3)
		Pr >  t			0.5901
	Week 84	n	13	16	
		LS Mean	12.055	7.932	4.123
		SEM	6.706	6.461	6.350
		95% CI	(-1.1,25.2)	(-4.8,20.6)	(-8.3,16.6)
		Pr >  t			0.5164
	Week 96	n	12	10	
		LS Mean	3.156	4.791	-1.634
		SEM	6.813	7.066	7.065
		95% CI	(-10.2,16.6)	(-9.1,18.7)	(-15.5,12.2)
		Pr >  t			0.8171
	Week 108	n	7	9	
		LS Mean	12.318	8.957	3.361
		SEM	7.686	7.231	8.058

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-2.8,27.4)	(-5.3,23.2)	(-12.5,19.2)
		Pr >  t			0.6767
	Week 120	n	10	8	
		LS Mean	5.628	5.650	-0.022
		SEM	7.089	7.436	7.686
		95% CI	(-8.3,19.6)	(-9.0,20.3)	(-15.1,15.1)
		Pr >  t			0.9977
	Week 132	n	9	4	
		LS Mean	10.559	5.491	5.068
		SEM	7.236	9.039	9.357
		95% CI	(-3.7,24.8)	(-12.3,23.2)	(-13.3,23.4)
		Pr >  t			0.5883
	Week 144	n	4	1	
		LS Mean	20.894	4.698	16.196
		SEM	9.037	15.48	16.58
		95% CI	( 3.1,38.6)	(-25.7,35.1)	(-16.4,48.7)
		Pr >  t			0.3289
	Week 156	n	5	1	
		LS Mean	17.625	4.698	12.927
		SEM	8.441	15.48	16.26
		95% CI	( 1.0,34.2)	(-25.7,35.1)	(-19.0,44.9)
		Pr >  t			0.4269
	Week 168	n	3		
		LS Mean	11.857		
		SEM	9.968		
		95% CI	(-7.7,31.4)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-5.429		
		SEM	15.47		
		95% CI	(-35.8,24.9)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	27.901		
		SEM	15.47		
		95% CI	(-2.5,58.3)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	-0.646	-4.292	3.646		
			SEM	5.389	5.058	4.547		
			95% CI	(-11.4,10.1)	(-14.4, 5.8)	( -5.3,12.6)		
					Pr >  t			0.4241
		Week 16	n	28	29			
			LS Mean	-0.280	0.830	-1.110		
			SEM	5.426	5.281	4.756		
			95% CI	(-11.1,10.5)	( -9.7,11.3)	(-10.5, 8.3)		
					Pr >  t			0.8158
		Week 24	n	21	25			
			LS Mean	2.551	-0.310	2.861		
			SEM	5.627	5.372	5.111		
			95% CI	( -8.6,13.7)	(-11.0,10.3)	( -7.2,12.9)		
					Pr >  t			0.5763
		Week 32	n	19	23			
			LS Mean	4.457	1.224	3.233		
			SEM	5.705	5.435	5.276		
			95% CI	( -6.9,15.8)	( -9.6,12.0)	( -7.2,13.6)		
					Pr >  t			0.5408
		Week 40	n	16	18			
			LS Mean	-2.628	4.056	-6.685		
			SEM	5.850	5.688	5.648		
			95% CI	(-14.2, 9.0)	( -7.2,15.3)	(-17.8, 4.4)		
					Pr >  t			0.2378
		Week 48	n	16	17			
			LS Mean	4.662	5.087	-0.424		
			SEM	5.850	5.740	5.701		
95% CI	( -6.9,16.3)		( -6.3,16.4)	(-11.7,10.8)				
			Pr >  t			0.9408		
Week 56	n	12	14					
	LS Mean	6.519	7.051	-0.531				
	SEM	6.138	5.928	6.195				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-5.6,18.7)	(-4.7,18.8)	(-12.7,11.7)
	Pr >  t			0.9317
	n	12	11	
	LS Mean	3.743	6.812	-3.070
	SEM	6.138	6.209	6.462
Week 72	95% CI	(-8.4,15.9)	(-5.4,19.1)	(-15.8, 9.6)
	Pr >  t			0.6351
	n	10	8	
	LS Mean	2.193	4.748	-2.555
	SEM	6.361	6.667	7.108
Week 84	95% CI	(-10.4,14.8)	(-8.4,17.9)	(-16.5,11.4)
	Pr >  t			0.7195
	n	8	8	
	LS Mean	6.539	8.915	-2.376
	SEM	6.736	6.667	7.401
Week 96	95% CI	(-6.8,19.8)	(-4.2,22.1)	(-16.9,12.2)
	Pr >  t			0.7484
	n	6	6	
	LS Mean	6.998	7.037	-0.040
	SEM	7.236	7.178	8.300
Week 108	95% CI	(-7.3,21.3)	(-7.1,21.2)	(-16.4,16.3)
	Pr >  t			0.9962
	n	4	5	
	LS Mean	14.932	5.768	9.164
	SEM	8.137	7.561	9.401
Week 120	95% CI	(-1.1,31.0)	(-9.1,20.7)	(-9.3,27.7)
	Pr >  t			0.3303
	n	4	4	
	LS Mean	14.930	10.551	4.378
	SEM	8.137	8.099	9.840
Week 132	95% CI	(-1.1,30.9)	(-5.4,26.5)	(-15.0,23.7)
	Pr >  t			0.6566
	n	3	2	
	LS Mean	8.172	3.791	4.381
	SEM	8.939	10.31	12.30
Week 144	95% CI	(-9.4,25.8)	(-16.5,24.1)	(-19.8,28.6)
	Pr >  t			0.7219
	n	3	1	
	LS Mean	24.838	3.007	21.831
	SEM	8.939	13.73	15.27

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Europe	Week 156	95% CI	( 7.3,42.4)	(-24.0,30.0)	(-8.2,51.9)
		Pr >  t			0.1538
		n	2	1	
	Week 168	LS Mean	18.725	3.007	15.718
		SEM	10.35	13.73	16.14
		95% CI	(-1.6,39.1)	(-24.0,30.0)	(-16.0,47.5)
	Week 8	Pr >  t			0.3307
		n	1		
		LS Mean	20.779		
	Week 16	SEM	13.73		
		95% CI	(-6.2,47.8)		
		Pr >  t			
	Week 24	n	66	68	
		LS Mean	-2.706	3.874	-6.580
		SEM	7.426	7.380	3.899
	Week 32	95% CI	(-17.4,12.0)	(-10.7,18.5)	(-14.3, 1.1)
		Pr >  t			0.0926
		n	58	48	
	Week 40	LS Mean	-4.916	2.825	-7.740
		SEM	7.466	7.478	4.274
		95% CI	(-19.7, 9.8)	(-11.9,17.6)	(-16.1, 0.7)
	Week 48	Pr >  t			0.0710
		n	51	36	
		LS Mean	-1.389	5.561	-6.951
Week 8	SEM	7.512	7.595	4.606	
	95% CI	(-16.2,13.4)	(-9.4,20.6)	(-16.0, 2.1)	
	Pr >  t			0.1321	
Week 16	n	43	30		
	LS Mean	-2.304	1.616	-3.920	
	SEM	7.628	7.763	4.885	
Week 24	95% CI	(-17.4,12.8)	(-13.7,16.9)	(-13.5, 5.7)	
	Pr >  t			0.4227	
	n	37	25		
Week 32	LS Mean	-0.723	1.951	-2.673	
	SEM	7.695	7.870	5.169	
	95% CI	(-15.9,14.5)	(-13.6,17.5)	(-12.8, 7.5)	
Week 40	Pr >  t			0.6053	
	n	33	21		
	LS Mean	-1.662	2.767	-4.429	
Week 48	SEM	7.751	7.999	5.437	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-17.0,13.6)	(-13.0,18.5)	(-15.1, 6.2)
	Pr >  t			0.4156
	n	29	20	
	LS Mean	-4.485	0.675	-5.160
	SEM	7.814	8.039	5.591
Week 64	95% CI	(-19.9,10.9)	(-15.2,16.5)	(-16.1, 5.8)
	Pr >  t			0.3564
	n	23	20	
	LS Mean	0.048	3.439	-3.391
	SEM	7.955	8.040	5.789
Week 72	95% CI	(-15.6,15.7)	(-12.4,19.3)	(-14.8, 8.0)
	Pr >  t			0.5583
	n	25	19	
	LS Mean	-3.276	4.023	-7.299
	SEM	7.906	8.079	5.773
Week 84	95% CI	(-18.9,12.3)	(-11.9,19.9)	(-18.6, 4.0)
	Pr >  t			0.2066
	n	22	17	
	LS Mean	3.177	2.745	0.432
	SEM	7.985	8.174	6.017
Week 96	95% CI	(-12.6,18.9)	(-13.4,18.9)	(-11.4,12.2)
	Pr >  t			0.9427
	n	20	13	
	LS Mean	0.715	7.395	-6.680
	SEM	8.056	8.443	6.469
Week 108	95% CI	(-15.2,16.6)	(-9.2,24.0)	(-19.4, 6.0)
	Pr >  t			0.3021
	n	15	11	
	LS Mean	-2.791	6.958	-9.749
	SEM	8.313	8.644	7.035
Week 120	95% CI	(-19.2,13.6)	(-10.1,24.0)	(-23.6, 4.1)
	Pr >  t			0.1662
	n	16	8	
	LS Mean	-4.326	3.543	-7.869
	SEM	8.257	9.115	7.544
Week 132	95% CI	(-20.6,11.9)	(-14.4,21.5)	(-22.7, 6.9)
	Pr >  t			0.2973
	n	12	3	
	LS Mean	-0.008	-6.662	6.654
	SEM	8.551	11.58	10.62

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.8,16.8)	(-29.4,16.1)	(-14.2,27.5)
		Pr >  t			0.5311
	Week 144	n	7	4	
		LS Mean	13.600	-1.122	14.722
		SEM	9.362	10.67	10.35
		95% CI	(-4.8,32.0)	(-22.1,19.8)	(-5.6,35.0)
		Pr >  t			0.1552
	Week 156	n	5	2	
		LS Mean	-3.463	14.202	-17.66
		SEM	10.08	13.21	13.48
		95% CI	(-23.3,16.3)	(-11.7,40.1)	(-44.1, 8.8)
		Pr >  t			0.1903
	Week 168	n	2	2	
		LS Mean	-8.470	5.867	-14.34
		SEM	13.20	13.21	15.95
		95% CI	(-34.4,17.4)	(-20.1,31.8)	(-45.6,17.0)
		Pr >  t			0.3690
	Week 180	n		1	
		LS Mean		8.990	
		SEM		17.18	
		95% CI		(-24.7,42.7)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		8.990	
		SEM		17.18	
		95% CI		(-24.7,42.7)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	-10.91	-10.44	-0.468
		SEM	4.547	4.623	6.557
		95% CI	(-20.0,-1.8)	(-19.6,-1.2)	(-13.5,12.6)
		Pr >  t			0.9433
	Week 16	n	13	12	
		LS Mean	-11.04	0.620	-11.66
		SEM	4.684	4.800	6.777
		95% CI	(-20.4,-1.7)	(-8.9,10.2)	(-25.2, 1.8)
		Pr >  t			0.0894
	Week 24	n	12	10	
		LS Mean	-5.205	-0.705	-4.501
		SEM	4.820	5.152	7.116

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-14.8, 4.4)	(-10.9, 9.5)	(-18.7, 9.6)
	Pr >  t			0.5288
	n	9	10	
	LS Mean	-5.829	-0.707	-5.123
	SEM	5.397	5.152	7.530
Week 40	95% CI	(-16.5, 4.9)	(-10.9, 9.5)	(-20.1, 9.8)
	Pr >  t			0.4980
	n	7	10	
	LS Mean	3.867	-5.706	9.572
	SEM	5.942	5.152	7.933
Week 48	95% CI	(-7.9, 15.6)	(-15.9, 4.5)	(-6.2, 25.3)
	Pr >  t			0.2303
	n	7	7	
	LS Mean	6.248	-6.458	12.706
	SEM	5.942	5.904	8.430
Week 56	95% CI	(-5.5, 18.0)	(-18.1, 5.2)	(-4.0, 29.4)
	Pr >  t			0.1345
	n	6	7	
	LS Mean	2.568	1.352	1.216
	SEM	6.323	5.904	8.716
Week 64	95% CI	(-9.9, 15.1)	(-10.3, 13.0)	(-16.0, 18.5)
	Pr >  t			0.8893
	n	4	7	
	LS Mean	-3.433	-8.367	4.934
	SEM	7.429	5.871	9.490
Week 72	95% CI	(-18.1, 11.3)	(-20.0, 3.3)	(-13.8, 23.7)
	Pr >  t			0.6040
	n	4	4	
	LS Mean	-3.433	-10.52	7.083
	SEM	7.429	7.368	10.48
Week 84	95% CI	(-18.1, 11.3)	(-25.1, 4.0)	(-13.6, 27.8)
	Pr >  t			0.5002
	n	4	5	
	LS Mean	1.081	1.696	-0.615
	SEM	7.431	6.710	10.04
Week 96	95% CI	(-13.6, 15.8)	(-11.6, 15.0)	(-20.5, 19.2)
	Pr >  t			0.9513
	n	3	2	
	LS Mean	1.897	-1.126	3.023
	SEM	8.394	9.979	13.06

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-14.7,18.5)	(-20.8,18.6)	(-22.8,28.8)
		Pr >  t			0.8173
		n	2	3	
	Week 120	LS Mean	23.156	0.656	22.499
		SEM	10.03	8.405	13.13
		95% CI	( 3.3,43.0)	(-16.0,17.3)	( -3.5,48.5)
	Week 132	Pr >  t			0.0888
		n	2	2	
		LS Mean	11.643	-22.64	34.283
	Week 8	SEM	10.04	9.993	14.18
		95% CI	( -8.2,31.5)	(-42.4,-2.9)	( 6.3,62.3)
		Pr >  t			0.0168
	Week 16	n	1	2	
		LS Mean	-5.562	-5.970	0.408
		SEM	13.83	9.993	17.07
	Week 24	95% CI	(-32.9,21.8)	(-25.7,13.8)	(-33.3,34.1)
		Pr >  t			0.9809
		n	16	19	
	Week 32	LS Mean	-8.133	7.051	-15.18
		SEM	5.519	5.274	6.539
		95% CI	(-19.3, 3.0)	( -3.6,17.7)	(-28.3,-2.0)
	Week 40	Pr >  t			0.0244
		n	12	14	
		LS Mean	-1.355	10.019	-11.37
	Week 8	SEM	5.941	5.711	7.160
		95% CI	(-13.3,10.6)	( -1.4,21.4)	(-25.7, 2.9)
		Pr >  t			0.1172
	Week 16	n	12	8	
LS Mean		-5.717	7.313	-13.03	
SEM		5.933	6.748	7.959	
Week 24	95% CI	(-17.6, 6.2)	( -6.1,20.7)	(-28.9, 2.8)	
	Pr >  t			0.1054	
	n	9	7		
Week 32	LS Mean	2.732	10.723	-7.992	
	SEM	6.405	6.993	8.484	
	95% CI	(-10.0,15.5)	( -3.2,24.6)	(-24.8, 8.8)	
Week 40	Pr >  t			0.3486	
	n	9	7		
	LS Mean	-0.954	8.340	-9.294	
		SEM	6.410	6.993	8.505

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-13.7,11.8)	(-5.5,22.2)	(-26.2, 7.6)
	Pr >  t			0.2772
	n	8	5	
	LS Mean	-6.630	13.106	-19.74
	SEM	6.602	7.689	9.232
Week 56	95% CI	(-19.8, 6.5)	(-2.1,28.3)	(-38.0,-1.4)
	Pr >  t			0.0347
	n	7	3	
	LS Mean	1.439	5.542	-4.103
	SEM	6.825	9.076	10.58
Week 64	95% CI	(-12.1,15.0)	(-12.4,23.5)	(-25.0,16.8)
	Pr >  t			0.6987
	n	5	3	
	LS Mean	4.221	5.545	-1.325
	SEM	7.509	9.076	11.04
Week 72	95% CI	(-10.7,19.1)	(-12.4,23.5)	(-23.2,20.5)
	Pr >  t			0.9047
	n	5	3	
	LS Mean	0.312	15.395	-15.08
	SEM	7.494	9.070	11.00
Week 84	95% CI	(-14.6,15.2)	(-2.5,33.3)	(-36.8, 6.7)
	Pr >  t			0.1726
	n	2	2	
	LS Mean	9.606	19.062	-9.456
	SEM	10.36	10.52	14.16
Week 96	95% CI	(-10.9,30.1)	(-1.7,39.9)	(-37.5,18.5)
	Pr >  t			0.5053
	n	3	2	
	LS Mean	-3.777	10.732	-14.51
	SEM	8.847	10.52	13.13
Week 108	95% CI	(-21.3,13.7)	(-10.1,31.5)	(-40.5,11.4)
	Pr >  t			0.2710
	n	1	2	
	LS Mean	2.124	10.732	-8.608
	SEM	13.75	10.52	16.81
Week 120	95% CI	(-25.1,29.3)	(-10.1,31.5)	(-41.9,24.6)
	Pr >  t			0.6094
	n	3	2	
	LS Mean	7.333	2.397	4.936
	SEM	8.847	10.52	13.13

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.2,24.8)	(-18.4,23.2)	(-21.0,30.9)
		Pr >  t			0.7075
	Week 132	n	1	1	
		LS Mean	-10.95	16.054	-27.01
		SEM	13.77	13.89	19.12
		95% CI	(-38.2,16.3)	(-11.4,43.5)	(-64.8,10.8)
		Pr >  t			0.1603
	Week 144	n	2		
		LS Mean	1.607		
		SEM	10.30		
		95% CI	(-18.8,22.0)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	22.376		
		SEM	13.77		
		95% CI	(-4.9,49.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	5.716		
		SEM	13.77		
		95% CI	(-21.5,33.0)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-10.95		
		SEM	13.77		
		95% CI	(-38.2,16.3)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	22.376		
		SEM	13.77		
		95% CI	(-4.9,49.6)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	4.271	6.085	-1.814
		SEM	6.899	10.69	11.66
		95% CI	(-10.0,18.6)	(-16.0,28.1)	(-25.9,22.2)
		Pr >  t			0.8777
	Week 16	n	13	4	
		LS Mean	11.180	-2.366	13.546
		SEM	7.255	11.68	12.50

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-3.7,26.1)	(-26.2,21.4)	(-12.0,39.1)
	Pr >  t			0.2870
	n	9	2	
	LS Mean	11.219	7.693	3.526
	SEM	7.837	13.92	14.86
Week 32	95% CI	(-4.7,27.1)	(-20.3,35.6)	(-26.3,33.4)
	Pr >  t			0.8134
	n	6	3	
	LS Mean	6.288	-1.215	7.503
	SEM	8.667	12.53	14.02
Week 40	95% CI	(-11.2,23.7)	(-26.6,24.1)	(-20.8,35.8)
	Pr >  t			0.5953
	n	6	2	
	LS Mean	3.916	-7.687	11.604
	SEM	8.764	13.92	15.31
Week 48	95% CI	(-13.7,21.5)	(-35.6,20.3)	(-19.1,42.3)
	Pr >  t			0.4519
	n	5	1	
	LS Mean	1.009	-2.372	3.381
	SEM	9.164	17.44	18.80
Week 56	95% CI	(-17.4,19.4)	(-37.1,32.4)	(-34.1,40.8)
	Pr >  t			0.8578
	n	5	1	
	LS Mean	4.341	-2.372	6.713
	SEM	9.164	17.44	18.80
Week 64	95% CI	(-14.0,22.7)	(-37.1,32.4)	(-30.8,44.2)
	Pr >  t			0.7221
	n	3	1	
	LS Mean	4.460	-2.372	6.832
	SEM	10.52	17.44	19.49
Week 72	95% CI	(-16.5,25.4)	(-37.1,32.4)	(-32.0,45.7)
	Pr >  t			0.7270
	n	4	1	
	LS Mean	5.314	-2.372	7.686
	SEM	9.715	17.44	19.08
Week 84	95% CI	(-14.1,24.7)	(-37.1,32.4)	(-30.3,45.7)
	Pr >  t			0.6882
	n	4	1	
	LS Mean	5.314	-2.372	7.686
	SEM	9.715	17.44	19.08

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-14.1,24.7)	(-37.1,32.4)	(-30.3,45.7)
	Pr >  t			0.6882
	n	3	1	
	LS Mean	4.463	-2.372	6.835
	SEM	10.52	17.44	19.49
Week 108	95% CI	(-16.5,25.4)	(-37.1,32.4)	(-32.0,45.7)
	Pr >  t			0.7269
	n	4		
	LS Mean	5.314		
	SEM	9.715		
Week 120	95% CI	(-14.1,24.7)		
	Pr >  t			
	n	3		
	LS Mean	-6.650		
	SEM	10.52		
Week 132	95% CI	(-27.6,14.3)		
	Pr >  t			
	n	3		
	LS Mean	4.460		
	SEM	10.52		
Week 144	95% CI	(-16.5,25.4)		
	Pr >  t			
	n	3		
	LS Mean	-2.961		
	SEM	10.52		
Week 156	95% CI	(-24.0,18.0)		
	Pr >  t			
	n	2		
	LS Mean	-12.93		
	SEM	11.91		
	95% CI	(-36.6,10.8)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Baseline ECOG performance status	0 Week 8	n	98	90			
		LS Mean	-3.652	-0.214	-3.438		
		SEM	3.790	3.699	2.959		
		95% CI	(-11.1, 3.8)	(-7.5, 7.1)	(-9.3, 2.4)		
						Pr >  t	0.2460
	Week 16	n	88	71			
		LS Mean	-1.843	1.800	-3.643		
		SEM	3.856	3.922	3.157		
		95% CI	(-9.4, 5.7)	(-5.9, 9.5)	(-9.8, 2.6)		
						Pr >  t	0.2492
	Week 24	n	75	54			
		LS Mean	-0.206	2.928	-3.134		
		SEM	3.913	4.054	3.407		
		95% CI	(-7.9, 7.5)	(-5.0, 10.9)	(-9.8, 3.6)		
						Pr >  t	0.3580
	Week 32	n	62	52			
		LS Mean	2.051	0.687	1.364		
		SEM	4.007	4.076	3.529		
		95% CI	(-5.8, 9.9)	(-7.3, 8.7)	(-5.6, 8.3)		
						Pr >  t	0.6993
	Week 40	n	51	46			
		LS Mean	1.597	-0.280	1.877		
		SEM	4.102	4.162	3.717		
		95% CI	(-6.5, 9.7)	(-8.5, 7.9)	(-5.4, 9.2)		
						Pr >  t	0.6136
	Week 48	n	50	37			
		LS Mean	2.551	1.259	1.292		
		SEM	4.112	4.299	3.880		
95% CI		(-5.5, 10.6)	(-7.2, 9.7)	(-6.3, 8.9)			
					Pr >  t	0.7393	
Week 56	n	43	33				
	LS Mean	0.582	-0.996	1.578			
	SEM	4.195	4.381	4.058			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.7, 8.8)	(-9.6, 7.6)	(-6.4, 9.5)
	Pr >  t			0.6974
	n	35	33	
	LS Mean	3.179	0.995	2.184
	SEM	4.323	4.381	4.194
Week 72	95% CI	(-5.3,11.7)	(-7.6, 9.6)	(-6.0,10.4)
	Pr >  t			0.6028
	n	35	31	
	LS Mean	-0.062	1.662	-1.724
	SEM	4.323	4.427	4.243
Week 84	95% CI	(-8.6, 8.4)	(-7.0,10.4)	(-10.0, 6.6)
	Pr >  t			0.6846
	n	31	29	
	LS Mean	5.547	3.931	1.616
	SEM	4.418	4.479	4.384
Week 96	95% CI	(-3.1,14.2)	(-4.9,12.7)	(-7.0,10.2)
	Pr >  t			0.7125
	n	27	22	
	LS Mean	3.028	4.988	-1.960
	SEM	4.518	4.725	4.741
Week 108	95% CI	(-5.8,11.9)	(-4.3,14.3)	(-11.3, 7.3)
	Pr >  t			0.6794
	n	19	20	
	LS Mean	4.339	4.346	-0.006
	SEM	4.869	4.823	5.158
Week 120	95% CI	(-5.2,13.9)	(-5.1,13.8)	(-10.1,10.1)
	Pr >  t			0.9990
	n	20	15	
	LS Mean	2.577	1.690	0.887
	SEM	4.798	5.165	5.430
Week 132	95% CI	(-6.8,12.0)	(-8.4,11.8)	(-9.8,11.5)
	Pr >  t			0.8703
	n	15	7	
	LS Mean	2.993	-1.072	4.065
	SEM	5.150	6.486	6.946
Week 144	95% CI	(-7.1,13.1)	(-13.8,11.7)	(-9.6,17.7)
	Pr >  t			0.5585
	n	10	5	
	LS Mean	15.465	-1.705	17.171
	SEM	5.745	7.327	8.162

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( -4.2,26.7)	(-16.1,12.7)	( -1.2,33.2)
		Pr >  t			0.0356
	Week 156	n	6	3	
		LS Mean	5.405	8.911	-3.506
		SEM	6.839	8.970	10.34
		95% CI	( -8.0,18.8)	( -8.7,26.5)	(-23.8,16.8)
		Pr >  t			0.7346
	Week 168	n	3	2	
		LS Mean	-0.562	4.564	-5.126
		SEM	8.962	10.68	13.19
		95% CI	(-18.1,17.0)	(-16.4,25.5)	(-31.0,20.8)
		Pr >  t			0.6976
	Week 180	n	1	1	
		LS Mean	-9.283	7.824	-17.11
		SEM	14.63	14.63	20.19
		95% CI	(-38.0,19.4)	(-20.9,36.5)	(-56.7,22.5)
		Pr >  t			0.3971
	Week 192	n	1	1	
		LS Mean	24.047	7.824	16.223
		SEM	14.63	14.63	20.19
		95% CI	( -4.7,52.8)	(-20.9,36.5)	(-23.4,55.8)
		Pr >  t			0.4220
1	Week 8	n	43	50	
		LS Mean	-2.827	3.277	-6.105
		SEM	4.434	4.629	4.517
		95% CI	(-11.6, 5.9)	( -5.9,12.4)	(-15.0, 2.8)
		Pr >  t			0.1784
	Week 16	n	35	35	
		LS Mean	-5.728	5.452	-11.18
		SEM	4.640	4.811	4.976
		95% CI	(-14.9, 3.4)	( -4.1,15.0)	(-21.0,-1.4)
		Pr >  t			0.0257
	Week 24	n	29	26	
		LS Mean	-1.629	4.795	-6.423
		SEM	4.828	5.150	5.386
		95% CI	(-11.2, 7.9)	( -5.4,15.0)	(-17.0, 4.2)
		Pr >  t			0.2341
	Week 32	n	23	21	
		LS Mean	-5.758	6.198	-11.96
		SEM	5.107	5.419	5.788

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-15.8, 4.3)	(-4.5,16.9)	(-23.3,-0.6)
	Pr >  t			0.0397
	n	23	16	
	LS Mean	-5.469	8.139	-13.61
	SEM	5.119	5.741	6.103
Week 48	95% CI	(-15.6, 4.6)	(-3.2,19.5)	(-25.6,-1.6)
	Pr >  t			0.0264
	n	18	14	
	LS Mean	-5.929	9.576	-15.51
	SEM	5.379	5.927	6.505
Week 56	95% CI	(-16.5, 4.7)	(-2.1,21.2)	(-28.3,-2.7)
	Pr >  t			0.0177
	n	15	12	
	LS Mean	-2.853	16.259	-19.11
	SEM	5.618	6.155	6.919
Week 64	95% CI	(-13.9, 8.2)	(-4.1,28.4)	(-32.7,-5.5)
	Pr >  t			0.0060
	n	11	9	
	LS Mean	-4.222	9.069	-13.29
	SEM	6.072	6.661	7.731
Week 72	95% CI	(-16.2, 7.7)	(-4.0,22.2)	(-28.5, 1.9)
	Pr >  t			0.0863
	n	12	4	
	LS Mean	-3.969	10.372	-14.34
	SEM	5.949	8.732	9.493
Week 84	95% CI	(-15.7, 7.7)	(-6.8,27.5)	(-33.0, 4.3)
	Pr >  t			0.1316
	n	8	4	
	LS Mean	0.481	10.372	-9.891
	SEM	6.712	8.732	9.974
Week 96	95% CI	(-12.7,13.7)	(-6.8,27.5)	(-29.5, 9.7)
	Pr >  t			0.3219
	n	8	2	
	LS Mean	-1.601	9.735	-11.34
	SEM	6.712	11.50	12.47
Week 108	95% CI	(-14.8,11.6)	(-12.9,32.3)	(-35.8,13.2)
	Pr >  t			0.3638
	n	6	1	
	LS Mean	0.643	16.286	-15.64
	SEM	7.374	15.61	16.61

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.9,15.1)	(-14.4,47.0)	(-48.3,17.0)
		Pr >  t			0.3469
	Week 120	n	8	1	
		LS Mean	-4.225	-17.04	12.818
		SEM	6.731	15.61	16.33
		95% CI	(-17.5, 9.0)	(-47.7,13.6)	(-19.3,44.9)
		Pr >  t			0.4331
	Week 132	n	5	1	
		LS Mean	-5.108	-0.374	-4.734
		SEM	7.855	15.61	16.83
		95% CI	(-20.5,10.3)	(-31.1,30.3)	(-37.8,28.4)
		Pr >  t			0.7787
	Week 144	n	5		
		LS Mean	-1.776		
		SEM	7.855		
		95% CI	(-17.2,13.7)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	-7.978		
		SEM	8.520		
		95% CI	(-24.7, 8.8)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	10.189		
		SEM	15.35		
		95% CI	(-20.0,40.4)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	2.040	1.330	0.710		
			SEM	5.775	6.681	6.982		
					95% CI	(-9.6,13.7)	(-12.2,14.8)	(-13.3,14.7)
					Pr >  t			0.9193
				Week 16	n	17	10	
					LS Mean	6.603	10.852	-4.249
					SEM	6.247	7.782	8.290
					95% CI	(-6.0,19.2)	(-4.7,26.4)	(-20.8,12.3)
					Pr >  t			0.6097
				Week 24	n	9	5	
					LS Mean	-2.576	20.121	-22.70
					SEM	7.352	9.681	10.99
					95% CI	(-17.2,12.1)	( 0.9,39.4)	(-44.5,-0.9)
					Pr >  t			0.0412
				Week 32	n	8	4	
					LS Mean	-8.524	10.898	-19.42
					SEM	7.639	10.49	11.88
					95% CI	(-23.7, 6.7)	(-9.9,31.7)	(-43.0, 4.1)
					Pr >  t			0.1050
				Week 40	n	5	4	
					LS Mean	-6.505	2.563	-9.069
					SEM	8.835	10.49	12.80
					95% CI	(-24.0,11.0)	(-18.2,23.4)	(-34.4,16.3)
			Pr >  t			0.4803		
		Week 48	n	5	3			
			LS Mean	6.829	17.705	-10.88		
			SEM	8.835	11.59	13.71		
			95% CI	(-10.7,24.4)	(-5.3,40.7)	(-38.0,16.3)		
			Pr >  t			0.4291		
		Week 56	n	4	3			
			LS Mean	7.474	-4.519	11.992		
			SEM	9.540	11.59	14.22		

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-11.4,26.4)	(-27.5,18.4)	(-16.2,40.2)
		Pr >  t			0.4008
		n	4	3	
		LS Mean	3.309	-4.519	7.827
		SEM	9.540	11.59	14.22
Week 72		95% CI	(-15.6,22.2)	(-27.5,18.4)	(-20.3,36.0)
		Pr >  t			0.5831
		n	4	3	
		LS Mean	3.309	12.148	-8.839
		SEM	9.540	11.59	14.22
Week 84		95% CI	(-15.6,22.2)	(-10.8,35.1)	(-37.0,19.3)
		Pr >  t			0.5355
		n	2	3	
		LS Mean	12.721	17.705	-4.984
		SEM	12.75	11.59	16.40
Week 96		95% CI	(-12.6,38.0)	(-5.3,40.7)	(-37.5,27.5)
		Pr >  t			0.7618
		n	1	3	
		LS Mean	-1.186	12.151	-13.34
		SEM	17.14	11.59	20.25
Week 108		95% CI	(-35.2,32.8)	(-10.8,35.1)	(-53.5,26.9)
		Pr >  t			0.5118
		n		2	
		LS Mean		8.257	
		SEM		13.39	
Week 120		95% CI		(-18.3,34.8)	
		Pr >  t			
		n	1	1	
		LS Mean	-1.186	-2.411	1.225
		SEM	17.14	17.69	24.30
Week 132		95% CI	(-35.2,32.8)	(-37.5,32.7)	(-47.1,49.5)
		Pr >  t			0.9599
		n		1	
		LS Mean		14.259	
		SEM		17.69	
Week 144		95% CI		(-20.8,49.3)	
		Pr >  t			
		n	1		
	LS Mean	-1.186			
	SEM	17.14			



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-35.2,32.8)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-1.440	3.607	-5.047
		SEM	3.524	3.513	2.928
		95% CI	(-8.4, 5.5)	(-3.3,10.5)	(-10.8, 0.7)
		Pr >  t			0.0855
	Week 16	n	83	81	
		LS Mean	-1.974	5.665	-7.639
		SEM	3.608	3.663	3.166
		95% CI	(-9.1, 5.1)	(-1.5,12.9)	(-13.9,-1.4)
		Pr >  t			0.0162
	Week 24	n	75	62	
		LS Mean	2.226	6.458	-4.232
		SEM	3.669	3.819	3.377
		95% CI	(-5.0, 9.4)	(-1.1,14.0)	(-10.9, 2.4)
		Pr >  t			0.2106
	Week 32	n	59	56	
		LS Mean	3.015	5.691	-2.676
		SEM	3.833	3.873	3.571
		95% CI	(-4.5,10.5)	(-1.9,13.3)	(-9.7, 4.3)
		Pr >  t			0.4539
	Week 40	n	52	48	
		LS Mean	4.849	5.324	-0.475
		SEM	3.903	3.977	3.743
		95% CI	(-2.8,12.5)	(-2.5,13.1)	(-7.8, 6.9)
		Pr >  t			0.8990
	Week 48	n	47	37	
		LS Mean	2.547	5.912	-3.365
		SEM	3.963	4.154	3.988
		95% CI	(-5.2,10.3)	(-2.2,14.1)	(-11.2, 4.5)
		Pr >  t			0.3990
	Week 56	n	41	31	
		LS Mean	2.854	8.108	-5.255
		SEM	4.050	4.296	4.221
		95% CI	(-5.1,10.8)	(-0.3,16.5)	(-13.5, 3.0)
		Pr >  t			0.2135
	Week 64	n	32	28	
		LS Mean	5.975	6.671	-0.696
		SEM	4.234	4.385	4.486

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-2.3,14.3)	(-1.9,15.3)	(-9.5, 8.1)	
	Pr >  t			0.8767	
	n	29	22		
	LS Mean	2.446	5.044	-2.598	
	SEM	4.321	4.625	4.798	
Week 84	95% CI	(-6.0,10.9)	(-4.0,14.1)	(-12.0, 6.8)	
	Pr >  t			0.5883	
	n	26	21		
	LS Mean	6.198	5.183	1.015	
	SEM	4.416	4.675	4.933	
Week 96	95% CI	(-2.5,14.9)	(-4.0,14.4)	(-8.7,10.7)	
	Pr >  t			0.8371	
	n	23	14		
	LS Mean	4.693	10.049	-5.356	
	SEM	4.539	5.201	5.534	
Week 108	95% CI	(-4.2,13.6)	(-0.2,20.3)	(-16.2, 5.5)	
	Pr >  t			0.3334	
	n	18	13		
	LS Mean	6.267	6.691	-0.424	
	SEM	4.822	5.316	5.870	
Week 120	95% CI	(-3.2,15.7)	(-3.7,17.1)	(-11.9,11.1)	
	Pr >  t			0.9425	
	n	19	10		
	LS Mean	3.993	2.891	1.101	
	SEM	4.760	5.765	6.232	
Week 132	95% CI	(-5.4,13.3)	(-8.4,14.2)	(-11.1,13.3)	
	Pr >  t			0.8598	
	n	13	4		
	LS Mean	5.343	2.378	2.965	
	SEM	5.272	8.088	8.726	
Week 144	95% CI	(-5.0,15.7)	(-13.5,18.2)	(-14.2,20.1)	
	Pr >  t			0.7341	
	n	8	1		
	LS Mean	18.946	-4.178	23.124	
	SEM	6.174	15.04	15.72	
Week 156	95% CI	( 6.8,31.1)	(-33.7,25.3)	(-7.7,54.0)	
	Pr >  t			0.1416	
	n	5	1		
	LS Mean	5.620	29.152	-23.53	
	SEM	7.363	15.04	16.22	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-8.8,20.1)	(-0.4,58.7)	(-55.4, 8.3)
		Pr >  t			0.1472
		n	3	1	
	Week 180	LS Mean	1.123	12.482	-11.36
		SEM	9.084	15.04	17.07
		95% CI	(-16.7,18.9)	(-17.0,42.0)	(-44.9,22.1)
	Week 180	Pr >  t			0.5060
		n	1	1	
		LS Mean	-7.680	12.482	-20.16
	Week 192	SEM	14.97	15.04	20.81
		95% CI	(-37.1,21.7)	(-17.0,42.0)	(-61.0,20.7)
		Pr >  t			0.3328
	Week 192	n	1	1	
		LS Mean	25.650	12.482	13.168
		SEM	14.97	15.04	20.81
	Week 8	95% CI	(-3.7,55.0)	(-17.0,42.0)	(-27.7,54.0)
		Pr >  t			0.5270
		n	17	16	
	Week 8	LS Mean	-9.620	-0.020	-9.600
		SEM	4.910	5.018	6.885
		95% CI	(-19.4, 0.2)	(-10.1,10.0)	(-23.4, 4.2)
	Week 16	Pr >  t			0.1684
		n	18	14	
		LS Mean	-9.117	-7.592	-1.525
	Week 16	SEM	4.842	5.201	7.014
		95% CI	(-18.8, 0.6)	(-18.0, 2.8)	(-15.5,12.5)
		Pr >  t			0.8285
	Week 24	n	16	13	
LS Mean		-9.499	-11.81	2.307	
SEM		4.994	5.289	7.181	
Week 24	95% CI	(-19.5, 0.5)	(-22.4,-1.3)	(-12.0,16.6)	
	Pr >  t			0.7490	
	n	15	13		
Week 32	LS Mean	-0.345	-8.805	8.460	
	SEM	5.050	5.299	7.230	
	95% CI	(-10.4, 9.7)	(-19.4, 1.8)	(-6.0,22.9)	
Week 32	Pr >  t			0.2460	
	n	14	10		
	LS Mean	-9.965	-6.083	-3.882	
Week 40	SEM	5.148	5.628	7.542	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48		95% CI	(-20.2, 0.3)	(-17.3, 5.1)	(-18.9,11.1)
		Pr >  t			0.6082
		n	14	11	
		LS Mean	-2.821	-4.774	1.952
		SEM	5.148	5.512	7.456
Week 56		95% CI	(-13.1, 7.5)	(-15.7, 6.2)	(-12.9,16.8)
		Pr >  t			0.7941
		n	11	11	
		LS Mean	-8.303	-4.773	-3.531
		SEM	5.423	5.512	7.652
Week 64		95% CI	(-19.1, 2.5)	(-15.7, 6.2)	(-18.7,11.7)
		Pr >  t			0.6457
		n	8	11	
		LS Mean	-9.672	-3.259	-6.413
		SEM	5.853	5.512	7.967
Week 72		95% CI	(-21.3, 1.9)	(-14.2, 7.7)	(-22.2, 9.4)
		Pr >  t			0.4229
		n	11	10	
		LS Mean	-9.819	-2.096	-7.722
		SEM	5.423	5.636	7.744
Week 84		95% CI	(-20.6, 1.0)	(-13.3, 9.1)	(-23.1, 7.7)
		Pr >  t			0.3214
		n	9	9	
		LS Mean	-1.880	3.210	-5.090
		SEM	5.680	5.778	8.032
Week 96		95% CI	(-13.2, 9.4)	(-8.3,14.7)	(-21.0,10.8)
		Pr >  t			0.5277
		n	8	7	
		LS Mean	-1.027	-2.780	1.753
		SEM	5.856	6.156	8.431
Week 108		95% CI	(-12.6,10.6)	(-15.0, 9.4)	(-14.9,18.5)
		Pr >  t			0.8357
		n	7	6	
		LS Mean	-4.353	4.874	-9.227
		SEM	6.071	6.433	8.784
Week 120		95% CI	(-16.4, 7.7)	(-7.9,17.6)	(-26.6, 8.2)
		Pr >  t			0.2955
		n	6	5	
		LS Mean	-0.849	-0.274	-0.575
		SEM	6.350	6.801	9.238

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132		95% CI	(-13.4,11.7)	(-13.7,13.2)	(-18.8,17.7)
		Pr >  t			0.9505
		n	5	3	
		LS Mean	-2.901	-10.12	7.216
		SEM	6.709	8.050	10.42
Week 144		95% CI	(-16.2,10.4)	(-26.0, 5.8)	(-13.3,27.8)
		Pr >  t			0.4896
		n	5	4	
		LS Mean	3.765	-5.317	9.082
		SEM	6.709	7.294	9.850
Week 156		95% CI	(-9.5,17.0)	(-19.7, 9.1)	(-10.4,28.5)
		Pr >  t			0.3578
		n	4	2	
		LS Mean	-1.866	-4.784	2.917
		SEM	7.209	9.385	11.79
Week 168		95% CI	(-16.1,12.4)	(-23.3,13.7)	(-20.3,26.1)
		Pr >  t			0.8047
		n	1	1	
		LS Mean	9.121	-5.229	14.350
		SEM	12.51	12.57	17.70
		95% CI	(-15.5,33.7)	(-30.0,19.5)	(-20.5,49.2)
		Pr >  t			0.4183

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	-9.586	-3.766	-5.821		
			SEM	9.322	9.594	3.437		
			95% CI	(-28.0, 8.8)	(-22.7,15.2)	(-12.6, 0.9)		
					Pr >  t			0.0915
		Week 16	n	69	55			
			LS Mean	-7.958	-4.032	-3.926		
			SEM	9.335	9.659	3.648		
			95% CI	(-26.4,10.5)	(-23.1,15.0)	(-11.1, 3.3)		
					Pr >  t			0.2826
		Week 24	n	54	46			
			LS Mean	-9.650	-3.822	-5.828		
			SEM	9.365	9.699	3.886		
			95% CI	(-28.2, 8.9)	(-23.0,15.3)	(-13.5, 1.8)		
					Pr >  t			0.1345
		Week 32	n	49	41			
			LS Mean	-3.768	-4.973	1.205		
			SEM	9.443	9.726	4.014		
			95% CI	(-22.4,14.9)	(-24.2,14.2)	(-6.7, 9.1)		
					Pr >  t			0.7641
		Week 40	n	40	33			
			LS Mean	-7.506	-6.256	-1.250		
			SEM	9.498	9.784	4.275		
			95% CI	(-26.3,11.3)	(-25.6,13.1)	(-9.6, 7.1)		
					Pr >  t			0.7701
		Week 48	n	38	28			
			LS Mean	-3.947	-5.289	1.342		
			SEM	9.512	9.841	4.431		
95% CI	(-22.7,14.8)		(-24.7,14.1)	(-7.4,10.0)				
			Pr >  t			0.7622		
Week 56	n	32	28					
	LS Mean	-7.855	-6.274	-1.582				
	SEM	9.565	9.842	4.541				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-26.7,11.0)	(-25.7,13.2)	(-10.5, 7.3)
	Pr >  t			0.7277
	n	23	26	
	LS Mean	-4.067	-7.025	2.958
	SEM	9.686	9.868	4.846
Week 72	95% CI	(-23.2,15.0)	(-26.5,12.5)	( -6.6,12.5)
	Pr >  t			0.5418
	n	27	25	
	LS Mean	-7.646	-3.100	-4.547
	SEM	9.624	9.880	4.751
Week 84	95% CI	(-26.6,11.3)	(-22.6,16.4)	(-13.9, 4.8)
	Pr >  t			0.3389
	n	23	22	
	LS Mean	-3.465	1.405	-4.870
	SEM	9.685	9.931	4.983
Week 96	95% CI	(-22.6,15.6)	(-18.2,21.0)	(-14.7, 4.9)
	Pr >  t			0.3287
	n	20	16	
	LS Mean	-2.360	-3.713	1.353
	SEM	9.748	10.09	5.411
Week 108	95% CI	(-21.6,16.9)	(-23.6,16.2)	( -9.3,12.0)
	Pr >  t			0.8027
	n	20	14	
	LS Mean	-6.316	-0.138	-6.178
	SEM	9.750	10.18	5.566
Week 120	95% CI	(-25.6,12.9)	(-20.2,19.9)	(-17.1, 4.7)
	Pr >  t			0.2674
	n	17	11	
	LS Mean	-4.226	-6.104	1.877
	SEM	9.834	10.35	6.021
Week 132	95% CI	(-23.6,15.2)	(-26.5,14.3)	( -9.9,13.7)
	Pr >  t			0.7553
	n	13	6	
	LS Mean	-8.766	-9.102	0.336
	SEM	10.00	11.01	7.318
Week 144	95% CI	(-28.5,11.0)	(-30.8,12.6)	(-14.0,14.7)
	Pr >  t			0.9634
	n	10	5	
	LS Mean	8.071	-7.632	15.703
	SEM	10.21	11.28	8.001

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.1,28.2)	(-29.8,14.6)	( 0.0,31.4)
		Pr >  t			0.0500
	Week 156	n	7	3	
		LS Mean	-5.015	2.971	-7.986
		SEM	10.60	12.32	9.816
		95% CI	(-25.9,15.9)	(-21.3,27.2)	(-27.3,11.3)
		Pr >  t			0.4161
	Week 168	n	3	2	
		LS Mean	-5.564	-1.420	-4.144
		SEM	12.13	13.51	12.72
		95% CI	(-29.4,18.3)	(-28.0,25.1)	(-29.1,20.8)
		Pr >  t			0.7448
	Week 180	n		1	
		LS Mean		1.838	
		SEM		16.55	
		95% CI		(-30.7,34.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		1.838	
		SEM		16.55	
		95% CI		(-30.7,34.3)	
		Pr >  t			
Second Line	Week 8	n	66	67	
		LS Mean	-0.417	2.629	-3.046
		SEM	3.243	3.243	3.538
		95% CI	( -6.8, 6.0)	( -3.8, 9.0)	(-10.0, 3.9)
		Pr >  t			0.3901
	Week 16	n	54	52	
		LS Mean	-1.941	7.192	-9.133
		SEM	3.420	3.502	3.869
		95% CI	( -8.7, 4.8)	( 0.3,14.1)	(-16.7,-1.5)
		Pr >  t			0.0188
	Week 24	n	49	35	
		LS Mean	5.422	8.521	-3.099
		SEM	3.513	3.866	4.258
		95% CI	( -1.5,12.3)	( 0.9,16.1)	(-11.5, 5.3)
		Pr >  t			0.4671
	Week 32	n	36	32	
		LS Mean	-0.473	7.229	-7.702
		SEM	3.795	3.969	4.553



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-7.9, 7.0)	(-0.6, 15.0)	(-16.6, 1.2)
	Pr >  t			0.0914
Week 40	n	33	29	
	LS Mean	2.696	8.131	-5.435
	SEM	3.875	4.092	4.712
	95% CI	(-4.9, 10.3)	(0.1, 16.2)	(-14.7, 3.8)
	Pr >  t			0.2492
Week 48	n	29	23	
	LS Mean	0.726	10.366	-9.641
	SEM	4.000	4.348	5.035
	95% CI	(-7.1, 8.6)	(1.8, 18.9)	(-19.5, 0.2)
	Pr >  t			0.0560
Week 56	n	25	17	
	LS Mean	5.912	13.047	-7.135
	SEM	4.152	4.745	5.504
	95% CI	(-2.2, 14.1)	(3.7, 22.4)	(-17.9, 3.7)
	Pr >  t			0.1954
Week 64	n	22	16	
	LS Mean	2.852	12.724	-9.872
	SEM	4.300	4.838	5.697
	95% CI	(-5.6, 11.3)	(3.2, 22.2)	(-21.1, 1.3)
	Pr >  t			0.0836
Week 72	n	20	10	
	LS Mean	2.593	7.269	-4.676
	SEM	4.419	5.667	6.499
	95% CI	(-6.1, 11.3)	(-3.9, 18.4)	(-17.4, 8.1)
	Pr >  t			0.4721
Week 84	n	16	11	
	LS Mean	10.000	4.515	5.486
	SEM	4.747	5.479	6.555
	95% CI	(0.7, 19.3)	(-6.2, 15.3)	(-7.4, 18.4)
	Pr >  t			0.4030
Week 96	n	15	8	
	LS Mean	2.152	17.509	-15.36
	SEM	4.837	6.146	7.191
	95% CI	(-7.3, 11.7)	(5.4, 29.6)	(-29.5, -1.2)
	Pr >  t			0.0331
Week 108	n	6	7	
	LS Mean	17.708	9.303	8.405
	SEM	6.785	6.465	8.845

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	( 4.4,31.0)	( -3.4,22.0)	( -9.0,25.8)
	Pr >  t			0.3423
	n	11	5	
	LS Mean	1.558	8.121	-6.563
	SEM	5.388	7.397	8.621
Week 132	95% CI	( -9.0,12.1)	( -6.4,22.6)	(-23.5,10.4)
	Pr >  t			0.4468
	n	7	2	
	LS Mean	10.507	10.154	0.353
	SEM	6.378	11.04	12.37
Week 144	95% CI	( -2.0,23.0)	(-11.5,31.8)	(-23.9,24.6)
	Pr >  t			0.9772
	n	5		
	LS Mean	4.311		
	SEM	7.294		
Week 156	95% CI	(-10.0,18.6)		
	Pr >  t			
	n	3		
	LS Mean	2.480		
	SEM	9.127		
Week 168	95% CI	(-15.4,20.4)		
	Pr >  t			
	n	1		
	LS Mean	8.053		
	SEM	15.23		
Week 180	95% CI	(-21.9,38.0)		
	Pr >  t			
	n	1		
	LS Mean	-8.617		
	SEM	15.23		
Week 192	95% CI	(-38.5,21.3)		
	Pr >  t			
	n	1		
	LS Mean	24.713		
	SEM	15.23		
	95% CI	( -5.2,54.6)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-5.457	0.407	-5.864
		SEM	9.149	9.580	3.934
		95% CI	(-23.6,12.7)	(-18.6,19.4)	(-13.6, 1.9)
		Pr >  t			0.1375
	Week 16	n	51	41	
		LS Mean	-3.349	2.510	-5.860
		SEM	9.178	9.700	4.259
		95% CI	(-21.5,14.8)	(-16.7,21.7)	(-14.2, 2.5)
		Pr >  t			0.1701
	Week 24	n	38	33	
		LS Mean	-5.637	4.633	-10.27
		SEM	9.228	9.768	4.632
		95% CI	(-23.9,12.6)	(-14.7,24.0)	(-19.4,-1.2)
		Pr >  t			0.0273
	Week 32	n	34	28	
		LS Mean	-1.204	1.995	-3.200
		SEM	9.365	9.820	4.845
		95% CI	(-19.7,17.3)	(-17.4,21.4)	(-12.7, 6.3)
		Pr >  t			0.5095
	Week 40	n	26	23	
		LS Mean	-2.011	-1.247	-0.764
		SEM	9.486	9.903	5.226
		95% CI	(-20.8,16.8)	(-20.8,18.4)	(-11.0, 9.5)
		Pr >  t			0.8838
	Week 48	n	24	17	
		LS Mean	-0.350	-0.568	0.217
		SEM	9.523	10.08	5.614
95% CI		(-19.2,18.5)	(-20.5,19.4)	(-10.8,11.2)	
	Pr >  t			0.9691	
Week 56	n	21	17		
	LS Mean	-3.555	-2.209	-1.347	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	9.599	10.08	5.731
		95% CI	(-22.5,15.4)	(-22.2,17.7)	(-12.6, 9.9)
		Pr >  t			0.8143
	Week 64	n	15	15	
		LS Mean	3.054	-5.017	8.070
		SEM	9.810	10.16	6.217
		95% CI	(-16.3,22.4)	(-25.1,15.1)	(-4.1,20.3)
		Pr >  t			0.1949
	Week 72	n	16	15	
		LS Mean	-2.076	1.142	-3.219
		SEM	9.765	10.16	6.147
		95% CI	(-21.4,17.2)	(-19.0,21.2)	(-15.3, 8.9)
		Pr >  t			0.6007
	Week 84	n	14	13	
		LS Mean	-0.436	5.102	-5.538
		SEM	9.860	10.27	6.470
		95% CI	(-19.9,19.0)	(-15.2,25.4)	(-18.2, 7.2)
		Pr >  t			0.3924
	Week 96	n	12	9	
		LS Mean	0.777	0.324	0.454
		SEM	9.986	10.62	7.191
		95% CI	(-18.9,20.5)	(-20.6,21.3)	(-13.7,14.6)
		Pr >  t			0.9497
	Week 108	n	13	8	
		LS Mean	-3.486	0.912	-4.398
		SEM	9.921	10.75	7.303
		95% CI	(-23.1,16.1)	(-20.3,22.1)	(-18.7, 9.9)
		Pr >  t			0.5473
	Week 120	n	11	6	
		LS Mean	-2.108	-5.807	3.699
		SEM	10.07	11.16	8.066
		95% CI	(-22.0,17.8)	(-27.8,16.2)	(-12.1,19.5)
		Pr >  t			0.6467
	Week 132	n	8	3	
		LS Mean	-8.449	-3.106	-5.342
		SEM	10.41	12.63	10.35
		95% CI	(-29.0,12.1)	(-28.0,21.8)	(-25.7,15.0)
		Pr >  t			0.6059
	Week 144	n	5	1	
		LS Mean	16.621	-9.760	26.381

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	11.14	17.29	16.19
		95% CI	(-5.3,38.6)	(-43.7,24.2)	(-5.4,58.2)
		Pr >  t			0.1037
	Week 168	n	3	1	
		LS Mean	-5.265	23.570	-28.83
		SEM	12.34	17.29	17.02
	Week 180	95% CI	(-29.5,19.0)	(-10.4,57.5)	(-62.3, 4.6)
		Pr >  t			0.0909
		n	2	1	
	Week 192	LS Mean	-9.033	6.900	-15.93
		SEM	13.66	17.29	18.01
		95% CI	(-35.9,17.8)	(-27.1,40.9)	(-51.3,19.4)
	Week 8	Pr >  t			0.3767
		n		1	
		LS Mean		6.900	
	Week 16	SEM		17.29	
		95% CI		(-27.1,40.9)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		6.900	
		SEM		17.29	
	Week 32	95% CI		(-27.1,40.9)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	-9.620	-0.020	-9.600	
	SEM	4.910	5.018	6.885	
	95% CI	(-19.4, 0.2)	(-10.1,10.0)	(-23.4, 4.2)	
Week 16	Pr >  t			0.1684	
	n	18	14		
	LS Mean	-9.117	-7.592	-1.525	
Week 24	SEM	4.842	5.201	7.014	
	95% CI	(-18.8, 0.6)	(-18.0, 2.8)	(-15.5,12.5)	
	Pr >  t			0.8285	
Week 32	n	16	13		
	LS Mean	-9.499	-11.81	2.307	
	SEM	4.994	5.289	7.181	
Week 32	95% CI	(-19.5, 0.5)	(-22.4,-1.3)	(-12.0,16.6)	
	Pr >  t			0.7490	
	n	15	13		
	LS Mean	-0.345	-8.805	8.460	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	N=169	N=172	
Week 40	95% CI	5.050	5.299	7.230	
	Pr >  t	(-10.4, 9.7)	(-19.4, 1.8)	(-6.0,22.9)	
	n	14	10	0.2460	
	LS Mean	-9.965	-6.083	-3.882	
	SEM	5.148	5.628	7.542	
Week 48	95% CI	(-20.2, 0.3)	(-17.3, 5.1)	(-18.9,11.1)	
	Pr >  t			0.6082	
	n	14	11		
	LS Mean	-2.821	-4.774	1.952	
	SEM	5.148	5.512	7.456	
Week 56	95% CI	(-13.1, 7.5)	(-15.7, 6.2)	(-12.9,16.8)	
	Pr >  t			0.7941	
	n	11	11		
	LS Mean	-8.303	-4.773	-3.531	
	SEM	5.423	5.512	7.652	
Week 64	95% CI	(-19.1, 2.5)	(-15.7, 6.2)	(-18.7,11.7)	
	Pr >  t			0.6457	
	n	8	11		
	LS Mean	-9.672	-3.259	-6.413	
	SEM	5.853	5.512	7.967	
Week 72	95% CI	(-21.3, 1.9)	(-14.2, 7.7)	(-22.2, 9.4)	
	Pr >  t			0.4229	
	n	11	10		
	LS Mean	-9.819	-2.096	-7.722	
	SEM	5.423	5.636	7.744	
Week 84	95% CI	(-20.6, 1.0)	(-13.3, 9.1)	(-23.1, 7.7)	
	Pr >  t			0.3214	
	n	9	9		
	LS Mean	-1.880	3.210	-5.090	
	SEM	5.680	5.778	8.032	
Week 96	95% CI	(-13.2, 9.4)	(-8.3,14.7)	(-21.0,10.8)	
	Pr >  t			0.5277	
	n	8	7		
	LS Mean	-1.027	-2.780	1.753	
	SEM	5.856	6.156	8.431	
Week 108	95% CI	(-12.6,10.6)	(-15.0, 9.4)	(-14.9,18.5)	
	Pr >  t			0.8357	
	n	7	6		
	LS Mean	-4.353	4.874	-9.227	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	6.071	6.433	8.784
		95% CI	(-16.4, 7.7)	(-7.9, 17.6)	(-26.6, 8.2)
		Pr >  t			0.2955
	Week 120	n	6	5	
		LS Mean	-0.849	-0.274	-0.575
		SEM	6.350	6.801	9.238
		95% CI	(-13.4, 11.7)	(-13.7, 13.2)	(-18.8, 17.7)
		Pr >  t			0.9505
	Week 132	n	5	3	
		LS Mean	-2.901	-10.12	7.216
		SEM	6.709	8.050	10.42
		95% CI	(-16.2, 10.4)	(-26.0, 5.8)	(-13.3, 27.8)
		Pr >  t			0.4896
	Week 144	n	5	4	
		LS Mean	3.765	-5.317	9.082
		SEM	6.709	7.294	9.850
		95% CI	(-9.5, 17.0)	(-19.7, 9.1)	(-10.4, 28.5)
		Pr >  t			0.3578
	Week 156	n	4	2	
		LS Mean	-1.866	-4.784	2.917
		SEM	7.209	9.385	11.79
		95% CI	(-16.1, 12.4)	(-23.3, 13.7)	(-20.3, 26.1)
		Pr >  t			0.8047
	Week 168	n	1	1	
		LS Mean	9.121	-5.229	14.350
		SEM	12.51	12.57	17.70
		95% CI	(-15.5, 33.7)	(-30.0, 19.5)	(-20.5, 49.2)
		Pr >  t			0.4183
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	0.323	6.418	-6.095
		SEM	6.347	5.837	7.078
		95% CI	(-12.4, 13.1)	(-5.3, 18.1)	(-20.3, 8.1)
		Pr >  t			0.3927
	Week 16	n	15	17	
		LS Mean	0.308	4.670	-4.362
		SEM	6.635	6.077	7.350
		95% CI	(-13.0, 13.6)	(-7.5, 16.8)	(-19.0, 10.3)
		Pr >  t			0.5549
	Week 24	n	14	11	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	0.879	7.960	-7.081
	SEM	6.719	6.583	7.901
	95% CI	(-12.6,14.3)	(-5.2,21.1)	(-22.8, 8.6)
	Pr >  t			0.3728
	n	12	9	
Week 40	LS Mean	-3.624	2.976	-6.599
	SEM	6.959	6.931	8.327
	95% CI	(-17.5,10.3)	(-10.8,16.8)	(-23.1, 9.9)
	Pr >  t			0.4301
	n	11	7	
Week 48	LS Mean	0.674	4.996	-4.323
	SEM	7.098	7.468	8.816
	95% CI	(-13.5,14.8)	(-9.8,19.8)	(-21.8,13.2)
	Pr >  t			0.6249
	n	8	6	
Week 56	LS Mean	2.061	2.210	-0.148
	SEM	7.541	7.783	9.446
	95% CI	(-12.9,17.1)	(-13.2,17.6)	(-18.8,18.5)
	Pr >  t			0.9875
	n	7	5	
Week 64	LS Mean	8.879	11.481	-2.602
	SEM	7.760	8.162	9.950
	95% CI	(-6.5,24.3)	(-4.7,27.6)	(-22.3,17.1)
	Pr >  t			0.7941
	n	5	3	
Week 72	LS Mean	0.927	1.165	-0.238
	SEM	8.408	9.564	11.58
	95% CI	(-15.7,17.6)	(-17.7,20.1)	(-23.1,22.6)
	Pr >  t			0.9836
	n	5	2	
Week 84	LS Mean	9.203	4.652	4.551
	SEM	8.448	11.07	12.88
	95% CI	(-7.5,25.9)	(-17.2,26.5)	(-20.9,30.0)
	Pr >  t			0.7242
	n	4	2	
Week 96	LS Mean	8.926	4.652	4.275
	SEM	8.919	11.07	13.20
	95% CI	(-8.7,26.6)	(-17.2,26.5)	(-21.8,30.3)
	Pr >  t			0.7464
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	-3.071	4.652	-7.723
		SEM	8.931	11.07	13.21
		95% CI	(-20.7,14.6)	(-17.2,26.5)	(-33.8,18.3)
		Pr >  t			0.5595
	Week 108	n	1	2	
		LS Mean	16.013	5.020	10.993
		SEM	14.57	11.03	17.50
		95% CI	(-12.8,44.8)	(-16.7,26.8)	(-23.6,45.5)
		Pr >  t			0.5308
	Week 120	n	5	1	
		LS Mean	5.871	5.103	0.768
		SEM	8.448	14.51	15.94
		95% CI	(-10.9,22.6)	(-23.5,33.8)	(-30.7,32.2)
		Pr >  t			0.9616
	Week 132	n	3	1	
		LS Mean	-3.948	5.103	-9.051
		SEM	9.737	14.51	16.66
		95% CI	(-23.2,15.3)	(-23.5,33.8)	(-41.9,23.8)
		Pr >  t			0.5877
	Week 144	n	3		
		LS Mean	-3.948		
		SEM	9.737		
		95% CI	(-23.2,15.3)		
		Pr >  t			
	Week 156	n	3		
		LS Mean	1.605		
		SEM	9.737		
		95% CI	(-17.6,20.8)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	6.908		
		SEM	14.56		
		95% CI	(-21.8,35.7)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-9.762		
		SEM	14.56		
		95% CI	(-38.5,19.0)		
		Pr >  t			
	Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	23.568		
		SEM	14.56		
		95% CI	(-5.2,52.3)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	-2.215	-0.741	-1.474
		SEM	4.132	4.135	4.567
		95% CI	(-10.4, 6.0)	(-8.9, 7.4)	(-10.5, 7.5)
		Pr >  t			0.7472
	Week 16	n	30	29	
		LS Mean	-0.908	7.890	-8.799
		SEM	4.304	4.556	5.079
		95% CI	(-9.4, 7.6)	(-1.1,16.9)	(-18.8, 1.2)
		Pr >  t			0.0846
	Week 24	n	26	20	
		LS Mean	10.412	6.492	3.920
		SEM	4.502	5.106	5.660
		95% CI	( 1.5,19.3)	(-3.6,16.6)	(-7.2,15.1)
		Pr >  t			0.4892
	Week 32	n	18	20	
		LS Mean	0.668	6.491	-5.823
		SEM	4.992	5.106	6.042
		95% CI	(-9.2,10.5)	(-3.6,16.6)	(-17.7, 6.1)
		Pr >  t			0.3360
	Week 40	n	18	19	
		LS Mean	1.653	8.416	-6.763
		SEM	4.991	5.174	6.095
		95% CI	(-8.2,11.5)	(-1.8,18.6)	(-18.8, 5.2)
		Pr >  t			0.2681
	Week 48	n	16	14	
		LS Mean	-4.529	12.222	-16.75
		SEM	5.154	5.602	6.596
		95% CI	(-14.7, 5.6)	( 1.2,23.3)	(-29.7,-3.8)
		Pr >  t			0.0116
	Week 56	n	14	10	
		LS Mean	2.767	13.184	-10.42
		SEM	5.356	6.201	7.271
		95% CI	(-7.8,13.3)	( 1.0,25.4)	(-24.7, 3.9)
		Pr >  t			0.1528

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	4.841	16.892	-12.05
		SEM	5.478	6.023	7.215
		95% CI	(-5.9,15.6)	(-5.0,28.7)	(-26.2, 2.1)
		Pr >  t			0.0958
Week 72		n	10	6	
		LS Mean	0.925	5.805	-4.880
		SEM	5.944	7.393	8.717
		95% CI	(-10.8,12.6)	(-8.7,20.3)	(-22.0,12.3)
		Pr >  t			0.5759
Week 84		n	8	7	
		LS Mean	14.383	6.469	7.913
		SEM	6.486	6.996	8.728
		95% CI	(-1.6,27.1)	(-7.3,20.2)	(-9.3,25.1)
		Pr >  t			0.3652
Week 96		n	6	5	
		LS Mean	3.091	24.700	-21.61
		SEM	7.180	7.906	9.990
		95% CI	(-11.0,17.2)	(-9.2,40.2)	(-41.3,-2.0)
		Pr >  t			0.0312
Week 108		n	2	4	
		LS Mean	19.585	12.723	6.863
		SEM	11.42	8.634	13.79
		95% CI	(-2.9,42.1)	(-4.3,29.7)	(-20.3,34.0)
		Pr >  t			0.6190
Week 120		n	4	4	
		LS Mean	-4.134	8.555	-12.69
		SEM	8.428	8.634	11.48
		95% CI	(-20.7,12.4)	(-8.4,25.5)	(-35.3, 9.9)
		Pr >  t			0.2698
Week 132		n	3	1	
		LS Mean	18.306	11.331	6.975
		SEM	9.555	15.84	18.09
		95% CI	(-0.5,37.1)	(-19.8,42.5)	(-28.6,42.6)
		Pr >  t			0.7001
Week 144		n	2		
		LS Mean	16.148		
		SEM	11.36		
		95% CI	(-6.2,38.5)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-1.991	0.172	-2.163		
			SEM	3.868	3.870	3.118		
			95% CI	(-9.6, 5.6)	(-7.4, 7.8)	(-8.3, 4.0)		
					Pr >  t			0.4883
		Week 16	n	79	68			
			LS Mean	-2.858	4.107	-6.965		
			SEM	3.910	4.068	3.378		
			95% CI	(-10.6, 4.8)	(-3.9, 12.1)	(-13.6, -0.3)		
					Pr >  t			0.0398
		Week 24	n	64	55			
			LS Mean	1.794	1.137	0.657		
			SEM	4.025	4.222	3.640		
			95% CI	(-6.1, 9.7)	(-7.2, 9.4)	(-6.5, 7.8)		
					Pr >  t			0.8569
		Week 32	n	49	53			
			LS Mean	3.188	1.831	1.357		
			SEM	4.208	4.246	3.831		
			95% CI	(-5.1, 11.5)	(-6.5, 10.2)	(-6.2, 8.9)		
					Pr >  t			0.7233
		Week 40	n	44	45			
			LS Mean	0.347	2.117	-1.770		
			SEM	4.276	4.342	4.013		
			95% CI	(-8.1, 8.8)	(-6.4, 10.7)	(-9.6, 6.1)		
					Pr >  t			0.6594
		Week 48	n	41	36			
			LS Mean	0.434	3.627	-3.193		
			SEM	4.322	4.493	4.222		
95% CI	(-8.1, 8.9)		(-5.2, 12.5)	(-11.5, 5.1)				
			Pr >  t			0.4497		
Week 56	n	33	32					
	LS Mean	-0.188	4.487	-4.675				
	SEM	4.476	4.584	4.478				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.0, 8.6)	(-4.5, 13.5)	(-13.5, 4.1)
		Pr >  t			0.2968
	Week 64	n	27	31	
		LS Mean	0.815	4.480	-3.665
		SEM	4.641	4.612	4.674
		95% CI	(-8.3, 9.9)	(-4.6, 13.5)	(-12.8, 5.5)
		Pr >  t			0.4331
	Week 72	n	26	26	
		LS Mean	-1.025	3.356	-4.381
		SEM	4.676	4.765	4.860
		95% CI	(-10.2, 8.2)	(-6.0, 12.7)	(-13.9, 5.2)
		Pr >  t			0.3675
	Week 84	n	22	23	
		LS Mean	7.329	7.474	-0.146
		SEM	4.858	4.883	5.133
		95% CI	(-2.2, 16.9)	(-2.1, 17.1)	(-10.2, 9.9)
		Pr >  t			0.9774
	Week 96	n	18	18	
		LS Mean	4.889	8.209	-3.320
		SEM	5.089	5.156	5.601
		95% CI	(-5.1, 14.9)	(-1.9, 18.3)	(-14.3, 7.7)
		Pr >  t			0.5535
	Week 108	n	14	14	
		LS Mean	2.511	7.116	-4.605
		SEM	5.432	5.494	6.209
		95% CI	(-8.2, 13.2)	(-3.7, 17.9)	(-16.8, 7.6)
		Pr >  t			0.4585
	Week 120	n	12	12	
		LS Mean	-2.313	2.527	-4.841
		SEM	5.668	5.732	6.622
		95% CI	(-13.4, 8.8)	(-8.7, 13.8)	(-17.8, 8.2)
		Pr >  t			0.4650
	Week 132	n	9	5	
		LS Mean	4.099	-0.520	4.619
		SEM	6.185	7.657	8.704
		95% CI	(-8.0, 16.2)	(-15.5, 14.5)	(-12.5, 21.7)
		Pr >  t			0.5958
	Week 144	n	7	4	
		LS Mean	10.569	1.705	8.864
		SEM	6.729	8.356	9.695

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-2.6,23.8)	(-14.7,18.1)	(-10.2,27.9)
		Pr >  t			0.3608
	Week 156	n	4	2	
		LS Mean	3.655	2.451	1.204
		SEM	8.296	11.17	13.13
		95% CI	(-12.6,19.9)	(-19.5,24.4)	(-24.6,27.0)
		Pr >  t			0.9270
	Week 168	n	2	1	
		LS Mean	2.661	2.706	-0.046
		SEM	11.12	15.32	18.37
		95% CI	(-19.2,24.5)	(-27.4,32.8)	(-36.1,36.0)
		Pr >  t			0.9980
Yes	Week 8	n	53	48	
		LS Mean	-3.391	4.959	-8.350
		SEM	4.085	4.252	3.989
		95% CI	(-11.5, 4.7)	(-3.4,13.4)	(-16.2,-0.5)
		Pr >  t			0.0376
	Week 16	n	45	39	
		LS Mean	-0.614	3.761	-4.376
		SEM	4.249	4.424	4.240
		95% CI	(-9.0, 7.8)	(-5.0,12.5)	(-12.7, 4.0)
		Pr >  t			0.3031
	Week 24	n	41	26	
		LS Mean	-2.239	11.166	-13.40
		SEM	4.300	4.712	4.625
		95% CI	(-10.7, 6.3)	(-1.9,20.5)	(-22.5,-4.3)
		Pr >  t			0.0040
	Week 32	n	37	20	
		LS Mean	-2.537	5.919	-8.456
		SEM	4.385	4.981	4.933
		95% CI	(-11.2, 6.1)	(-3.9,15.7)	(-18.2, 1.2)
		Pr >  t			0.0874
	Week 40	n	31	17	
		LS Mean	0.562	4.402	-3.840
		SEM	4.500	5.188	5.212
		95% CI	(-8.3, 9.4)	(-5.8,14.6)	(-14.1, 6.4)
		Pr >  t			0.4617
	Week 48	n	28	15	
		LS Mean	1.982	5.936	-3.954
		SEM	4.571	5.332	5.417



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.0,11.0)	(-4.6,16.4)	(-14.6, 6.7)
		Pr >  t			0.4658
	Week 56	n	26	13	
		LS Mean	2.002	4.038	-2.035
		SEM	4.626	5.511	5.641
		95% CI	(-7.1,11.1)	(-6.8,14.9)	(-13.1, 9.1)
		Pr >  t			0.7184
	Week 64	n	20	11	
		LS Mean	3.903	1.289	2.614
		SEM	4.845	5.742	6.045
		95% CI	(-5.6,13.4)	(-10.0,12.6)	(-9.3,14.5)
		Pr >  t			0.6657
	Week 72	n	22	9	
		LS Mean	0.511	6.464	-5.953
		SEM	4.764	6.052	6.278
		95% CI	(-8.9, 9.9)	(-5.4,18.4)	(-18.3, 6.4)
		Pr >  t			0.3435
	Week 84	n	18	10	
		LS Mean	2.028	3.681	-1.652
		SEM	4.957	5.886	6.262
		95% CI	(-7.7,11.8)	(-7.9,15.3)	(-14.0,10.6)
		Pr >  t			0.7920
	Week 96	n	17	6	
		LS Mean	0.317	3.873	-3.556
		SEM	5.004	6.829	7.198
		95% CI	(-9.5,10.2)	(-9.5,17.3)	(-17.7,10.6)
		Pr >  t			0.6215
	Week 108	n	12	7	
		LS Mean	5.700	7.203	-1.503
		SEM	5.437	6.509	7.204
		95% CI	(-5.0,16.4)	(-5.6,20.0)	(-15.7,12.6)
		Pr >  t			0.8348
	Week 120	n	16	4	
		LS Mean	4.441	2.225	2.216
		SEM	5.075	7.845	8.212
		95% CI	(-5.5,14.4)	(-13.2,17.6)	(-13.9,18.3)
		Pr >  t			0.7874
	Week 132	n	11	3	
		LS Mean	-0.002	2.978	-2.980
		SEM	5.559	8.740	9.342

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.9,10.9)	(-14.2,20.1)	(-21.3,15.4)
		Pr >  t			0.7498
	Week 144	n	8	1	
		LS Mean	11.199	-4.713	15.912
		SEM	6.055	13.96	14.55
		95% CI	(-0.7,23.1)	(-32.1,22.7)	(-12.7,44.5)
		Pr >  t			0.2747
	Week 156	n	6	1	
		LS Mean	0.482	28.617	-28.14
		SEM	6.659	13.96	14.80
		95% CI	(-12.6,13.6)	(-1.2,56.0)	(-57.2, 0.9)
		Pr >  t			0.0579
	Week 168	n	2	1	
		LS Mean	3.284	11.947	-8.662
		SEM	10.17	13.96	16.68
		95% CI	(-16.7,23.3)	(-15.5,39.4)	(-41.4,24.1)
		Pr >  t			0.6037
	Week 180	n	1	1	
		LS Mean	-9.993	11.947	-21.94
		SEM	13.82	13.96	19.13
		95% CI	(-37.1,17.2)	(-15.5,39.4)	(-59.5,15.6)
		Pr >  t			0.2519
	Week 192	n	1	1	
		LS Mean	23.337	11.947	11.390
		SEM	13.82	13.96	19.13
		95% CI	(-3.8,50.5)	(-15.5,39.4)	(-26.2,49.0)
		Pr >  t			0.5518

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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Final

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-10.79	-3.293	-7.495
			SEM	8.017	8.997	7.426
			95% CI	(-26.9, 5.3)	(-21.4,14.8)	(-22.3, 7.3)
			Pr >  t			0.3167
		Week 16	n	14	17	
			LS Mean	-9.256	1.716	-10.97
			SEM	8.123	9.207	7.863
			95% CI	(-25.6, 7.1)	(-16.8,20.2)	(-26.6, 4.7)
			Pr >  t			0.1671
		Week 24	n	14	11	
			LS Mean	-4.494	-2.379	-2.115
			SEM	8.123	9.570	8.293
			95% CI	(-20.8,11.8)	(-21.6,16.8)	(-18.6,14.4)
			Pr >  t			0.7993
		Week 32	n	10	10	
			LS Mean	-12.01	-3.743	-8.263
			SEM	8.703	9.698	8.725
			95% CI	(-29.4, 5.4)	(-23.2,15.7)	(-25.6, 9.0)
			Pr >  t			0.3459
		Week 40	n	8	10	
			LS Mean	-10.67	0.432	-11.10
			SEM	8.977	9.688	8.979
			95% CI	(-28.6, 7.2)	(-19.0,19.8)	(-28.9, 6.7)
			Pr >  t			0.2191
		Week 48	n	7	11	
			LS Mean	-16.21	4.283	-20.50
			SEM	9.146	9.603	9.084
95% CI	(-34.4, 2.0)		(-15.0,23.5)	(-38.5,-2.5)		
	Pr >  t			0.0260		
Week 56	n	6	9			
	LS Mean	-4.770	-0.294	-4.476		
	SEM	9.362	9.814	9.537		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-23.4,13.8)	(-19.9,19.3)	(-23.3,14.4)
		Pr >  t			0.6396
	Week 64	n	5	8	
		LS Mean	-10.94	-5.699	-5.244
		SEM	9.669	9.945	9.968
		95% CI	(-30.1, 8.3)	(-25.6,14.2)	(-24.9,14.5)
		Pr >  t			0.5997
	Week 72	n	7	7	
		LS Mean	-10.40	2.756	-13.15
		SEM	9.124	10.11	9.620
		95% CI	(-28.6, 7.8)	(-17.4,22.9)	(-32.2, 5.9)
		Pr >  t			0.1739
	Week 84	n	7	7	
		LS Mean	-5.636	5.138	-10.77
		SEM	9.124	10.11	9.620
		95% CI	(-23.8,12.5)	(-15.0,25.3)	(-29.8, 8.3)
		Pr >  t			0.2648
	Week 96	n	5	6	
		LS Mean	-7.555	1.640	-9.195
		SEM	9.665	10.32	10.34
		95% CI	(-26.7,11.6)	(-18.9,22.2)	(-29.6,11.2)
		Pr >  t			0.3754
	Week 108	n	4	6	
		LS Mean	-11.34	7.197	-18.54
		SEM	10.12	10.32	10.77
		95% CI	(-31.4, 8.7)	(-13.4,27.8)	(-39.8, 2.7)
		Pr >  t			0.0870
	Week 120	n	4	4	
		LS Mean	-3.191	8.318	-11.51
		SEM	10.12	11.02	11.45
		95% CI	(-23.3,16.9)	(-13.6,30.2)	(-34.1,11.1)
		Pr >  t			0.3161
	Week 132	n	3	1	
		LS Mean	-7.392	7.486	-14.88
		SEM	10.81	15.88	16.61
		95% CI	(-28.8,14.0)	(-23.8,38.8)	(-47.6,17.9)
		Pr >  t			0.3714
	Week 144	n	1	1	
		LS Mean	48.530	-2.981	51.512
		SEM	15.26	15.90	19.82

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	( 18.4,78.6)	(-34.3,28.4)	( 12.4,90.6)
		Pr >  t			0.0100
		n	35	37	
	Week 16	LS Mean	12.009	17.844	-5.835
		SEM	9.826	10.15	4.529
		95% CI	( -7.4,31.4)	( -2.2,37.9)	(-14.8, 3.1)
	Week 24	Pr >  t			0.1994
		n	34	30	
		LS Mean	12.765	21.713	-8.948
	Week 32	SEM	10.11	10.23	4.720
		95% CI	( -7.2,32.7)	( 1.5,41.9)	(-18.3, 0.4)
		Pr >  t			0.0596
	Week 40	n	32	23	
		LS Mean	13.831	26.908	-13.08
		SEM	10.13	10.34	5.044
	Week 48	95% CI	( -6.2,33.8)	( 6.5,47.3)	(-23.0,-3.1)
		Pr >  t			0.0102
		n	21	22	
	Week 56	LS Mean	20.463	20.267	0.196
		SEM	10.29	10.37	5.437
		95% CI	( 0.2,40.8)	( -0.2,40.7)	(-10.5,10.9)
	Week 64	Pr >  t			0.9713
		n	20	20	
		LS Mean	21.344	23.431	-2.087
	Week 8	SEM	10.33	10.42	5.582
		95% CI	( 1.0,41.7)	( 2.9,44.0)	(-13.1, 8.9)
		Pr >  t			0.7088
	Week 16	n	19	12	
LS Mean		12.751	23.107	-10.36	
SEM		10.35	10.75	6.214	
Week 24	95% CI	( -7.7,33.2)	( 1.9,44.3)	(-22.6, 1.9)	
	Pr >  t			0.0966	
	n	16	8		
Week 32	LS Mean	17.513	26.273	-8.759	
	SEM	10.45	11.15	7.023	
	95% CI	( -3.1,38.1)	( 4.3,48.3)	(-22.6, 5.1)	
Week 40	Pr >  t			0.2131	
	n	12	11		
	LS Mean	22.292	25.472	-3.180	
Week 48	SEM	10.65	10.83	6.825	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.3,43.3)	( 4.1,46.8)	(-16.6,10.2)
		Pr >  t			0.6416
	Week 72	n	13	7	
		LS Mean	13.790	23.493	-9.703
		SEM	10.60	11.32	7.490
		95% CI	( -7.1,34.7)	( 1.2,45.8)	(-24.4, 5.0)
		Pr >  t			0.1959
	Week 84	n	12	6	
		LS Mean	25.502	32.115	-6.613
		SEM	10.65	11.54	7.877
		95% CI	( 4.5,46.5)	( 9.4,54.8)	(-22.1, 8.9)
		Pr >  t			0.4017
	Week 96	n	7	6	
		LS Mean	20.417	31.154	-10.74
		SEM	11.20	11.54	8.606
		95% CI	( -1.6,42.5)	( 8.4,53.9)	(-27.7, 6.2)
		Pr >  t			0.2129
	Week 108	n	5	3	
		LS Mean	19.863	27.384	-7.521
		SEM	11.71	12.90	10.92
		95% CI	( -3.2,42.9)	( 2.0,52.8)	(-29.0,14.0)
		Pr >  t			0.4915
	Week 120	n	8	3	
		LS Mean	19.086	27.384	-8.297
		SEM	11.07	12.90	10.22
		95% CI	( -2.7,40.9)	( 2.0,52.8)	(-28.4,11.8)
		Pr >  t			0.4174
	Week 132	n	2	1	
		LS Mean	37.815	24.982	12.833
		SEM	14.00	17.28	17.59
		95% CI	( 10.3,65.3)	( -9.0,59.0)	(-21.8,47.4)
		Pr >  t			0.4662
	Week 144	n	2		
		LS Mean	16.632		
		SEM	14.04		
		95% CI	(-11.0,44.2)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	8.297		
		SEM	14.04		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.3,35.9)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	-1.530	2.530	-4.060
		SEM	3.653	3.790	3.556
		95% CI	(-8.7, 5.7)	(-4.9,10.0)	(-11.1, 2.9)
		Pr >  t			0.2545
	Week 16	n	70	52	
		LS Mean	-1.774	0.442	-2.216
		SEM	3.741	3.978	3.786
		95% CI	(-9.1, 5.6)	(-7.4, 8.3)	(-9.7, 5.2)
		Pr >  t			0.5588
	Week 24	n	54	40	
		LS Mean	0.390	0.442	-0.052
		SEM	3.887	4.192	4.120
		95% CI	(-7.3, 8.0)	(-7.8, 8.7)	(-8.2, 8.0)
		Pr >  t			0.9899
	Week 32	n	50	36	
		LS Mean	0.978	3.415	-2.436
		SEM	3.948	4.269	4.243
		95% CI	(-6.8, 8.8)	(-5.0,11.8)	(-10.8, 5.9)
		Pr >  t			0.5662
	Week 40	n	42	28	
		LS Mean	-1.631	-0.586	-1.045
		SEM	4.055	4.492	4.550
		95% CI	(-9.6, 6.4)	(-9.4, 8.2)	(-10.0, 7.9)
		Pr >  t			0.8184
	Week 48	n	38	24	
		LS Mean	5.659	0.450	5.209
		SEM	4.122	4.637	4.752
		95% CI	(-2.5,13.8)	(-8.7, 9.6)	(-4.1,14.5)
		Pr >  t			0.2734
	Week 56	n	33	24	
		LS Mean	0.766	2.795	-2.029
		SEM	4.224	4.640	4.847
		95% CI	(-7.5, 9.1)	(-6.3,11.9)	(-11.5, 7.5)
		Pr >  t			0.6757
	Week 64	n	27	19	
		LS Mean	0.113	2.918	-2.805
		SEM	4.385	4.890	5.224

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.5, 8.7)	(-6.7, 12.5)	(-13.1, 7.5)
		Pr >  t			0.5914
	Week 72	n	26	17	
		LS Mean	1.646	2.823	-1.177
		SEM	4.420	5.021	5.375
		95% CI	(-7.0, 10.3)	(-7.0, 12.7)	(-11.7, 9.4)
		Pr >  t			0.8268
	Week 84	n	18	16	
		LS Mean	3.405	0.569	2.837
		SEM	4.827	5.099	5.768
		95% CI	(-6.1, 12.9)	(-9.4, 10.6)	(-8.5, 14.2)
		Pr >  t			0.6230
	Week 96	n	20	10	
		LS Mean	3.685	3.377	0.308
		SEM	4.697	5.818	6.323
		95% CI	(-5.5, 12.9)	(-8.0, 14.8)	(-12.1, 12.7)
		Pr >  t			0.9611
	Week 108	n	14	10	
		LS Mean	5.289	2.668	2.621
		SEM	5.162	5.818	6.670
		95% CI	(-4.8, 15.4)	(-8.8, 14.1)	(-10.5, 15.7)
		Pr >  t			0.6945
	Week 120	n	14	7	
		LS Mean	2.518	-5.773	8.290
		SEM	5.145	6.538	7.303
		95% CI	(-7.6, 12.6)	(-18.6, 7.1)	(-6.0, 22.6)
		Pr >  t			0.2566
	Week 132	n	12	5	
		LS Mean	-4.118	-6.209	2.091
		SEM	5.392	7.385	8.222
		95% CI	(-14.7, 6.5)	(-20.7, 8.3)	(-14.0, 18.2)
		Pr >  t			0.7993
	Week 144	n	11	4	
		LS Mean	6.789	-2.221	9.010
		SEM	5.517	8.052	8.913
		95% CI	(-4.0, 17.6)	(-18.0, 13.6)	(-8.5, 26.5)
		Pr >  t			0.3124
	Week 156	n	8	3	
		LS Mean	3.627	8.204	-4.576
		SEM	6.131	9.050	10.17



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168	95% CI	(-8.4,15.7)	(-9.6,26.0)	(-24.5,15.4)
	Pr >  t			0.6529
	n	4	2	
	LS Mean	2.716	3.887	-1.171
	SEM	7.950	10.77	12.78
Week 180	95% CI	(-12.9,18.3)	(-17.3,25.0)	(-26.3,23.9)
	Pr >  t			0.9270
	n	1	1	
	LS Mean	-10.17	6.883	-17.05
	SEM	14.72	14.76	20.46
Week 192	95% CI	(-39.1,18.7)	(-22.1,35.9)	(-57.2,23.1)
	Pr >  t			0.4047
	n	1	1	
	LS Mean	23.159	6.883	16.277
	SEM	14.72	14.76	20.46
	95% CI	(-5.7,52.0)	(-22.1,35.9)	(-23.9,56.4)
	Pr >  t			0.4265

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	-1.530	2.530	-4.060		
			SEM	3.653	3.790	3.556		
			95% CI	(-8.7, 5.7)	(-4.9, 10.0)	(-11.1, 2.9)		
					Pr >  t			0.2545
		Week 16	n	70	52			
			LS Mean	-1.774	0.442	-2.216		
			SEM	3.741	3.978	3.786		
			95% CI	(-9.1, 5.6)	(-7.4, 8.3)	(-9.7, 5.2)		
					Pr >  t			0.5588
		Week 24	n	54	40			
			LS Mean	0.390	0.442	-0.052		
			SEM	3.887	4.192	4.120		
			95% CI	(-7.3, 8.0)	(-7.8, 8.7)	(-8.2, 8.0)		
					Pr >  t			0.9899
		Week 32	n	50	36			
			LS Mean	0.978	3.415	-2.436		
			SEM	3.948	4.269	4.243		
			95% CI	(-6.8, 8.8)	(-5.0, 11.8)	(-10.8, 5.9)		
					Pr >  t			0.5662
		Week 40	n	42	28			
			LS Mean	-1.631	-0.586	-1.045		
			SEM	4.055	4.492	4.550		
			95% CI	(-9.6, 6.4)	(-9.4, 8.2)	(-10.0, 7.9)		
			Pr >  t			0.8184		
Week 48	n	38	24					
	LS Mean	5.659	0.450	5.209				
	SEM	4.122	4.637	4.752				
	95% CI	(-2.5, 13.8)	(-8.7, 9.6)	(-4.1, 14.5)				
			Pr >  t			0.2734		
Week 56	n	33	24					
	LS Mean	0.766	2.795	-2.029				
		SEM	4.224	4.640	4.847			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.5, 9.1)	(-6.3, 11.9)	(-11.5, 7.5)
	Pr >  t			0.6757
	n	27	19	
	LS Mean	0.113	2.918	-2.805
	SEM	4.385	4.890	5.224
Week 72	95% CI	(-8.5, 8.7)	(-6.7, 12.5)	(-13.1, 7.5)
	Pr >  t			0.5914
	n	26	17	
	LS Mean	1.646	2.823	-1.177
	SEM	4.420	5.021	5.375
Week 84	95% CI	(-7.0, 10.3)	(-7.0, 12.7)	(-11.7, 9.4)
	Pr >  t			0.8268
	n	18	16	
	LS Mean	3.405	0.569	2.837
	SEM	4.827	5.099	5.768
Week 96	95% CI	(-6.1, 12.9)	(-9.4, 10.6)	(-8.5, 14.2)
	Pr >  t			0.6230
	n	20	10	
	LS Mean	3.685	3.377	0.308
	SEM	4.697	5.818	6.323
Week 108	95% CI	(-5.5, 12.9)	(-8.0, 14.8)	(-12.1, 12.7)
	Pr >  t			0.9611
	n	14	10	
	LS Mean	5.289	2.668	2.621
	SEM	5.162	5.818	6.670
Week 120	95% CI	(-4.8, 15.4)	(-8.8, 14.1)	(-10.5, 15.7)
	Pr >  t			0.6945
	n	14	7	
	LS Mean	2.518	-5.773	8.290
	SEM	5.145	6.538	7.303
Week 132	95% CI	(-7.6, 12.6)	(-18.6, 7.1)	(-6.0, 22.6)
	Pr >  t			0.2566
	n	12	5	
	LS Mean	-4.118	-6.209	2.091
	SEM	5.392	7.385	8.222
Week 144	95% CI	(-14.7, 6.5)	(-20.7, 8.3)	(-14.0, 18.2)
	Pr >  t			0.7993
	n	11	4	
Week 144	LS Mean	6.789	-2.221	9.010
	SEM	5.517	8.052	8.913

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.0,17.6)	(-18.0,13.6)	(-8.5,26.5)
		Pr >  t			0.3124
	Week 156	n	8	3	
		LS Mean	3.627	8.204	-4.576
		SEM	6.131	9.050	10.17
		95% CI	(-8.4,15.7)	(-9.6,26.0)	(-24.5,15.4)
		Pr >  t			0.6529
	Week 168	n	4	2	
		LS Mean	2.716	3.887	-1.171
		SEM	7.950	10.77	12.78
		95% CI	(-12.9,18.3)	(-17.3,25.0)	(-26.3,23.9)
		Pr >  t			0.9270
	Week 180	n	1	1	
		LS Mean	-10.17	6.883	-17.05
		SEM	14.72	14.76	20.46
		95% CI	(-39.1,18.7)	(-22.1,35.9)	(-57.2,23.1)
		Pr >  t			0.4047
	Week 192	n	1	1	
		LS Mean	23.159	6.883	16.277
		SEM	14.72	14.76	20.46
		95% CI	(-5.7,52.0)	(-22.1,35.9)	(-23.9,56.4)
		Pr >  t			0.4265
Exon 9	Week 8	n	53	64	
		LS Mean	-4.388	2.045	-6.433
		SEM	5.525	5.879	3.721
		95% CI	(-15.3, 6.5)	(-9.6,13.7)	(-13.8, 0.9)
		Pr >  t			0.0851
	Week 16	n	48	48	
		LS Mean	-3.982	5.904	-9.886
		SEM	5.643	5.991	3.980
		95% CI	(-15.1, 7.2)	(-5.9,17.7)	(-17.7,-2.1)
		Pr >  t			0.0136
	Week 24	n	46	36	
		LS Mean	-1.829	8.312	-10.14
		SEM	5.660	6.120	4.220
		95% CI	(-13.0, 9.3)	(-3.8,20.4)	(-18.4,-1.8)
		Pr >  t			0.0168
	Week 32	n	31	33	
		LS Mean	0.651	3.355	-2.704
		SEM	5.937	6.171	4.542

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-11.1,12.4)	(-8.8,15.5)	(-11.6, 6.2)
	Pr >  t			0.5519
Week 40	n	28	30	
	LS Mean	1.982	6.871	-4.890
	SEM	6.002	6.223	4.692
	95% CI	(-9.9,13.8)	(-5.4,19.1)	(-14.1, 4.3)
	Pr >  t			0.2980
Week 48	n	26	23	
	LS Mean	-5.840	8.617	-14.46
	SEM	6.045	6.392	4.964
	95% CI	(-17.8, 6.1)	(-4.0,21.2)	(-24.2,-4.7)
	Pr >  t			0.0038
Week 56	n	22	17	
	LS Mean	0.814	8.006	-7.191
	SEM	6.153	6.633	5.395
	95% CI	(-11.3,12.9)	(-5.1,21.1)	(-17.8, 3.4)
	Pr >  t			0.1831
Week 64	n	17	19	
	LS Mean	2.386	5.632	-3.245
	SEM	6.360	6.539	5.521
	95% CI	(-10.1,14.9)	(-7.3,18.5)	(-14.1, 7.6)
	Pr >  t			0.5568
Week 72	n	20	14	
	LS Mean	-3.360	8.309	-11.67
	SEM	6.231	6.821	5.706
	95% CI	(-15.6, 8.9)	(-5.1,21.7)	(-22.9,-0.5)
	Pr >  t			0.0413
Week 84	n	19	13	
	LS Mean	5.877	13.594	-7.717
	SEM	6.263	6.898	5.839
	95% CI	(-6.5,18.2)	( 0.0,27.2)	(-19.2, 3.8)
	Pr >  t			0.1868
Week 96	n	12	12	
	LS Mean	1.738	11.547	-9.809
	SEM	6.719	6.989	6.424
	95% CI	(-11.5,15.0)	(-2.2,25.3)	(-22.4, 2.8)
	Pr >  t			0.1273
Week 108	n	9	9	
	LS Mean	-0.211	13.124	-13.34
	SEM	7.107	7.362	7.209

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120		95% CI	(-14.2,13.8)	(-1.4,27.6)	(-27.5, 0.8)
		Pr >  t			0.0648
		n	12	7	
		LS Mean	2.370	13.482	-11.11
		SEM	6.737	7.768	7.273
Week 132		95% CI	(-10.9,15.6)	(-1.8,28.8)	(-25.4, 3.2)
		Pr >  t			0.1271
		n	5	2	
		LS Mean	8.538	11.548	-3.009
		SEM	8.198	11.30	11.92
Week 144		95% CI	(-7.6,24.6)	(-10.7,33.7)	(-26.4,20.4)
		Pr >  t			0.8008
		n	3	1	
		LS Mean	18.722	4.083	14.639
		SEM	9.634	14.95	16.24
Week 156		95% CI	(-0.2,37.6)	(-25.3,33.4)	(-17.3,46.5)
		Pr >  t			0.3677
		n	2		
		LS Mean	-7.976		
		SEM	11.17		
		95% CI	(-29.9,14.0)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-26: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Dyspnoe“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73	
			LS Mean	3.399	4.199	-0.800
			SEM	2.889	2.913	2.725
			95% CI	(-2.3, 9.1)	(-1.5, 9.9)	(-6.2, 4.6)
			Pr >  t			0.7692
	Week 16	n	67	56		
		LS Mean	3.858	3.795	0.063	
		SEM	2.950	3.124	2.983	
		95% CI	(-2.0, 9.7)	(-2.4, 9.9)	(-5.8, 5.9)	
		Pr >  t			0.9832	
	Week 24	n	61	46		
		LS Mean	1.615	4.491	-2.876	
		SEM	3.023	3.249	3.179	
		95% CI	(-4.3, 7.6)	(-1.9, 10.9)	(-9.1, 3.4)	
		Pr >  t			0.3659	
	Week 32	n	52	41		
		LS Mean	2.103	3.138	-1.035	
		SEM	3.158	3.355	3.356	
		95% CI	(-4.1, 8.3)	(-3.5, 9.7)	(-7.6, 5.6)	
		Pr >  t			0.7580	
	Week 40	n	45	36		
		LS Mean	0.502	6.066	-5.564	
		SEM	3.251	3.478	3.545	
		95% CI	(-5.9, 6.9)	(-0.8, 12.9)	(-12.5, 1.4)	
Pr >  t				0.1170		
Week 48	n	42	30			
	LS Mean	1.770	5.319	-3.549		
	SEM	3.301	3.633	3.742		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-4.7, 8.3)	(-1.8,12.5)	(-10.9, 3.8)
	Pr >  t			0.3432
	n	35	24	
	LS Mean	3.541	4.400	-0.859
	SEM	3.437	3.854	4.075
Week 64	95% CI	(-3.2,10.3)	(-3.2,12.0)	(-8.9, 7.1)
	Pr >  t			0.8331
	n	25	25	
	LS Mean	-0.433	4.202	-4.635
	SEM	3.735	3.813	4.299
Week 72	95% CI	(-7.8, 6.9)	(-3.3,11.7)	(-13.1, 3.8)
	Pr >  t			0.2813
	n	27	20	
	LS Mean	6.022	2.514	3.508
	SEM	3.662	4.057	4.455
Week 84	95% CI	(-1.2,13.2)	(-5.5,10.5)	(-5.2,12.3)
	Pr >  t			0.4313
	n	23	19	
	LS Mean	1.993	3.000	-1.008
	SEM	3.842	4.119	4.645
Week 96	95% CI	(-5.6, 9.5)	(-5.1,11.1)	(-10.1, 8.1)
	Pr >  t			0.8283
	n	20	13	
	LS Mean	0.204	1.979	-1.775
	SEM	4.000	4.645	5.237
Week 108	95% CI	(-7.7, 8.1)	(-7.1,11.1)	(-12.1, 8.5)
	Pr >  t			0.7348
	n	17	13	
	LS Mean	-0.151	4.690	-4.841
	SEM	4.204	4.646	5.395
Week 120	95% CI	(-8.4, 8.1)	(-4.4,13.8)	(-15.4, 5.7)
	Pr >  t			0.3697
	n	17	12	
	LS Mean	4.206	4.774	-0.567
	SEM	4.203	4.775	5.506
Week 132	95% CI	(-4.0,12.5)	(-4.6,14.1)	(-11.4,10.2)
	Pr >  t			0.9180
	n	13	6	
	LS Mean	3.769	15.736	-11.97
	SEM	4.589	6.193	7.019



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.2,12.8)	(-3.6,27.9)	(-25.7, 1.8)
		Pr >  t			0.0886
	Week 144	n	11	4	
		LS Mean	5.412	3.401	2.011
		SEM	4.867	7.348	8.217
		95% CI	(-4.1,15.0)	(-11.0,17.8)	(-14.1,18.1)
		Pr >  t			0.8067
	Week 156	n	7	2	
		LS Mean	3.618	3.996	-0.378
		SEM	5.774	10.02	11.12
		95% CI	(-7.7,15.0)	(-15.7,23.7)	(-22.2,21.4)
		Pr >  t			0.9729
	Week 168	n	3	1	
		LS Mean	7.987	4.039	3.948
		SEM	8.282	13.90	15.86
		95% CI	(-8.3,24.2)	(-23.2,31.3)	(-27.2,35.1)
		Pr >  t			0.8035
	Week 180	n	1	1	
		LS Mean	31.822	4.039	27.783
		SEM	13.87	13.90	19.38
		95% CI	(-4.6,59.1)	(-23.2,31.3)	(-10.3,65.8)
		Pr >  t			0.1521
	Week 192	n	1	1	
		LS Mean	31.822	4.039	27.783
		SEM	13.87	13.90	19.38
		95% CI	(-4.6,59.1)	(-23.2,31.3)	(-10.3,65.8)
		Pr >  t			0.1521
Present	Week 8	n	65	67	
		LS Mean	0.456	1.268	-0.812
		SEM	3.637	3.737	3.179
		95% CI	(-6.7, 7.6)	(-6.1, 8.6)	(-7.1, 5.4)
		Pr >  t			0.7985
	Week 16	n	57	51	
		LS Mean	-0.988	1.660	-2.649
		SEM	3.790	3.929	3.453
		95% CI	(-8.5, 6.5)	(-6.1, 9.4)	(-9.4, 4.1)
		Pr >  t			0.4435
	Week 24	n	44	35	
		LS Mean	0.872	8.904	-8.032
		SEM	3.932	4.243	3.920

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-6.9, 8.6)	( 0.6,17.3)	(-15.7,-0.3)
	Pr >  t			0.0410
	n	34	32	
	LS Mean	-1.532	-0.249	-1.283
	SEM	4.144	4.322	4.189
Week 40	95% CI	(-9.7, 6.6)	(-8.8, 8.3)	(-9.5, 6.9)
	Pr >  t			0.7595
	n	30	26	
	LS Mean	1.018	3.500	-2.482
	SEM	4.246	4.503	4.477
Week 48	95% CI	(-7.3, 9.4)	(-5.4,12.4)	(-11.3, 6.3)
	Pr >  t			0.5795
	n	27	21	
	LS Mean	2.245	8.100	-5.855
	SEM	4.330	4.718	4.772
Week 56	95% CI	(-6.3,10.8)	(-1.2,17.4)	(-15.2, 3.5)
	Pr >  t			0.2203
	n	24	21	
	LS Mean	-2.424	3.290	-5.714
	SEM	4.439	4.717	4.874
Week 64	95% CI	(-11.2, 6.3)	(-6.0,12.6)	(-15.3, 3.9)
	Pr >  t			0.2415
	n	22	17	
	LS Mean	2.792	4.152	-1.360
	SEM	4.525	4.960	5.187
Week 72	95% CI	(-6.1,11.7)	(-5.6,13.9)	(-11.5, 8.8)
	Pr >  t			0.7933
	n	21	15	
	LS Mean	3.632	5.417	-1.785
	SEM	4.576	5.123	5.385
Week 84	95% CI	(-5.4,12.6)	(-4.6,15.5)	(-12.4, 8.8)
	Pr >  t			0.7403
	n	17	14	
	LS Mean	3.882	5.798	-1.916
	SEM	4.831	5.215	5.674
Week 96	95% CI	(-5.6,13.4)	(-4.4,16.0)	(-13.1, 9.2)
	Pr >  t			0.7357
	n	15	11	
	LS Mean	1.934	14.284	-12.35
	SEM	4.970	5.583	6.147

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108		95% CI	(-7.8,11.7)	(-3.3,25.3)	(-24.4,-0.3)
		Pr >  t			0.0449
		n	9	8	
		LS Mean	-3.374	8.117	-11.49
		SEM	5.813	6.169	7.317
Week 120		95% CI	(-14.8, 8.0)	(-4.0,20.2)	(-25.9, 2.9)
		Pr >  t			0.1168
		n	11	4	
		LS Mean	1.568	-6.781	8.349
		SEM	5.442	7.952	8.652
Week 132		95% CI	(-9.1,12.3)	(-22.4, 8.8)	(-8.6,25.3)
		Pr >  t			0.3349
		n	7	2	
		LS Mean	4.188	11.418	-7.230
		SEM	6.333	10.61	11.59
Week 144		95% CI	(-8.2,16.6)	(-9.4,32.3)	(-30.0,15.5)
		Pr >  t			0.5331
		n	4	1	
		LS Mean	10.792	5.007	5.785
		SEM	7.775	14.56	15.97
Week 156		95% CI	(-4.5,26.1)	(-23.6,33.6)	(-25.6,37.2)
		Pr >  t			0.7174
		n	3	1	
		LS Mean	-7.120	5.007	-12.13
		SEM	8.823	14.56	16.48
Week 168		95% CI	(-24.4,10.2)	(-23.6,33.6)	(-44.5,20.2)
		Pr >  t			0.4622
		n	1	1	
		LS Mean	-0.248	5.007	-5.256
		SEM	14.52	14.56	20.11
	95% CI	(-28.8,28.3)	(-23.6,33.6)	(-44.8,34.3)	
	Pr >  t			0.7940	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Presence of Lung Metastases (L)	No	Week 8	n	98	84	
			LS Mean	3.000	2.412	0.588
			SEM	2.391	2.538	2.464
			95% CI	(-1.7, 7.7)	(-2.6, 7.4)	(-4.3, 5.4)
			Pr >  t			0.8115
		Week 16	n	86	68	
			LS Mean	3.896	4.110	-0.214
			SEM	2.463	2.674	2.663
			95% CI	(-1.0, 8.7)	(-1.1, 9.4)	(-5.4, 5.0)
			Pr >  t			0.9360
		Week 24	n	73	48	
			LS Mean	0.391	5.764	-5.373
			SEM	2.557	2.929	2.988
			95% CI	(-4.6, 5.4)	( 0.0,11.5)	(-11.2, 0.5)
			Pr >  t			0.0726
		Week 32	n	60	43	
			LS Mean	1.182	3.082	-1.900
			SEM	2.710	3.030	3.172
			95% CI	(-4.1, 6.5)	(-2.9, 9.0)	(-8.1, 4.3)
			Pr >  t			0.5493
		Week 40	n	50	38	
			LS Mean	1.567	4.375	-2.808
			SEM	2.830	3.146	3.373
			95% CI	(-4.0, 7.1)	(-1.8,10.6)	(-9.4, 3.8)
Pr >  t				0.4054		
Week 48	n	48	31			
	LS Mean	1.333	3.529	-2.197		
	SEM	2.860	3.328	3.569		
	95% CI	(-4.3, 7.0)	(-3.0,10.1)	(-9.2, 4.8)		
	Pr >  t			0.5383		
Week 56	n	41	25			
	LS Mean	1.900	5.081	-3.181		
	SEM	2.976	3.551	3.870		
	95% CI	(-3.9, 7.7)	(-1.9,12.1)	(-10.8, 4.4)		
	Pr >  t			0.4113		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n		30	24	
	LS Mean		0.020	3.648	-3.628
	SEM		3.244	3.598	4.127
	95% CI		(-6.3, 6.4)	(-3.4, 10.7)	(-11.7, 4.5)
	Pr >  t				0.3795
Week 72	n		32	19	
	LS Mean		5.384	1.854	3.530
	SEM		3.185	3.880	4.330
	95% CI		(-0.9, 11.6)	(-5.8, 9.5)	(-5.0, 12.0)
	Pr >  t				0.4151
Week 84	n		26	19	
	LS Mean		0.907	1.921	-1.014
	SEM		3.411	3.880	4.485
	95% CI		(-5.8, 7.6)	(-5.7, 9.5)	(-9.8, 7.8)
	Pr >  t				0.8212
Week 96	n		23	14	
	LS Mean		2.146	3.141	-0.995
	SEM		3.537	4.317	4.965
	95% CI		(-4.8, 9.1)	(-5.3, 11.6)	(-10.7, 8.7)
	Pr >  t				0.8412
Week 108	n		19	13	
	LS Mean		-0.475	4.393	-4.868
	SEM		3.785	4.435	5.236
	95% CI		(-7.9, 7.0)	(-4.3, 13.1)	(-15.1, 5.4)
	Pr >  t				0.3527
Week 120	n		19	11	
	LS Mean		3.344	4.675	-1.331
	SEM		3.771	4.725	5.484
	95% CI		(-4.1, 10.7)	(-4.6, 13.9)	(-12.1, 9.4)
	Pr >  t				0.8083
Week 132	n		15	5	
	LS Mean		4.268	18.141	-13.87
	SEM		4.116	6.534	7.285
	95% CI		(-3.8, 12.3)	( 5.3, 31.0)	(-28.2, 0.4)
	Pr >  t				0.0572
Week 144	n		12	3	
	LS Mean		4.591	3.449	1.143
	SEM		4.464	8.229	9.012
	95% CI		(-4.2, 13.4)	(-12.7, 19.6)	(-16.5, 18.8)
	Pr >  t				0.8991

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 156	n	7	2	
		LS Mean	3.252	3.766	-0.515
		SEM	5.581	9.929	11.10
		95% CI	(-7.7,14.2)	(-15.7,23.3)	(-22.3,21.3)
		Pr >  t			0.9630
	Week 168	n	3	1	
		LS Mean	7.651	3.822	3.830
		SEM	8.150	13.84	15.86
		95% CI	(-8.3,23.6)	(-23.3,31.0)	(-27.3,34.9)
		Pr >  t			0.8092
	Week 180	n	1	1	
		LS Mean	31.509	3.822	27.687
		SEM	13.80	13.84	19.37
		95% CI	(-4.4,58.6)	(-23.3,31.0)	(-10.3,65.7)
		Pr >  t			0.1533
	Week 192	n	1	1	
		LS Mean	31.509	3.822	27.687
		SEM	13.80	13.84	19.37
		95% CI	(-4.4,58.6)	(-23.3,31.0)	(-10.3,65.7)
		Pr >  t			0.1533
Yes	Week 8	n	44	56	
		LS Mean	6.888	9.990	-3.102
		SEM	5.921	5.654	3.721
		95% CI	(-4.8,18.6)	(-1.2,21.1)	(-10.4, 4.2)
		Pr >  t			0.4053
	Week 16	n	38	39	
		LS Mean	3.698	7.821	-4.123
		SEM	6.117	6.031	4.112
		95% CI	(-8.4,15.7)	(-4.1,19.7)	(-12.2, 4.0)
		Pr >  t			0.3169
	Week 24	n	32	33	
		LS Mean	10.078	14.305	-4.227
		SEM	6.218	6.118	4.389
		95% CI	(-2.2,22.3)	(-2.3,26.4)	(-12.9, 4.4)
		Pr >  t			0.3361
	Week 32	n	26	30	
		LS Mean	5.789	6.623	-0.834
		SEM	6.349	6.182	4.654
		95% CI	(-6.7,18.3)	(-5.5,18.8)	(-10.0, 8.3)
		Pr >  t			0.8579

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	n		25	24	
	LS Mean		5.348	12.844	-7.496
	SEM		6.379	6.329	4.887
	95% CI		(-7.2,17.9)	(0.4,25.3)	(-17.1, 2.1)
	Pr >  t				0.1259
Week 48	n		21	20	
	LS Mean		9.701	17.856	-8.155
	SEM		6.500	6.471	5.222
	95% CI		(-3.1,22.5)	(5.1,30.6)	(-18.4, 2.1)
	Pr >  t				0.1191
Week 56	n		18	20	
	LS Mean		5.907	9.448	-3.540
	SEM		6.627	6.471	5.379
	95% CI		(-7.1,19.0)	(-3.3,22.2)	(-14.1, 7.0)
	Pr >  t				0.5108
Week 64	n		17	18	
	LS Mean		9.645	11.928	-2.283
	SEM		6.680	6.561	5.551
	95% CI		(-3.5,22.8)	(-1.0,24.8)	(-13.2, 8.6)
	Pr >  t				0.6810
Week 72	n		16	16	
	LS Mean		10.706	13.151	-2.445
	SEM		6.739	6.672	5.749
	95% CI		(-2.6,24.0)	(0.0,26.3)	(-13.7, 8.8)
	Pr >  t				0.6708
Week 84	n		14	14	
	LS Mean		12.834	14.328	-1.494
	SEM		6.869	6.806	6.053
	95% CI		(-0.7,26.3)	(0.9,27.7)	(-13.4,10.4)
	Pr >  t				0.8051
Week 96	n		12	10	
	LS Mean		5.262	21.044	-15.78
	SEM		7.045	7.221	6.702
	95% CI		(-8.6,19.1)	(6.8,35.2)	(-28.9,-2.6)
	Pr >  t				0.0189
Week 108	n		7	8	
	LS Mean		2.772	15.647	-12.87
	SEM		7.848	7.564	7.871
	95% CI		(-12.7,18.2)	(0.8,30.5)	(-28.3, 2.6)
	Pr >  t				0.1024

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	n		9	5	
	LS Mean		9.179	2.739	6.440
	SEM		7.446	8.505	8.420
	95% CI		(-5.5,23.8)	(-14.0,19.4)	(-10.1,23.0)
	Pr >  t				0.4447
Week 132	n		5	3	
	LS Mean		9.285	15.803	-6.518
	SEM		8.544	9.936	10.72
	95% CI		(-7.5,26.1)	(-3.7,35.3)	(-27.6,14.5)
	Pr >  t				0.5433
Week 144	n		3	2	
	LS Mean		21.980	11.022	10.958
	SEM		9.966	11.49	13.21
	95% CI		( 2.4,41.6)	(-11.5,33.6)	(-15.0,36.9)
	Pr >  t				0.4071
Week 156	n		3	1	
	LS Mean		-0.215	12.385	-12.60
	SEM		9.976	15.20	16.55
	95% CI		(-19.8,19.4)	(-17.5,42.3)	(-45.1,19.9)
	Pr >  t				0.4467
Week 168	n		1	1	
	LS Mean		6.371	12.385	-6.014
	SEM		15.26	15.20	20.18
	95% CI		(-23.6,36.3)	(-17.5,42.3)	(-45.7,33.6)
	Pr >  t				0.7658

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	2.402	2.916	-0.515		
			SEM	2.291	2.342	2.130		
			95% CI	(-2.1, 6.9)	(-1.7, 7.5)	(-4.7, 3.7)		
					Pr >  t			0.8092
		Week 16	n	119	97			
			LS Mean	1.985	3.404	-1.420		
			SEM	2.364	2.505	2.340		
			95% CI	(-2.7, 6.6)	(-1.5, 8.3)	(-6.0, 3.2)		
					Pr >  t			0.5442
		Week 24	n	100	75			
			LS Mean	1.519	7.735	-6.216		
			SEM	2.443	2.650	2.559		
			95% CI	(-3.3, 6.3)	( 2.5,12.9)	(-11.2,-1.2)		
					Pr >  t			0.0153
		Week 32	n	82	69			
			LS Mean	1.105	2.361	-1.256		
			SEM	2.563	2.710	2.701		
			95% CI	(-3.9, 6.1)	(-3.0, 7.7)	(-6.6, 4.0)		
					Pr >  t			0.6420
		Week 40	n	73	58			
			LS Mean	1.135	5.278	-4.143		
			SEM	2.624	2.824	2.863		
			95% CI	(-4.0, 6.3)	(-0.3,10.8)	(-9.8, 1.5)		
			Pr >  t			0.1482		
Week 48	n	66	48					
	LS Mean	1.988	6.792	-4.804				
	SEM	2.678	2.952	3.039				
	95% CI	(-3.3, 7.2)	( 1.0,12.6)	(-10.8, 1.2)				
			Pr >  t			0.1142		
Week 56	n	56	43					
	LS Mean	1.785	4.401	-2.616				
	SEM	2.776	3.035	3.207				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.7, 7.2)	(-1.6, 10.4)	(-8.9, 3.7)
		Pr >  t			0.4149
	Week 64	n	45	41	
		LS Mean	1.168	4.650	-3.481
		SEM	2.924	3.074	3.374
		95% CI	(-4.6, 6.9)	(-1.4, 10.7)	(-10.1, 3.1)
		Pr >  t			0.3023
	Week 72	n	46	34	
		LS Mean	5.197	4.203	0.994
		SEM	2.910	3.231	3.506
		95% CI	(-0.5, 10.9)	(-2.1, 10.5)	(-5.9, 7.9)
		Pr >  t			0.7769
	Week 84	n	37	32	
		LS Mean	2.969	4.659	-1.690
		SEM	3.093	3.287	3.699
		95% CI	(-3.1, 9.0)	(-1.8, 11.1)	(-8.9, 5.6)
		Pr >  t			0.6478
	Week 96	n	33	23	
		LS Mean	1.915	8.332	-6.417
		SEM	3.188	3.632	4.089
		95% CI	(-4.3, 8.2)	( 1.2, 15.5)	(-14.4, 1.6)
		Pr >  t			0.1167
	Week 108	n	24	20	
		LS Mean	-2.544	5.038	-7.582
		SEM	3.524	3.804	4.493
		95% CI	(-9.5, 4.4)	(-2.4, 12.5)	(-16.4, 1.2)
		Pr >  t			0.0917
	Week 120	n	25	16	
		LS Mean	3.318	2.450	0.869
		SEM	3.471	4.111	4.723
		95% CI	(-3.5, 10.1)	(-5.6, 10.5)	(-8.4, 10.1)
		Pr >  t			0.8541
	Week 132	n	19	8	
		LS Mean	4.409	15.087	-10.68
		SEM	3.810	5.373	6.057
		95% CI	(-3.1, 11.9)	( 4.5, 25.6)	(-22.6, 1.2)
		Pr >  t			0.0781
	Week 144	n	14	5	
		LS Mean	7.458	4.191	3.268
		SEM	4.245	6.580	7.397

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.9,15.8)	(-8.7,17.1)	(-11.2,17.8)
		Pr >  t			0.6588
	Week 156	n	10	3	
		LS Mean	0.549	4.724	-4.175
		SEM	4.856	8.288	9.251
		95% CI	(-9.0,10.1)	(-11.5,21.0)	(-22.3,14.0)
		Pr >  t			0.6518
	Week 168	n	4	2	
		LS Mean	6.139	4.756	1.383
		SEM	7.224	10.02	12.08
		95% CI	(-8.0,20.3)	(-14.9,24.4)	(-22.3,25.1)
		Pr >  t			0.9089
	Week 180	n	1	1	
		LS Mean	31.519	4.693	26.827
		SEM	13.97	13.98	19.59
		95% CI	( 4.1,58.9)	(-22.7,32.1)	(-11.6,65.3)
		Pr >  t			0.1711
	Week 192	n	1	1	
		LS Mean	31.519	4.693	26.827
		SEM	13.97	13.98	19.59
		95% CI	( 4.1,58.9)	(-22.7,32.1)	(-11.6,65.3)
		Pr >  t			0.1711
Yes	Week 8	n	5	9	
		LS Mean	-13.17	-4.413	-8.759
		SEM	6.550	4.780	8.193
		95% CI	(-26.4, 0.0)	(-14.0, 5.2)	(-25.3, 7.7)
		Pr >  t			0.2907
	Week 16	n	5	9	
		LS Mean	-13.17	-8.175	-4.998
		SEM	6.550	4.756	8.179
		95% CI	(-26.4, 0.0)	(-17.7, 1.4)	(-21.5,11.5)
		Pr >  t			0.5443
	Week 24	n	5	5	
		LS Mean	-13.17	-15.36	2.186
		SEM	6.550	6.541	9.314
		95% CI	(-26.4, 0.0)	(-28.5,-2.2)	(-16.6,20.9)
		Pr >  t			0.8155
	Week 32	n	4	3	
		LS Mean	-18.98	-13.22	-5.753
		SEM	7.307	8.759	11.48

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-33.7,-4.3)	(-30.8, 4.4)	(-28.8,17.3)
		Pr >  t			0.6186
	Week 40	n	2	3	
		LS Mean	-24.15	-2.706	-21.44
		SEM	10.79	8.675	13.79
		95% CI	(-45.8,-2.5)	(-20.1,14.7)	(-49.1, 6.2)
		Pr >  t			0.1262
	Week 48	n	3	2	
		LS Mean	-9.609	2.265	-11.87
		SEM	8.548	10.87	13.66
		95% CI	(-26.8, 7.6)	(-19.6,24.1)	(-39.3,15.6)
		Pr >  t			0.3887
	Week 56	n	3	1	
		LS Mean	-20.72	-12.65	-8.070
		SEM	8.548	15.17	17.63
		95% CI	(-37.9,-3.5)	(-43.1,17.8)	(-43.5,27.3)
		Pr >  t			0.6491
	Week 64	n	2		
		LS Mean	-7.481		
		SEM	10.79		
		95% CI	(-29.1,14.2)		
		Pr >  t			
	Week 72	n	2		
		LS Mean	-7.265		
		SEM	10.77		
		95% CI	(-28.9,14.4)		
		Pr >  t			
	Week 84	n	3		
		LS Mean	-9.609		
		SEM	8.548		
		95% CI	(-26.8, 7.6)		
		Pr >  t			
	Week 96	n	2		
		LS Mean	-24.15		
		SEM	10.79		
		95% CI	(-45.8,-2.5)		
		Pr >  t			
	Week 108	n	2		
		LS Mean	2.584		
		SEM	10.54		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-18.6,23.8)
		Pr >  t		
	Week 120	n	3	
		LS Mean	-9.609	
		SEM	8.548	
		95% CI		(-26.8, 7.6)
		Pr >  t		
	Week 132	n	1	
		LS Mean	-14.30	
		SEM	15.71	
		95% CI		(-45.8,17.2)
		Pr >  t		
	Week 144	n	1	
		LS Mean	-14.30	
		SEM	15.71	
		95% CI		(-45.8,17.2)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	2.498	5.621	-3.123		
			SEM	2.753	2.874	2.780		
			95% CI	(-2.9, 7.9)	(-0.0, 11.3)	(-8.6, 2.3)		
					Pr >  t			0.2622
		Week 16	n	70	52			
			LS Mean	3.979	7.320	-3.341		
			SEM	2.825	3.122	3.030		
			95% CI	(-1.6, 9.5)	( 1.2, 13.5)	(-9.3, 2.6)		
					Pr >  t			0.2709
		Week 24	n	61	37			
			LS Mean	2.964	11.738	-8.774		
			SEM	2.907	3.389	3.341		
			95% CI	(-2.8, 8.7)	( 5.1, 18.4)	(-15.3, -2.2)		
					Pr >  t			0.0089
		Week 32	n	48	33			
			LS Mean	1.181	4.145	-2.964		
			SEM	3.068	3.479	3.551		
			95% CI	(-4.9, 7.2)	(-2.7, 11.0)	(-9.9, 4.0)		
					Pr >  t			0.4043
		Week 40	n	42	31			
			LS Mean	2.496	8.371	-5.875		
			SEM	3.152	3.531	3.677		
			95% CI	(-3.7, 8.7)	( 1.4, 15.3)	(-13.1, 1.3)		
			Pr >  t			0.1106		
Week 48	n	40	25					
	LS Mean	2.520	4.422	-1.901				
	SEM	3.184	3.715	3.880				
	95% CI	(-3.7, 8.8)	(-2.9, 11.7)	(-9.5, 5.7)				
			Pr >  t			0.6243		
Week 56	n	35	20					
	LS Mean	2.690	8.987	-6.297				
	SEM	3.274	3.940	4.171				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-3.7, 9.1)	(-1.2, 16.7)	(-14.5, 1.9)
	Pr >  t			0.1315
	n	29	18	
	LS Mean	1.871	7.518	-5.647
Week 72	SEM	3.415	4.060	4.395
	95% CI	(-4.8, 8.6)	(-0.5, 15.5)	(-14.3, 3.0)
	Pr >  t			0.1993
	n	28	18	
Week 84	LS Mean	6.240	5.614	0.626
	SEM	3.446	4.057	4.417
	95% CI	(-0.5, 13.0)	(-2.4, 13.6)	(-8.0, 9.3)
	Pr >  t			0.8874
Week 96	n	27	17	
	LS Mean	4.642	3.628	1.014
	SEM	3.496	4.125	4.503
	95% CI	(-2.2, 11.5)	(-4.5, 11.7)	(-7.8, 9.9)
Week 108	Pr >  t			0.8219
	n	23	14	
	LS Mean	1.956	13.013	-11.06
	SEM	3.635	4.369	4.840
Week 120	95% CI	(-5.2, 9.1)	(-4.4, 21.6)	(-20.6, -1.6)
	Pr >  t			0.0226
	n	19	12	
	LS Mean	1.010	6.963	-5.953
Week 132	SEM	3.848	4.588	5.185
	95% CI	(-6.5, 8.6)	(-2.0, 16.0)	(-16.1, 4.2)
	Pr >  t			0.2512
	n	18	8	
Week 144	LS Mean	5.817	7.552	-1.735
	SEM	3.895	5.278	5.844
	95% CI	(-1.8, 13.5)	(-2.8, 17.9)	(-13.2, 9.7)
	Pr >  t			0.7666
Week 132	n	11	4	
	LS Mean	-0.534	4.225	-4.759
	SEM	4.582	6.936	7.755
	95% CI	(-9.5, 8.5)	(-9.4, 17.8)	(-20.0, 10.5)
Week 144	Pr >  t			0.5396
	n	11	4	
	LS Mean	2.626	6.163	-3.537
	SEM	4.568	6.940	7.760

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.3,11.6)	(-7.5,19.8)	(-18.8,11.7)	
		Pr >  t			0.6486	
	Week 156	n	5	2		
		LS Mean	-1.584	6.468	-8.052	
		SEM	6.214	9.403	10.87	
		95% CI	(-13.8,10.6)	(-12.0,24.9)	(-29.4,13.3)	
		Pr >  t			0.4589	
	Week 168	n	1	2		
		LS Mean	23.973	6.468	17.505	
		SEM	12.90	9.403	15.68	
		95% CI	(-1.4,49.3)	(-12.0,24.9)	(-13.3,48.3)	
		Pr >  t			0.2647	
	Week 180	n		1		
		LS Mean		6.564		
		SEM		12.98		
		95% CI		(-18.9,32.0)		
		Pr >  t				
	Week 192	n		1		
		LS Mean		6.564		
		SEM		12.98		
		95% CI		(-18.9,32.0)		
		Pr >  t				
	>= 65 Years	Week 8	n	63	71	
			LS Mean	0.272	-2.470	2.742
			SEM	4.035	4.002	3.084
			95% CI	(-7.7, 8.2)	(-10.4, 5.4)	(-3.3, 8.8)
		Pr >  t			0.3744	
	Week 16	n	54	55		
		LS Mean	-2.645	-3.998	1.353	
		SEM	4.179	4.108	3.373	
		95% CI	(-10.9, 5.6)	(-12.1, 4.1)	(-5.3, 8.0)	
		Pr >  t			0.6884	
	Week 24	n	44	44		
		LS Mean	-2.416	-1.118	-1.298	
		SEM	4.304	4.229	3.702	
		95% CI	(-10.9, 6.1)	(-9.5, 7.2)	(-8.6, 6.0)	
		Pr >  t			0.7260	
	Week 32	n	38	40		
		LS Mean	-1.958	-3.585	1.627	
		SEM	4.455	4.341	3.898	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.7, 6.8)	(-12.1, 5.0)	(-6.0, 9.3)
		Pr >  t			0.6765
	Week 40	n	33	31	
		LS Mean	-3.627	-1.058	-2.570
		SEM	4.565	4.581	4.233
		95% CI	(-12.6, 5.4)	(-10.1, 8.0)	(-10.9, 5.7)
		Pr >  t			0.5440
	Week 48	n	29	26	
		LS Mean	-0.700	5.692	-6.393
		SEM	4.670	4.744	4.517
		95% CI	(-9.9, 8.5)	(-3.6, 15.0)	(-15.3, 2.5)
		Pr >  t			0.1575
	Week 56	n	24	25	
		LS Mean	-2.839	-3.270	0.431
		SEM	4.846	4.779	4.738
		95% CI	(-12.4, 6.7)	(-12.7, 6.1)	(-8.9, 9.7)
		Pr >  t			0.9276
	Week 64	n	18	24	
		LS Mean	-1.326	-1.563	0.237
		SEM	5.165	4.822	5.107
		95% CI	(-11.5, 8.8)	(-11.0, 7.9)	(-9.8, 10.3)
		Pr >  t			0.9630
	Week 72	n	20	17	
		LS Mean	1.593	-0.453	2.045
		SEM	5.045	5.218	5.365
		95% CI	(-8.3, 11.5)	(-10.7, 9.8)	(-8.5, 12.6)
		Pr >  t			0.7031
	Week 84	n	13	16	
		LS Mean	-1.811	2.545	-4.356
		SEM	5.613	5.295	5.973
		95% CI	(-12.8, 9.2)	(-7.9, 13.0)	(-16.1, 7.4)
		Pr >  t			0.4660
	Week 96	n	12	10	
		LS Mean	-1.798	-0.712	-1.086
		SEM	5.743	6.049	6.761
		95% CI	(-13.1, 9.5)	(-12.6, 11.2)	(-14.4, 12.2)
		Pr >  t			0.8725
	Week 108	n	7	9	
		LS Mean	-7.756	3.784	-11.54
		SEM	6.801	6.250	7.842

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.1, 5.6)	(-8.5,16.1)	(-26.9, 3.9)
		Pr >  t			0.1416
	Week 120	n	10	8	
		LS Mean	-2.916	-5.491	2.575
		SEM	6.073	6.498	7.432
		95% CI	(-14.8, 9.0)	(-18.3, 7.3)	(-12.0,17.2)
		Pr >  t			0.7291
	Week 132	n	9	4	
		LS Mean	7.317	22.882	-15.56
		SEM	6.262	8.367	9.236
		95% CI	(-5.0,19.6)	(-6.5,39.3)	(-33.7, 2.6)
		Pr >  t			0.0924
	Week 144	n	4	1	
		LS Mean	17.301	-0.551	17.852
		SEM	8.368	15.38	16.81
		95% CI	(-0.9,33.7)	(-30.7,29.6)	(-15.2,50.9)
		Pr >  t			0.2886
	Week 156	n	5	1	
		LS Mean	0.053	-0.551	0.604
		SEM	7.683	15.38	16.48
		95% CI	(-15.0,15.1)	(-30.7,29.6)	(-31.8,33.0)
		Pr >  t			0.9708
	Week 168	n	3		
		LS Mean	-2.859		
		SEM	9.417		
		95% CI	(-21.3,15.6)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	28.402		
		SEM	15.37		
		95% CI	(-1.8,58.6)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	28.402		
		SEM	15.37		
		95% CI	(-1.8,58.6)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	3.510	-0.521	4.031		
			SEM	5.071	4.788	4.418		
			95% CI	(-6.6,13.6)	(-10.0, 9.0)	(-4.7,12.8)		
					Pr >  t			0.3629
		Week 16	n	28	29			
			LS Mean	0.126	-0.083	0.209		
			SEM	5.124	5.048	4.663		
			95% CI	(-10.1,10.3)	(-10.1, 9.9)	(-9.0, 9.4)		
					Pr >  t			0.9643
		Week 24	n	21	25			
			LS Mean	2.622	3.823	-1.201		
			SEM	5.367	5.155	5.074		
			95% CI	(-8.0,13.3)	(-6.4,14.0)	(-11.2, 8.8)		
					Pr >  t			0.8130
		Week 32	n	19	23			
			LS Mean	-2.286	-2.027	-0.259		
			SEM	5.460	5.231	5.265		
			95% CI	(-13.1, 8.5)	(-12.4, 8.3)	(-10.6,10.1)		
					Pr >  t			0.9608
		Week 40	n	16	18			
			LS Mean	-2.524	5.650	-8.174		
			SEM	5.638	5.538	5.697		
			95% CI	(-13.7, 8.6)	(-5.3,16.6)	(-19.4, 3.0)		
					Pr >  t			0.1525
		Week 48	n	16	17			
			LS Mean	-0.440	5.372	-5.812		
			SEM	5.638	5.597	5.756		
95% CI	(-11.6,10.7)		(-5.7,16.4)	(-17.1, 5.5)				
			Pr >  t			0.3135		
Week 56	n	12	14					
	LS Mean	1.352	-4.598	5.949				
	SEM	5.985	5.821	6.327				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.5,13.2)	(-16.1, 6.9)	(-6.5,18.4)
	Pr >  t			0.3478
	n	12	11	
	LS Mean	4.129	4.466	-0.337
	SEM	5.985	6.159	6.636
Week 72	95% CI	(-7.7,16.0)	(-7.7,16.6)	(-13.4,12.7)
	Pr >  t			0.9595
	n	10	8	
	LS Mean	8.048	9.371	-1.323
	SEM	6.245	6.688	7.364
Week 84	95% CI	(-4.3,20.4)	(-3.8,22.5)	(-15.8,13.2)
	Pr >  t			0.8575
	n	8	8	
	LS Mean	2.212	9.371	-7.159
	SEM	6.692	6.688	7.692
Week 96	95% CI	(-11.0,15.4)	(-3.8,22.5)	(-22.3, 8.0)
	Pr >  t			0.3526
	n	6	6	
	LS Mean	-2.841	19.852	-22.69
	SEM	7.279	7.281	8.697
Week 108	95% CI	(-17.2,11.5)	( 5.5,34.2)	(-39.8,-5.6)
	Pr >  t			0.0094
	n	4	5	
	LS Mean	-2.763	10.939	-13.70
	SEM	8.321	7.723	9.928
Week 120	95% CI	(-19.1,13.6)	(-4.3,26.1)	(-33.2, 5.8)
	Pr >  t			0.1684
	n	4	4	
	LS Mean	5.570	2.322	3.247
	SEM	8.321	8.339	10.41
Week 132	95% CI	(-10.8,21.9)	(-14.1,18.7)	(-17.2,23.7)
	Pr >  t			0.7553
	n	3	2	
	LS Mean	7.721	11.216	-3.495
	SEM	9.238	10.83	13.13
Week 144	95% CI	(-10.4,25.9)	(-10.1,32.5)	(-29.3,22.3)
	Pr >  t			0.7903
	n	3	1	
	LS Mean	18.835	4.529	14.305
	SEM	9.238	14.62	16.40

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.7,37.0)	(-24.2,33.3)	(-17.9,46.6)
		Pr >  t			0.3836
	Week 156	n	2	1	
		LS Mean	-5.027	4.529	-9.556
		SEM	10.83	14.62	17.34
		95% CI	(-26.3,16.3)	(-24.2,33.3)	(-43.7,24.6)
		Pr >  t			0.5820
	Week 168	n	1		
		LS Mean	1.877		
		SEM	14.59		
		95% CI	(-26.8,30.6)		
		Pr >  t			
	Week 8	n	66	68	
		LS Mean	2.850	3.469	-0.619
		SEM	5.566	5.556	3.179
		95% CI	( -8.2,13.9)	( -7.5,14.5)	( -6.9, 5.6)
		Pr >  t			0.8457
	Week 16	n	58	48	
		LS Mean	4.049	3.983	0.066
		SEM	5.606	5.681	3.530
		95% CI	( -7.0,15.1)	( -7.2,15.2)	( -6.9, 7.0)
		Pr >  t			0.9850
	Week 24	n	51	36	
		LS Mean	1.459	6.928	-5.470
		SEM	5.653	5.812	3.859
		95% CI	( -9.7,12.6)	( -4.6,18.4)	(-13.1, 2.1)
		Pr >  t			0.1570
	Week 32	n	43	30	
		LS Mean	1.460	3.235	-1.775
		SEM	5.793	6.001	4.142
		95% CI	(-10.0,12.9)	( -8.6,15.1)	( -9.9, 6.4)
		Pr >  t			0.6684
	Week 40	n	37	25	
		LS Mean	2.378	4.342	-1.964
		SEM	5.868	6.129	4.422
		95% CI	( -9.2,14.0)	( -7.7,16.4)	(-10.6, 6.7)
		Pr >  t			0.6571
	Week 48	n	33	21	
		LS Mean	3.976	8.652	-4.676
		SEM	5.931	6.268	4.692

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-7.7,15.7)	(-3.7,21.0)	(-13.9, 4.5)
	Pr >  t			0.3194
	n	29	20	
	LS Mean	2.343	7.265	-4.923
	SEM	6.009	6.312	4.848
Week 64	95% CI	(-9.5,14.2)	(-5.2,19.7)	(-14.4, 4.6)
	Pr >  t			0.3103
	n	23	20	
	LS Mean	1.476	5.559	-4.083
	SEM	6.168	6.314	5.046
Week 72	95% CI	(-10.7,13.6)	(-6.9,18.0)	(-14.0, 5.8)
	Pr >  t			0.4187
	n	25	19	
	LS Mean	2.831	3.889	-1.058
	SEM	6.108	6.358	5.029
Week 84	95% CI	(-9.2,14.9)	(-8.6,16.4)	(-10.9, 8.8)
	Pr >  t			0.8334
	n	22	17	
	LS Mean	4.563	4.624	-0.060
	SEM	6.204	6.462	5.273
Week 96	95% CI	(-7.7,16.8)	(-8.1,17.4)	(-10.4,10.3)
	Pr >  t			0.9909
	n	20	13	
	LS Mean	3.320	6.356	-3.036
	SEM	6.283	6.758	5.717
Week 108	95% CI	(-9.1,15.7)	(-6.9,19.7)	(-14.3, 8.2)
	Pr >  t			0.5955
	n	15	11	
	LS Mean	-2.434	5.502	-7.936
	SEM	6.563	6.977	6.268
Week 120	95% CI	(-15.4,10.5)	(-8.2,19.2)	(-20.2, 4.4)
	Pr >  t			0.2058
	n	16	8	
	LS Mean	4.696	-2.555	7.252
	SEM	6.496	7.481	6.760
Week 132	95% CI	(-8.1,17.5)	(-17.3,12.2)	(-6.0,20.5)
	Pr >  t			0.2838
	n	12	3	
	LS Mean	5.924	3.489	2.436
	SEM	6.824	10.01	9.710

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.5,19.4)	(-16.2,23.1)	(-16.6,21.5)
		Pr >  t			0.8020
	Week 144	n	7	4	
		LS Mean	3.119	3.615	-0.496
		SEM	7.689	9.088	9.447
		95% CI	(-12.0,18.2)	(-14.2,21.5)	(-19.0,18.1)
		Pr >  t			0.9582
	Week 156	n	5	2	
		LS Mean	-2.366	4.138	-6.504
		SEM	8.437	11.63	12.41
		95% CI	(-18.9,14.2)	(-18.7,27.0)	(-30.9,17.9)
		Pr >  t			0.6004
	Week 168	n	2	2	
		LS Mean	12.805	4.138	8.667
		SEM	11.60	11.63	14.74
		95% CI	(-10.0,35.6)	(-18.7,27.0)	(-20.3,37.6)
		Pr >  t			0.5568
	Week 180	n		1	
		LS Mean		3.956	
		SEM		15.49	
		95% CI		(-26.5,34.4)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		3.956	
		SEM		15.49	
		95% CI		(-26.5,34.4)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	-4.908	-6.036	1.128
		SEM	2.264	2.329	3.267
		95% CI	(-9.4,-0.4)	(-10.6,-1.4)	(-5.3, 7.6)
		Pr >  t			0.7304
	Week 16	n	13	12	
		LS Mean	-4.813	-0.568	-4.245
		SEM	2.342	2.418	3.378
		95% CI	(-9.4,-0.2)	(-5.3, 4.2)	(-10.9, 2.4)
		Pr >  t			0.2110
	Week 24	n	12	10	
		LS Mean	-4.711	-2.972	-1.739
		SEM	2.432	2.645	3.603



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-9.5, 0.1)	(-8.2, 2.3)	(-8.9, 5.4)
	Pr >  t			0.6300
	n	9	10	
	LS Mean	-3.849	-6.305	2.456
	SEM	2.797	2.645	3.857
Week 40	95% CI	(-9.4, 1.7)	(-11.5,-1.1)	(-5.2,10.1)
	Pr >  t			0.5253
	n	7	10	
	LS Mean	-7.724	-6.305	-1.420
	SEM	3.157	2.645	4.127
Week 48	95% CI	(-14.0,-1.5)	(-11.5,-1.1)	(-9.6, 6.7)
	Pr >  t			0.7313
	n	7	7	
	LS Mean	-7.724	-6.701	-1.024
	SEM	3.157	3.151	4.454
Week 56	95% CI	(-14.0,-1.5)	(-12.9,-0.5)	(-9.8, 7.8)
	Pr >  t			0.8185
	n	6	7	
	LS Mean	-8.152	-1.529	-6.623
	SEM	3.419	3.147	4.650
Week 64	95% CI	(-14.9,-1.4)	(-7.7, 4.7)	(-15.8, 2.6)
	Pr >  t			0.1564
	n	4	7	
	LS Mean	-0.894	-1.928	1.034
	SEM	4.166	3.150	5.223
Week 72	95% CI	(-9.1, 7.3)	(-8.2, 4.3)	(-9.3,11.4)
	Pr >  t			0.8433
	n	4	4	
	LS Mean	7.439	-6.902	14.341
	SEM	4.166	4.147	5.871
Week 84	95% CI	(-0.8,15.7)	(-15.1, 1.3)	( 2.7,25.9)
	Pr >  t			0.0157
	n	4	5	
	LS Mean	-0.601	-6.459	5.858
	SEM	4.163	3.712	5.579
Week 96	95% CI	(-8.8, 7.6)	(-13.8, 0.9)	(-5.2,16.9)
	Pr >  t			0.2954
	n	3	2	
	LS Mean	-10.86	-6.505	-4.355
	SEM	4.815	5.830	7.550

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-20.4,-1.3)	(-18.0, 5.0)	(-19.3,10.6)
		Pr >  t			0.5649
		n	2	3	
	Week 120	LS Mean	-5.675	-6.298	0.623
		SEM	5.838	4.780	7.541
		95% CI	(-17.2, 5.9)	(-15.7, 3.1)	(-14.3,15.5)
	Week 120	Pr >  t			0.9343
		n	2	2	
		LS Mean	3.887	9.600	-5.713
	Week 132	SEM	5.885	5.843	8.295
		95% CI	(-7.7,15.5)	(-1.9,21.1)	(-22.1,10.7)
		Pr >  t			0.4921
	Week 132	n	1	2	
		LS Mean	-4.830	-7.065	2.235
		SEM	8.241	5.843	10.09
	Week 8	95% CI	(-21.1,11.5)	(-18.6, 4.5)	(-17.7,22.2)
		Pr >  t			0.8249
		n	16	19	
	Week 8	LS Mean	1.714	10.977	-9.263
		SEM	4.955	4.804	6.141
		95% CI	(-8.2,11.6)	(-1.4,20.6)	(-21.5, 3.0)
	Week 16	Pr >  t			0.1357
		n	12	14	
		LS Mean	1.077	5.823	-4.746
Week 16	SEM	5.562	5.425	6.956	
	95% CI	(-10.0,12.2)	(-5.0,16.6)	(-18.6, 9.1)	
	Pr >  t			0.4968	
Week 24	n	12	8		
	LS Mean	2.590	15.819	-13.23	
	SEM	5.580	6.865	8.063	
Week 24	95% CI	(-8.5,13.7)	(-2.2,29.4)	(-29.2, 2.8)	
	Pr >  t			0.1037	
	n	9	7		
Week 32	LS Mean	8.396	12.201	-3.805	
	SEM	6.288	7.223	8.790	
	95% CI	(-4.1,20.9)	(-2.1,26.5)	(-21.2,13.6)	
Week 32	Pr >  t			0.6659	
	n	9	7		
	LS Mean	1.769	16.962	-15.19	
Week 40	SEM	6.332	7.223	8.836	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-10.8,14.3)	( 2.6,31.3)	(-32.7, 2.3)
	Pr >  t			0.0881
	n	8	5	
	LS Mean	5.794	13.328	-7.534
	SEM	6.600	8.203	9.856
Week 56	95% CI	( -7.3,18.9)	( -2.9,29.6)	(-27.0,12.0)
	Pr >  t			0.4460
	n	7	3	
	LS Mean	3.649	20.590	-16.94
	SEM	6.918	10.10	11.68
Week 64	95% CI	(-10.1,17.4)	( 0.6,40.6)	(-40.0, 6.1)
	Pr >  t			0.1492
	n	5	3	
	LS Mean	-2.037	-1.630	-0.407
	SEM	7.906	10.10	12.31
Week 72	95% CI	(-17.7,13.6)	(-21.6,18.3)	(-24.7,23.9)
	Pr >  t			0.9737
	n	5	3	
	LS Mean	8.518	0.775	7.743
	SEM	7.854	10.09	12.25
Week 84	95% CI	( -7.0,24.1)	(-19.2,20.7)	(-16.5,32.0)
	Pr >  t			0.5283
	n	2	2	
	LS Mean	1.616	-3.263	4.879
	SEM	11.78	12.01	16.39
Week 96	95% CI	(-21.7,24.9)	(-27.0,20.5)	(-27.5,37.3)
	Pr >  t			0.7665
	n	3	2	
	LS Mean	12.470	-3.263	15.733
	SEM	9.725	12.01	15.06
Week 108	95% CI	( -6.8,31.7)	(-27.0,20.5)	(-14.0,45.5)
	Pr >  t			0.2979
	n	1	2	
	LS Mean	33.583	13.402	20.181
	SEM	16.18	12.01	19.80
Week 120	95% CI	( 1.6,65.6)	(-10.4,37.2)	(-19.0,59.4)
	Pr >  t			0.3100
	n	3	2	
	LS Mean	1.360	13.402	-12.04
	SEM	9.725	12.01	15.06

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-17.9,20.6)	(-10.4,37.2)	(-41.8,17.7)
		Pr >  t			0.4252
	Week 132	n	1	1	
		LS Mean	1.404	91.860	-90.46
		SEM	16.17	16.37	22.71
		95% CI	(-30.6,33.4)	( 59.5, 124)	( -135, -45)
		Pr >  t			0.0001
	Week 144	n	2		
		LS Mean	18.578		
		SEM	11.65		
		95% CI	( -4.5,41.6)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	34.734		
		SEM	16.17		
		95% CI	( 2.7,66.8)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	1.404		
		SEM	16.17		
		95% CI	(-30.6,33.4)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	34.734		
		SEM	16.17		
		95% CI	( 2.7,66.8)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	34.734		
		SEM	16.17		
		95% CI	( 2.7,66.8)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	4.189	5.828	-1.639
		SEM	3.190	5.202	5.765
		95% CI	( -2.2,10.5)	( -4.5,16.2)	(-13.1, 9.8)
		Pr >  t			0.7770
	Week 16	n	13	4	
		LS Mean	2.848	-0.737	3.585
		SEM	3.538	6.080	6.507

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-4.2, 9.9)	(-12.8, 11.4)	(-9.4, 16.5)
	Pr >  t			0.5832
	n	9	2	
	LS Mean	2.605	15.588	-12.98
	SEM	4.199	8.306	8.803
Week 32	95% CI	(-5.8, 11.0)	(-0.9, 32.1)	(-30.5, 4.5)
	Pr >  t			0.1441
	n	6	3	
	LS Mean	-1.078	-0.851	-0.227
	SEM	5.192	6.888	7.957
Week 40	95% CI	(-11.4, 9.3)	(-14.6, 12.9)	(-16.1, 15.6)
	Pr >  t			0.9773
	n	6	2	
	LS Mean	7.122	-1.050	8.172
	SEM	5.304	8.306	9.262
Week 48	95% CI	(-3.4, 17.7)	(-17.6, 15.5)	(-10.3, 26.6)
	Pr >  t			0.3802
	n	5	1	
	LS Mean	2.243	-0.399	2.642
	SEM	5.691	11.58	12.58
Week 56	95% CI	(-9.1, 13.6)	(-23.4, 22.6)	(-22.4, 27.7)
	Pr >  t			0.8342
	n	5	1	
	LS Mean	2.243	-0.399	2.642
	SEM	5.691	11.58	12.58
Week 64	95% CI	(-9.1, 13.6)	(-23.4, 22.6)	(-22.4, 27.7)
	Pr >  t			0.8342
	n	3	1	
	LS Mean	-1.396	-0.399	-0.996
	SEM	7.028	11.58	13.20
Week 72	95% CI	(-15.4, 12.6)	(-23.4, 22.6)	(-27.3, 25.3)
	Pr >  t			0.9400
	n	4	1	
	LS Mean	6.871	-0.399	7.270
	SEM	6.209	11.58	12.80
Week 84	95% CI	(-5.5, 19.2)	(-23.4, 22.6)	(-18.2, 32.7)
	Pr >  t			0.5715
	n	4	1	
	LS Mean	-1.462	-0.399	-1.062
	SEM	6.209	11.58	12.80

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-13.8,10.9)	(-23.4,22.6)	(-26.5,24.4)
	Pr >  t			0.9340
	n	3	1	
	LS Mean	-1.396	-0.399	-0.996
	SEM	7.028	11.58	13.20
Week 108	95% CI	(-15.4,12.6)	(-23.4,22.6)	(-27.3,25.3)
	Pr >  t			0.9400
	n	4		
	LS Mean	-1.462		
	SEM	6.209		
Week 120	95% CI	(-13.8,10.9)		
	Pr >  t			
	n	3		
	LS Mean	-1.396		
	SEM	7.028		
Week 132	95% CI	(-15.4,12.6)		
	Pr >  t			
	n	3		
	LS Mean	-1.396		
	SEM	7.028		
Week 144	95% CI	(-15.4,12.6)		
	Pr >  t			
	n	3		
	LS Mean	-1.802		
	SEM	7.088		
Week 156	95% CI	(-15.9,12.3)		
	Pr >  t			
	n	2		
	LS Mean	-1.810		
	SEM	8.530		
	95% CI	(-18.8,15.2)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	4.532	3.895	0.637	
		SEM	2.971	2.901	2.407	
		95% CI	(-1.3,10.4)	(-1.8, 9.6)	(-4.1, 5.4)	
			Pr >  t			0.7914
	Week 16	n	88	71		
		LS Mean	2.895	4.624	-1.729	
		SEM	3.037	3.120	2.601	
		95% CI	(-3.1, 8.9)	(-1.5,10.8)	(-6.8, 3.4)	
			Pr >  t			0.5064
	Week 24	n	75	54		
		LS Mean	3.315	8.416	-5.100	
		SEM	3.096	3.255	2.845	
		95% CI	(-2.8, 9.4)	( 2.0,14.8)	(-10.7, 0.5)	
			Pr >  t			0.0734
	Week 32	n	62	52		
		LS Mean	4.568	2.008	2.559	
		SEM	3.195	3.278	2.965	
		95% CI	(-1.7,10.9)	(-4.4, 8.5)	(-3.3, 8.4)	
			Pr >  t			0.3883
	Week 40	n	51	46		
		LS Mean	4.259	3.900	0.358	
		SEM	3.295	3.369	3.153	
		95% CI	(-2.2,10.7)	(-2.7,10.5)	(-5.8, 6.5)	
			Pr >  t			0.9096
	Week 48	n	50	37		
		LS Mean	4.453	7.636	-3.182	
		SEM	3.306	3.511	3.315	
95% CI		(-2.0,11.0)	( 0.7,14.5)	(-9.7, 3.3)		
		Pr >  t			0.3373	
Week 56	n	43	33			
	LS Mean	4.694	6.688	-1.995		
	SEM	3.391	3.596	3.489		
	95% CI	(-2.0,11.4)	(-0.4,13.8)	(-8.8, 4.9)		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.5676
	Week 64	n	35	33	
		LS Mean	3.955	5.539	-1.584
		SEM	3.525	3.596	3.623
		95% CI	(-3.0,10.9)	(-1.5,12.6)	(-8.7, 5.5)
		Pr >  t			0.6619
	Week 72	n	35	31	
		LS Mean	6.176	4.653	1.524
		SEM	3.525	3.643	3.670
		95% CI	(-0.7,13.1)	(-2.5,11.8)	(-5.7, 8.7)
		Pr >  t			0.6781
	Week 84	n	31	29	
		LS Mean	3.952	2.816	1.136
		SEM	3.625	3.697	3.808
		95% CI	(-3.2,11.1)	(-4.4,10.1)	(-6.3, 8.6)
		Pr >  t			0.7654
	Week 96	n	27	22	
		LS Mean	2.602	9.237	-6.635
		SEM	3.726	3.950	4.156
		95% CI	(-4.7, 9.9)	( 1.5,17.0)	(-14.8, 1.5)
		Pr >  t			0.1107
	Week 108	n	19	20	
		LS Mean	3.348	7.374	-4.026
		SEM	4.086	4.049	4.559
		95% CI	(-4.7,11.4)	(-0.6,15.3)	(-13.0, 4.9)
		Pr >  t			0.3774
	Week 120	n	20	15	
		LS Mean	3.551	3.154	0.398
		SEM	4.013	4.393	4.820
		95% CI	(-4.3,11.4)	(-5.5,11.8)	(-9.1, 9.9)
		Pr >  t			0.9342
	Week 132	n	15	7	
		LS Mean	8.362	17.453	-9.091
		SEM	4.370	5.694	6.264
		95% CI	(-0.2,16.9)	( 6.3,28.6)	(-21.4, 3.2)
		Pr >  t			0.1470
	Week 144	n	10	5	
		LS Mean	10.118	5.070	5.048
		SEM	4.958	6.506	7.409
		95% CI	( 0.4,19.8)	(-7.7,17.8)	(-9.5,19.6)



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.4958
	Week 156	n 6	3	
		LS Mean 4.503	5.572	-1.069
		SEM 6.029	8.072	9.446
		95% CI (-7.3,16.3)	(-10.3,21.4)	(-19.6,17.5)
		Pr >  t		0.9099
	Week 168	n 3	2	
		LS Mean 9.971	5.592	4.379
		SEM 8.060	9.683	12.10
		95% CI (-5.8,25.8)	(-13.4,24.6)	(-19.4,28.1)
		Pr >  t		0.7175
	Week 180	n 1	1	
		LS Mean 33.914	5.587	28.327
		SEM 13.38	13.38	18.60
		95% CI ( 7.7,60.2)	(-20.7,31.8)	(-8.2,64.8)
		Pr >  t		0.1281
	Week 192	n 1	1	
		LS Mean 33.914	5.587	28.327
		SEM 13.38	13.38	18.60
		95% CI ( 7.7,60.2)	(-20.7,31.8)	(-8.2,64.8)
		Pr >  t		0.1281
1	Week 8	n 43	50	
		LS Mean -3.143	-0.364	-2.779
		SEM 3.982	4.131	4.160
		95% CI (-11.0, 4.7)	(-8.5, 7.8)	(-11.0, 5.4)
		Pr >  t		0.5049
	Week 16	n 35	35	
		LS Mean -0.515	-1.220	0.705
		SEM 4.221	4.342	4.670
		95% CI (-8.8, 7.8)	(-9.8, 7.4)	(-8.5, 9.9)
		Pr >  t		0.8801
	Week 24	n 29	26	
		LS Mean -3.154	0.362	-3.516
		SEM 4.440	4.739	5.141
		95% CI (-11.9, 5.6)	(-9.0, 9.7)	(-13.6, 6.6)
		Pr >  t		0.4945
	Week 32	n 23	21	
		LS Mean -9.244	0.096	-9.340
		SEM 4.773	5.060	5.603
		95% CI (-18.6, 0.2)	(-9.9,10.1)	(-20.4, 1.7)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.0964
	Week 40	n	23	16	
		LS Mean	-7.667	7.880	-15.55
		SEM	4.783	5.437	5.953
		95% CI	(-17.1, 1.8)	(-2.8,18.6)	(-27.3,-3.8)
		Pr >  t			0.0094
	Week 48	n	18	14	
		LS Mean	-4.005	3.007	-7.012
		SEM	5.091	5.653	6.410
		95% CI	(-14.0, 6.0)	(-8.1,14.1)	(-19.6, 5.6)
		Pr >  t			0.2747
	Week 56	n	15	12	
		LS Mean	-7.850	-3.844	-4.006
		SEM	5.370	5.915	6.871
		95% CI	(-18.4, 2.7)	(-15.5, 7.8)	(-17.5, 9.5)
		Pr >  t			0.5602
	Week 64	n	11	9	
		LS Mean	-5.628	0.317	-5.945
		SEM	5.895	6.498	7.782
		95% CI	(-17.2, 6.0)	(-12.5,13.1)	(-21.2, 9.4)
		Pr >  t			0.4453
	Week 72	n	12	4	
		LS Mean	3.433	3.179	0.254
		SEM	5.748	8.817	9.711
		95% CI	(-7.9,14.7)	(-14.2,20.5)	(-18.8,19.3)
		Pr >  t			0.9791
	Week 84	n	8	4	
		LS Mean	2.183	19.846	-17.66
		SEM	6.628	8.817	10.24
		95% CI	(-10.8,15.2)	( 2.5,37.2)	(-37.8, 2.5)
		Pr >  t			0.0852
	Week 96	n	8	2	
		LS Mean	-1.983	0.325	-2.308
		SEM	6.628	11.84	12.93
		95% CI	(-15.0,11.0)	(-23.0,23.6)	(-27.7,23.1)
		Pr >  t			0.8585
	Week 108	n	6	1	
		LS Mean	-14.51	1.240	-15.75
		SEM	7.375	16.28	17.38
		95% CI	(-29.0,-0.0)	(-30.8,33.3)	(-49.9,18.4)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.3654
	Week 120	n	8	1
		LS Mean	2.713	1.240
		SEM	6.641	16.28
		95% CI	(-10.3,15.8)	(-30.8,33.3)
		Pr >  t		(-32.1,35.1)
	Week 132	n	5	1
		LS Mean	-7.902	1.240
		SEM	7.911	16.28
		95% CI	(-23.5, 7.6)	(-30.8,33.3)
		Pr >  t		(-43.8,25.5)
	Week 144	n	5	
		LS Mean	-1.234	
		SEM	7.911	
		95% CI	(-16.8,14.3)	
		Pr >  t		0.6041
	Week 156	n	4	
		LS Mean	-8.106	
		SEM	8.647	
		95% CI	(-25.1, 8.9)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	-4.630	
		SEM	16.05	
		95% CI	(-36.2,26.9)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	5.706	6.569	-0.863		
			SEM	6.436	7.554	7.892		
			95% CI	(-7.3,18.8)	(-8.7,21.9)	(-16.7,15.0)		
					Pr >  t			0.9134
		Week 16	n	17	10			
			LS Mean	1.152	15.719	-14.57		
			SEM	6.792	8.351	8.684		
			95% CI	(-12.5,14.8)	(-1.0,32.5)	(-31.9, 2.8)		
					Pr >  t			0.0987
		Week 24	n	9	5			
			LS Mean	8.144	25.907	-17.76		
			SEM	7.496	9.680	10.62		
			95% CI	(-6.9,23.1)	( 6.6,45.2)	(-38.8, 3.3)		
					Pr >  t			0.0976
		Week 32	n	8	4			
			LS Mean	1.370	25.056	-23.69		
			SEM	7.710	10.21	11.28		
			95% CI	(-14.0,16.8)	( 4.8,45.3)	(-46.0,-1.3)		
					Pr >  t			0.0381
		Week 40	n	5	4			
			LS Mean	0.861	8.388	-7.527		
			SEM	8.561	10.21	11.94		
			95% CI	(-16.2,17.9)	(-11.9,28.7)	(-31.2,16.1)		
			Pr >  t			0.5299		
Week 48	n	5	3					
	LS Mean	7.529	17.379	-9.850				
	SEM	8.561	10.99	12.62				
	95% CI	(-9.5,24.5)	(-4.4,39.2)	(-34.9,15.2)				
			Pr >  t			0.4368		
Week 56	n	4	3					
	LS Mean	-0.417	6.269	-6.686				
	SEM	9.073	10.99	13.00				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	95% CI	(-18.4,17.6)	(-15.5,28.1)	(-32.4,19.1)	
	Pr >  t			0.6081	
	n	4	3		
	LS Mean	7.915	6.269	1.646	
	SEM	9.073	10.99	13.00	
Week 72	95% CI	(-10.1,25.9)	(-15.5,28.1)	(-24.1,27.4)	
	Pr >  t			0.8995	
	n	4	3		
	LS Mean	7.915	6.269	1.646	
	SEM	9.073	10.99	13.00	
Week 84	95% CI	(-10.1,25.9)	(-15.5,28.1)	(-24.1,27.4)	
	Pr >  t			0.8995	
	n	2	3		
	LS Mean	4.082	6.269	-2.187	
	SEM	11.44	10.99	14.66	
Week 96	95% CI	(-18.6,26.8)	(-15.5,28.1)	(-31.2,26.9)	
	Pr >  t			0.8817	
	n	1	3		
	LS Mean	37.126	6.269	30.857	
	SEM	14.83	10.99	17.60	
Week 108	95% CI	( 7.7,66.5)	(-15.5,28.1)	( -4.0,65.8)	
	Pr >  t			0.0825	
	n		2		
	LS Mean		37.359		
	SEM		12.30		
Week 120	95% CI		( 13.0,61.7)		
	Pr >  t				
	n	1	1		
	LS Mean	3.796	30.684	-26.89	
	SEM	14.83	15.56	20.76	
Week 132	95% CI	(-25.6,33.2)	( -0.2,61.5)	(-68.1,14.3)	
	Pr >  t			0.1984	
	n		1		
	LS Mean		97.354		
	SEM		15.56		
Week 144	95% CI		( 66.5, 128)		
	Pr >  t				
	n	1			
	LS Mean	3.796			
	SEM	14.83			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.6,33.2)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-0.358	1.988	-2.346
		SEM	2.640	2.630	2.298
		95% CI	(-5.5, 4.8)	(-3.2, 7.2)	(-6.9, 2.2)
		Pr >  t			0.3076
	Week 16	n	83	81	
		LS Mean	-0.547	0.411	-0.959
		SEM	2.725	2.786	2.528
		95% CI	(-5.9, 4.8)	(-5.1, 5.9)	(-5.9, 4.0)
		Pr >  t			0.7047
	Week 24	n	75	62	
		LS Mean	-2.426	5.429	-7.856
		SEM	2.791	2.952	2.740
		95% CI	(-7.9, 3.1)	(-0.4,11.2)	(-13.2,-2.5)
		Pr >  t			0.0043
	Week 32	n	59	56	
		LS Mean	-1.684	-0.514	-1.169
		SEM	2.977	3.011	2.938
		95% CI	(-7.5, 4.2)	(-6.4, 5.4)	(-6.9, 4.6)
		Pr >  t			0.6908
	Week 40	n	52	48	
		LS Mean	-2.545	4.762	-7.306
		SEM	3.053	3.127	3.114
		95% CI	(-8.5, 3.5)	(-1.4,10.9)	(-13.4,-1.2)
		Pr >  t			0.0192
	Week 48	n	47	37	
		LS Mean	-1.244	4.550	-5.794
		SEM	3.118	3.317	3.364
		95% CI	(-7.4, 4.9)	(-2.0,11.1)	(-12.4, 0.8)
		Pr >  t			0.0853
	Week 56	n	41	31	
		LS Mean	-1.000	5.271	-6.271
		SEM	3.213	3.467	3.600
		95% CI	(-7.3, 5.3)	(-1.5,12.1)	(-13.3, 0.8)
		Pr >  t			0.0818
	Week 64	n	32	28	
		LS Mean	-1.571	1.166	-2.737
		SEM	3.411	3.564	3.866

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72		95% CI	(-8.3, 5.1)	(-5.8, 8.2)	(-10.3, 4.8)
		Pr >  t			0.4791
		n	29	22	
		LS Mean	2.470	4.389	-1.919
		SEM	3.503	3.815	4.176
Week 84		95% CI	(-4.4, 9.3)	(-3.1, 11.9)	(-10.1, 6.3)
		Pr >  t			0.6459
		n	26	21	
		LS Mean	-3.100	3.089	-6.190
		SEM	3.605	3.868	4.310
Week 96		95% CI	(-10.2, 4.0)	(-4.5, 10.7)	(-14.6, 2.3)
		Pr >  t			0.1512
		n	23	14	
		LS Mean	-4.790	8.846	-13.64
		SEM	3.735	4.411	4.901
Week 108		95% CI	(-12.1, 2.5)	(0.2, 17.5)	(-23.3, -4.0)
		Pr >  t			0.0055
		n	18	13	
		LS Mean	-1.792	1.645	-3.437
		SEM	4.029	4.527	5.227
Week 120		95% CI	(-9.7, 6.1)	(-7.2, 10.5)	(-13.7, 6.8)
		Pr >  t			0.5110
		n	19	10	
		LS Mean	4.707	0.853	3.854
		SEM	3.964	4.982	5.579
Week 132		95% CI	(-3.1, 12.5)	(-8.9, 10.6)	(-7.1, 14.8)
		Pr >  t			0.4898
		n	13	4	
		LS Mean	2.236	3.983	-1.747
		SEM	4.492	7.258	7.966
Week 144		95% CI	(-6.6, 11.1)	(-10.3, 18.2)	(-17.4, 13.9)
		Pr >  t			0.8264
		n	8	1	
		LS Mean	-0.146	2.042	-2.188
		SEM	5.397	13.85	14.55
Week 156		95% CI	(-10.7, 10.4)	(-25.1, 29.2)	(-30.7, 26.4)
		Pr >  t			0.8805
		n	5	1	
		LS Mean	2.037	2.042	-0.005
		SEM	6.561	13.85	15.02

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-10.8,14.9)	(-25.1,29.2)	(-29.5,29.5)
		Pr >  t			0.9997
		n	3	1	
		LS Mean	4.962	2.042	2.920
		SEM	8.223	13.85	15.81
	Week 180	95% CI	(-11.2,21.1)	(-25.1,29.2)	(-28.1,34.0)
		Pr >  t			0.8536
		n	1	1	
		LS Mean	28.693	2.042	26.651
		SEM	13.80	13.85	19.31
	Week 192	95% CI	( 1.6,55.8)	(-25.1,29.2)	(-11.2,64.5)
		Pr >  t			0.1679
		n	1	1	
		LS Mean	28.693	2.042	26.651
		SEM	13.80	13.85	19.31
	Week 8	95% CI	( 1.6,55.8)	(-25.1,29.2)	(-11.2,64.5)
		Pr >  t			0.1679
		n	17	16	
		LS Mean	2.860	-3.179	6.039
		SEM	4.269	4.479	6.085
	Week 16	95% CI	( -5.6,11.3)	(-12.1, 5.7)	( -6.0,18.1)
		Pr >  t			0.3232
		n	18	14	
		LS Mean	-0.689	-4.402	3.713
		SEM	4.179	4.698	6.197
	Week 24	95% CI	( -9.0, 7.6)	(-13.7, 4.9)	( -8.6,16.0)
		Pr >  t			0.5504
		n	16	13	
LS Mean		1.775	-9.054	10.830	
SEM		4.393	4.814	6.413	
Week 32	95% CI	( -6.9,10.5)	(-18.6, 0.5)	( -1.9,23.5)	
	Pr >  t			0.0939	
	n	15	13		
	LS Mean	0.876	-8.000	8.876	
	SEM	4.478	4.827	6.503	
Week 40	95% CI	( -8.0, 9.7)	(-17.6, 1.6)	( -4.0,21.7)	
	Pr >  t			0.1748	
	n	14	10		
	LS Mean	-0.268	-7.043	6.775	
	SEM	4.608	5.270	6.918	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	N=169	N=172	
Week 48		95% CI	(-9.4, 8.9)	(-17.5, 3.4)	(-6.9,20.4)
		Pr >  t			0.3290
		n	14	11	
		LS Mean	-0.267	-1.300	1.033
		SEM	4.608	5.107	6.792
Week 56		95% CI	(-9.4, 8.9)	(-11.4, 8.8)	(-12.4,14.5)
		Pr >  t			0.8794
		n	11	11	
		LS Mean	-5.192	-10.39	5.199
		SEM	4.991	5.107	7.074
Week 64		95% CI	(-15.1, 4.7)	(-20.5,-0.3)	(-8.8,19.2)
		Pr >  t			0.4635
		n	8	11	
		LS Mean	-3.778	1.730	-5.508
		SEM	5.587	5.107	7.515
Week 72		95% CI	(-14.8, 7.2)	(-8.4,11.8)	(-20.3, 9.3)
		Pr >  t			0.4646
		n	11	10	
		LS Mean	0.868	-7.016	7.884
		SEM	4.991	5.269	7.192
Week 84		95% CI	(-9.0,10.7)	(-17.4, 3.4)	(-6.3,22.1)
		Pr >  t			0.2746
		n	9	9	
		LS Mean	7.818	-2.550	10.367
		SEM	5.353	5.460	7.593
Week 96		95% CI	(-2.7,18.4)	(-13.3, 8.2)	(-4.6,25.4)
		Pr >  t			0.1739
		n	8	7	
		LS Mean	4.786	-1.162	5.948
		SEM	5.593	5.970	8.133
Week 108		95% CI	(-6.2,15.8)	(-12.9,10.6)	(-10.1,22.0)
		Pr >  t			0.4655
		n	7	6	
		LS Mean	-8.821	-3.144	-5.677
		SEM	5.879	6.342	8.604
Week 120		95% CI	(-20.4, 2.8)	(-15.6, 9.4)	(-22.6,11.3)
		Pr >  t			0.5101
		n	6	5	
	LS Mean	-10.08	-10.53	0.447	
	SEM	6.247	6.823	9.198	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-22.4, 2.2)	(-24.0, 2.9)	(-17.7, 18.6)
	Pr >  t			0.9613
	n	5	3	
	LS Mean	1.461	-5.650	7.111
	SEM	6.716	8.411	10.72
Week 144	95% CI	(-11.8, 14.7)	(-22.2, 10.9)	(-14.0, 28.2)
	Pr >  t			0.5077
	n	5	4	
	LS Mean	14.797	-5.547	20.344
	SEM	6.716	7.456	9.988
Week 156	95% CI	( 1.6, 28.0)	(-20.2, 9.1)	( 0.7, 40.0)
	Pr >  t			0.0427
	n	4	2	
	LS Mean	-5.995	-5.107	-0.887
	SEM	7.360	10.05	12.42
Week 168	95% CI	(-20.5, 8.5)	(-24.9, 14.7)	(-25.3, 23.6)
	Pr >  t			0.9431
	n	1	1	
	LS Mean	-0.340	-5.080	4.740
	SEM	13.80	13.85	19.53
	95% CI	(-27.5, 26.8)	(-32.4, 22.2)	(-33.7, 43.2)
	Pr >  t			0.8084

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	5.477	8.974	-3.496		
			SEM	3.871	3.778	2.920		
					95% CI	(-2.2,13.1)	( 1.5,16.4)	(-9.2, 2.3)
					Pr >  t			0.2322
				Week 16	n	60	51	
					LS Mean	6.680	11.540	-4.861
					SEM	3.953	3.994	3.135
					95% CI	(-1.1,14.5)	( 3.7,19.4)	(-11.0, 1.3)
					Pr >  t			0.1219
				Week 24	n	51	42	
					LS Mean	5.572	12.670	-7.098
					SEM	4.020	4.089	3.352
					95% CI	(-2.4,13.5)	( 4.6,20.7)	(-13.7,-0.5)
					Pr >  t			0.0348
				Week 32	n	46	36	
					LS Mean	5.018	7.715	-2.697
					SEM	4.102	4.218	3.524
					95% CI	(-3.1,13.1)	(-0.6,16.0)	(-9.6, 4.2)
					Pr >  t			0.4445
				Week 40	n	40	33	
					LS Mean	6.824	12.029	-5.205
					SEM	4.176	4.274	3.674
					95% CI	(-1.4,15.0)	( 3.6,20.4)	(-12.4, 2.0)
			Pr >  t			0.1571		
		Week 48	n	37	28			
			LS Mean	5.840	16.326	-10.49		
			SEM	4.217	4.385	3.847		
			95% CI	(-2.5,14.1)	( 7.7,25.0)	(-18.0,-2.9)		
			Pr >  t			0.0066		
		Week 56	n	33	23			
			LS Mean	6.389	6.403	-0.014		
			SEM	4.287	4.536	4.093		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-2.0,14.8)	(-2.5,15.3)	(-8.1, 8.0)	
	Pr >  t			0.9973	
	n	26	20		
	LS Mean	7.762	8.182	-0.420	
	SEM	4.445	4.660	4.391	
Week 72	95% CI	(-1.0,16.5)	(-1.0,17.3)	(-9.0, 8.2)	
	Pr >  t			0.9239	
	n	28	17		
	LS Mean	8.309	8.700	-0.391	
	SEM	4.393	4.817	4.507	
Week 84	95% CI	(-0.3,17.0)	(-0.8,18.2)	(-9.2, 8.5)	
	Pr >  t			0.9309	
	n	23	17		
	LS Mean	7.614	5.222	2.392	
	SEM	4.537	4.819	4.649	
Week 96	95% CI	(-1.3,16.5)	(-4.3,14.7)	(-6.7,11.5)	
	Pr >  t			0.6070	
	n	23	11		
	LS Mean	4.424	10.663	-6.239	
	SEM	4.539	5.348	5.197	
Week 108	95% CI	(-4.5,13.4)	( 0.2,21.2)	(-16.4, 4.0)	
	Pr >  t			0.2303	
	n	15	13		
	LS Mean	1.668	9.992	-8.324	
	SEM	4.948	5.125	5.342	
Week 120	95% CI	(-8.1,11.4)	(-0.1,20.1)	(-18.8, 2.2)	
	Pr >  t			0.1196	
	n	16	9		
	LS Mean	4.152	6.820	-2.668	
	SEM	4.881	5.654	5.794	
Week 132	95% CI	(-5.4,13.7)	(-4.3,17.9)	(-14.0, 8.7)	
	Pr >  t			0.6453	
	n	14	5		
	LS Mean	8.140	24.025	-15.88	
	SEM	5.027	6.827	7.046	
Week 144	95% CI	(-1.7,18.0)	(10.6,37.4)	(-29.7,-2.1)	
	Pr >  t			0.0244	
	n	8	3		
	LS Mean	5.214	9.681	-4.468	
	SEM	5.839	8.281	8.969	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-6.3,16.7)	(-6.6,25.9)	(-22.1,13.1)
		Pr >  t			0.6185
		n	7	2	
	Week 168	LS Mean	5.777	10.094	-4.318
		SEM	6.083	9.793	10.52
		95% CI	(-6.2,17.7)	(-9.1,29.3)	(-25.0,16.3)
	Week 180	Pr >  t			0.6817
		n	4	2	
		LS Mean	10.038	10.094	-0.057
	Week 192	SEM	7.386	9.793	11.32
		95% CI	(-4.5,24.5)	(-9.1,29.3)	(-22.3,22.2)
		Pr >  t			0.9960
	Week 8	n	1	1	
		LS Mean	35.340	10.129	25.211
		SEM	13.31	13.32	18.23
	Week 16	95% CI	( 9.2,61.5)	(-16.0,36.3)	(-10.6,61.0)
		Pr >  t			0.1671
		n	1	1	
	Week 24	LS Mean	35.340	10.129	25.211
		SEM	13.31	13.32	18.23
		95% CI	( 9.2,61.5)	(-16.0,36.3)	(-10.6,61.0)
	Week 32	Pr >  t			0.1671
		n	18	17	
		LS Mean	6.500	2.006	4.494
Week 8	SEM	4.980	5.140	7.160	
	95% CI	(-3.4,16.4)	(-8.2,12.2)	(-9.7,18.7)	
	Pr >  t			0.5319	
Week 16	n	17	11		
	LS Mean	6.230	8.481	-2.251	
	SEM	5.123	6.242	8.141	
Week 24	95% CI	(-3.9,16.4)	(-3.9,20.8)	(-18.4,13.9)	
	Pr >  t			0.7827	
	n	15	5		
Week 32	LS Mean	2.476	20.121	-17.65	
	SEM	5.437	8.750	10.38	
	95% CI	(-8.3,13.3)	( 2.8,37.4)	(-38.2, 2.9)	
Week 8	Pr >  t			0.0911	
	n	13	5		
	LS Mean	4.833	6.787	-1.954	
Week 16	SEM	5.719	8.750	10.53	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-6.5,16.2)	(-10.5,24.1)	(-22.8,18.8)	
	Pr >  t			0.8530	
	n	11	5		
	LS Mean	-0.305	6.787	-7.092	
	SEM	6.076	8.750	10.72	
Week 48	95% CI	(-12.3,11.7)	(-10.5,24.1)	(-28.3,14.1)	
	Pr >  t			0.5093	
	n	11	2		
	LS Mean	7.207	-0.286	7.493	
	SEM	6.081	12.84	14.26	
Week 56	95% CI	(-4.8,19.2)	(-25.6,25.1)	(-20.6,35.6)	
	Pr >  t			0.5999	
	n	8	2		
	LS Mean	2.225	16.379	-14.15	
	SEM	6.824	12.84	14.58	
Week 64	95% CI	(-11.3,15.7)	(-9.0,41.7)	(-42.9,14.6)	
	Pr >  t			0.3331	
	n	7	3		
	LS Mean	2.266	13.968	-11.70	
	SEM	7.190	10.81	13.03	
Week 72	95% CI	(-11.9,16.5)	(-7.4,35.3)	(-37.4,14.0)	
	Pr >  t			0.3702	
	n	7	3		
	LS Mean	10.632	2.858	7.774	
	SEM	7.200	10.81	13.03	
Week 84	95% CI	(-3.6,24.9)	(-18.5,24.2)	(-17.9,33.5)	
	Pr >  t			0.5515	
	n	7	2		
	LS Mean	10.634	-0.286	10.920	
	SEM	7.200	12.84	14.76	
Week 96	95% CI	(-3.6,24.9)	(-25.6,25.1)	(-18.2,40.1)	
	Pr >  t			0.4604	
	n	6	3		
	LS Mean	6.015	13.968	-7.953	
	SEM	7.651	10.81	13.28	
Week 108	95% CI	(-9.1,21.1)	(-7.4,35.3)	(-34.2,18.3)	
	Pr >  t			0.5501	
	n	7	2		
	LS Mean	-3.652	24.134	-27.79	
	SEM	7.200	12.82	14.73	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-17.9,10.6)	(-1.2,49.4)	(-56.9, 1.3)
		Pr >  t			0.0609
		n	6	1	
	Week 132	LS Mean	17.125	9.147	7.978
		SEM	7.651	17.58	19.19
		95% CI	( 2.0,32.2)	(-25.6,43.8)	(-29.9,45.9)
	Week 144	Pr >  t			0.6781
		n	4		
		LS Mean	10.767		
	Week 156	SEM	9.037		
		95% CI	( -7.1,28.6)		
		Pr >  t			
	Week 8	n	5		
		LS Mean	22.952		
		SEM	8.232		
Week 16	95% CI	( 6.7,39.2)			
	Pr >  t				
	n	3			
Week 24	LS Mean	1.432			
	SEM	10.25			
	95% CI	(-18.8,21.7)			
Week 32	Pr >  t				
	n	59	57		
	LS Mean	1.042	0.156	0.886	
Week 16	SEM	2.861	3.007	3.164	
	95% CI	( -4.6, 6.7)	( -5.8, 6.1)	( -5.3, 7.1)	
	Pr >  t			0.7796	
Week 24	n	47	44		
	LS Mean	-1.373	-4.158	2.785	
	SEM	3.041	3.232	3.528	
Week 32	95% CI	( -7.4, 4.6)	(-10.5, 2.2)	( -4.2, 9.7)	
	Pr >  t			0.4304	
	n	39	34		
Week 8	LS Mean	0.176	1.382	-1.205	
	SEM	3.219	3.504	3.895	
	95% CI	( -6.2, 6.5)	( -5.5, 8.3)	( -8.9, 6.5)	
Week 16	Pr >  t			0.7572	
	n	27	32		
	LS Mean	-1.952	-2.065	0.113	
Week 24	SEM	3.630	3.563	4.262	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.1, 5.2)	(-9.1, 4.9)	(-8.3, 8.5)
		Pr >  t			0.9788
	Week 40	n	24	24	
		LS Mean	-2.489	0.468	-2.957
		SEM	3.763	3.893	4.635
		95% CI	(-9.9, 4.9)	(-7.2, 8.1)	(-12.1, 6.1)
		Pr >  t			0.5237
	Week 48	n	21	21	
		LS Mean	-0.328	-1.241	0.914
		SEM	3.925	4.057	4.909
		95% CI	(-8.0, 7.4)	(-9.2, 6.7)	(-8.7, 10.6)
		Pr >  t			0.8524
	Week 56	n	18	20	
		LS Mean	-1.283	3.456	-4.739
		SEM	4.126	4.121	5.133
		95% CI	(-9.4, 6.8)	(-4.6, 11.6)	(-14.8, 5.3)
		Pr >  t			0.3563
	Week 64	n	14	19	
		LS Mean	-3.725	1.729	-5.455
		SEM	4.500	4.190	5.498
		95% CI	(-12.6, 5.1)	(-6.5, 10.0)	(-16.3, 5.3)
		Pr >  t			0.3216
	Week 72	n	13	15	
		LS Mean	4.503	2.418	2.085
		SEM	4.624	4.528	5.860
		95% CI	(-4.6, 13.6)	(-6.5, 11.3)	(-9.4, 13.6)
		Pr >  t			0.7222
	Week 84	n	10	14	
		LS Mean	-2.921	7.654	-10.57
		SEM	5.153	4.634	6.329
		95% CI	(-13.0, 7.2)	(-1.5, 16.8)	(-23.0, 1.9)
		Pr >  t			0.0953
	Week 96	n	6	10	
		LS Mean	1.798	6.811	-5.012
		SEM	6.316	5.232	7.729
		95% CI	(-10.6, 14.2)	(-3.5, 17.1)	(-20.2, 10.2)
		Pr >  t			0.5170
	Week 108	n	4	6	
		LS Mean	13.228	2.605	10.623
		SEM	7.571	6.405	9.506



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-1.6,28.1)	(-10.0,15.2)	(-8.1,29.3)
	Pr >  t			0.2643
	n	6	6	
	LS Mean	0.339	0.125	0.214
	SEM	6.318	6.408	8.568
Week 132	95% CI	(-12.1,12.7)	(-12.5,12.7)	(-16.6,17.0)
	Pr >  t			0.9800
	n	2	3	
	LS Mean	-2.928	5.597	-8.525
	SEM	10.38	8.639	13.21
Week 144	95% CI	(-23.3,17.5)	(-11.4,22.6)	(-34.5,17.4)
	Pr >  t			0.5190
	n	2	2	
	LS Mean	-3.110	0.576	-3.686
	SEM	10.34	10.42	14.45
Week 156	95% CI	(-23.4,17.2)	(-19.9,21.1)	(-32.1,24.7)
	Pr >  t			0.7988
	n		1	
	LS Mean		0.721	
	SEM		14.44	
	95% CI		(-27.7,29.1)	
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-0.166	0.724	-0.889
		SEM	7.528	7.785	3.412
		95% CI	(-15.1,14.7)	(-14.7,16.1)	(-7.6, 5.8)
		Pr >  t			0.7945
	Week 16	n	51	41	
		LS Mean	0.577	1.760	-1.183
		SEM	7.554	7.908	3.739
		95% CI	(-14.4,15.5)	(-13.9,17.4)	(-8.5, 6.2)
		Pr >  t			0.7520
	Week 24	n	38	33	
		LS Mean	-0.282	11.037	-11.32
		SEM	7.615	7.992	4.123
		95% CI	(-15.4,14.8)	(-4.8,26.9)	(-19.4,-3.2)
		Pr >  t			0.0063
	Week 32	n	34	28	
		LS Mean	2.262	4.293	-2.031
		SEM	7.769	8.067	4.350
		95% CI	(-13.1,17.6)	(-11.7,20.3)	(-10.6, 6.5)
		Pr >  t			0.6409
	Week 40	n	26	23	
		LS Mean	1.261	3.483	-2.222
		SEM	7.894	8.170	4.750
		95% CI	(-14.3,16.9)	(-12.7,19.6)	(-11.6, 7.1)
		Pr >  t			0.6401
	Week 48	n	24	17	
		LS Mean	5.128	5.820	-0.692
		SEM	7.938	8.360	5.138
95% CI		(-10.6,20.8)	(-10.7,22.3)	(-10.8, 9.4)	
	Pr >  t			0.8929	
Week 56	n	21	17		
	LS Mean	1.859	2.912	-1.053	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	8.015	8.361	5.259
		95% CI	(-14.0,17.7)	(-13.6,19.4)	(-11.4, 9.3)
		Pr >  t			0.8413
	Week 64	n	15	15	
		LS Mean	5.005	0.762	4.244
		SEM	8.250	8.455	5.752
		95% CI	(-11.3,21.3)	(-15.9,17.5)	( -7.1,15.5)
		Pr >  t			0.4610
	Week 72	n	16	15	
		LS Mean	4.018	2.804	1.214
		SEM	8.201	8.456	5.681
		95% CI	(-12.2,20.2)	(-13.9,19.5)	( -9.9,12.4)
		Pr >  t			0.8309
	Week 84	n	14	13	
		LS Mean	-0.304	5.841	-6.145
		SEM	8.307	8.572	6.005
		95% CI	(-16.7,16.1)	(-11.1,22.8)	(-17.9, 5.6)
		Pr >  t			0.3066
	Week 96	n	12	9	
		LS Mean	-0.179	5.124	-5.303
		SEM	8.449	8.957	6.724
		95% CI	(-16.9,16.5)	(-12.5,22.8)	(-18.5, 7.9)
		Pr >  t			0.4306
	Week 108	n	13	8	
		LS Mean	0.073	5.567	-5.494
		SEM	8.374	9.109	6.836
		95% CI	(-16.5,16.6)	(-12.4,23.5)	(-18.9, 7.9)
		Pr >  t			0.4219
	Week 120	n	11	6	
		LS Mean	9.953	5.415	4.538
		SEM	8.536	9.545	7.593
		95% CI	( -6.9,26.8)	(-13.4,24.2)	(-10.4,19.5)
		Pr >  t			0.5503
	Week 132	n	8	3	
		LS Mean	1.286	31.333	-30.05
		SEM	8.920	11.12	9.836
		95% CI	(-16.3,18.9)	( 9.5,53.2)	(-49.4, -11)
		Pr >  t			0.0024
	Week 144	n	5	1	
		LS Mean	-2.273	5.424	-7.697

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	9.700	15.92	15.53
		95% CI	(-21.4,16.8)	(-25.8,36.7)	(-38.2,22.8)
		Pr >  t			0.6205
	Week 168	n	3	1	
		LS Mean	-3.078	5.424	-8.502
		SEM	10.96	15.92	16.35
	Week 180	95% CI	(-24.6,18.5)	(-25.8,36.7)	(-40.6,23.6)
		Pr >  t			0.6033
		n	2	1	
	Week 192	LS Mean	11.971	5.424	6.547
		SEM	12.34	15.92	17.30
		95% CI	(-12.3,36.2)	(-25.8,36.7)	(-27.4,40.5)
	Week 8	Pr >  t			0.7053
		n		1	
		LS Mean		5.424	
	Week 16	SEM		15.92	
		95% CI		(-25.8,36.7)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		5.424	
		SEM		15.92	
	Week 32	95% CI		(-25.8,36.7)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	2.860	-3.179	6.039	
	SEM	4.269	4.479	6.085	
	95% CI	(-5.6,11.3)	(-12.1, 5.7)	(-6.0,18.1)	
Week 16	Pr >  t			0.3232	
	n	18	14		
	LS Mean	-0.689	-4.402	3.713	
Week 24	SEM	4.179	4.698	6.197	
	95% CI	(-9.0, 7.6)	(-13.7, 4.9)	(-8.6,16.0)	
	Pr >  t			0.5504	
Week 32	n	16	13		
	LS Mean	1.775	-9.054	10.830	
	SEM	4.393	4.814	6.413	
Week 32	95% CI	(-6.9,10.5)	(-18.6, 0.5)	(-1.9,23.5)	
	Pr >  t			0.0939	
Week 32	n	15	13		
	LS Mean	0.876	-8.000	8.876	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.478	4.827	6.503
		95% CI	(-8.0, 9.7)	(-17.6, 1.6)	(-4.0, 21.7)
		Pr >  t			0.1748
	Week 40	n	14	10	
		LS Mean	-0.268	-7.043	6.775
		SEM	4.608	5.270	6.918
		95% CI	(-9.4, 8.9)	(-17.5, 3.4)	(-6.9, 20.4)
		Pr >  t			0.3290
	Week 48	n	14	11	
		LS Mean	-0.267	-1.300	1.033
		SEM	4.608	5.107	6.792
		95% CI	(-9.4, 8.9)	(-11.4, 8.8)	(-12.4, 14.5)
		Pr >  t			0.8794
	Week 56	n	11	11	
		LS Mean	-5.192	-10.39	5.199
		SEM	4.991	5.107	7.074
		95% CI	(-15.1, 4.7)	(-20.5, -0.3)	(-8.8, 19.2)
		Pr >  t			0.4635
	Week 64	n	8	11	
		LS Mean	-3.778	1.730	-5.508
		SEM	5.587	5.107	7.515
		95% CI	(-14.8, 7.2)	(-8.4, 11.8)	(-20.3, 9.3)
		Pr >  t			0.4646
	Week 72	n	11	10	
		LS Mean	0.868	-7.016	7.884
		SEM	4.991	5.269	7.192
		95% CI	(-9.0, 10.7)	(-17.4, 3.4)	(-6.3, 22.1)
		Pr >  t			0.2746
	Week 84	n	9	9	
		LS Mean	7.818	-2.550	10.367
		SEM	5.353	5.460	7.593
		95% CI	(-2.7, 18.4)	(-13.3, 8.2)	(-4.6, 25.4)
		Pr >  t			0.1739
	Week 96	n	8	7	
		LS Mean	4.786	-1.162	5.948
		SEM	5.593	5.970	8.133
		95% CI	(-6.2, 15.8)	(-12.9, 10.6)	(-10.1, 22.0)
		Pr >  t			0.4655
	Week 108	n	7	6	
		LS Mean	-8.821	-3.144	-5.677

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.879	6.342	8.604
		95% CI	(-20.4, 2.8)	(-15.6, 9.4)	(-22.6,11.3)
		Pr >  t			0.5101
	Week 120	n	6	5	
		LS Mean	-10.08	-10.53	0.447
		SEM	6.247	6.823	9.198
		95% CI	(-22.4, 2.2)	(-24.0, 2.9)	(-17.7,18.6)
		Pr >  t			0.9613
	Week 132	n	5	3	
		LS Mean	1.461	-5.650	7.111
		SEM	6.716	8.411	10.72
		95% CI	(-11.8,14.7)	(-22.2,10.9)	(-14.0,28.2)
		Pr >  t			0.5077
	Week 144	n	5	4	
		LS Mean	14.797	-5.547	20.344
		SEM	6.716	7.456	9.988
		95% CI	( 1.6,28.0)	(-20.2, 9.1)	( 0.7,40.0)
		Pr >  t			0.0427
	Week 156	n	4	2	
		LS Mean	-5.995	-5.107	-0.887
		SEM	7.360	10.05	12.42
		95% CI	(-20.5, 8.5)	(-24.9,14.7)	(-25.3,23.6)
		Pr >  t			0.9431
	Week 168	n	1	1	
		LS Mean	-0.340	-5.080	4.740
		SEM	13.80	13.85	19.53
		95% CI	(-27.5,26.8)	(-32.4,22.2)	(-33.7,43.2)
		Pr >  t			0.8084
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	2.240	4.826	-2.585
		SEM	6.114	5.593	6.746
		95% CI	(-10.1,14.6)	( -6.4,16.1)	(-16.1,11.0)
		Pr >  t			0.7031
	Week 16	n	15	17	
		LS Mean	9.001	9.225	-0.224
		SEM	6.376	5.803	7.033
		95% CI	( -3.8,21.8)	( -2.4,20.9)	(-14.3,13.9)
		Pr >  t			0.9747
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	2.684	14.609	-11.92
		SEM	6.455	6.252	7.536
		95% CI	(-10.3,15.6)	( 2.1,27.1)	(-26.9, 3.1)
		Pr >  t			0.1179
	Week 32	n	12	9	
		LS Mean	-2.448	9.670	-12.12
		SEM	6.677	6.568	7.926
		95% CI	(-15.8,10.9)	( -3.4,22.7)	(-27.9, 3.6)
		Pr >  t			0.1300
	Week 40	n	11	7	
		LS Mean	-0.407	11.924	-12.33
		SEM	6.807	7.055	8.380
		95% CI	(-14.0,13.2)	( -2.1,25.9)	(-29.0, 4.3)
		Pr >  t			0.1442
	Week 48	n	8	6	
		LS Mean	0.972	13.384	-12.41
		SEM	7.199	7.340	8.943
		95% CI	(-13.4,15.3)	( -1.2,27.9)	(-30.1, 5.3)
		Pr >  t			0.1678
	Week 56	n	7	5	
		LS Mean	1.708	22.001	-20.29
		SEM	7.389	7.680	9.386
		95% CI	(-13.0,16.4)	( 6.8,37.2)	(-38.9,-1.7)
		Pr >  t			0.0324
	Week 64	n	5	3	
		LS Mean	2.349	17.642	-15.29
		SEM	7.971	8.963	10.87
		95% CI	(-13.5,18.2)	( -0.1,35.3)	(-36.8, 6.2)
		Pr >  t			0.1616
	Week 72	n	5	2	
		LS Mean	9.204	22.318	-13.11
		SEM	8.015	10.34	12.06
		95% CI	( -6.7,25.1)	( 1.9,42.7)	(-36.9,10.7)
		Pr >  t			0.2785
	Week 84	n	4	2	
		LS Mean	3.433	22.318	-18.88
		SEM	8.434	10.34	12.35
		95% CI	(-13.3,20.1)	( 1.9,42.7)	(-43.3, 5.5)
		Pr >  t			0.1282
	Week 96	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	LS Mean	-5.884	22.318	-28.20
	SEM	8.446	10.34	12.36
	95% CI	(-22.6,10.8)	( 1.9,42.7)	(-52.6,-3.8)
	Pr >  t			0.0237
	n	1	2	
Week 120	LS Mean	-3.753	21.180	-24.93
	SEM	13.59	10.29	16.28
	95% CI	(-30.6,23.1)	( 0.9,41.5)	(-57.1, 7.2)
	Pr >  t			0.1276
	n	5	1	
Week 132	LS Mean	2.538	29.903	-27.36
	SEM	8.015	13.49	14.86
	95% CI	(-13.4,18.4)	( 3.3,56.5)	(-56.7, 2.0)
	Pr >  t			0.0673
	n	3	1	
Week 144	LS Mean	-1.660	29.903	-31.56
	SEM	9.171	13.49	15.52
	95% CI	(-19.8,16.5)	( 3.3,56.5)	(-62.2,-0.9)
	Pr >  t			0.0436
	n	3		
Week 156	LS Mean	9.450		
	SEM	9.171		
	95% CI	( -8.7,27.6)		
	Pr >  t			
	n	3		
Week 168	LS Mean	9.450		
	SEM	9.171		
	95% CI	( -8.7,27.6)		
	Pr >  t			
	n	1		
Week 180	LS Mean	-1.860		
	SEM	13.57		
	95% CI	(-28.7,24.9)		
	Pr >  t			
	n	1		
Week 192	LS Mean	31.470		
	SEM	13.57		
	95% CI	( 4.7,58.3)		
	Pr >  t			
	n	1		



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	31.470		
		SEM	13.57		
		95% CI	( 4.7,58.3)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	3.442	3.855	-0.412
		SEM	3.330	3.336	3.826
		95% CI	( -3.1,10.0)	( -2.7,10.4)	( -7.9, 7.1)
		Pr >  t			0.9142
	Week 16	n	30	29	
		LS Mean	-1.026	2.092	-3.118
		SEM	3.518	3.752	4.327
		95% CI	( -8.0, 5.9)	( -5.3, 9.5)	(-11.6, 5.4)
		Pr >  t			0.4718
	Week 24	n	26	20	
		LS Mean	0.115	1.994	-1.879
		SEM	3.730	4.316	4.912
		95% CI	( -7.2, 7.5)	( -6.5,10.5)	(-11.5, 7.8)
		Pr >  t			0.7023
	Week 32	n	18	20	
		LS Mean	-2.901	-4.672	1.771
		SEM	4.275	4.316	5.329
		95% CI	(-11.3, 5.5)	(-13.2, 3.8)	( -8.7,12.3)
		Pr >  t			0.7399
	Week 40	n	18	19	
		LS Mean	-2.166	6.323	-8.489
		SEM	4.277	4.392	5.391
		95% CI	(-10.6, 6.3)	( -2.3,15.0)	(-19.1, 2.1)
		Pr >  t			0.1163
	Week 48	n	16	14	
		LS Mean	-0.831	4.674	-5.505
		SEM	4.451	4.872	5.928
		95% CI	( -9.6, 7.9)	( -4.9,14.3)	(-17.2, 6.2)
		Pr >  t			0.3537
	Week 56	n	14	10	
		LS Mean	1.769	6.792	-5.023
		SEM	4.671	5.516	6.634
		95% CI	( -7.4,11.0)	( -4.1,17.6)	(-18.1, 8.0)
		Pr >  t			0.4495

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n		13	11	
	LS Mean		-0.611	-2.597	1.985
	SEM		4.802	5.323	6.572
	95% CI		(-10.1, 8.8)	(-13.1, 7.9)	(-10.9,14.9)
	Pr >  t				0.7628
Week 72	n		10	6	
	LS Mean		3.037	0.752	2.285
	SEM		5.306	6.776	8.133
	95% CI		(-7.4,13.5)	(-12.6,14.1)	(-13.7,18.3)
	Pr >  t				0.7789
Week 84	n		8	7	
	LS Mean		-2.780	-8.972	6.192
	SEM		5.900	6.357	8.144
	95% CI		(-14.4, 8.8)	(-21.5, 3.5)	(-9.8,22.2)
	Pr >  t				0.4476
Week 96	n		6	5	
	LS Mean		1.881	9.158	-7.277
	SEM		6.616	7.313	9.441
	95% CI		(-11.1,14.9)	(-5.2,23.5)	(-25.8,11.3)
	Pr >  t				0.4414
Week 108	n		2	4	
	LS Mean		-6.664	-5.701	-0.963
	SEM		10.96	8.059	13.27
	95% CI		(-28.2,14.9)	(-21.6,10.1)	(-27.1,25.1)
	Pr >  t				0.9422
Week 120	n		4	4	
	LS Mean		3.789	-5.701	9.490
	SEM		7.900	8.059	10.94
	95% CI		(-11.7,19.3)	(-21.6,10.1)	(-12.0,31.0)
	Pr >  t				0.3862
Week 132	n		3	1	
	LS Mean		17.822	-7.938	25.760
	SEM		9.070	15.34	17.56
	95% CI		(-0.0,35.7)	(-38.1,22.2)	(-8.8,60.3)
	Pr >  t				0.1434
Week 144	n		2		
	LS Mean		-2.379		
	SEM		10.88		
	95% CI		(-23.8,19.0)		
	Pr >  t				

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	2.249	1.873	0.376		
			SEM	3.260	3.267	2.739		
			95% CI	(-4.2, 8.7)	(-4.6, 8.3)	(-5.0, 5.8)		
					Pr >  t			0.8908
		Week 16	n	79	68			
			LS Mean	0.018	1.546	-1.529		
			SEM	3.306	3.483	3.009		
			95% CI	(-6.5, 6.5)	(-5.3, 8.4)	(-7.4, 4.4)		
					Pr >  t			0.6115
		Week 24	n	64	55			
			LS Mean	0.954	3.930	-2.976		
			SEM	3.437	3.654	3.291		
			95% CI	(-5.8, 7.7)	(-3.3, 11.1)	(-9.4, 3.5)		
					Pr >  t			0.3661
		Week 32	n	49	53			
			LS Mean	0.359	-0.760	1.119		
			SEM	3.654	3.682	3.499		
			95% CI	(-6.8, 7.5)	(-8.0, 6.5)	(-5.7, 8.0)		
					Pr >  t			0.7492
		Week 40	n	44	45			
			LS Mean	0.204	2.764	-2.560		
			SEM	3.731	3.793	3.696		
			95% CI	(-7.1, 7.5)	(-4.7, 10.2)	(-9.8, 4.7)		
			Pr >  t			0.4887		
Week 48	n	41	36					
	LS Mean	2.334	5.745	-3.411				
	SEM	3.783	3.967	3.925				
	95% CI	(-5.1, 9.8)	(-2.0, 13.5)	(-11.1, 4.3)				
			Pr >  t			0.3850		
Week 56	n	33	32					
	LS Mean	0.390	1.183	-0.793				
	SEM	3.961	4.071	4.203				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.4, 8.2)	(-6.8, 9.2)	(-9.0, 7.5)
		Pr >  t			0.8504
	Week 64	n	27	31	
		LS Mean	0.828	1.421	-0.593
		SEM	4.149	4.102	4.414
		95% CI	(-7.3, 9.0)	(-6.6, 9.5)	(-9.3, 8.1)
		Pr >  t			0.8932
	Week 72	n	26	26	
		LS Mean	4.864	0.497	4.367
		SEM	4.188	4.277	4.613
		95% CI	(-3.4, 13.1)	(-7.9, 8.9)	(-4.7, 13.4)
		Pr >  t			0.3440
	Week 84	n	22	23	
		LS Mean	1.494	-1.914	3.408
		SEM	4.399	4.410	4.906
		95% CI	(-7.1, 10.1)	(-10.6, 6.7)	(-6.2, 13.0)
		Pr >  t			0.4874
	Week 96	n	18	18	
		LS Mean	1.747	3.802	-2.055
		SEM	4.657	4.717	5.403
		95% CI	(-7.4, 10.9)	(-5.5, 13.1)	(-12.7, 8.5)
		Pr >  t			0.7037
	Week 108	n	14	14	
		LS Mean	-4.244	1.865	-6.108
		SEM	5.036	5.091	6.043
		95% CI	(-14.1, 5.6)	(-8.1, 11.9)	(-18.0, 5.7)
		Pr >  t			0.3123
	Week 120	n	12	12	
		LS Mean	6.897	-4.660	11.557
		SEM	5.295	5.353	6.474
		95% CI	(-3.5, 17.3)	(-15.2, 5.8)	(-1.1, 24.3)
		Pr >  t			0.0746
	Week 132	n	9	5	
		LS Mean	6.195	17.005	-10.81
		SEM	5.859	7.418	8.636
		95% CI	(-5.3, 17.7)	( 2.4, 31.6)	(-27.8, 6.1)
		Pr >  t			0.2110
	Week 144	n	7	4	
		LS Mean	1.951	0.913	1.038
		SEM	6.443	8.152	9.653

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.7,14.6)	(-15.1,16.9)	(-17.9,20.0)
		Pr >  t			0.9144
	Week 156	n	4	2	
		LS Mean	-4.105	1.794	-5.899
		SEM	8.099	11.08	13.17
		95% CI	(-20.0,11.8)	(-19.9,23.5)	(-31.8,20.0)
		Pr >  t			0.6544
	Week 168	n	2	1	
		LS Mean	11.718	2.013	9.705
		SEM	11.03	15.34	18.50
		95% CI	(-9.9,33.4)	(-28.1,32.1)	(-26.6,46.0)
		Pr >  t			0.6000
Yes	Week 8	n	53	48	
		LS Mean	1.359	3.898	-2.539
		SEM	3.081	3.206	3.079
		95% CI	(-4.7, 7.5)	(-2.4,10.2)	(-8.6, 3.5)
		Pr >  t			0.4106
	Week 16	n	45	39	
		LS Mean	4.015	4.742	-0.727
		SEM	3.232	3.366	3.308
		95% CI	(-2.4,10.4)	(-1.9,11.4)	(-7.2, 5.8)
		Pr >  t			0.8263
	Week 24	n	41	26	
		LS Mean	1.481	10.228	-8.747
		SEM	3.282	3.636	3.662
		95% CI	(-5.0, 8.0)	( 3.1,17.4)	(-16.0,-1.5)
		Pr >  t			0.0175
	Week 32	n	37	20	
		LS Mean	0.686	5.741	-5.055
		SEM	3.366	3.890	3.945
		95% CI	(-6.0, 7.3)	(-1.9,13.4)	(-12.8, 2.7)
		Pr >  t			0.2010
	Week 40	n	31	17	
		LS Mean	0.880	8.447	-7.566
		SEM	3.477	4.085	4.202
		95% CI	(-6.0, 7.7)	( 0.4,16.5)	(-15.8, 0.7)
		Pr >  t			0.0725
	Week 48	n	28	15	
		LS Mean	0.931	6.327	-5.396
		SEM	3.544	4.220	4.388

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-6.1, 7.9)	(-2.0,14.6)	(-14.0, 3.2)
	Pr >  t			0.2195
	n	26	13	
	LS Mean	1.759	8.846	-7.087
	SEM	3.594	4.386	4.591
Week 64	95% CI	(-5.3, 8.8)	( 0.2,17.5)	(-16.1, 1.9)
	Pr >  t			0.1233
	n	20	11	
	LS Mean	1.327	9.318	-7.991
	SEM	3.801	4.601	4.957
Week 72	95% CI	(-6.2, 8.8)	( 0.3,18.4)	(-17.7, 1.7)
	Pr >  t			0.1076
	n	22	9	
	LS Mean	5.007	10.053	-5.046
	SEM	3.725	4.887	5.167
Week 84	95% CI	(-2.3,12.3)	( 0.4,19.7)	(-15.2, 5.1)
	Pr >  t			0.3291
	n	18	10	
	LS Mean	4.264	16.661	-12.40
	SEM	3.908	4.734	5.151
Week 96	95% CI	(-3.4,12.0)	( 7.4,26.0)	(-22.5,-2.3)
	Pr >  t			0.0164
	n	17	6	
	LS Mean	0.028	15.892	-15.86
	SEM	3.951	5.594	5.991
Week 108	95% CI	(-7.7, 7.8)	( 4.9,26.9)	(-27.6,-4.1)
	Pr >  t			0.0083
	n	12	7	
	LS Mean	1.888	13.706	-11.82
	SEM	4.354	5.301	5.995
Week 120	95% CI	(-6.7,10.4)	( 3.3,24.1)	(-23.6,-0.0)
	Pr >  t			0.0491
	n	16	4	
	LS Mean	0.345	18.633	-18.29
	SEM	4.018	6.506	6.889
Week 132	95% CI	(-7.6, 8.3)	( 5.9,31.4)	(-31.8,-4.8)
	Pr >  t			0.0082
	n	11	3	
	LS Mean	1.974	11.405	-9.431
	SEM	4.467	7.303	7.884

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.8,10.8)	(-2.9,25.7)	(-24.9, 6.1)
		Pr >  t			0.2321
	Week 144	n	8	1	
		LS Mean	10.831	9.463	1.368
		SEM	4.921	11.88	12.43
		95% CI	( 1.2,20.5)	(-13.9,32.8)	(-23.0,25.8)
		Pr >  t			0.9124
	Week 156	n	6	1	
		LS Mean	3.390	9.463	-6.073
		SEM	5.470	11.88	12.65
		95% CI	( -7.4,14.1)	(-13.9,32.8)	(-30.9,18.8)
		Pr >  t			0.6313
	Week 168	n	2	1	
		LS Mean	-0.325	9.463	-9.788
		SEM	8.585	11.88	14.27
		95% CI	(-17.2,16.5)	(-13.9,32.8)	(-37.8,18.3)
		Pr >  t			0.4931
	Week 180	n	1	1	
		LS Mean	31.201	9.463	21.737
		SEM	11.78	11.88	16.39
		95% CI	( 8.1,54.3)	(-13.9,32.8)	(-10.5,53.9)
		Pr >  t			0.1855
	Week 192	n	1	1	
		LS Mean	31.201	9.463	21.737
		SEM	11.78	11.88	16.39
		95% CI	( 8.1,54.3)	(-13.9,32.8)	(-10.5,53.9)
		Pr >  t			0.1855

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	5.963	8.098	-2.135
			SEM	4.276	4.653	4.499
			95% CI	(-2.5,14.4)	(-1.1,17.3)	(-11.0, 6.8)
		Pr >  t			0.6360	
		Week 16	n	35	22	
			LS Mean	6.142	3.541	2.600
			SEM	4.456	5.266	5.121
			95% CI	(-2.7,15.0)	(-6.9,14.0)	(-7.5,12.7)
		Pr >  t			0.6122	
		Week 24	n	28	16	
			LS Mean	7.094	14.848	-7.754
			SEM	4.632	5.648	5.693
			95% CI	(-2.1,16.3)	( 3.7,26.0)	(-19.0, 3.5)
		Pr >  t			0.1746	
		Week 32	n	22	16	
			LS Mean	4.106	6.160	-2.053
			SEM	4.928	5.663	5.887
			95% CI	(-5.6,13.8)	(-5.0,17.3)	(-13.6, 9.5)
		Pr >  t			0.7275	
		Week 40	n	19	12	
			LS Mean	4.411	15.004	-10.59
			SEM	5.087	6.058	6.394
			95% CI	(-5.6,14.5)	( 3.1,26.9)	(-23.2, 2.0)
		Pr >  t			0.0987	
		Week 48	n	16	10	
			LS Mean	10.653	14.585	-3.932
			SEM	5.283	6.355	6.832
95% CI	( 0.2,21.1)		( 2.1,27.1)	(-17.4, 9.5)		
Pr >  t			0.5654			
Week 56	n	14	7			
	LS Mean	2.021	12.371	-10.35		
		SEM	5.460	7.035	7.603	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.7,12.8)	(-1.5,26.2)	(-25.3, 4.6)
	Pr >  t			0.1744
	n	8	7	
	LS Mean	8.253	26.419	-18.17
	SEM	6.348	7.035	8.281
Week 72	95% CI	(-4.2,20.7)	(12.6,40.3)	(-34.5,-1.9)
	Pr >  t			0.0289
	n	12	6	
	LS Mean	10.020	18.520	-8.500
	SEM	5.676	7.383	8.083
Week 84	95% CI	(-1.2,21.2)	(4.0,33.1)	(-24.4, 7.4)
	Pr >  t			0.2937
	n	8	5	
	LS Mean	4.948	21.523	-16.57
	SEM	6.395	7.835	8.975
Week 96	95% CI	(-7.6,17.5)	(6.1,36.9)	(-34.2, 1.1)
	Pr >  t			0.0656
	n	5	5	
	LS Mean	4.725	21.523	-16.80
	SEM	7.470	7.835	9.770
Week 108	95% CI	(-10.0,19.4)	(6.1,36.9)	(-36.0, 2.4)
	Pr >  t			0.0865
	n	7	5	
	LS Mean	10.024	21.523	-11.50
	SEM	6.675	7.835	9.176
Week 120	95% CI	(-3.1,23.2)	(6.1,36.9)	(-29.5, 6.6)
	Pr >  t			0.2110
	n	5	3	
	LS Mean	24.878	12.719	12.159
	SEM	7.482	9.397	11.07
Week 132	95% CI	(10.2,39.6)	(-5.8,31.2)	(-9.6,33.9)
	Pr >  t			0.2727
	n	2	2	
	LS Mean	7.412	21.296	-13.88
	SEM	10.73	10.96	14.61
Week 144	95% CI	(-13.7,28.5)	(-0.3,42.9)	(-42.6,14.9)
	Pr >  t			0.3426
	n	2		
	LS Mean	6.839		
	SEM	10.73		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.3,28.0)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	6.789		
		SEM	10.75		
		95% CI	(-14.4,27.9)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	7.362		
		SEM	14.64		
		95% CI	(-21.4,36.2)		
		Pr >  t			
Positive	Week 8	n	98	104	
		LS Mean	-0.694	-0.355	-0.339
		SEM	2.756	2.722	2.344
		95% CI	(-6.1, 4.7)	(-5.7, 5.0)	(-4.9, 4.3)
		Pr >  t			0.8851
	Week 16	n	87	84	
		LS Mean	-0.985	1.278	-2.263
		SEM	2.825	2.827	2.522
		95% CI	(-6.5, 4.6)	(-4.3, 6.8)	(-7.2, 2.7)
		Pr >  t			0.3699
	Week 24	n	76	65	
		LS Mean	-2.042	2.650	-4.692
		SEM	2.905	2.977	2.741
		95% CI	(-7.8, 3.7)	(-3.2, 8.5)	(-10.1, 0.7)
		Pr >  t			0.0874
	Week 32	n	62	57	
		LS Mean	-2.616	-1.036	-1.580
		SEM	3.024	3.069	2.933
		95% CI	(-8.6, 3.3)	(-7.1, 5.0)	(-7.3, 4.2)
		Pr >  t			0.5902
	Week 40	n	54	50	
		LS Mean	-1.563	0.895	-2.458
		SEM	3.103	3.167	3.099
		95% CI	(-7.7, 4.5)	(-5.3, 7.1)	(-8.5, 3.6)
		Pr >  t			0.4280
	Week 48	n	52	41	
		LS Mean	-2.252	2.911	-5.164
		SEM	3.125	3.302	3.259

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-8.4, 3.9)	(-3.6, 9.4)	(-11.6, 1.2)
	Pr >  t			0.1134
Week 56	n	44	38	
	LS Mean	-1.199	0.436	-1.635
	SEM	3.230	3.359	3.419
	95% CI	(-7.5, 5.1)	(-6.2, 7.0)	(-8.3, 5.1)
	Pr >  t			0.6327
Week 64	n	39	35	
	LS Mean	-2.340	-2.041	-0.299
	SEM	3.315	3.425	3.564
	95% CI	(-8.9, 4.2)	(-8.8, 4.7)	(-7.3, 6.7)
	Pr >  t			0.9331
Week 72	n	36	29	
	LS Mean	1.958	-1.043	3.000
	SEM	3.376	3.588	3.776
	95% CI	(-4.7, 8.6)	(-8.1, 6.0)	(-4.4, 10.4)
	Pr >  t			0.4270
Week 84	n	32	28	
	LS Mean	0.473	-0.910	1.383
	SEM	3.481	3.620	3.892
	95% CI	(-6.4, 7.3)	(-8.0, 6.2)	(-6.3, 9.0)
	Pr >  t			0.7223
Week 96	n	30	19	
	LS Mean	-1.864	2.833	-4.697
	SEM	3.527	4.040	4.332
	95% CI	(-8.8, 5.1)	(-5.1, 10.8)	(-13.2, 3.8)
	Pr >  t			0.2784
Week 108	n	18	16	
	LS Mean	-6.369	0.622	-6.991
	SEM	4.085	4.266	4.981
	95% CI	(-14.4, 1.6)	(-7.7, 9.0)	(-16.8, 2.8)
	Pr >  t			0.1607
Week 120	n	23	13	
	LS Mean	-3.456	-1.837	-1.619
	SEM	3.788	4.574	5.029
	95% CI	(-10.9, 4.0)	(-10.8, 7.1)	(-11.5, 8.2)
	Pr >  t			0.7475
Week 132	n	18	6	
	LS Mean	0.941	11.988	-11.05
	SEM	4.086	6.141	6.657

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-7.1, 9.0)	(-0.1,24.0)	(-24.1, 2.0)
	Pr >  t			0.0973
Week 144	n	13	5	
	LS Mean	4.262	-0.173	4.435
	SEM	4.528	6.631	7.388
	95% CI	(-4.6,13.1)	(-13.2,12.8)	(-10.1,18.9)
	Pr >  t			0.5484
Week 156	n	8	3	
	LS Mean	-3.169	0.391	-3.560
	SEM	5.442	8.290	9.395
	95% CI	(-13.8, 7.5)	(-15.9,16.7)	(-22.0,14.9)
	Pr >  t			0.7048
Week 168	n	3	2	
	LS Mean	4.153	0.436	3.717
	SEM	8.260	9.986	12.56
	95% CI	(-12.1,20.4)	(-19.2,20.0)	(-20.9,28.4)
	Pr >  t			0.7674
Week 180	n	1	1	
	LS Mean	27.990	0.384	27.606
	SEM	13.86	13.86	19.35
	95% CI	( 0.8,55.2)	(-26.8,27.6)	(-10.4,65.6)
	Pr >  t			0.1539
Week 192	n	1	1	
	LS Mean	27.990	0.384	27.606
	SEM	13.86	13.86	19.35
	95% CI	( 0.8,55.2)	(-26.8,27.6)	(-10.4,65.6)
	Pr >  t			0.1539

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	-0.402	-0.350	-0.052		
			SEM	2.775	2.733	2.362		
			95% CI	(-5.9, 5.1)	(-5.7, 5.0)	(-4.7, 4.6)		
					Pr >  t			0.9823
		Week 16	n	85	84			
			LS Mean	-1.073	1.287	-2.360		
			SEM	2.846	2.838	2.541		
			95% CI	(-6.7, 4.5)	(-4.3, 6.9)	(-7.4, 2.6)		
					Pr >  t			0.3533
		Week 24	n	75	65			
			LS Mean	-1.991	2.665	-4.657		
			SEM	2.923	2.987	2.756		
			95% CI	(-7.7, 3.8)	(-3.2, 8.5)	(-10.1, 0.8)		
					Pr >  t			0.0915
		Week 32	n	61	57			
			LS Mean	-2.571	-1.019	-1.552		
			SEM	3.045	3.079	2.949		
			95% CI	(-8.6, 3.4)	(-7.1, 5.0)	(-7.3, 4.2)		
					Pr >  t			0.5989
		Week 40	n	53	50			
			LS Mean	-1.831	0.913	-2.743		
			SEM	3.125	3.176	3.117		
			95% CI	(-8.0, 4.3)	(-5.3, 7.2)	(-8.9, 3.4)		
					Pr >  t			0.3791
		Week 48	n	51	41			
			LS Mean	-2.541	2.934	-5.475		
			SEM	3.148	3.310	3.276		
95% CI	(-8.7, 3.6)		(-3.6, 9.4)	(-11.9, 1.0)				
			Pr >  t			0.0950		
Week 56	n	43	38					
	LS Mean	-0.736	0.458	-1.194				
	SEM	3.256	3.367	3.440				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.1, 5.7)	(-6.2, 7.1)	(-7.9, 5.6)
	Pr >  t			0.7286
	n	39	35	
	LS Mean	-2.356	-2.019	-0.338
	SEM	3.326	3.433	3.569
Week 72	95% CI	(-8.9, 4.2)	(-8.8, 4.7)	(-7.3, 6.7)
	Pr >  t			0.9247
	n	35	29	
	LS Mean	2.155	-1.018	3.173
	SEM	3.408	3.594	3.800
Week 84	95% CI	(-4.5, 8.8)	(-8.1, 6.0)	(-4.3, 10.6)
	Pr >  t			0.4038
	n	31	28	
	LS Mean	-0.431	-0.886	0.455
	SEM	3.518	3.627	3.920
Week 96	95% CI	(-7.3, 6.5)	(-8.0, 6.2)	(-7.2, 8.1)
	Pr >  t			0.9076
	n	29	19	
	LS Mean	-1.751	2.861	-4.612
	SEM	3.567	4.044	4.359
Week 108	95% CI	(-8.8, 5.3)	(-5.1, 10.8)	(-13.2, 3.9)
	Pr >  t			0.2902
	n	18	16	
	LS Mean	-6.395	0.652	-7.047
	SEM	4.092	4.269	4.981
Week 120	95% CI	(-14.4, 1.6)	(-7.7, 9.0)	(-16.8, 2.7)
	Pr >  t			0.1574
	n	23	13	
	LS Mean	-3.477	-1.809	-1.669
	SEM	3.796	4.576	5.028
Week 132	95% CI	(-10.9, 4.0)	(-10.8, 7.2)	(-11.5, 8.2)
	Pr >  t			0.7401
	n	18	6	
	LS Mean	0.912	12.019	-11.11
	SEM	4.093	6.137	6.652
Week 144	95% CI	(-7.1, 8.9)	(-0.0, 24.1)	(-24.2, 1.9)
	Pr >  t			0.0952
	n	13	5	
	LS Mean	4.238	-0.129	4.368
	SEM	4.532	6.627	7.381

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive Negative	Week 156	95% CI	(-4.7,13.1)	(-13.1,12.9)	(-10.1,18.8)
		Pr >  t			0.5541
		n	8	3	
	Week 168	LS Mean	-3.198	0.428	-3.626
		SEM	5.443	8.282	9.383
		95% CI	(-13.9, 7.5)	(-15.8,16.7)	(-22.0,14.8)
	Week 180	Pr >  t			0.6993
		n	3	2	
		LS Mean	4.143	0.473	3.670
	Week 192	SEM	8.253	9.973	12.55
		95% CI	(-12.0,20.3)	(-19.1,20.0)	(-20.9,28.3)
		Pr >  t			0.7700
	Week 8	n	1	1	
		LS Mean	28.019	0.423	27.596
		SEM	13.84	13.84	19.31
	Week 16	95% CI	( 0.9,55.2)	(-26.7,27.6)	(-10.3,65.5)
		Pr >  t			0.1534
		n	1	1	
	Week 24	LS Mean	28.019	0.423	27.596
		SEM	13.84	13.84	19.31
		95% CI	( 0.9,55.2)	(-26.7,27.6)	(-10.3,65.5)
	Week 32	Pr >  t			0.1534
		n	42	35	
		LS Mean	5.963	8.098	-2.135
Week 8	SEM	4.276	4.653	4.499	
	95% CI	(-2.5,14.4)	(-1.1,17.3)	(-11.0, 6.8)	
	Pr >  t			0.6360	
Week 16	n	35	22		
	LS Mean	6.142	3.541	2.600	
	SEM	4.456	5.266	5.121	
Week 24	95% CI	(-2.7,15.0)	(-6.9,14.0)	(-7.5,12.7)	
	Pr >  t			0.6122	
	n	28	16		
Week 32	LS Mean	7.094	14.848	-7.754	
	SEM	4.632	5.648	5.693	
	95% CI	(-2.1,16.3)	( 3.7,26.0)	(-19.0, 3.5)	
Week 8	Pr >  t			0.1746	
	n	22	16		
	LS Mean	4.106	6.160	-2.053	
Week 16	SEM	4.928	5.663	5.887	
	95% CI				
	Pr >  t				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-5.6,13.8)	(-5.0,17.3)	(-13.6, 9.5)
	Pr >  t			0.7275
	n	19	12	
	LS Mean	4.411	15.004	-10.59
	SEM	5.087	6.058	6.394
Week 48	95% CI	(-5.6,14.5)	( 3.1,26.9)	(-23.2, 2.0)
	Pr >  t			0.0987
	n	16	10	
	LS Mean	10.653	14.585	-3.932
	SEM	5.283	6.355	6.832
Week 56	95% CI	( 0.2,21.1)	( 2.1,27.1)	(-17.4, 9.5)
	Pr >  t			0.5654
	n	14	7	
	LS Mean	2.021	12.371	-10.35
	SEM	5.460	7.035	7.603
Week 64	95% CI	(-8.7,12.8)	(-1.5,26.2)	(-25.3, 4.6)
	Pr >  t			0.1744
	n	8	7	
	LS Mean	8.253	26.419	-18.17
	SEM	6.348	7.035	8.281
Week 72	95% CI	(-4.2,20.7)	( 12.6,40.3)	(-34.5,-1.9)
	Pr >  t			0.0289
	n	12	6	
	LS Mean	10.020	18.520	-8.500
	SEM	5.676	7.383	8.083
Week 84	95% CI	(-1.2,21.2)	( 4.0,33.1)	(-24.4, 7.4)
	Pr >  t			0.2937
	n	8	5	
	LS Mean	4.948	21.523	-16.57
	SEM	6.395	7.835	8.975
Week 96	95% CI	(-7.6,17.5)	( 6.1,36.9)	(-34.2, 1.1)
	Pr >  t			0.0656
	n	5	5	
	LS Mean	4.725	21.523	-16.80
	SEM	7.470	7.835	9.770
Week 108	95% CI	(-10.0,19.4)	( 6.1,36.9)	(-36.0, 2.4)
	Pr >  t			0.0865
	n	7	5	
	LS Mean	10.024	21.523	-11.50
	SEM	6.675	7.835	9.176

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-3.1,23.2)	(-6.1,36.9)	(-29.5, 6.6)
	Pr >  t			0.2110
	n	5	3	
	LS Mean	24.878	12.719	12.159
	SEM	7.482	9.397	11.07
Week 132	95% CI	(10.2,39.6)	(-5.8,31.2)	(-9.6,33.9)
	Pr >  t			0.2727
	n	2	2	
	LS Mean	7.412	21.296	-13.88
	SEM	10.73	10.96	14.61
Week 144	95% CI	(-13.7,28.5)	(-0.3,42.9)	(-42.6,14.9)
	Pr >  t			0.3426
	n	2		
	LS Mean	6.839		
	SEM	10.73		
Week 156	95% CI	(-14.3,28.0)		
	Pr >  t			
	n	2		
	LS Mean	6.789		
	SEM	10.75		
Week 168	95% CI	(-14.4,27.9)		
	Pr >  t			
	n	1		
	LS Mean	7.362		
	SEM	14.64		
	95% CI	(-21.4,36.2)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60	
		LS Mean	3.369	2.598	0.772	
	SEM	5.520	5.711	2.866		
	95% CI	(-7.6,14.3)	(-8.7,13.9)	(-4.9, 6.4)		
	Pr >  t			0.7879		
	Week 16	n	59	49		
		LS Mean	4.261	4.102	0.160	
		SEM	5.558	5.786	3.104	
		95% CI	(-6.8,15.3)	(-7.4,15.6)	(-5.9, 6.3)	
	Week 24	Pr >  t			0.9590	
		n	54	41		
		LS Mean	-0.185	4.950	-5.135	
		SEM	5.579	5.861	3.294	
	Week 32	95% CI	(-11.3,10.9)	(-6.7,16.6)	(-11.6, 1.3)	
		Pr >  t			0.1196	
		n	48	37		
		LS Mean	0.008	3.466	-3.457	
	Week 40	SEM	5.613	5.905	3.444	
		95% CI	(-11.1,11.1)	(-8.2,15.2)	(-10.2, 3.3)	
		Pr >  t			0.3158	
		n	43	33		
	Week 48	LS Mean	-0.839	4.685	-5.524	
		SEM	5.648	5.958	3.603	
		95% CI	(-12.0,10.4)	(-7.1,16.5)	(-12.6, 1.6)	
Pr >  t				0.1257		
Week 56	n	41	28			
	LS Mean	0.429	4.086	-3.657		
	SEM	5.665	6.044	3.775		
	95% CI	(-10.8,11.7)	(-7.9,16.1)	(-11.1, 3.8)		
Week 56	Pr >  t			0.3329		
	n	35	22			
	LS Mean	2.560	4.447	-1.888		
	SEM	5.726	6.198	4.114		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.8,13.9)	(-7.8,16.7)	(-10.0, 6.2)
		Pr >  t			0.6465
	Week 64	n	26	23	
		LS Mean	-1.353	2.746	-4.099
		SEM	5.869	6.169	4.290
		95% CI	(-13.0,10.3)	(-9.5,15.0)	(-12.5, 4.3)
		Pr >  t			0.3396
	Week 72	n	28	18	
		LS Mean	4.871	2.483	2.388
		SEM	5.830	6.348	4.489
		95% CI	(-6.7,16.4)	(-10.1,15.0)	(-6.4,11.2)
		Pr >  t			0.5948
	Week 84	n	22	18	
		LS Mean	1.095	2.556	-1.460
		SEM	6.022	6.348	4.683
		95% CI	(-10.8,13.0)	(-10.0,15.1)	(-10.7, 7.7)
		Pr >  t			0.7552
	Week 96	n	21	13	
		LS Mean	0.873	1.507	-0.634
		SEM	5.998	6.652	5.127
		95% CI	(-11.0,12.7)	(-11.6,14.6)	(-10.7, 9.4)
		Pr >  t			0.9016
	Week 108	n	17	12	
		LS Mean	-1.067	4.424	-5.491
		SEM	6.221	6.740	5.430
		95% CI	(-13.4,11.2)	(-8.9,17.7)	(-16.1, 5.2)
		Pr >  t			0.3122
	Week 120	n	18	11	
		LS Mean	3.056	4.552	-1.496
		SEM	6.107	6.842	5.506
		95% CI	(-9.0,15.1)	(-8.9,18.1)	(-12.3, 9.3)
		Pr >  t			0.7859
	Week 132	n	13	5	
		LS Mean	2.862	18.043	-15.18
		SEM	6.475	8.156	7.339
		95% CI	(-9.9,15.6)	( 2.0,34.1)	(-29.6,-0.8)
		Pr >  t			0.0389
	Week 144	n	12	3	
		LS Mean	4.027	3.295	0.731
		SEM	6.476	9.524	8.904

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.8,16.8)	(-15.4,22.0)	(-16.7,18.2)
		Pr >  t			0.9346
	Week 156	n	7	2	
		LS Mean	2.707	3.612	-0.905
		SEM	7.336	10.98	10.95
		95% CI	(-11.7,17.1)	(-17.9,25.2)	(-22.4,20.6)
		Pr >  t			0.9341
	Week 168	n	3	1	
		LS Mean	7.063	3.644	3.418
		SEM	9.376	14.51	15.62
		95% CI	(-11.4,25.5)	(-24.8,32.1)	(-27.2,34.1)
		Pr >  t			0.8268
	Week 180	n	1	1	
		LS Mean	30.885	3.644	27.241
		SEM	14.42	14.51	19.07
		95% CI	( 2.6,59.2)	(-24.8,32.1)	(-10.2,64.7)
		Pr >  t			0.1536
	Week 192	n	1	1	
		LS Mean	30.885	3.644	27.241
		SEM	14.42	14.51	19.07
		95% CI	( 2.6,59.2)	(-24.8,32.1)	(-10.2,64.7)
		Pr >  t			0.1536
Yes	Week 8	n	73	80	
		LS Mean	-0.734	1.379	-2.113
		SEM	3.912	3.952	3.014
		95% CI	(-8.4, 7.0)	(-6.4, 9.2)	(-8.0, 3.8)
		Pr >  t			0.4837
	Week 16	n	65	58	
		LS Mean	-2.328	0.168	-2.496
		SEM	4.035	4.158	3.291
		95% CI	(-10.3, 5.6)	(-8.0, 8.4)	(-9.0, 4.0)
		Pr >  t			0.4487
	Week 24	n	51	40	
		LS Mean	1.170	6.329	-5.159
		SEM	4.140	4.420	3.716
		95% CI	(-7.0, 9.3)	(-2.4,15.0)	(-12.5, 2.1)
		Pr >  t			0.1656
	Week 32	n	38	36	
		LS Mean	-0.257	-1.761	1.504
		SEM	4.384	4.502	4.005

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.9, 8.4)	(-10.6, 7.1)	(-6.4, 9.4)
		Pr >  t			0.7075
	Week 40	n	32	29	
		LS Mean	1.153	3.745	-2.592
		SEM	4.519	4.668	4.324
		95% CI	(-7.7,10.0)	(-5.4,12.9)	(-11.1, 5.9)
		Pr >  t			0.5490
	Week 48	n	28	23	
		LS Mean	2.442	7.746	-5.303
		SEM	4.623	4.879	4.648
		95% CI	(-6.6,11.5)	(-1.8,17.3)	(-14.4, 3.8)
		Pr >  t			0.2543
	Week 56	n	24	23	
		LS Mean	-2.593	1.903	-4.496
		SEM	4.766	4.879	4.784
		95% CI	(-12.0, 6.8)	(-7.7,11.5)	(-13.9, 4.9)
		Pr >  t			0.3477
	Week 64	n	21	19	
		LS Mean	2.773	4.350	-1.578
		SEM	4.901	5.073	5.110
		95% CI	(-6.9,12.4)	(-5.6,14.3)	(-11.6, 8.5)
		Pr >  t			0.7576
	Week 72	n	20	17	
		LS Mean	3.666	3.609	0.056
		SEM	4.955	5.200	5.285
		95% CI	(-6.1,13.4)	(-6.6,13.8)	(-10.3,10.4)
		Pr >  t			0.9915
	Week 84	n	18	15	
		LS Mean	3.421	4.592	-1.171
		SEM	5.058	5.358	5.537
		95% CI	(-6.5,13.4)	(-5.9,15.1)	(-12.0, 9.7)
		Pr >  t			0.8326
	Week 96	n	14	11	
		LS Mean	-0.457	13.335	-13.79
		SEM	5.380	5.809	6.241
		95% CI	(-11.0,10.1)	( 1.9,24.7)	(-26.0,-1.5)
		Pr >  t			0.0274
	Week 108	n	9	9	
		LS Mean	-3.561	6.456	-10.02
		SEM	6.083	6.150	7.154

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.5, 8.4)	(-5.6, 18.5)	(-24.1, 4.0)
		Pr >  t			0.1619
	Week 120	n	10	5	
		LS Mean	1.726	-5.913	7.639
		SEM	5.914	7.479	8.203
		95% CI	(-9.9, 13.3)	(-20.6, 8.8)	(-8.5, 23.7)
		Pr >  t			0.3520
	Week 132	n	7	3	
		LS Mean	3.980	7.147	-3.167
		SEM	6.590	9.088	10.13
		95% CI	(-9.0, 16.9)	(-10.7, 25.0)	(-23.1, 16.7)
		Pr >  t			0.7546
	Week 144	n	3	2	
		LS Mean	14.888	2.382	12.505
		SEM	9.035	10.78	13.21
		95% CI	(-2.9, 32.6)	(-18.8, 23.5)	(-13.4, 38.4)
		Pr >  t			0.3442
	Week 156	n	3	1	
		LS Mean	-7.249	3.699	-10.95
		SEM	9.046	14.73	16.59
		95% CI	(-25.0, 10.5)	(-25.2, 32.6)	(-43.5, 21.6)
		Pr >  t			0.5095
	Week 168	n	1	1	
		LS Mean	-0.570	3.699	-4.269
		SEM	14.73	14.73	20.26
		95% CI	(-29.5, 28.4)	(-25.2, 32.6)	(-44.1, 35.5)
		Pr >  t			0.8331

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-6.212	4.207	-10.42
			SEM	4.557	4.670	4.805
			95% CI	(-15.3, 2.9)	(-5.2,13.6)	(-19.9,-0.9)
			Pr >  t			0.0318
		Week 16	n	14	17	
			LS Mean	-7.466	6.004	-13.47
			SEM	4.684	5.080	5.374
			95% CI	(-16.8, 1.9)	(-4.2,16.2)	(-24.1,-2.8)
			Pr >  t			0.0133
		Week 24	n	14	11	
			LS Mean	-0.323	-0.614	0.291
			SEM	4.684	5.696	5.961
			95% CI	(-9.7, 9.0)	(-12.0,10.7)	(-11.5,12.1)
			Pr >  t			0.9612
		Week 32	n	10	10	
			LS Mean	-3.406	1.658	-5.064
			SEM	5.674	5.864	6.539
			95% CI	(-14.6, 7.8)	(-10.0,13.3)	(-18.0, 7.8)
			Pr >  t			0.4398
		Week 40	n	8	10	
			LS Mean	-2.767	-5.192	2.425
			SEM	6.115	5.858	6.922
			95% CI	(-14.8, 9.3)	(-16.8, 6.5)	(-11.2,16.1)
			Pr >  t			0.7265
		Week 48	n	7	11	
			LS Mean	-1.960	6.978	-8.938
			SEM	6.398	5.700	7.047
95% CI	(-14.6,10.7)		(-4.4,18.3)	(-22.8, 5.0)		
	Pr >  t			0.2062		
Week 56	n	6	9			
	LS Mean	-3.923	-1.609	-2.313		
	SEM	6.775	6.057	7.656		



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.3, 9.4)	(-13.6, 10.4)	(-17.4, 12.8)
		Pr >  t			0.7628
	Week 64	n	5	8	
		LS Mean	-3.470	-5.910	2.440
		SEM	7.248	6.285	8.249
		95% CI	(-17.8, 10.8)	(-18.4, 6.6)	(-13.8, 18.7)
		Pr >  t			0.7677
	Week 72	n	7	7	
		LS Mean	-4.182	-0.977	-3.205
		SEM	6.409	6.570	7.763
		95% CI	(-16.8, 8.5)	(-14.0, 12.0)	(-18.5, 12.1)
		Pr >  t			0.6801
	Week 84	n	7	7	
		LS Mean	0.579	3.786	-3.206
		SEM	6.409	6.570	7.763
		95% CI	(-12.1, 13.2)	(-9.2, 16.8)	(-18.5, 12.1)
		Pr >  t			0.6800
	Week 96	n	5	6	
		LS Mean	-4.074	-0.364	-3.709
		SEM	7.248	6.922	8.745
		95% CI	(-18.4, 10.2)	(-14.1, 13.3)	(-20.9, 13.5)
		Pr >  t			0.6719
	Week 108	n	4	6	
		LS Mean	4.366	10.746	-6.379
		SEM	7.907	6.922	9.302
		95% CI	(-11.2, 20.0)	(-3.0, 24.4)	(-24.7, 12.0)
		Pr >  t			0.4936
	Week 120	n	4	4	
		LS Mean	-4.403	-8.121	3.718
		SEM	7.911	8.032	10.16
		95% CI	(-20.0, 11.2)	(-24.0, 7.7)	(-16.3, 23.8)
		Pr >  t			0.7149
	Week 132	n	3	1	
		LS Mean	-3.808	86.402	-90.21
		SEM	8.891	14.58	16.36
		95% CI	(-21.3, 13.7)	(57.7, 115)	(-122, -58)
		Pr >  t			<.0001
	Week 144	n	1	1	
		LS Mean	-4.035	-1.898	-2.137
		SEM	14.50	14.61	20.00

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-32.6,24.6)	(-30.7,26.9)	(-41.6,37.3)
		Pr >  t			0.9150
		n	35	37	
	Week 16	LS Mean	-1.757	-1.315	-0.442
		SEM	8.669	9.117	4.035
		95% CI	(-18.8,15.3)	(-19.3,16.6)	(-8.4, 7.5)
	Week 24	Pr >  t			0.9129
		n	34	30	
		LS Mean	-3.282	-2.680	-0.602
	Week 32	SEM	9.036	9.206	4.241
		95% CI	(-21.1,14.5)	(-20.8,15.4)	(-8.9, 7.7)
		Pr >  t			0.8872
	Week 40	n	32	23	
		LS Mean	-3.913	2.179	-6.092
		SEM	9.059	9.350	4.599
	Week 48	95% CI	(-21.7,13.9)	(-16.2,20.6)	(-15.1, 3.0)
		Pr >  t			0.1863
		n	21	22	
	Week 56	LS Mean	-6.154	-5.015	-1.140
		SEM	9.282	9.380	5.086
		95% CI	(-24.4,12.1)	(-23.5,13.4)	(-11.1, 8.9)
	Week 64	Pr >  t			0.8228
		n	20	20	
		LS Mean	-8.075	7.202	-15.28
	Week 8	SEM	9.318	9.440	5.255
		95% CI	(-26.4,10.3)	(-11.4,25.8)	(-25.6,-4.9)
		Pr >  t			0.0039
	Week 16	n	19	12	
		LS Mean	-11.00	-4.878	-6.121
		SEM	9.348	9.852	6.029
	Week 24	95% CI	(-29.4, 7.4)	(-24.3,14.5)	(-18.0, 5.7)
		Pr >  t			0.3106
		n	16	8	
	Week 32	LS Mean	-6.154	9.330	-15.48
		SEM	9.476	10.36	6.983
		95% CI	(-24.8,12.5)	(-11.0,29.7)	(-29.2,-1.8)
	Week 40	Pr >  t			0.0272
		n	12	11	
		LS Mean	-11.21	6.277	-17.49
	Week 48	SEM	9.732	9.959	6.752

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-30.4, 7.9)	(-30.8,-4.2)
		Pr >  t		0.0099
	Week 72	n	13	7
		LS Mean	1.045	-1.199
		SEM	9.661	10.56
		95% CI	(-18.0,20.1)	(-22.0,19.6)
		Pr >  t		0.7655
	Week 84	n	12	6
		LS Mean	-6.428	0.131
		SEM	9.733	10.84
		95% CI	(-25.6,12.7)	(-21.2,21.4)
		Pr >  t		0.4115
	Week 96	n	7	6
		LS Mean	-11.66	11.602
		SEM	10.42	10.83
		95% CI	(-32.2, 8.8)	( -9.7,32.9)
		Pr >  t		0.0086
	Week 108	n	5	3
		LS Mean	-1.257	5.677
		SEM	11.04	12.50
		95% CI	(-23.0,20.5)	(-18.9,30.3)
		Pr >  t		0.5434
	Week 120	n	8	3
		LS Mean	10.106	5.677
		SEM	10.23	12.50
		95% CI	(-10.0,30.2)	(-18.9,30.3)
		Pr >  t		0.6769
	Week 132	n	2	1
		LS Mean	-7.166	17.409
		SEM	13.83	17.63
		95% CI	(-34.4,20.0)	(-17.2,52.1)
		Pr >  t		0.1919
	Week 144	n	2	
		LS Mean	-6.200	
		SEM	13.85	
		95% CI	(-33.4,21.0)	
		Pr >  t		
	Week 156	n	2	
		LS Mean	-6.200	
		SEM	13.85	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-33.4,21.0)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	3.138	4.222	-1.084
		SEM	3.085	3.217	3.030
		95% CI	(-2.9, 9.2)	(-2.1,10.6)	(-7.0, 4.9)
		Pr >  t			0.7208
	Week 16	n	70	52	
		LS Mean	3.982	3.238	0.744
		SEM	3.165	3.389	3.239
		95% CI	(-2.3,10.2)	(-3.4, 9.9)	(-5.6, 7.1)
		Pr >  t			0.8184
	Week 24	n	54	40	
		LS Mean	2.401	8.711	-6.310
		SEM	3.302	3.588	3.547
		95% CI	(-4.1, 8.9)	( 1.6,15.8)	(-13.3, 0.7)
		Pr >  t			0.0760
	Week 32	n	50	36	
		LS Mean	3.029	3.976	-0.947
		SEM	3.359	3.660	3.661
		95% CI	(-3.6, 9.6)	(-3.2,11.2)	(-8.1, 6.2)
		Pr >  t			0.7961
	Week 40	n	42	28	
		LS Mean	3.022	5.205	-2.183
		SEM	3.460	3.868	3.947
		95% CI	(-3.8, 9.8)	(-2.4,12.8)	(-9.9, 5.6)
		Pr >  t			0.5804
	Week 48	n	38	24	
		LS Mean	4.821	11.012	-6.190
		SEM	3.523	4.002	4.132
		95% CI	(-2.1,11.8)	( 3.1,18.9)	(-14.3, 1.9)
		Pr >  t			0.1346
	Week 56	n	33	24	
		LS Mean	1.648	3.769	-2.121
		SEM	3.618	4.005	4.220
		95% CI	(-5.5, 8.8)	(-4.1,11.6)	(-10.4, 6.2)
		Pr >  t			0.6155
	Week 64	n	27	19	
		LS Mean	4.609	6.016	-1.407
		SEM	3.769	4.237	4.569

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-2.8,12.0)	(-2.3,14.3)	(-10.4, 7.6)
		Pr >  t			0.7582
	Week 72	n	26	17	
		LS Mean	7.641	7.398	0.243
		SEM	3.801	4.357	4.708
		95% CI	( 0.2,15.1)	(-1.2,16.0)	(-9.0, 9.5)
		Pr >  t			0.9589
	Week 84	n	18	16	
		LS Mean	6.626	5.670	0.956
		SEM	4.179	4.430	5.067
		95% CI	(-1.6,14.8)	(-3.0,14.4)	(-9.0,10.9)
		Pr >  t			0.8503
	Week 96	n	20	10	
		LS Mean	5.757	9.080	-3.324
		SEM	4.058	5.090	5.572
		95% CI	(-2.2,13.7)	(-0.9,19.1)	(-14.3, 7.6)
		Pr >  t			0.5510
	Week 108	n	14	10	
		LS Mean	-4.362	3.306	-7.668
		SEM	4.489	5.090	5.887
		95% CI	(-13.2, 4.5)	(-6.7,13.3)	(-19.2, 3.9)
		Pr >  t			0.1931
	Week 120	n	14	7	
		LS Mean	-1.351	1.061	-2.412
		SEM	4.473	5.748	6.462
		95% CI	(-10.1, 7.4)	(-10.2,12.3)	(-15.1,10.3)
		Pr >  t			0.7090
	Week 132	n	12	5	
		LS Mean	3.055	4.753	-1.698
		SEM	4.701	6.520	7.294
		95% CI	(-6.2,12.3)	(-8.0,17.5)	(-16.0,12.6)
		Pr >  t			0.8160
	Week 144	n	11	4	
		LS Mean	10.330	4.693	5.636
		SEM	4.816	7.125	7.919
		95% CI	( 0.9,19.8)	(-9.3,18.7)	(-9.9,21.2)
		Pr >  t			0.4768
	Week 156	n	8	3	
		LS Mean	1.530	5.002	-3.472
		SEM	5.380	8.028	9.055

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.0,12.1)	(-10.8,20.8)	(-21.2,14.3)
		Pr >  t			0.7015
	Week 168	n	4	2	
		LS Mean	7.235	5.016	2.219
		SEM	7.033	9.582	11.40
		95% CI	(-6.6,21.0)	(-13.8,23.8)	(-20.2,24.6)
		Pr >  t			0.8457
	Week 180	n	1	1	
		LS Mean	32.756	4.832	27.923
		SEM	13.13	13.17	18.29
		95% CI	( 7.0,58.5)	(-21.0,30.7)	(-8.0,63.8)
		Pr >  t			0.1273
	Week 192	n	1	1	
		LS Mean	32.756	4.832	27.923
		SEM	13.13	13.17	18.29
		95% CI	( 7.0,58.5)	(-21.0,30.7)	(-8.0,63.8)
		Pr >  t			0.1273

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	3.138	4.222	-1.084		
			SEM	3.085	3.217	3.030		
			95% CI	(-2.9, 9.2)	(-2.1, 10.6)	(-7.0, 4.9)		
					Pr >  t			0.7208
		Week 16	n	70	52			
			LS Mean	3.982	3.238	0.744		
			SEM	3.165	3.389	3.239		
			95% CI	(-2.3, 10.2)	(-3.4, 9.9)	(-5.6, 7.1)		
					Pr >  t			0.8184
		Week 24	n	54	40			
			LS Mean	2.401	8.711	-6.310		
			SEM	3.302	3.588	3.547		
			95% CI	(-4.1, 8.9)	( 1.6, 15.8)	(-13.3, 0.7)		
					Pr >  t			0.0760
		Week 32	n	50	36			
			LS Mean	3.029	3.976	-0.947		
			SEM	3.359	3.660	3.661		
			95% CI	(-3.6, 9.6)	(-3.2, 11.2)	(-8.1, 6.2)		
					Pr >  t			0.7961
		Week 40	n	42	28			
			LS Mean	3.022	5.205	-2.183		
			SEM	3.460	3.868	3.947		
			95% CI	(-3.8, 9.8)	(-2.4, 12.8)	(-9.9, 5.6)		
			Pr >  t			0.5804		
Week 48	n	38	24					
	LS Mean	4.821	11.012	-6.190				
	SEM	3.523	4.002	4.132				
	95% CI	(-2.1, 11.8)	( 3.1, 18.9)	(-14.3, 1.9)				
			Pr >  t			0.1346		
Week 56	n	33	24					
	LS Mean	1.648	3.769	-2.121				
		SEM	3.618	4.005	4.220			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.5, 8.8)	(-4.1, 11.6)	(-10.4, 6.2)
		Pr >  t			0.6155
	Week 64	n	27	19	
		LS Mean	4.609	6.016	-1.407
		SEM	3.769	4.237	4.569
		95% CI	(-2.8, 12.0)	(-2.3, 14.3)	(-10.4, 7.6)
		Pr >  t			0.7582
	Week 72	n	26	17	
		LS Mean	7.641	7.398	0.243
		SEM	3.801	4.357	4.708
		95% CI	(0.2, 15.1)	(-1.2, 16.0)	(-9.0, 9.5)
		Pr >  t			0.9589
	Week 84	n	18	16	
		LS Mean	6.626	5.670	0.956
		SEM	4.179	4.430	5.067
		95% CI	(-1.6, 14.8)	(-3.0, 14.4)	(-9.0, 10.9)
		Pr >  t			0.8503
	Week 96	n	20	10	
		LS Mean	5.757	9.080	-3.324
		SEM	4.058	5.090	5.572
		95% CI	(-2.2, 13.7)	(-0.9, 19.1)	(-14.3, 7.6)
		Pr >  t			0.5510
	Week 108	n	14	10	
		LS Mean	-4.362	3.306	-7.668
		SEM	4.489	5.090	5.887
		95% CI	(-13.2, 4.5)	(-6.7, 13.3)	(-19.2, 3.9)
		Pr >  t			0.1931
	Week 120	n	14	7	
		LS Mean	-1.351	1.061	-2.412
		SEM	4.473	5.748	6.462
		95% CI	(-10.1, 7.4)	(-10.2, 12.3)	(-15.1, 10.3)
		Pr >  t			0.7090
	Week 132	n	12	5	
		LS Mean	3.055	4.753	-1.698
		SEM	4.701	6.520	7.294
		95% CI	(-6.2, 12.3)	(-8.0, 17.5)	(-16.0, 12.6)
		Pr >  t			0.8160
	Week 144	n	11	4	
		LS Mean	10.330	4.693	5.636
		SEM	4.816	7.125	7.919



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	( 0.9,19.8)	( -9.3,18.7)	( -9.9,21.2)
		Pr >  t			0.4768
		n	8	3	
		LS Mean	1.530	5.002	-3.472
	Week 168	SEM	5.380	8.028	9.055
		95% CI	( -9.0,12.1)	(-10.8,20.8)	(-21.2,14.3)
		Pr >  t			0.7015
		n	4	2	
	Week 180	LS Mean	7.235	5.016	2.219
		SEM	7.033	9.582	11.40
		95% CI	( -6.6,21.0)	(-13.8,23.8)	(-20.2,24.6)
		Pr >  t			0.8457
Week 192	n	1	1		
	LS Mean	32.756	4.832	27.923	
	SEM	13.13	13.17	18.29	
	95% CI	( 7.0,58.5)	(-21.0,30.7)	( -8.0,63.8)	
Week 8	Pr >  t			0.1273	
	n	1	1		
	LS Mean	32.756	4.832	27.923	
	SEM	13.13	13.17	18.29	
Week 16	95% CI	( 7.0,58.5)	(-21.0,30.7)	( -8.0,63.8)	
	Pr >  t			0.1273	
	n	53	64		
	LS Mean	-2.016	0.337	-2.352	
Week 24	SEM	3.965	4.203	3.053	
	95% CI	( -9.8, 5.8)	( -8.0, 8.6)	( -8.4, 3.6)	
	Pr >  t			0.4414	
	n	48	48		
Week 32	LS Mean	-3.884	0.642	-4.525	
	SEM	4.095	4.363	3.331	
	95% CI	(-12.0, 4.2)	( -8.0, 9.2)	(-11.1, 2.0)	
	Pr >  t			0.1749	
Week 8	n	46	36		
	LS Mean	-2.199	1.495	-3.694	
	SEM	4.116	4.553	3.612	
	95% CI	(-10.3, 5.9)	( -7.5,10.5)	(-10.8, 3.4)	
Week 16	Pr >  t			0.3069	
	n	31	33		
	LS Mean	-4.940	-2.560	-2.379	
Week 24	SEM	4.553	4.622	4.019	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.9, 4.0)	(-11.7, 6.5)	(-10.3, 5.5)
		Pr >  t			0.5541
	Week 40	n	28	30	
		LS Mean	-6.139	3.472	-9.612
		SEM	4.642	4.699	4.205
		95% CI	(-15.3, 3.0)	(-5.8, 12.7)	(-17.9, -1.4)
		Pr >  t			0.0226
	Week 48	n	26	23	
		LS Mean	-8.024	0.982	-9.007
		SEM	4.710	4.945	4.550
		95% CI	(-17.3, 1.2)	(-8.7, 10.7)	(-17.9, -0.1)
		Pr >  t			0.0482
	Week 56	n	22	17	
		LS Mean	-4.889	3.426	-8.315
		SEM	4.878	5.297	5.089
		95% CI	(-14.5, 4.7)	(-7.0, 13.8)	(-18.3, 1.7)
		Pr >  t			0.1028
	Week 64	n	17	19	
		LS Mean	-8.367	1.032	-9.400
		SEM	5.180	5.161	5.245
		95% CI	(-18.5, 1.8)	(-9.1, 11.2)	(-19.7, 0.9)
		Pr >  t			0.0736
	Week 72	n	20	14	
		LS Mean	-0.331	-1.248	0.917
		SEM	4.987	5.565	5.465
		95% CI	(-10.1, 9.5)	(-12.2, 9.7)	(-9.8, 11.6)
		Pr >  t			0.8667
	Week 84	n	19	13	
		LS Mean	-3.455	2.085	-5.540
		SEM	5.046	5.679	5.631
		95% CI	(-13.4, 6.5)	(-9.1, 13.2)	(-16.6, 5.5)
		Pr >  t			0.3256
	Week 96	n	12	12	
		LS Mean	-8.245	5.629	-13.87
		SEM	5.690	5.805	6.333
		95% CI	(-19.4, 2.9)	(-5.8, 17.0)	(-26.3, -1.4)
		Pr >  t			0.0288
	Week 108	n	9	9	
		LS Mean	1.587	9.157	-7.570
		SEM	6.216	6.321	7.255

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.6,13.8)	(-3.3,21.6)	(-21.8, 6.7)
		Pr >  t			0.2971
	Week 120	n	12	7	
		LS Mean	5.946	-2.266	8.213
		SEM	5.696	6.865	7.323
		95% CI	(-5.2,17.1)	(-15.7,11.2)	(-6.2,22.6)
		Pr >  t			0.2625
	Week 132	n	5	2	
		LS Mean	-4.917	51.764	-56.68
		SEM	7.647	11.26	12.62
		95% CI	(-19.9,10.1)	(29.7,73.9)	(-81.5, -32)
		Pr >  t			<.0001
	Week 144	n	3	1	
		LS Mean	-4.879	-0.031	-4.848
		SEM	9.405	15.47	17.37
		95% CI	(-23.3,13.6)	(-30.4,30.4)	(-39.0,29.3)
		Pr >  t			0.7803
	Week 156	n	2		
		LS Mean	-5.258		
		SEM	11.22		
		95% CI	(-27.3,16.8)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-27: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schlaflosigkeit“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv			
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	0.661	1.192	-0.530		
			SEM	3.777	3.952	3.843		
			95% CI	(-6.8, 8.1)	(-6.6, 9.0)	(-8.1, 7.0)		
							Pr >  t	0.8903
		Week 16	n	70	52			
			LS Mean	-2.144	8.224	-10.37		
			SEM	3.874	4.290	4.178		
			95% CI	(-9.8, 5.5)	(-0.2, 16.7)	(-18.6, -2.2)		
							Pr >  t	0.0135
		Week 24	n	61	37			
			LS Mean	3.451	3.437	0.014		
			SEM	3.988	4.654	4.600		
			95% CI	(-4.4, 11.3)	(-5.7, 12.6)	(-9.0, 9.1)		
							Pr >  t	0.9977
		Week 32	n	48	33			
			LS Mean	-3.441	-0.873	-2.568		
			SEM	4.212	4.778	4.890		
			95% CI	(-11.7, 4.8)	(-10.3, 8.5)	(-12.2, 7.0)		
							Pr >  t	0.5997
		Week 40	n	42	31			
			LS Mean	-0.468	-3.702	3.234		
			SEM	4.328	4.849	5.064		
			95% CI	(-9.0, 8.0)	(-13.2, 5.8)	(-6.7, 13.2)		
					Pr >  t	0.5233		
Week 48	n	40	25					
	LS Mean	2.227	3.434	-1.207				
	SEM	4.372	5.103	5.344				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-6.4,10.8)	(-6.6,13.5)	(-11.7, 9.3)
	Pr >  t			0.8214
	n	35	20	
	LS Mean	0.636	4.973	-4.337
	SEM	4.498	5.412	5.745
Week 64	95% CI	(-8.2, 9.5)	(-5.7,15.6)	(-15.6, 6.9)
	Pr >  t			0.4505
	n	29	18	
	LS Mean	-2.059	-3.232	1.172
	SEM	4.694	5.578	6.057
Week 72	95% CI	(-11.3, 7.2)	(-14.2, 7.7)	(-10.7,13.1)
	Pr >  t			0.8466
	n	28	18	
	LS Mean	1.382	3.447	-2.066
	SEM	4.736	5.573	6.086
Week 84	95% CI	(-7.9,10.7)	(-7.5,14.4)	(-14.0, 9.9)
	Pr >  t			0.7344
	n	27	17	
	LS Mean	-2.312	3.859	-6.171
	SEM	4.805	5.668	6.204
Week 96	95% CI	(-11.8, 7.1)	(-7.3,15.0)	(-18.3, 6.0)
	Pr >  t			0.3203
	n	23	14	
	LS Mean	-3.497	3.910	-7.407
	SEM	4.997	6.003	6.667
Week 108	95% CI	(-13.3, 6.3)	(-7.9,15.7)	(-20.5, 5.7)
	Pr >  t			0.2669
	n	19	12	
	LS Mean	0.266	4.964	-4.698
	SEM	5.288	6.306	7.141
Week 120	95% CI	(-10.1,10.7)	(-7.4,17.3)	(-18.7, 9.3)
	Pr >  t			0.5108
	n	18	8	
	LS Mean	3.434	10.028	-6.594
	SEM	5.354	7.258	8.048
Week 132	95% CI	(-7.1,13.9)	(-4.2,24.3)	(-22.4, 9.2)
	Pr >  t			0.4128
	n	11	4	
	LS Mean	-8.661	-1.503	-7.157
	SEM	6.300	9.542	10.68

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.0, 3.7)	(-20.2,17.2)	(-28.1,13.8)
		Pr >  t			0.5029
	Week 144	n	11	4	
		LS Mean	2.486	2.152	0.334
		SEM	6.280	9.548	10.69
		95% CI	(-9.8,14.8)	(-16.6,20.9)	(-20.6,21.3)
		Pr >  t			0.9751
	Week 156	n	5	2	
		LS Mean	-4.268	5.708	-9.976
		SEM	8.547	12.94	14.96
		95% CI	(-21.0,12.5)	(-19.7,31.1)	(-39.3,19.4)
		Pr >  t			0.5051
	Week 168	n	1	2	
		LS Mean	-12.58	-10.96	-1.619
		SEM	17.75	12.94	21.58
		95% CI	(-47.4,22.3)	(-36.4,14.4)	(-44.0,40.7)
		Pr >  t			0.9402
	Week 180	n		1	
		LS Mean		11.418	
		SEM		17.86	
		95% CI		(-23.6,46.5)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-21.91	
		SEM		17.86	
		95% CI		(-57.0,13.2)	
		Pr >  t			
>= 65 Years	Week 8	n	63	71	
		LS Mean	4.938	4.960	-0.022
		SEM	5.721	5.696	4.147
		95% CI	(-6.3,16.2)	(-6.3,16.2)	(-8.2, 8.1)
		Pr >  t			0.9957
	Week 16	n	54	55	
		LS Mean	4.405	5.589	-1.185
		SEM	5.879	5.806	4.476
		95% CI	(-7.2,16.0)	(-5.9,17.0)	(-10.0, 7.6)
		Pr >  t			0.7914
	Week 24	n	44	44	
		LS Mean	6.234	7.459	-1.225
		SEM	6.013	5.934	4.839

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.6,18.1)	(-4.2,19.2)	(-10.7, 8.3)
		Pr >  t			0.8002
	Week 32	n	38	40	
		LS Mean	7.535	4.989	2.546
		SEM	6.167	6.048	5.056
		95% CI	(-4.6,19.7)	(-6.9,16.9)	(-7.4,12.5)
		Pr >  t			0.6148
	Week 40	n	33	31	
		LS Mean	5.880	5.287	0.592
		SEM	6.283	6.293	5.429
		95% CI	(-6.5,18.3)	(-7.1,17.7)	(-10.1,11.3)
		Pr >  t			0.9132
	Week 48	n	29	26	
		LS Mean	9.329	5.564	3.765
		SEM	6.391	6.463	5.745
		95% CI	(-3.3,21.9)	(-7.2,18.3)	(-7.5,15.0)
		Pr >  t			0.5125
	Week 56	n	24	25	
		LS Mean	7.042	6.905	0.138
		SEM	6.573	6.499	5.991
		95% CI	(-5.9,20.0)	(-5.9,19.7)	(-11.6,11.9)
		Pr >  t			0.9817
	Week 64	n	18	24	
		LS Mean	-0.320	3.326	-3.646
		SEM	6.906	6.545	6.404
		95% CI	(-13.9,13.3)	(-9.6,16.2)	(-16.2, 8.9)
		Pr >  t			0.5693
	Week 72	n	20	17	
		LS Mean	1.427	7.043	-5.616
		SEM	6.782	6.958	6.697
		95% CI	(-11.9,14.8)	(-6.6,20.7)	(-18.8, 7.5)
		Pr >  t			0.4020
	Week 84	n	13	16	
		LS Mean	14.684	4.389	10.295
		SEM	7.377	7.039	7.380
		95% CI	( 0.2,29.2)	(-9.5,18.2)	(-4.2,24.8)
		Pr >  t			0.1634
	Week 96	n	12	10	
		LS Mean	6.772	11.010	-4.238
		SEM	7.518	7.846	8.281

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.0,21.5)	(-4.4,26.4)	(-20.5,12.0)
		Pr >  t			0.6090
	Week 108	n	7	9	
		LS Mean	13.871	4.613	9.258
		SEM	8.667	8.064	9.522
		95% CI	(-3.2,30.9)	(-11.2,20.5)	(-9.4,28.0)
		Pr >  t			0.3313
	Week 120	n	10	8	
		LS Mean	5.834	-5.158	10.992
		SEM	7.880	8.334	9.055
		95% CI	(-9.6,21.3)	(-21.5,11.2)	(-6.8,28.8)
		Pr >  t			0.2252
	Week 132	n	9	4	
		LS Mean	22.148	8.212	13.936
		SEM	8.077	10.41	11.13
		95% CI	( 6.3,38.0)	(-12.2,28.6)	(-7.9,35.8)
		Pr >  t			0.2111
	Week 144	n	4	1	
		LS Mean	15.029	4.372	10.657
		SEM	10.41	18.47	19.99
		95% CI	(-5.4,35.5)	(-31.9,40.6)	(-28.6,49.9)
		Pr >  t			0.5942
	Week 156	n	5	1	
		LS Mean	13.241	4.372	8.869
		SEM	9.643	18.47	19.61
		95% CI	(-5.7,32.2)	(-31.9,40.6)	(-29.6,47.4)
		Pr >  t			0.6512
	Week 168	n	3		
		LS Mean	33.619		
		SEM	11.59		
		95% CI	( 10.9,56.4)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	54.242		
		SEM	18.46		
		95% CI	( 18.0,90.5)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	54.242		
		SEM	18.46		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI Pr >  t	( 18.0,90.5)	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	1.786	1.784	0.002		
			SEM	3.254	3.320	3.056		
			95% CI	(-4.6, 8.2)	(-4.7, 8.3)	(-6.0, 6.0)		
					Pr >  t			0.9995
		Week 16	n	111	91			
			LS Mean	-0.203	6.019	-6.222		
			SEM	3.339	3.525	3.306		
			95% CI	(-6.8, 6.4)	(-0.9, 12.9)	(-12.7, 0.3)		
					Pr >  t			0.0602
		Week 24	n	96	70			
			LS Mean	5.651	4.787	0.864		
			SEM	3.424	3.713	3.569		
			95% CI	(-1.1, 12.4)	(-2.5, 12.1)	(-6.1, 7.9)		
					Pr >  t			0.8088
		Week 32	n	77	61			
			LS Mean	0.208	1.913	-1.706		
			SEM	3.584	3.826	3.797		
			95% CI	(-6.8, 7.2)	(-5.6, 9.4)	(-9.2, 5.7)		
					Pr >  t			0.6535
		Week 40	n	69	52			
			LS Mean	2.479	0.880	1.598		
			SEM	3.655	3.966	3.994		
			95% CI	(-4.7, 9.7)	(-6.9, 8.7)	(-6.2, 9.4)		
			Pr >  t			0.6892		
Week 48	n	62	41					
	LS Mean	5.589	4.601	0.988				
	SEM	3.727	4.177	4.268				
	95% CI	(-1.7, 12.9)	(-3.6, 12.8)	(-7.4, 9.4)				
			Pr >  t			0.8171		
Week 56	n	53	35					
	LS Mean	4.085	4.754	-0.669				
	SEM	3.843	4.338	4.528				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.5,11.6)	(-3.8,13.3)	(-9.6, 8.2)
		Pr >  t			0.8825
	Week 64	n	44	33	
		LS Mean	-0.961	0.256	-1.217
		SEM	3.995	4.404	4.723
		95% CI	(-8.8, 6.9)	(-8.4, 8.9)	(-10.5, 8.0)
		Pr >  t			0.7967
	Week 72	n	45	28	
		LS Mean	3.386	4.598	-1.213
		SEM	3.978	4.595	4.886
		95% CI	(-4.4,11.2)	(-4.4,13.6)	(-10.8, 8.4)
		Pr >  t			0.8040
	Week 84	n	39	27	
		LS Mean	4.324	4.710	-0.386
		SEM	4.123	4.641	5.037
		95% CI	(-3.8,12.4)	(-4.4,13.8)	(-10.3, 9.5)
		Pr >  t			0.9389
	Week 96	n	34	19	
		LS Mean	0.869	6.912	-6.043
		SEM	4.258	5.143	5.611
		95% CI	(-7.5, 9.2)	(-3.2,17.0)	(-17.1, 5.0)
		Pr >  t			0.2817
	Week 108	n	26	17	
		LS Mean	5.078	5.818	-0.739
		SEM	4.586	5.331	6.022
		95% CI	(-3.9,14.1)	(-4.6,16.3)	(-12.6,11.1)
		Pr >  t			0.9023
	Week 120	n	27	11	
		LS Mean	5.528	6.069	-0.542
		SEM	4.531	6.201	6.772
		95% CI	(-3.4,14.4)	(-6.1,18.2)	(-13.8,12.7)
		Pr >  t			0.9363
	Week 132	n	20	6	
		LS Mean	5.090	3.209	1.882
		SEM	4.959	7.868	8.563
		95% CI	(-4.6,14.8)	(-12.2,18.6)	(-14.9,18.7)
		Pr >  t			0.8261
	Week 144	n	15	4	
		LS Mean	7.198	3.469	3.728
		SEM	5.442	9.372	10.22

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.5,17.9)	(-14.9,21.9)	(-16.3,23.8)
		Pr >  t			0.7153
	Week 156	n	10	2	
		LS Mean	3.885	7.128	-3.244
		SEM	6.327	12.84	13.85
		95% CI	(-8.5,16.3)	(-18.1,32.3)	(-30.4,23.9)
		Pr >  t			0.8148
	Week 168	n	4	2	
		LS Mean	19.473	-9.537	29.010
		SEM	9.283	12.84	15.42
		95% CI	( 1.3,37.7)	(-34.7,15.6)	(-1.2,59.3)
		Pr >  t			0.0602
	Week 180	n	1	1	
		LS Mean	49.270	12.732	36.538
		SEM	17.80	17.83	24.93
		95% CI	( 14.4,84.2)	(-22.2,47.7)	(-12.4,85.4)
		Pr >  t			0.1430
	Week 192	n	1	1	
		LS Mean	49.270	-20.60	69.868
		SEM	17.80	17.83	24.93
		95% CI	( 14.4,84.2)	(-55.6,14.4)	( 21.0, 119)
		Pr >  t			0.0051
>= 75 Years	Week 8	n	17	19	
		LS Mean	-6.956	-2.449	-4.507
		SEM	5.181	4.722	6.958
		95% CI	(-17.2, 3.3)	(-11.8, 6.9)	(-18.3, 9.3)
		Pr >  t			0.5186
	Week 16	n	13	16	
		LS Mean	-7.566	-2.485	-5.081
		SEM	5.815	5.122	7.692
		95% CI	(-19.1, 4.0)	(-12.6, 7.7)	(-20.3,10.2)
		Pr >  t			0.5102
	Week 24	n	9	11	
		LS Mean	-22.05	-4.198	-17.85
		SEM	6.749	6.023	9.003
		95% CI	(-35.4,-8.7)	(-16.1, 7.7)	(-35.6,-0.1)
		Pr >  t			0.0494
	Week 32	n	9	12	
		LS Mean	-3.883	-9.755	5.872
		SEM	6.749	5.838	8.876

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-17.2, 9.5)	(-21.3, 1.8)	(-11.7, 23.4)
		Pr >  t			0.5094
	Week 40	n	6	10	
		LS Mean	-15.49	-12.78	-2.704
		SEM	7.994	6.260	10.11
		95% CI	(-31.3, 0.3)	(-25.2, -0.4)	(-22.7, 17.3)
		Pr >  t			0.7894
	Week 48	n	7	10	
		LS Mean	-12.46	-8.551	-3.912
		SEM	7.503	6.281	9.738
		95% CI	(-27.3, 2.4)	(-21.0, 3.9)	(-23.1, 15.3)
		Pr >  t			0.6885
	Week 56	n	6	10	
		LS Mean	-17.57	-2.494	-15.08
		SEM	7.981	6.291	10.11
		95% CI	(-33.3, -1.8)	(-14.9, 9.9)	(-35.0, 4.9)
		Pr >  t			0.1378
	Week 64	n	3	9	
		LS Mean	-20.19	-11.96	-8.235
		SEM	10.76	6.564	12.56
		95% CI	(-41.4, 1.0)	(-24.9, 1.0)	(-33.0, 16.6)
		Pr >  t			0.5129
	Week 72	n	3	7	
		LS Mean	-42.41	-4.423	-37.99
		SEM	10.76	7.284	12.95
		95% CI	(-63.6, -21)	(-18.8, 10.0)	(-63.5, -12)
		Pr >  t			0.0038
	Week 84	n	1	6	
		LS Mean	-27.66	-10.79	-16.87
		SEM	17.88	7.764	19.45
		95% CI	(-63.0, 7.6)	(-26.1, 4.5)	(-55.3, 21.5)
		Pr >  t			0.3870
	Week 96	n	1	5	
		LS Mean	-27.66	-3.970	-23.69
		SEM	17.88	8.391	19.72
		95% CI	(-63.0, 7.6)	(-20.5, 12.6)	(-62.6, 15.2)
		Pr >  t			0.2313
	Week 108	n		4	
		LS Mean		-10.54	
		SEM		9.254	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-28.8, 7.7)
		Pr >  t		
	Week 120	n	1	5
		LS Mean	-27.66	-17.30
		SEM	17.91	8.391
		95% CI	(-63.0, 7.7)	(-33.9,-0.7)
		Pr >  t		
	Week 132	n		2
		LS Mean		-7.620
		SEM		12.62
		95% CI		(-32.5,17.3)
		Pr >  t		
	Week 144	n		1
		LS Mean		-8.920
		SEM		17.53
		95% CI		(-43.5,25.7)
		Pr >  t		
	Week 156	n		1
		LS Mean		-8.920
		SEM		17.53
		95% CI		(-43.5,25.7)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	10.915	6.604	4.311		
			SEM	5.106	4.803	4.393		
			95% CI	( 0.8,21.1)	( -2.9,16.2)	( -4.4,13.0)		
					Pr >  t			0.3279
		Week 16	n	30	30			
			LS Mean	8.739	8.069	0.670		
			SEM	5.154	5.047	4.638		
			95% CI	( -1.5,19.0)	( -2.0,18.1)	( -8.5, 9.8)		
					Pr >  t			0.8853
		Week 24	n	21	26			
			LS Mean	8.786	6.559	2.227		
			SEM	5.440	5.147	5.093		
			95% CI	( -2.0,19.6)	( -3.7,16.8)	( -7.8,12.3)		
					Pr >  t			0.6623
		Week 32	n	19	24			
			LS Mean	9.112	4.170	4.943		
			SEM	5.541	5.217	5.285		
			95% CI	( -1.9,20.1)	( -6.2,14.5)	( -5.5,15.4)		
					Pr >  t			0.3506
		Week 40	n	16	19			
			LS Mean	8.620	-0.426	9.046		
			SEM	5.713	5.501	5.701		
			95% CI	( -2.7,19.9)	(-11.3,10.5)	( -2.2,20.3)		
					Pr >  t			0.1138
		Week 48	n	16	18			
			LS Mean	8.620	7.442	1.178		
			SEM	5.713	5.557	5.758		
95% CI	( -2.7,19.9)		( -3.6,18.4)	(-10.2,12.5)				
			Pr >  t			0.8381		
Week 56	n	12	14					
	LS Mean	8.494	10.460	-1.966				
	SEM	6.053	5.842	6.376				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.5,20.5)	(-14.5,10.6)
		Pr >  t		0.7580
	Week 64	n	12	11
		LS Mean	8.493	3.324
		SEM	6.053	6.177
		95% CI	(-3.5,20.5)	(-8.9,15.5)
		Pr >  t		0.4401
	Week 72	n	10	9
		LS Mean	10.082	7.582
		SEM	6.310	6.498
		95% CI	(-2.4,22.5)	(-5.2,20.4)
		Pr >  t		0.7290
	Week 84	n	8	8
		LS Mean	11.667	8.377
		SEM	6.759	6.713
		95% CI	(-1.7,25.0)	(-4.9,21.6)
		Pr >  t		0.6709
	Week 96	n	6	6
		LS Mean	3.426	10.319
		SEM	7.350	7.308
		95% CI	(-11.0,17.9)	(-4.1,24.7)
		Pr >  t		0.4316
	Week 108	n	4	5
		LS Mean	10.208	4.522
		SEM	8.390	7.751
		95% CI	(-6.3,26.7)	(-10.7,19.8)
		Pr >  t		0.5695
	Week 120	n	4	4
		LS Mean	18.541	3.948
		SEM	8.390	8.368
		95% CI	( 2.0,35.0)	(-12.5,20.4)
		Pr >  t		0.1643
	Week 132	n	3	2
		LS Mean	22.548	6.109
		SEM	9.305	10.87
		95% CI	( 4.2,40.8)	(-15.3,27.5)
		Pr >  t		0.2135
	Week 144	n	3	1
		LS Mean	11.438	5.633
		SEM	9.305	14.67
				5.805
				16.46



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.9,29.7)	(-23.2,34.5)	(-26.6,38.2)
		Pr >  t			0.7245
	Week 156	n	2	1	
		LS Mean	-3.411	5.633	-9.044
		SEM	10.90	14.67	17.41
		95% CI	(-24.8,18.0)	(-23.2,34.5)	(-43.3,25.2)
		Pr >  t			0.6037
	Week 168	n	1		
		LS Mean	42.311		
		SEM	14.67		
		95% CI	( 13.5,71.2)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	0.139	-0.245	0.384
		SEM	11.89	11.79	7.665
		95% CI	(-23.6,23.9)	(-23.7,23.2)	(-14.9,15.7)
		Pr >  t			0.9602
	Week 16	n	15	14	
		LS Mean	-3.511	4.586	-8.097
		SEM	11.95	11.01	7.986
		95% CI	(-27.4,20.3)	(-17.4,26.6)	(-24.0, 7.8)
		Pr >  t			0.3142
	Week 24	n	12	11	
		LS Mean	11.316	-0.965	12.281
		SEM	12.16	11.95	8.553
		95% CI	(-12.9,35.6)	(-24.8,22.8)	( -4.7,29.3)
		Pr >  t			0.1549
	Week 32	n	8	9	
		LS Mean	5.693	1.382	4.311
		SEM	12.65	12.24	9.552
		95% CI	(-19.5,30.9)	(-23.0,25.7)	(-14.6,23.3)
		Pr >  t			0.6527
	Week 40	n	6	7	
		LS Mean	23.147	-4.159	27.305
		SEM	13.10	12.56	10.53
		95% CI	( -2.9,49.2)	(-29.1,20.8)	( 6.5,48.2)
		Pr >  t			0.0107
	Week 48	n	4	6	
		LS Mean	8.806	-2.502	11.308
		SEM	13.90	12.80	11.74

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-18.8,36.4)	(-27.9,22.9)	(-11.9,34.5)
		Pr >  t			0.3372
	Week 56	n	4	6	
		LS Mean	5.944	7.557	-1.612
		SEM	13.90	12.81	11.76
		95% CI	(-21.6,33.5)	(-17.9,33.0)	(-24.9,21.6)
		Pr >  t			0.8911
	Week 64	n	4	4	
		LS Mean	2.146	-0.776	2.922
		SEM	13.92	13.60	12.61
		95% CI	(-25.5,29.8)	(-27.7,26.2)	(-22.0,27.8)
		Pr >  t			0.8170
	Week 72	n	4	4	
		LS Mean	10.479	-0.776	11.255
		SEM	13.92	13.60	12.61
		95% CI	(-17.1,38.1)	(-27.7,26.2)	(-13.7,36.2)
		Pr >  t			0.3735
	Week 84	n	4	4	
		LS Mean	8.806	-0.776	9.582
		SEM	13.90	13.60	12.61
		95% CI	(-18.8,36.4)	(-27.7,26.2)	(-15.4,34.5)
		Pr >  t			0.4487
	Week 96	n	3	2	
		LS Mean	21.288	-2.503	23.791
		SEM	14.65	15.72	15.57
		95% CI	(-7.7,50.3)	(-33.6,28.6)	(-7.0,54.6)
		Pr >  t			0.1287
	Week 108	n	3	3	
		LS Mean	10.175	-4.705	14.879
		SEM	14.65	14.37	14.20
		95% CI	(-18.9,39.2)	(-33.2,23.8)	(-13.2,42.9)
		Pr >  t			0.2964
	Week 120	n	2	1	
		LS Mean	14.588	-4.208	18.796
		SEM	16.01	19.24	20.16
		95% CI	(-17.1,46.3)	(-42.2,33.8)	(-21.1,58.7)
		Pr >  t			0.3528
	Week 132	n	2	1	
		LS Mean	55.107	-4.208	59.315
		SEM	15.99	19.24	20.19

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(23.5,86.8)	(-42.2,33.8)	(19.4,99.2)
		Pr >  t			0.0039
	Week 156	n	1		
		LS Mean	8.864		
		SEM	19.50		
		95% CI	(-29.7,47.4)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	8.864		
		SEM	19.50		
		95% CI	(-29.7,47.4)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	-0.781	1.454	-2.235
		SEM	3.952	4.170	3.794
		95% CI	(-8.6, 7.0)	(-6.8, 9.7)	(-9.7, 5.2)
		Pr >  t			0.5562
	Week 16	n	79	61	
		LS Mean	-2.211	5.963	-8.174
		SEM	4.102	4.529	4.209
		95% CI	(-10.3, 5.9)	(-2.9,14.9)	(-16.4, 0.1)
		Pr >  t			0.0527
	Week 24	n	71	43	
		LS Mean	1.063	5.881	-4.819
		SEM	4.193	4.847	4.628
		95% CI	(-7.2, 9.3)	(-3.6,15.4)	(-13.9, 4.3)
		Pr >  t			0.2982
	Week 32	n	59	39	
		LS Mean	-2.900	1.291	-4.192
		SEM	4.390	4.979	4.860
		95% CI	(-11.5, 5.7)	(-8.5,11.1)	(-13.7, 5.4)
		Pr >  t			0.3887
	Week 40	n	52	35	
		LS Mean	-4.042	1.319	-5.360
		SEM	4.495	5.098	5.075
		95% CI	(-12.9, 4.8)	(-8.7,11.3)	(-15.3, 4.6)
		Pr >  t			0.2912
	Week 48	n	48	26	
		LS Mean	2.631	4.383	-1.752
		SEM	4.564	5.467	5.502

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.3,11.6)	(-6.4,15.1)	(-12.6, 9.0)
		Pr >  t			0.7503
	Week 56	n	42	24	
		LS Mean	0.109	3.026	-2.917
		SEM	4.685	5.579	5.718
		95% CI	(-9.1, 9.3)	(-7.9,14.0)	(-14.1, 8.3)
		Pr >  t			0.6101
	Week 64	n	30	26	
		LS Mean	-6.267	-1.037	-5.230
		SEM	5.048	5.469	5.923
		95% CI	(-16.2, 3.6)	(-11.8, 9.7)	(-16.9, 6.4)
		Pr >  t			0.3775
	Week 72	n	34	21	
		LS Mean	-3.669	5.602	-9.271
		SEM	4.906	5.777	6.092
		95% CI	(-13.3, 6.0)	(-5.7,16.9)	(-21.2, 2.7)
		Pr >  t			0.1284
	Week 84	n	28	20	
		LS Mean	-0.666	3.631	-4.298
		SEM	5.147	5.852	6.349
		95% CI	(-10.8, 9.4)	(-7.9,15.1)	(-16.8, 8.2)
		Pr >  t			0.4986
	Week 96	n	26	15	
		LS Mean	-4.567	3.447	-8.014
		SEM	5.233	6.359	6.895
		95% CI	(-14.8, 5.7)	(-9.0,15.9)	(-21.5, 5.5)
		Pr >  t			0.2454
	Week 108	n	19	12	
		LS Mean	1.413	5.271	-3.858
		SEM	5.726	6.829	7.677
		95% CI	(-9.8,12.7)	(-8.1,18.7)	(-18.9,11.2)
		Pr >  t			0.6154
	Week 120	n	22	10	
		LS Mean	-1.092	3.357	-4.449
		SEM	5.477	7.266	7.904
		95% CI	(-11.8, 9.7)	(-10.9,17.6)	(-20.0,11.1)
		Pr >  t			0.5736
	Week 132	n	15	4	
		LS Mean	-7.317	-1.211	-6.106
		SEM	6.154	10.38	11.19

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.4, 4.8)	(-21.6,19.2)	(-28.1,15.8)
		Pr >  t			0.5853
	Week 144	n	12	4	
		LS Mean	3.305	2.433	0.872
		SEM	6.611	10.39	11.46
		95% CI	(-9.7,16.3)	(-17.9,22.8)	(-21.6,23.4)
		Pr >  t			0.9394
	Week 156	n	7	2	
		LS Mean	3.940	6.135	-2.195
		SEM	8.102	14.10	15.62
		95% CI	(-12.0,19.8)	(-21.5,33.8)	(-32.8,28.5)
		Pr >  t			0.8883
	Week 168	n	2	2	
		LS Mean	16.746	-10.53	27.276
		SEM	13.97	14.10	19.32
		95% CI	(-10.7,44.2)	(-38.2,17.1)	(-10.6,65.2)
		Pr >  t			0.1584
	Week 180	n	1	1	
		LS Mean	44.913	11.632	33.281
		SEM	19.41	19.48	27.13
		95% CI	( 6.8,83.0)	(-26.6,49.9)	(-20.0,86.5)
		Pr >  t			0.2202
	Week 192	n	1	1	
		LS Mean	44.913	-21.70	66.611
		SEM	19.41	19.48	27.13
		95% CI	( 6.8,83.0)	(-59.9,16.5)	( 13.4, 120)
		Pr >  t			0.0143

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Geographic Region 1 (L)	Asia	Week 8	n	30	35	
			LS Mean	9.882	7.473	2.409
			SEM	5.051	4.714	4.424
			95% CI	(-0.2,19.9)	(-1.9,16.9)	(-6.3,11.2)
			Pr >  t			0.5869
		Week 16	n	28	29	
			LS Mean	9.891	9.087	0.803
			SEM	5.106	4.969	4.683
			95% CI	(-0.3,20.1)	(-0.8,19.0)	(-8.4,10.1)
			Pr >  t			0.8640
		Week 24	n	21	25	
			LS Mean	8.810	7.559	1.251
			SEM	5.339	5.078	5.077
			95% CI	(-1.8,19.4)	(-2.5,17.6)	(-8.8,11.3)
			Pr >  t			0.8057
		Week 32	n	19	23	
			LS Mean	9.131	5.099	4.032
			SEM	5.440	5.154	5.275
			95% CI	(-1.7,19.9)	(-5.1,15.3)	(-6.4,14.4)
			Pr >  t			0.4454
		Week 40	n	16	18	
			LS Mean	8.620	0.264	8.355
			SEM	5.613	5.463	5.708
			95% CI	(-2.5,19.7)	(-10.5,11.1)	(-2.9,19.6)
Pr >  t				0.1445		
Week 48	n	16	17			
	LS Mean	8.620	8.582	0.037		
	SEM	5.613	5.525	5.771		
	95% CI	(-2.5,19.7)	(-2.4,19.5)	(-11.3,11.4)		
	Pr >  t			0.9948		
Week 56	n	12	14			
	LS Mean	8.471	11.247	-2.776		
	SEM	5.955	5.750	6.329		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-3.3,20.2)	(-0.1,22.6)	(-15.2, 9.7)
	Pr >  t			0.6613
	n	12	11	
	LS Mean	8.470	4.113	4.357
	SEM	5.955	6.087	6.641
Week 72	95% CI	(-3.3,20.2)	(-7.9,16.1)	(-8.7,17.4)
	Pr >  t			0.5123
	n	10	8	
	LS Mean	10.043	9.190	0.854
	SEM	6.212	6.626	7.354
Week 84	95% CI	(-2.2,22.3)	(-3.9,22.2)	(-13.6,15.3)
	Pr >  t			0.9077
	n	8	8	
	LS Mean	11.618	9.190	2.428
	SEM	6.664	6.626	7.686
Week 96	95% CI	(-1.5,24.8)	(-3.9,22.2)	(-12.7,17.5)
	Pr >  t			0.7523
	n	6	6	
	LS Mean	3.389	11.115	-7.727
	SEM	7.257	7.222	8.700
Week 108	95% CI	(-10.9,17.7)	(-3.1,25.3)	(-24.8, 9.4)
	Pr >  t			0.3750
	n	4	5	
	LS Mean	10.157	5.319	4.838
	SEM	8.298	7.666	9.927
Week 120	95% CI	(-6.2,26.5)	(-9.8,20.4)	(-14.7,24.4)
	Pr >  t			0.6263
	n	4	4	
	LS Mean	18.489	4.743	13.747
	SEM	8.298	8.283	10.41
Week 132	95% CI	( 2.2,34.8)	(-11.6,21.0)	(-6.7,34.2)
	Pr >  t			0.1875
	n	3	2	
	LS Mean	22.496	6.946	15.550
	SEM	9.213	10.78	13.12
Week 144	95% CI	( 4.4,40.6)	(-14.3,28.2)	(-10.2,41.3)
	Pr >  t			0.2366
	n	3	1	
	LS Mean	11.386	6.501	4.885
	SEM	9.213	14.57	16.37

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Europe	Week 156	95% CI	(-6.7,29.5)	(-22.2,35.2)	(-27.3,37.1)
		Pr >  t			0.7655
		n	2	1	
	Week 168	LS Mean	-3.459	6.501	-9.960
		SEM	10.80	14.57	17.31
		95% CI	(-24.7,17.8)	(-22.2,35.2)	(-44.0,24.1)
	Week 8	Pr >  t			0.5654
		n	1		
		LS Mean	42.309		
	Week 16	SEM	14.56		
		95% CI	(13.7,70.9)		
		Pr >  t			
	Week 24	n	66	68	
		LS Mean	-2.993	-1.731	-1.262
		SEM	7.734	7.769	4.406
	Week 32	95% CI	(-18.3,12.3)	(-17.1,13.6)	(-9.9, 7.4)
		Pr >  t			0.7748
		n	58	48	
	Week 40	LS Mean	-8.036	1.951	-9.987
		SEM	7.788	7.921	4.860
		95% CI	(-23.4, 7.4)	(-13.7,17.6)	(-19.5,-0.4)
	Week 48	Pr >  t			0.0405
		n	51	36	
		LS Mean	0.498	-1.075	1.573
Week 8	SEM	7.850	8.094	5.299	
	95% CI	(-15.0,16.0)	(-17.1,14.9)	(-8.8,12.0)	
	Pr >  t			0.7668	
Week 16	n	43	30		
	LS Mean	-4.937	-4.385	-0.551	
	SEM	8.033	8.346	5.676	
Week 24	95% CI	(-20.8,10.9)	(-20.9,12.1)	(-11.7,10.6)	
	Pr >  t			0.9226	
	n	37	25		
Week 32	LS Mean	-3.915	-6.009	2.094	
	SEM	8.130	8.512	6.052	
	95% CI	(-20.0,12.1)	(-22.8,10.8)	(-9.8,14.0)	
Week 40	Pr >  t			0.7295	
	n	33	21		
	LS Mean	3.523	1.539	1.984	
Week 48	SEM	8.213	8.696	6.409	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-12.7,19.7)	(-15.6,18.7)	(-10.6,14.6)
	Pr >  t			0.7570
	n	29	20	
	LS Mean	-4.165	-3.576	-0.589
	SEM	8.311	8.751	6.616
Week 64	95% CI	(-20.6,12.2)	(-20.8,13.7)	(-13.6,12.4)
	Pr >  t			0.9291
	n	23	20	
	LS Mean	-9.240	-8.475	-0.765
	SEM	8.520	8.753	6.878
Week 72	95% CI	(-26.0, 7.6)	(-25.7, 8.8)	(-14.3,12.7)
	Pr >  t			0.9114
	n	25	19	
	LS Mean	-7.456	-2.244	-5.212
	SEM	8.442	8.810	6.855
Week 84	95% CI	(-24.1, 9.2)	(-19.6,15.1)	(-18.7, 8.2)
	Pr >  t			0.4473
	n	22	17	
	LS Mean	-0.086	-0.780	0.695
	SEM	8.565	8.946	7.178
Week 96	95% CI	(-17.0,16.8)	(-18.4,16.8)	(-13.4,14.8)
	Pr >  t			0.9230
	n	20	13	
	LS Mean	-3.512	0.045	-3.557
	SEM	8.669	9.332	7.770
Week 108	95% CI	(-20.6,13.6)	(-18.3,18.4)	(-18.8,11.7)
	Pr >  t			0.6473
	n	15	11	
	LS Mean	-5.725	3.549	-9.274
	SEM	9.039	9.616	8.499
Week 120	95% CI	(-23.5,12.1)	(-15.4,22.5)	(-26.0, 7.4)
	Pr >  t			0.2756
	n	16	8	
	LS Mean	-1.971	-1.345	-0.626
	SEM	8.953	10.28	9.159
Week 132	95% CI	(-19.6,15.7)	(-21.6,18.9)	(-18.6,17.4)
	Pr >  t			0.9455
	n	12	3	
	LS Mean	-5.321	-12.34	7.018
	SEM	9.382	13.64	13.11

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-23.8,13.1)	(-39.1,14.4)	(-18.7,32.8)
		Pr >  t			0.5927
	Week 144	n	7	4	
		LS Mean	3.467	-2.848	6.315
		SEM	10.53	12.41	12.76
		95% CI	(-17.2,24.2)	(-27.2,21.5)	(-18.7,31.4)
		Pr >  t			0.6207
	Week 156	n	5	2	
		LS Mean	-7.853	0.880	-8.733
		SEM	11.52	15.80	16.74
		95% CI	(-30.5,14.8)	(-30.1,31.9)	(-41.6,24.1)
		Pr >  t			0.6020
	Week 168	n	2	2	
		LS Mean	-11.93	-15.78	3.857
		SEM	15.72	15.80	19.87
		95% CI	(-42.8,18.9)	(-46.8,15.2)	(-35.1,42.9)
		Pr >  t			0.8461
	Week 180	n		1	
		LS Mean		6.466	
		SEM		20.96	
		95% CI		(-34.7,47.6)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-26.86	
		SEM		20.96	
		95% CI		(-68.0,14.3)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	-5.615	-5.433	-0.182
		SEM	5.924	5.954	8.407
		95% CI	(-17.5, 6.2)	(-17.3, 6.5)	(-17.0,16.6)
		Pr >  t			0.9828
	Week 16	n	13	12	
		LS Mean	-9.639	-2.532	-7.107
		SEM	6.049	6.158	8.626
		95% CI	(-21.7, 2.4)	(-14.8, 9.8)	(-24.3,10.1)
		Pr >  t			0.4130
	Week 24	n	12	10	
		LS Mean	-5.956	1.042	-6.998
		SEM	6.215	6.584	9.051

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-18.4, 6.4)	(-12.1,14.1)	(-25.0,11.0)
	Pr >  t			0.4419
	n	9	10	
	LS Mean	-8.514	-2.291	-6.223
	SEM	6.888	6.584	9.522
Week 40	95% CI	(-22.2, 5.2)	(-15.4,10.8)	(-25.2,12.7)
	Pr >  t			0.5153
	n	7	10	
	LS Mean	0.434	-5.624	6.058
	SEM	7.519	6.584	9.993
Week 48	95% CI	(-14.5,15.3)	(-18.7, 7.5)	(-13.8,25.9)
	Pr >  t			0.5458
	n	7	7	
	LS Mean	0.434	-9.702	10.136
	SEM	7.519	7.456	10.56
Week 56	95% CI	(-14.5,15.3)	(-24.5, 5.1)	(-10.8,31.1)
	Pr >  t			0.3396
	n	6	7	
	LS Mean	-9.464	9.052	-18.52
	SEM	7.974	7.448	10.91
Week 64	95% CI	(-25.3, 6.3)	(-5.7,23.8)	(-40.1, 3.1)
	Pr >  t			0.0925
	n	4	7	
	LS Mean	-8.512	1.728	-10.24
	SEM	9.306	7.455	11.91
Week 72	95% CI	(-26.9, 9.9)	(-13.1,16.5)	(-33.8,13.3)
	Pr >  t			0.3914
	n	4	4	
	LS Mean	8.155	7.815	0.340
	SEM	9.306	9.237	13.10
Week 84	95% CI	(-10.2,26.6)	(-10.4,26.1)	(-25.6,26.2)
	Pr >  t			0.9793
	n	4	5	
	LS Mean	-8.789	-0.254	-8.535
	SEM	9.293	8.460	12.56
Week 96	95% CI	(-27.2, 9.6)	(-17.0,16.5)	(-33.4,16.3)
	Pr >  t			0.4980
	n	3	2	
	LS Mean	-9.108	-4.770	-4.338
	SEM	10.47	12.38	16.21

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-29.8,11.6)	(-29.2,19.7)	(-36.4,27.7)
		Pr >  t			0.7894
		n	2	3	
	Week 120	LS Mean	8.557	-12.81	21.366
		SEM	12.45	10.41	16.23
		95% CI	(-16.0,33.2)	(-33.4, 7.8)	(-10.7,53.4)
	Week 120	Pr >  t			0.1899
		n	2	2	
		LS Mean	7.754	3.718	4.036
	Week 132	SEM	12.45	12.39	17.54
		95% CI	(-16.8,32.3)	(-20.8,28.2)	(-30.6,38.7)
		Pr >  t			0.8183
	Week 132	n	1	2	
		LS Mean	-5.005	3.718	-8.723
		SEM	17.06	12.39	21.06
	Week 8	95% CI	(-38.7,28.7)	(-20.8,28.2)	(-50.3,32.9)
		Pr >  t			0.6793
		n	16	19	
	Week 8	LS Mean	-0.724	-1.560	0.835
		SEM	6.536	6.350	7.954
		95% CI	(-13.8,12.3)	(-14.2,11.1)	(-15.0,16.7)
	Week 16	Pr >  t			0.9166
		n	12	14	
		LS Mean	8.481	8.909	-0.428
Week 16	SEM	7.210	7.037	8.868	
	95% CI	(-5.9,22.8)	(-5.1,22.9)	(-18.0,17.2)	
	Pr >  t			0.9617	
Week 24	n	12	8		
	LS Mean	6.422	13.019	-6.597	
	SEM	7.223	8.584	10.05	
Week 24	95% CI	(-8.0,20.8)	(-4.0,30.0)	(-26.5,13.3)	
	Pr >  t			0.5129	
	n	9	7		
Week 32	LS Mean	5.126	5.675	-0.549	
	SEM	7.940	8.948	10.83	
	95% CI	(-10.6,20.9)	(-12.0,23.4)	(-22.0,20.9)	
Week 32	Pr >  t			0.9596	
	n	9	7		
	LS Mean	7.547	15.200	-7.653	
Week 40	SEM	7.971	8.948	10.86	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-8.3,23.4)	(-2.5,32.9)	(-29.2,13.9)
	Pr >  t			0.4824
	n	8	5	
	LS Mean	-0.381	0.418	-0.799
	SEM	8.268	9.997	11.94
Week 56	95% CI	(-16.8,16.0)	(-19.4,20.2)	(-24.4,22.8)
	Pr >  t			0.9467
	n	7	3	
	LS Mean	17.801	-1.958	19.759
	SEM	8.613	12.03	13.91
Week 64	95% CI	( 0.7,34.9)	(-25.7,21.8)	(-7.7,47.3)
	Pr >  t			0.1578
	n	5	3	
	LS Mean	2.257	-1.955	4.212
	SEM	9.623	12.03	14.60
Week 72	95% CI	(-16.8,21.3)	(-25.7,21.8)	(-24.6,33.1)
	Pr >  t			0.7734
	n	5	3	
	LS Mean	9.883	3.422	6.462
	SEM	9.589	12.01	14.55
Week 84	95% CI	(-9.1,28.9)	(-20.3,27.2)	(-22.3,35.2)
	Pr >  t			0.6576
	n	2	2	
	LS Mean	21.109	-12.63	33.742
	SEM	13.82	14.11	19.10
Week 96	95% CI	(-6.2,48.4)	(-40.5,15.3)	(-4.0,71.5)
	Pr >  t			0.0795
	n	3	2	
	LS Mean	8.608	20.702	-12.09
	SEM	11.59	14.11	17.62
Week 108	95% CI	(-14.3,31.5)	(-7.2,48.6)	(-46.9,22.7)
	Pr >  t			0.4936
	n	1	2	
	LS Mean	25.369	4.037	21.332
	SEM	18.69	14.11	22.88
Week 120	95% CI	(-11.6,62.3)	(-23.9,31.9)	(-23.9,66.6)
	Pr >  t			0.3528
	n	3	2	
Week 120	LS Mean	-2.505	-12.63	10.128
	SEM	11.59	14.11	17.62

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-25.4,20.4)	(-40.5,15.3)	(-24.7,45.0)
		Pr >  t			0.5664
	Week 132	n	1	1	
		LS Mean	62.779	19.817	42.962
		SEM	18.69	18.94	26.14
		95% CI	( 25.8,99.8)	(-17.6,57.3)	( -8.8,94.7)
		Pr >  t			0.1027
	Week 144	n	2		
		LS Mean	33.557		
		SEM	13.69		
		95% CI	( 6.5,60.6)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	62.779		
		SEM	18.69		
		95% CI	( 25.8,99.8)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	62.779		
		SEM	18.69		
		95% CI	( 25.8,99.8)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	62.779		
		SEM	18.69		
		95% CI	( 25.8,99.8)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	62.779		
		SEM	18.69		
		95% CI	( 25.8,99.8)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	15.583	14.392	1.191
		SEM	7.387	11.46	12.51
		95% CI	( 0.3,30.8)	( -9.2,38.0)	(-24.5,26.9)
		Pr >  t			0.9248
	Week 16	n	13	4	
		LS Mean	15.871	14.733	1.138
		SEM	7.817	12.63	13.52

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-0.1,31.9)	(-10.9,40.4)	(-26.4,28.7)
	Pr >  t			0.9334
	n	9	2	
	LS Mean	15.416	7.831	7.585
	SEM	8.532	15.34	16.37
Week 32	95% CI	(-1.9,32.7)	(-22.9,38.6)	(-25.2,40.4)
	Pr >  t			0.6450
	n	6	3	
	LS Mean	11.670	7.811	3.859
	SEM	9.552	13.68	15.38
Week 40	95% CI	(-7.5,30.8)	(-19.8,35.4)	(-27.1,34.8)
	Pr >  t			0.8030
	n	6	2	
	LS Mean	2.887	5.847	-2.960
	SEM	9.680	15.35	16.95
Week 48	95% CI	(-16.5,22.3)	(-24.9,36.6)	(-36.9,31.0)
	Pr >  t			0.8620
	n	5	1	
	LS Mean	7.601	7.772	-0.171
	SEM	10.14	19.53	21.07
Week 56	95% CI	(-12.7,27.9)	(-31.1,46.7)	(-42.1,41.8)
	Pr >  t			0.9935
	n	5	1	
	LS Mean	14.269	7.772	6.497
	SEM	10.14	19.53	21.07
Week 64	95% CI	(-6.0,34.6)	(-31.1,46.7)	(-35.5,48.5)
	Pr >  t			0.7587
	n	3	1	
	LS Mean	9.576	7.772	1.804
	SEM	11.74	19.53	21.89
Week 72	95% CI	(-13.8,33.0)	(-31.1,46.7)	(-41.8,45.4)
	Pr >  t			0.9345
	n	4	1	
	LS Mean	0.943	7.772	-6.829
	SEM	10.79	19.53	21.39
Week 84	95% CI	(-20.6,22.5)	(-31.1,46.7)	(-49.4,35.8)
	Pr >  t			0.7504
	n	4	1	
	LS Mean	-7.389	7.772	-15.16
	SEM	10.79	19.53	21.39

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-28.9,14.2)	(-31.1,46.7)	(-57.8,27.4)
	Pr >  t			0.4806
	n	3	1	
	LS Mean	-1.534	7.772	-9.306
	SEM	11.74	19.53	21.89
Week 108	95% CI	(-24.9,21.9)	(-31.1,46.7)	(-52.9,34.3)
	Pr >  t			0.6719
	n	4		
	LS Mean	17.611		
	SEM	10.79		
Week 120	95% CI	(-3.9,39.2)		
	Pr >  t			
	n	3		
	LS Mean	9.576		
	SEM	11.74		
Week 132	95% CI	(-13.8,33.0)		
	Pr >  t			
	n	3		
	LS Mean	-1.534		
	SEM	11.74		
Week 144	95% CI	(-24.9,21.9)		
	Pr >  t			
	n	3		
	LS Mean	-3.883		
	SEM	11.75		
Week 156	95% CI	(-27.3,19.5)		
	Pr >  t			
	n	2		
	LS Mean	10.547		
	SEM	13.38		
	95% CI	(-16.1,37.2)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Baseline ECOG performance status	0 Week 8	n	98	90	
		LS Mean	3.206	0.962	2.244
		SEM	3.882	3.799	3.154
		95% CI	(-4.4,10.8)	(-6.5, 8.4)	(-4.0, 8.4)
		Pr >  t			0.4771
	Week 16	n	88	71	
		LS Mean	0.885	5.315	-4.430
		SEM	3.967	4.085	3.403
		95% CI	(-6.9, 8.7)	(-2.7,13.3)	(-11.1, 2.3)
		Pr >  t			0.1935
	Week 24	n	75	54	
		LS Mean	5.225	4.970	0.255
		SEM	4.041	4.261	3.720
		95% CI	(-2.7,13.2)	(-3.4,13.3)	(-7.0, 7.6)
		Pr >  t			0.9454
	Week 32	n	62	52	
		LS Mean	1.843	2.261	-0.417
		SEM	4.172	4.290	3.877
		95% CI	(-6.4,10.0)	(-6.2,10.7)	(-8.0, 7.2)
		Pr >  t			0.9143
	Week 40	n	51	46	
		LS Mean	4.455	-1.320	5.774
		SEM	4.300	4.410	4.120
		95% CI	(-4.0,12.9)	(-10.0, 7.3)	(-2.3,13.9)
Pr >  t				0.1614	
Week 48	n	50	37		
	LS Mean	6.539	4.770	1.769	
	SEM	4.314	4.594	4.330	
	95% CI	(-1.9,15.0)	(-4.3,13.8)	(-6.7,10.3)	
	Pr >  t			0.6830	
Week 56	n	43	33		
	LS Mean	3.359	5.174	-1.815	
	SEM	4.426	4.702	4.558	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.3,12.1)	(-4.1,14.4)	(-10.8, 7.1)
		Pr >  t			0.6907
	Week 64	n	35	33	
		LS Mean	-1.047	-0.895	-0.152
		SEM	4.601	4.703	4.734
		95% CI	(-10.1, 8.0)	(-10.1, 8.3)	(-9.4, 9.1)
		Pr >  t			0.9744
	Week 72	n	35	31	
		LS Mean	2.045	4.008	-1.962
		SEM	4.601	4.764	4.795
		95% CI	(-7.0,11.1)	(-5.3,13.4)	(-11.4, 7.4)
		Pr >  t			0.6825
	Week 84	n	31	29	
		LS Mean	4.402	3.925	0.477
		SEM	4.732	4.833	4.975
		95% CI	(-4.9,13.7)	(-5.6,13.4)	(-9.3,10.2)
		Pr >  t			0.9236
	Week 96	n	27	22	
		LS Mean	-0.202	7.285	-7.487
		SEM	4.863	5.160	5.428
		95% CI	(-9.8, 9.3)	(-2.8,17.4)	(-18.1, 3.2)
		Pr >  t			0.1681
	Week 108	n	19	20	
		LS Mean	1.585	4.668	-3.082
		SEM	5.330	5.288	5.948
		95% CI	(-8.9,12.0)	(-5.7,15.0)	(-14.8, 8.6)
		Pr >  t			0.6044
	Week 120	n	20	15	
		LS Mean	3.650	1.918	1.732
		SEM	5.233	5.735	6.287
		95% CI	(-6.6,13.9)	(-9.3,13.2)	(-10.6,14.1)
		Pr >  t			0.7830
	Week 132	n	15	7	
		LS Mean	10.717	3.355	7.361
		SEM	5.699	7.423	8.163
		95% CI	(-0.5,21.9)	(-11.2,17.9)	(-8.7,23.4)
		Pr >  t			0.3674
	Week 144	n	10	5	
		LS Mean	13.172	2.688	10.484
		SEM	6.462	8.477	9.650

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 0.5,25.9)	(-13.9,19.3)	( -8.4,29.4)
		Pr >  t			0.2775
	Week 156	n	6	3	
		LS Mean	10.979	5.332	5.647
		SEM	7.852	10.51	12.30
		95% CI	( -4.4,26.4)	(-15.3,26.0)	(-18.5,29.8)
		Pr >  t			0.6462
	Week 168	n	3	2	
		LS Mean	15.407	-9.877	25.284
		SEM	10.49	12.61	15.75
		95% CI	( -5.2,36.0)	(-34.6,14.9)	( -5.6,56.2)
		Pr >  t			0.1087
	Week 180	n	1	1	
		LS Mean	51.237	12.008	39.230
		SEM	17.41	17.42	24.20
		95% CI	( 17.1,85.4)	(-22.2,46.2)	( -8.3,86.7)
		Pr >  t			0.1053
	Week 192	n	1	1	
		LS Mean	51.237	-21.32	72.560
		SEM	17.41	17.42	24.20
		95% CI	( 17.1,85.4)	(-55.5,12.9)	( 25.1, 120)
		Pr >  t			0.0028
1	Week 8	n	43	50	
		LS Mean	0.223	4.088	-3.865
		SEM	5.808	6.054	5.907
		95% CI	(-11.3,11.7)	( -7.9,16.1)	(-15.5, 7.8)
		Pr >  t			0.5139
	Week 16	n	35	35	
		LS Mean	-0.493	6.911	-7.404
		SEM	6.072	6.286	6.487
		95% CI	(-12.5,11.5)	( -5.5,19.3)	(-20.2, 5.4)
		Pr >  t			0.2551
	Week 24	n	29	26	
		LS Mean	2.552	3.944	-1.393
		SEM	6.314	6.729	7.019
		95% CI	( -9.9,15.0)	( -9.3,17.2)	(-15.2,12.4)
		Pr >  t			0.8429
	Week 32	n	23	21	
		LS Mean	-1.233	-0.691	-0.542
		SEM	6.671	7.076	7.538

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-14.4,11.9)	(-14.6,13.3)	(-15.4,14.3)
	Pr >  t			0.9428
	n	23	16	
	LS Mean	-4.017	3.994	-8.011
	SEM	6.686	7.486	7.938
Week 48	95% CI	(-17.2, 9.2)	(-10.8,18.7)	(-23.6, 7.6)
	Pr >  t			0.3137
	n	18	14	
	LS Mean	-0.862	1.096	-1.958
	SEM	7.020	7.725	8.458
Week 56	95% CI	(-14.7,13.0)	(-14.1,16.3)	(-18.6,14.7)
	Pr >  t			0.8170
	n	15	12	
	LS Mean	2.880	4.842	-1.962
	SEM	7.327	8.019	8.991
Week 64	95% CI	(-11.6,17.3)	(-10.9,20.6)	(-19.6,15.7)
	Pr >  t			0.8274
	n	11	9	
	LS Mean	-2.376	1.093	-3.469
	SEM	7.911	8.668	10.04
Week 72	95% CI	(-17.9,13.2)	(-16.0,18.1)	(-23.2,16.3)
	Pr >  t			0.7298
	n	12	4	
	LS Mean	-1.097	8.946	-10.04
	SEM	7.753	11.34	12.31
Week 84	95% CI	(-16.4,14.2)	(-13.3,31.2)	(-34.2,14.2)
	Pr >  t			0.4151
	n	8	4	
	LS Mean	1.980	0.613	1.367
	SEM	8.733	11.34	12.93
Week 96	95% CI	(-15.2,19.2)	(-21.7,22.9)	(-24.1,26.8)
	Pr >  t			0.9159
	n	8	2	
	LS Mean	1.980	-1.402	3.382
	SEM	8.733	14.91	16.15
Week 108	95% CI	(-15.2,19.2)	(-30.7,27.9)	(-28.4,35.1)
	Pr >  t			0.8343
	n	6	1	
Week 108	LS Mean	15.430	-1.604	17.033
	SEM	9.585	20.22	21.51

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.4,34.3)	(-25.3,59.3)
		Pr >  t		0.4290
	Week 120	n	8	1
		LS Mean	6.269	-1.604
		SEM	8.758	20.22
		95% CI	(-11.0,23.5)	(-41.4,38.2)
		Pr >  t		(-33.7,49.5)
	Week 132	n	5	1
		LS Mean	-13.33	-1.604
		SEM	10.21	20.22
		95% CI	(-33.4, 6.7)	(-41.4,38.2)
		Pr >  t		(-54.6,31.1)
	Week 144	n	5	
		LS Mean	-6.659	
		SEM	10.21	
		95% CI	(-26.7,13.4)	
		Pr >  t		0.5911
	Week 156	n	4	
		LS Mean	-8.866	
		SEM	11.06	
		95% CI	(-30.6,12.9)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	32.371	
		SEM	19.89	
		95% CI	(-6.7,71.5)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L)	Primary resistant	Week 8	n	21	16			
			LS Mean	2.790	6.837	-4.046		
			SEM	5.883	7.038	7.326		
			95% CI	(-9.1,14.7)	(-7.4,21.1)	(-18.7,10.6)		
					Pr >  t			0.5829
		Week 16	n	17	10			
			LS Mean	-0.174	21.403	-21.58		
			SEM	6.358	8.250	8.659		
			95% CI	(-13.0,12.6)	(-4.8,38.0)	(-38.8,-4.3)		
					Pr >  t			0.0149
		Week 24	n	9	5			
			LS Mean	1.725	1.844	-0.119		
			SEM	7.483	10.07	11.32		
			95% CI	(-13.2,16.6)	(-18.2,21.9)	(-22.6,22.3)		
					Pr >  t			0.9916
		Week 32	n	8	4			
			LS Mean	-9.829	-6.991	-2.837		
			SEM	7.771	10.89	12.28		
			95% CI	(-25.3, 5.6)	(-28.6,14.6)	(-27.2,21.5)		
					Pr >  t			0.8178
		Week 40	n	5	4			
			LS Mean	1.540	1.344	0.197		
			SEM	9.045	10.89	13.26		
			95% CI	(-16.4,19.5)	(-20.3,22.9)	(-26.1,26.5)		
			Pr >  t			0.9882		
Week 48	n	5	3					
	LS Mean	14.872	3.276	11.597				
	SEM	9.045	12.02	14.20				
	95% CI	(-3.1,32.8)	(-20.5,27.1)	(-16.5,39.7)				
			Pr >  t			0.4158		
Week 56	n	4	3					
	LS Mean	3.155	3.276	-0.120				
	SEM	9.796	12.02	14.73				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-16.3,22.6)	(-20.5,27.1)	(-29.3,29.1)
		Pr >  t			0.9935
		n	4	3	
		LS Mean	3.155	-7.834	10.990
		SEM	9.796	12.02	14.73
Week 72		95% CI	(-16.3,22.6)	(-31.7,16.0)	(-18.2,40.2)
		Pr >  t			0.4573
		n	4	3	
		LS Mean	11.488	3.276	8.212
		SEM	9.796	12.02	14.73
Week 84		95% CI	(-7.9,30.9)	(-20.5,27.1)	(-21.0,37.4)
		Pr >  t			0.5784
		n	2	3	
		LS Mean	9.149	-7.834	16.983
		SEM	13.14	12.02	16.98
Week 96		95% CI	(-16.9,35.2)	(-31.7,16.0)	(-16.7,50.6)
		Pr >  t			0.3195
		n	1	3	
		LS Mean	-0.944	25.499	-26.44
		SEM	17.68	12.02	20.96
Week 108		95% CI	(-36.0,34.2)	( 1.7,49.3)	(-68.1,15.2)
		Pr >  t			0.2103
		n		2	
		LS Mean		21.696	
		SEM		13.89	
Week 120		95% CI		( -5.8,49.2)	
		Pr >  t			
		n	1	1	
		LS Mean	-0.944	-11.75	10.802
		SEM	17.68	18.34	25.13
Week 132		95% CI	(-36.0,34.2)	(-48.1,24.6)	(-39.1,60.7)
		Pr >  t			0.6684
		n		1	
		LS Mean		21.595	
		SEM		18.34	
Week 144		95% CI		(-14.8,58.0)	
		Pr >  t			
		n	1		
		LS Mean	-0.944		
		SEM	17.68		



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-36.0,34.2)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	5.562	6.000	-0.439
		SEM	3.855	3.842	3.291
		95% CI	(-2.0,13.1)	(-1.6,13.6)	(-6.9, 6.0)
		Pr >  t			0.8940
	Week 16	n	83	81	
		LS Mean	3.701	9.569	-5.868
		SEM	3.965	4.041	3.588
		95% CI	(-4.1,11.5)	(1.6,17.5)	(-12.9, 1.2)
		Pr >  t			0.1025
	Week 24	n	75	62	
		LS Mean	7.527	8.770	-1.243
		SEM	4.047	4.249	3.859
		95% CI	(-0.4,15.5)	(0.4,17.1)	(-8.8, 6.3)
		Pr >  t			0.7474
	Week 32	n	59	56	
		LS Mean	6.215	5.247	0.968
		SEM	4.271	4.322	4.110
		95% CI	(-2.2,14.6)	(-3.2,13.7)	(-7.1, 9.0)
		Pr >  t			0.8138
	Week 40	n	52	48	
		LS Mean	7.751	3.978	3.773
		SEM	4.365	4.464	4.333
		95% CI	(-0.8,16.3)	(-4.8,12.7)	(-4.7,12.3)
		Pr >  t			0.3841
	Week 48	n	47	37	
		LS Mean	6.610	8.202	-1.591
		SEM	4.446	4.698	4.651
		95% CI	(-2.1,15.3)	(-1.0,17.4)	(-10.7, 7.5)
		Pr >  t			0.7323
	Week 56	n	41	31	
		LS Mean	5.658	10.325	-4.668
		SEM	4.564	4.884	4.950
		95% CI	(-3.3,14.6)	(0.7,19.9)	(-14.4, 5.0)
		Pr >  t			0.3460
	Week 64	n	32	28	
		LS Mean	2.210	4.454	-2.244
		SEM	4.809	5.005	5.292

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-7.2,11.7)	(-5.4,14.3)	(-12.6, 8.1)	
	Pr >  t			0.6716	
	n	29	22		
	LS Mean	2.232	7.171	-4.938	
	SEM	4.924	5.320	5.689	
Week 84	95% CI	(-7.4,11.9)	(-3.3,17.6)	(-16.1, 6.2)	
	Pr >  t			0.3855	
	n	26	21		
	LS Mean	4.710	5.587	-0.877	
	SEM	5.052	5.386	5.862	
Week 96	95% CI	(-5.2,14.6)	(-5.0,16.2)	(-12.4,10.6)	
	Pr >  t			0.8811	
	n	23	14		
	LS Mean	2.643	4.389	-1.746	
	SEM	5.214	6.071	6.624	
Week 108	95% CI	(-7.6,12.9)	(-7.5,16.3)	(-14.7,11.3)	
	Pr >  t			0.7922	
	n	18	13		
	LS Mean	6.925	3.714	3.211	
	SEM	5.582	6.218	7.046	
Week 120	95% CI	(-4.0,17.9)	(-8.5,15.9)	(-10.6,17.0)	
	Pr >  t			0.6487	
	n	19	10		
	LS Mean	6.994	9.952	-2.958	
	SEM	5.499	6.798	7.500	
Week 132	95% CI	(-3.8,17.8)	(-3.4,23.3)	(-17.7,11.8)	
	Pr >  t			0.6934	
	n	13	4		
	LS Mean	11.100	2.800	8.301	
	SEM	6.169	9.737	10.62	
Week 144	95% CI	(-1.0,23.2)	(-16.3,21.9)	(-12.5,29.1)	
	Pr >  t			0.4344	
	n	8	1		
	LS Mean	21.803	15.304	6.499	
	SEM	7.325	18.38	19.27	
Week 156	95% CI	( 7.4,36.2)	(-20.8,51.4)	(-31.3,44.3)	
	Pr >  t			0.7359	
	n	5	1		
	LS Mean	20.391	15.304	5.087	
	SEM	8.829	18.38	19.89	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	( 3.1,37.7)	(-20.8,51.4)	(-33.9,44.1)
		Pr >  t			0.7982
		n	3	1	
	Week 180	LS Mean	18.345	-18.03	36.371
		SEM	10.99	18.38	20.94
		95% CI	( -3.2,39.9)	(-54.1,18.0)	( -4.7,77.5)
	Week 192	Pr >  t			0.0827
		n	1	1	
		LS Mean	53.960	15.304	38.656
	Week 8	SEM	18.30	18.38	25.54
		95% CI	( 18.0,89.9)	(-20.8,51.4)	(-11.5,88.8)
		Pr >  t			0.1305
	Week 16	n	1	1	
		LS Mean	53.960	-18.03	71.986
		SEM	18.30	18.38	25.54
	Week 24	95% CI	( 18.0,89.9)	(-54.1,18.0)	( 21.9, 122)
		Pr >  t			0.0049
		n	17	16	
	Week 32	LS Mean	-12.90	-11.33	-1.577
		SEM	6.035	6.228	8.536
		95% CI	(-24.9,-0.9)	(-23.7, 1.1)	(-18.6,15.4)
	Week 40	Pr >  t			0.8539
		n	18	14	
		LS Mean	-10.37	-12.57	2.203
	Week 8	SEM	5.927	6.495	8.688
		95% CI	(-22.2, 1.4)	(-25.5, 0.3)	(-15.1,19.5)
		Pr >  t			0.8005
	Week 16	n	16	13	
LS Mean		-2.785	-4.881	2.096	
SEM		6.149	6.631	8.935	
Week 24	95% CI	(-15.0, 9.5)	(-18.1, 8.3)	(-15.7,19.9)	
	Pr >  t			0.8151	
	n	15	13		
Week 32	LS Mean	-12.35	-8.140	-4.210	
	SEM	6.252	6.646	9.026	
	95% CI	(-24.8, 0.1)	(-21.3, 5.1)	(-22.1,13.7)	
Week 40	Pr >  t			0.6421	
	n	14	10		
	LS Mean	-14.13	-13.31	-0.816	
		SEM	6.389	7.141	9.485

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48		95% CI	(-26.8,-1.4)	(-27.5, 0.8)	(-19.6,18.0)
		Pr >  t			0.9316
		n	14	11	
		LS Mean	-2.223	-9.984	7.761
		SEM	6.389	6.966	9.353
Week 56		95% CI	(-14.9,10.5)	(-23.8, 3.8)	(-10.8,26.3)
		Pr >  t			0.4086
		n	11	11	
		LS Mean	-6.897	-9.984	3.088
		SEM	6.811	6.966	9.652
Week 64		95% CI	(-20.4, 6.6)	(-23.8, 3.8)	(-16.0,22.2)
		Pr >  t			0.7497
		n	8	11	
		LS Mean	-12.53	-13.01	0.489
		SEM	7.465	6.966	10.13
Week 72		95% CI	(-27.3, 2.2)	(-26.8, 0.8)	(-19.6,20.5)
		Pr >  t			0.9616
		n	11	10	
		LS Mean	-3.867	-4.059	0.192
		SEM	6.811	7.152	9.783
Week 84		95% CI	(-17.4, 9.6)	(-18.2,10.1)	(-19.2,19.6)
		Pr >  t			0.9844
		n	9	9	
		LS Mean	2.451	-0.239	2.690
		SEM	7.207	7.364	10.22
Week 96		95% CI	(-11.8,16.7)	(-14.8,14.3)	(-17.5,22.9)
		Pr >  t			0.7929
		n	8	7	
		LS Mean	-4.160	-1.378	-2.782
		SEM	7.469	7.929	10.82
Week 108		95% CI	(-18.9,10.6)	(-17.0,14.3)	(-24.2,18.6)
		Pr >  t			0.7974
		n	7	6	
		LS Mean	-8.396	-3.735	-4.661
		SEM	7.788	8.340	11.34
Week 120		95% CI	(-23.8, 7.0)	(-20.2,12.7)	(-27.0,17.7)
		Pr >  t			0.6815
		n	6	5	
		LS Mean	-2.352	-16.13	13.776
		SEM	8.198	8.881	12.01

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-18.5,13.8)	(-33.6, 1.4)	(-9.9,37.5)
	Pr >  t			0.2527
	n	5	3	
	LS Mean	-13.71	-9.781	-3.933
	SEM	8.728	10.70	13.74
Week 144	95% CI	(-30.9, 3.5)	(-30.9,11.3)	(-31.0,23.1)
	Pr >  t			0.7749
	n	5	4	
	LS Mean	-13.72	-10.71	-3.005
	SEM	8.728	9.601	12.90
Week 156	95% CI	(-30.9, 3.5)	(-29.6, 8.2)	(-28.4,22.4)
	Pr >  t			0.8160
	n	4	2	
	LS Mean	-24.73	-9.449	-15.28
	SEM	9.461	12.61	15.71
Week 168	95% CI	(-43.4,-6.1)	(-34.3,15.4)	(-46.2,15.7)
	Pr >  t			0.3317
	n	1	1	
	LS Mean	24.190	-9.995	34.185
	SEM	17.03	17.12	24.11
	95% CI	(-9.3,57.7)	(-43.7,23.7)	(-13.3,81.7)
	Pr >  t			0.1574

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73	
			LS Mean	8.055	13.581	-5.525
		SEM	10.21	10.49	3.953	
		95% CI	(-12.1,28.2)	(-7.1,34.3)	(-13.3, 2.3)	
		Pr >  t			0.1631	
		Week 16	n	69	55	
			LS Mean	6.429	14.065	-7.637
		SEM	10.23	10.58	4.232	
		95% CI	(-13.8,26.6)	(-6.8,35.0)	(-16.0, 0.7)	
		Pr >  t			0.0719	
		Week 24	n	54	46	
			LS Mean	13.848	14.897	-1.049
		SEM	10.27	10.64	4.547	
		95% CI	(-6.4,34.1)	(-6.1,35.9)	(-10.0, 7.9)	
		Pr >  t			0.8177	
		Week 32	n	49	41	
			LS Mean	7.387	11.666	-4.280
		SEM	10.38	10.68	4.715	
		95% CI	(-13.1,27.9)	(-9.4,32.8)	(-13.5, 5.0)	
		Pr >  t			0.3645	
		Week 40	n	40	33	
			LS Mean	6.557	7.894	-1.337
		SEM	10.46	10.77	5.064	
		95% CI	(-14.1,27.2)	(-13.4,29.2)	(-11.3, 8.6)	
		Pr >  t			0.7918	
		Week 48	n	38	28	
			LS Mean	16.106	12.256	3.850
		SEM	10.48	10.85	5.272	
95% CI	(-4.6,36.8)	(-9.2,33.7)	(-6.5,14.2)			
Pr >  t			0.4656			
Week 56	n	32	28			
	LS Mean	10.316	13.231	-2.915		
SEM	10.55	10.85	5.417			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.5,31.1)	(-8.2,34.6)	(-13.6, 7.7)
	Pr >  t			0.5907
	n	23	26	
	LS Mean	6.657	7.438	-0.781
	SEM	10.72	10.89	5.823
Week 72	95% CI	(-14.5,27.8)	(-14.1,28.9)	(-12.2,10.7)
	Pr >  t			0.8934
	n	27	25	
	LS Mean	8.877	15.771	-6.894
	SEM	10.63	10.91	5.697
Week 84	95% CI	(-12.1,29.9)	(-5.8,37.3)	(-18.1, 4.3)
	Pr >  t			0.2266
	n	23	22	
	LS Mean	14.941	14.413	0.529
	SEM	10.72	10.98	6.000
Week 96	95% CI	(-6.2,36.1)	(-7.3,36.1)	(-11.3,12.3)
	Pr >  t			0.9298
	n	20	16	
	LS Mean	8.637	18.427	-9.791
	SEM	10.81	11.21	6.561
Week 108	95% CI	(-12.7,30.0)	(-3.7,40.5)	(-22.7, 3.1)
	Pr >  t			0.1360
	n	20	14	
	LS Mean	8.326	18.021	-9.695
	SEM	10.81	11.33	6.763
Week 120	95% CI	(-13.0,29.7)	(-4.3,40.4)	(-23.0, 3.6)
	Pr >  t			0.1520
	n	17	11	
	LS Mean	15.839	9.657	6.183
	SEM	10.93	11.58	7.354
Week 132	95% CI	(-5.7,37.4)	(-13.2,32.5)	(-8.3,20.6)
	Pr >  t			0.4007
	n	13	6	
	LS Mean	6.313	9.998	-3.685
	SEM	11.17	12.50	9.022
Week 144	95% CI	(-15.7,28.3)	(-14.6,34.6)	(-21.4,14.0)
	Pr >  t			0.6830
	n	10	5	
	LS Mean	10.754	12.545	-1.791
	SEM	11.47	12.88	9.896

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.8,33.3)	(-12.8,37.9)	(-21.2,17.6)
		Pr >  t			0.8564
	Week 156	n	7	3	
		LS Mean	2.914	14.985	-12.07
		SEM	12.00	14.31	12.21
		95% CI	(-20.7,26.5)	(-13.1,43.1)	(-36.0,11.9)
		Pr >  t			0.3230
	Week 168	n	3	2	
		LS Mean	15.172	-0.362	15.534
		SEM	14.11	15.91	15.90
		95% CI	(-12.6,42.9)	(-31.6,30.9)	(-15.7,46.7)
		Pr >  t			0.3288
	Week 180	n		1	
		LS Mean		21.739	
		SEM		19.94	
		95% CI		(-17.4,60.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-11.59	
		SEM		19.94	
		95% CI		(-50.7,27.5)	
		Pr >  t			
Second Line	Week 8	n	66	67	
		LS Mean	6.444	1.645	4.799
		SEM	3.562	3.607	3.976
		95% CI	(-0.6,13.5)	(-5.5, 8.8)	(-3.0,12.6)
		Pr >  t			0.2283
	Week 16	n	54	52	
		LS Mean	4.453	8.887	-4.434
		SEM	3.787	3.914	4.374
		95% CI	(-3.0,11.9)	( 1.2,16.6)	(-13.0, 4.2)
		Pr >  t			0.3113
	Week 24	n	49	35	
		LS Mean	4.668	5.192	-0.525
		SEM	3.907	4.374	4.862
		95% CI	(-3.0,12.4)	(-3.4,13.8)	(-10.1, 9.0)
		Pr >  t			0.9141
	Week 32	n	36	32	
		LS Mean	4.865	1.637	3.228
		SEM	4.278	4.507	5.238



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-3.5,13.3)	(-7.2,10.5)	(-7.1,13.5)
	Pr >  t			0.5379
Week 40	n	33	29	
	LS Mean	7.170	3.020	4.150
	SEM	4.382	4.668	5.442
	95% CI	(-1.4,15.8)	(-6.2,12.2)	(-6.5,14.8)
	Pr >  t			0.4460
Week 48	n	29	23	
	LS Mean	1.968	6.237	-4.269
	SEM	4.545	5.000	5.857
	95% CI	(-7.0,10.9)	(-3.6,16.1)	(-15.8, 7.2)
	Pr >  t			0.4663
Week 56	n	25	17	
	LS Mean	6.290	8.632	-2.342
	SEM	4.744	5.505	6.452
	95% CI	(-3.0,15.6)	(-2.2,19.4)	(-15.0,10.3)
	Pr >  t			0.7167
Week 64	n	22	16	
	LS Mean	0.305	3.505	-3.200
	SEM	4.934	5.623	6.693
	95% CI	(-9.4,10.0)	(-7.5,14.5)	(-16.3, 9.9)
	Pr >  t			0.6327
Week 72	n	20	10	
	LS Mean	3.463	1.507	1.956
	SEM	5.087	6.670	7.697
	95% CI	(-6.5,13.5)	(-11.6,14.6)	(-13.2,17.1)
	Pr >  t			0.7995
Week 84	n	16	11	
	LS Mean	0.530	1.781	-1.251
	SEM	5.512	6.433	7.770
	95% CI	(-10.3,11.4)	(-10.9,14.4)	(-16.5,14.0)
	Pr >  t			0.8721
Week 96	n	15	8	
	LS Mean	1.533	2.812	-1.279
	SEM	5.626	7.271	8.564
	95% CI	(-9.5,12.6)	(-11.5,17.1)	(-18.1,15.5)
	Pr >  t			0.8814
Week 108	n	6	7	
	LS Mean	20.025	-2.998	23.024
	SEM	8.077	7.671	10.62

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	( 4.2,35.9)	(-18.1,12.1)	( 2.2,43.9)
	Pr >  t			0.0305
Week 120	n	11	5	
	LS Mean	1.113	6.481	-5.367
	SEM	6.319	8.831	10.33
	95% CI	(-11.3,13.5)	(-10.9,23.8)	(-25.7,14.9)
	Pr >  t			0.6036
Week 132	n	7	2	
	LS Mean	18.458	11.311	7.147
	SEM	7.571	13.34	14.96
	95% CI	( 3.6,33.3)	(-14.9,37.5)	(-22.2,36.5)
	Pr >  t			0.6330
Week 144	n	5		
	LS Mean	16.711		
	SEM	8.709		
	95% CI	( -0.4,33.8)		
	Pr >  t			
Week 156	n	3		
	LS Mean	25.042		
	SEM	10.98		
	95% CI	( 3.5,46.6)		
	Pr >  t			
Week 168	n	1		
	LS Mean	56.173		
	SEM	18.48		
	95% CI	( 19.9,92.5)		
	Pr >  t			
Week 180	n	1		
	LS Mean	56.173		
	SEM	18.48		
	95% CI	( 19.9,92.5)		
	Pr >  t			
Week 192	n	1		
	LS Mean	56.173		
	SEM	18.48		
	95% CI	( 19.9,92.5)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	10.621	17.504	-6.883
		SEM	9.903	10.25	4.445
		95% CI	(-9.0,30.3)	(-2.8,37.8)	(-15.6, 1.9)
		Pr >  t			0.1229
	Week 16	n	51	41	
		LS Mean	7.648	18.683	-11.03
		SEM	9.929	10.40	4.861
		95% CI	(-12.0,27.3)	(-1.9,39.3)	(-20.6,-1.5)
		Pr >  t			0.0240
	Week 24	n	38	33	
		LS Mean	14.772	16.769	-1.997
		SEM	10.01	10.51	5.331
		95% CI	(-5.1,34.6)	(-4.0,37.6)	(-12.5, 8.5)
		Pr >  t			0.7082
	Week 32	n	34	28	
		LS Mean	9.626	13.364	-3.737
		SEM	10.19	10.59	5.604
		95% CI	(-10.6,29.8)	(-7.6,34.3)	(-14.8, 7.3)
		Pr >  t			0.5052
	Week 40	n	26	23	
		LS Mean	9.469	10.275	-0.807
		SEM	10.35	10.72	6.095
		95% CI	(-11.0,30.0)	(-10.9,31.5)	(-12.8,11.2)
		Pr >  t			0.8948
	Week 48	n	24	17	
		LS Mean	17.732	15.233	2.499
		SEM	10.40	10.95	6.582
95% CI		(-2.8,38.3)	(-6.4,36.9)	(-10.4,15.4)	
	Pr >  t			0.7044	
Week 56	n	21	17		
	LS Mean	11.240	16.876	-5.635	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	10.50	10.95	6.731
		95% CI	(-9.5,32.0)	(-4.8,38.5)	(-18.9, 7.6)
		Pr >  t			0.4029
	Week 64	n	15	15	
		LS Mean	8.539	9.161	-0.622
		SEM	10.78	11.07	7.354
		95% CI	(-12.8,29.8)	(-12.7,31.0)	(-15.1,13.8)
		Pr >  t			0.9327
	Week 72	n	16	15	
		LS Mean	6.494	17.250	-10.76
		SEM	10.72	11.07	7.264
		95% CI	(-14.7,27.7)	(-4.6,39.1)	(-25.0, 3.5)
		Pr >  t			0.1393
	Week 84	n	14	13	
		LS Mean	12.627	12.300	0.327
		SEM	10.85	11.21	7.668
		95% CI	(-8.8,34.1)	(-9.8,34.4)	(-14.7,15.4)
		Pr >  t			0.9660
	Week 96	n	12	9	
		LS Mean	6.311	19.862	-13.55
		SEM	11.02	11.68	8.569
		95% CI	(-15.5,28.1)	(-3.2,42.9)	(-30.4, 3.3)
		Pr >  t			0.1143
	Week 108	n	13	8	
		LS Mean	8.752	20.936	-12.18
		SEM	10.93	11.87	8.710
		95% CI	(-12.8,30.3)	(-2.5,44.3)	(-29.3, 4.9)
		Pr >  t			0.1624
	Week 120	n	11	6	
		LS Mean	16.896	16.105	0.790
		SEM	11.13	12.40	9.657
		95% CI	(-5.1,38.9)	(-8.3,40.6)	(-18.2,19.8)
		Pr >  t			0.9348
	Week 132	n	8	3	
		LS Mean	8.545	11.155	-2.609
		SEM	11.60	14.33	12.47
		95% CI	(-14.3,31.4)	(-17.0,39.3)	(-27.1,21.9)
		Pr >  t			0.8343
	Week 144	n	5	1	
		LS Mean	18.546	24.230	-5.685

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	12.55	20.31	19.64
		95% CI	(-6.2,43.3)	(-15.7,64.1)	(-44.3,32.9)
		Pr >  t			0.7724
	Week 168	n	3	1	
		LS Mean	17.131	24.230	-7.100
		SEM	14.11	20.31	20.67
	Week 180	95% CI	(-10.6,44.9)	(-15.7,64.1)	(-47.7,33.5)
		Pr >  t			0.7313
		n	2	1	
	Week 192	LS Mean	3.535	-9.100	12.634
		SEM	15.82	20.31	21.87
		95% CI	(-27.5,34.6)	(-49.0,30.8)	(-30.3,55.6)
	Week 8	Pr >  t			0.5637
		n		1	
		LS Mean		24.230	
	Week 16	SEM		20.31	
		95% CI		(-15.7,64.1)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-9.100	
		SEM		20.31	
	Week 32	95% CI		(-49.0,30.8)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	-12.90	-11.33	-1.577	
	SEM	6.035	6.228	8.536	
	95% CI	(-24.9,-0.9)	(-23.7, 1.1)	(-18.6,15.4)	
Week 16	Pr >  t			0.8539	
	n	18	14		
	LS Mean	-10.37	-12.57	2.203	
Week 24	SEM	5.927	6.495	8.688	
	95% CI	(-22.2, 1.4)	(-25.5, 0.3)	(-15.1,19.5)	
	Pr >  t			0.8005	
Week 32	n	16	13		
	LS Mean	-2.785	-4.881	2.096	
	SEM	6.149	6.631	8.935	
Week 8	95% CI	(-15.0, 9.5)	(-18.1, 8.3)	(-15.7,19.9)	
	Pr >  t			0.8151	
	n	15	13		
Week 16	LS Mean	-12.35	-8.140	-4.210	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	6.252	6.646	9.026
		95% CI	(-24.8, 0.1)	(-21.3, 5.1)	(-22.1,13.7)
		Pr >  t			0.6421
	Week 40	n	14	10	
		LS Mean	-14.13	-13.31	-0.816
		SEM	6.389	7.141	9.485
		95% CI	(-26.8,-1.4)	(-27.5, 0.8)	(-19.6,18.0)
		Pr >  t			0.9316
	Week 48	n	14	11	
		LS Mean	-2.223	-9.984	7.761
		SEM	6.389	6.966	9.353
		95% CI	(-14.9,10.5)	(-23.8, 3.8)	(-10.8,26.3)
		Pr >  t			0.4086
	Week 56	n	11	11	
		LS Mean	-6.897	-9.984	3.088
		SEM	6.811	6.966	9.652
		95% CI	(-20.4, 6.6)	(-23.8, 3.8)	(-16.0,22.2)
		Pr >  t			0.7497
	Week 64	n	8	11	
		LS Mean	-12.53	-13.01	0.489
		SEM	7.465	6.966	10.13
		95% CI	(-27.3, 2.2)	(-26.8, 0.8)	(-19.6,20.5)
		Pr >  t			0.9616
	Week 72	n	11	10	
		LS Mean	-3.867	-4.059	0.192
		SEM	6.811	7.152	9.783
		95% CI	(-17.4, 9.6)	(-18.2,10.1)	(-19.2,19.6)
		Pr >  t			0.9844
	Week 84	n	9	9	
		LS Mean	2.451	-0.239	2.690
		SEM	7.207	7.364	10.22
		95% CI	(-11.8,16.7)	(-14.8,14.3)	(-17.5,22.9)
		Pr >  t			0.7929
	Week 96	n	8	7	
		LS Mean	-4.160	-1.378	-2.782
		SEM	7.469	7.929	10.82
		95% CI	(-18.9,10.6)	(-17.0,14.3)	(-24.2,18.6)
		Pr >  t			0.7974
	Week 108	n	7	6	
		LS Mean	-8.396	-3.735	-4.661

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	7.788	8.340	11.34
		95% CI	(-23.8, 7.0)	(-20.2,12.7)	(-27.0,17.7)
		Pr >  t			0.6815
	Week 120	n	6	5	
		LS Mean	-2.352	-16.13	13.776
		SEM	8.198	8.881	12.01
		95% CI	(-18.5,13.8)	(-33.6, 1.4)	(-9.9,37.5)
		Pr >  t			0.2527
	Week 132	n	5	3	
		LS Mean	-13.71	-9.781	-3.933
		SEM	8.728	10.70	13.74
		95% CI	(-30.9, 3.5)	(-30.9,11.3)	(-31.0,23.1)
		Pr >  t			0.7749
	Week 144	n	5	4	
		LS Mean	-13.72	-10.71	-3.005
		SEM	8.728	9.601	12.90
		95% CI	(-30.9, 3.5)	(-29.6, 8.2)	(-28.4,22.4)
		Pr >  t			0.8160
	Week 156	n	4	2	
		LS Mean	-24.73	-9.449	-15.28
		SEM	9.461	12.61	15.71
		95% CI	(-43.4,-6.1)	(-34.3,15.4)	(-46.2,15.7)
		Pr >  t			0.3317
	Week 168	n	1	1	
		LS Mean	24.190	-9.995	34.185
		SEM	17.03	17.12	24.11
		95% CI	(-9.3,57.7)	(-43.7,23.7)	(-13.3,81.7)
		Pr >  t			0.1574
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	6.688	5.015	1.673
		SEM	7.234	6.402	7.884
		95% CI	(-7.8,21.2)	(-7.8,17.8)	(-14.0,17.4)
		Pr >  t			0.8326
	Week 16	n	15	17	
		LS Mean	3.303	11.002	-7.699
		SEM	7.580	6.751	8.233
		95% CI	(-11.8,18.5)	(-2.5,24.5)	(-24.1, 8.7)
		Pr >  t			0.3525
	Week 24	n	14	11	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	0.348	5.283	-4.935
		SEM	7.734	7.437	9.056
		95% CI	(-15.1,15.8)	(-9.5,20.1)	(-22.9,13.0)
		Pr >  t			0.5870
	Week 32	n	12	9	
		LS Mean	-1.844	7.490	-9.334
		SEM	8.089	7.923	9.707
		95% CI	(-18.0,14.3)	(-8.2,23.2)	(-28.6, 9.9)
		Pr >  t			0.3382
	Week 40	n	11	7	
		LS Mean	1.119	2.554	-1.434
		SEM	8.268	8.711	10.34
		95% CI	(-15.3,17.6)	(-14.7,19.8)	(-21.9,19.0)
		Pr >  t			0.8899
	Week 48	n	8	6	
		LS Mean	-2.867	2.454	-5.322
		SEM	8.909	9.154	11.23
		95% CI	(-20.5,14.8)	(-15.6,20.6)	(-27.5,16.9)
		Pr >  t			0.6362
	Week 56	n	7	5	
		LS Mean	10.809	8.609	2.199
		SEM	9.167	9.673	11.92
		95% CI	(-7.4,29.0)	(-10.5,27.7)	(-21.3,25.7)
		Pr >  t			0.8538
	Week 64	n	5	3	
		LS Mean	-13.73	1.650	-15.38
		SEM	10.06	11.61	14.16
		95% CI	(-33.6, 6.2)	(-21.3,24.6)	(-43.3,12.6)
		Pr >  t			0.2789
	Week 72	n	5	2	
		LS Mean	-9.424	4.426	-13.85
		SEM	10.08	13.64	15.90
		95% CI	(-29.4,10.5)	(-22.5,31.4)	(-45.2,17.5)
		Pr >  t			0.3849
	Week 84	n	4	2	
		LS Mean	-8.983	4.426	-13.41
		SEM	10.75	13.64	16.34
		95% CI	(-30.2,12.3)	(-22.5,31.4)	(-45.7,18.8)
		Pr >  t			0.4130
	Week 96	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	-3.489	4.426	-7.915
		SEM	10.77	13.64	16.35
		95% CI	(-24.8,17.8)	(-22.5,31.4)	(-40.2,24.4)
		Pr >  t			0.6289
	Week 108	n	1	2	
		LS Mean	44.047	-0.334	44.381
		SEM	18.34	13.59	22.04
		95% CI	( 7.8,80.3)	(-27.2,26.5)	( 0.9,87.9)
		Pr >  t			0.0457
	Week 120	n	5	1	
		LS Mean	3.908	4.938	-1.029
		SEM	10.08	18.25	19.97
		95% CI	(-16.0,23.9)	(-31.1,41.0)	(-40.5,38.4)
		Pr >  t			0.9590
	Week 132	n	3	1	
		LS Mean	21.160	4.938	16.223
		SEM	11.87	18.25	20.94
		95% CI	( -2.3,44.6)	(-31.1,41.0)	(-25.1,57.6)
		Pr >  t			0.4396
	Week 144	n	3		
		LS Mean	10.050		
		SEM	11.87		
		95% CI	(-13.4,33.5)		
		Pr >  t			
	Week 156	n	3		
		LS Mean	21.160		
		SEM	11.87		
		95% CI	( -2.3,44.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	51.164		
		SEM	18.32		
		95% CI	( 15.0,87.3)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	51.164		
		SEM	18.32		
		95% CI	( 15.0,87.3)		
		Pr >  t			
	Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	51.164		
		SEM	18.32		
		95% CI	( 15.0,87.3)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	2.620	-3.040	5.659
		SEM	4.630	4.607	5.201
		95% CI	( -6.5,11.8)	(-12.1, 6.1)	( -4.6,15.9)
		Pr >  t			0.2778
	Week 16	n	30	29	
		LS Mean	1.141	4.168	-3.028
		SEM	4.853	5.123	5.803
		95% CI	( -8.4,10.7)	( -5.9,14.3)	(-14.5, 8.4)
		Pr >  t			0.6023
	Week 24	n	26	20	
		LS Mean	3.551	1.956	1.595
		SEM	5.107	5.810	6.519
		95% CI	( -6.5,13.6)	( -9.5,13.4)	(-11.2,14.4)
		Pr >  t			0.8069
	Week 32	n	18	20	
		LS Mean	3.993	-4.711	8.704
		SEM	5.748	5.810	7.021
		95% CI	( -7.3,15.3)	(-16.2, 6.7)	( -5.1,22.5)
		Pr >  t			0.2160
	Week 40	n	18	19	
		LS Mean	5.374	-0.648	6.022
		SEM	5.751	5.901	7.096
		95% CI	( -6.0,16.7)	(-12.3,11.0)	( -7.9,20.0)
		Pr >  t			0.3967
	Week 48	n	16	14	
		LS Mean	-1.706	2.386	-4.092
		SEM	5.953	6.467	7.742
		95% CI	(-13.4,10.0)	(-10.3,15.1)	(-19.3,11.1)
		Pr >  t			0.5975
	Week 56	n	14	10	
		LS Mean	-1.483	3.649	-5.132
		SEM	6.212	7.237	8.598
		95% CI	(-13.7,10.7)	(-10.6,17.9)	(-22.0,11.8)
		Pr >  t			0.5509

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n		13	11	
	LS Mean		-1.219	1.026	-2.245
	SEM		6.368	7.005	8.526
	95% CI		(-13.8,11.3)	(-12.8,14.8)	(-19.0,14.5)
	Pr >  t				0.7925
Week 72	n		10	6	
	LS Mean		-3.400	-2.452	-0.949
	SEM		6.967	8.758	10.42
	95% CI		(-17.1,10.3)	(-19.7,14.8)	(-21.4,19.5)
	Pr >  t				0.9275
Week 84	n		8	7	
	LS Mean		0.906	-2.028	2.934
	SEM		7.671	8.250	10.44
	95% CI		(-14.2,16.0)	(-18.3,14.2)	(-17.6,23.5)
	Pr >  t				0.7788
Week 96	n		6	5	
	LS Mean		0.785	-5.805	6.590
	SEM		8.549	9.408	12.03
	95% CI		(-16.0,17.6)	(-24.3,12.7)	(-17.1,30.2)
	Pr >  t				0.5841
Week 108	n		2	4	
	LS Mean		-2.481	-14.19	11.713
	SEM		13.85	10.32	16.74
	95% CI		(-29.7,24.8)	(-34.5, 6.1)	(-21.2,44.6)
	Pr >  t				0.4847
Week 120	n		4	4	
	LS Mean		-11.81	2.471	-14.28
	SEM		10.11	10.32	13.86
	95% CI		(-31.7, 8.1)	(-17.8,22.8)	(-41.5,13.0)
	Pr >  t				0.3036
Week 132	n		3	1	
	LS Mean		20.583	14.325	6.258
	SEM		11.53	19.30	22.07
	95% CI		(-2.1,43.3)	(-23.7,52.3)	(-37.2,49.7)
	Pr >  t				0.7769
Week 144	n		2		
	LS Mean		17.026		
	SEM		13.76		
	95% CI		(-10.0,44.1)		
	Pr >  t				

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Estrogen Receptor Status (L)	Negative	Week 8	n	2		
			LS Mean	-27.78		
			SEM			
			95% CI	( , )		
		Pr >  t				
		Week 16	n	2		
			LS Mean	-27.78		
			SEM			
			95% CI	( , )		
		Pr >  t				
		Week 24	n	1		
			LS Mean	-27.78		
			SEM	0.000		
			95% CI	(-27.8, -28)		
		Pr >  t				
		Week 32	n	1		
			LS Mean	-27.78		
			SEM	0.000		
			95% CI	(-27.8, -28)		
		Pr >  t				
		Week 40	n	1		
			LS Mean	-27.78		
			SEM	0.000		
			95% CI	(-27.8, -28)		
Pr >  t						
Week 48	n	1				
	LS Mean	5.551				
	SEM	0.000				
	95% CI	( 5.6, 5.6)				
Pr >  t						
Week 56	n	1				
	LS Mean	-27.78				
	SEM	0.000				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv				
		95% CI	(-27.8, -28)						
		Pr >  t							
	Week 72	n	1						
		LS Mean	-27.78						
		SEM	0.000						
		95% CI	(-27.8, -28)						
		Pr >  t							
	Week 84	n	1						
		LS Mean	-27.78						
		SEM	0.000						
		95% CI	(-27.8, -28)						
		Pr >  t							
	Week 96	n	1						
		LS Mean	-27.78						
		SEM	0.000						
		95% CI	(-27.8, -28)						
		Pr >  t							
Positive	Week 8	n	140	140					
		LS Mean	1.702	1.865	-0.163				
		SEM	3.127	3.170	2.809				
		95% CI	(-4.4, 7.8)	(-4.4, 8.1)	(-5.7, 5.4)				
		Pr >  t			0.9537				
		Week 16	n	122	107				
			LS Mean	-0.171	5.613	-5.784			
			SEM	3.214	3.347	3.046			
			95% CI	(-6.5, 6.1)	(-1.0, 12.2)	(-11.8, 0.2)			
			Pr >  t			0.0579			
			Week 24	n	104	81			
				LS Mean	3.801	4.331	-0.530		
				SEM	3.301	3.525	3.312		
				95% CI	(-2.7, 10.3)	(-2.6, 11.3)	(-7.0, 6.0)		
				Pr >  t			0.8730		
				Week 32	n	85	73		
					LS Mean	0.446	1.010	-0.565	
					SEM	3.444	3.606	3.499	
					95% CI	(-6.3, 7.2)	(-6.1, 8.1)	(-7.4, 6.3)	
					Pr >  t			0.8718	
					Week 40	n	74	62	
						LS Mean	1.539	-0.424	1.963
						SEM	3.529	3.732	3.702

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-5.4, 8.5)	(-7.8, 6.9)	(-5.3, 9.2)
	Pr >  t			0.5961
Week 48	n	68	51	
	LS Mean	4.125	3.311	0.814
	SEM	3.584	3.886	3.909
	95% CI	(-2.9,11.2)	(-4.3,10.9)	(-6.9, 8.5)
	Pr >  t			0.8350
Week 56	n	58	45	
	LS Mean	2.737	4.662	-1.924
	SEM	3.696	3.996	4.122
	95% CI	(-4.5,10.0)	(-3.2,12.5)	(-10.0, 6.2)
	Pr >  t			0.6407
Week 64	n	47	42	
	LS Mean	-2.062	-0.921	-1.140
	SEM	3.863	4.062	4.339
	95% CI	(-9.6, 5.5)	(-8.9, 7.1)	(-9.7, 7.4)
	Pr >  t			0.7927
Week 72	n	47	35	
	LS Mean	0.620	4.087	-3.466
	SEM	3.866	4.246	4.513
	95% CI	(-7.0, 8.2)	(-4.2,12.4)	(-12.3, 5.4)
	Pr >  t			0.4426
Week 84	n	39	33	
	LS Mean	3.061	3.018	0.044
	SEM	4.053	4.311	4.722
	95% CI	(-4.9,11.0)	(-5.4,11.5)	(-9.2, 9.3)
	Pr >  t			0.9926
Week 96	n	34	24	
	LS Mean	-0.432	6.042	-6.474
	SEM	4.190	4.711	5.207
	95% CI	(-8.7, 7.8)	(-3.2,15.3)	(-16.7, 3.7)
	Pr >  t			0.2139
Week 108	n	26	21	
	LS Mean	4.055	3.822	0.233
	SEM	4.526	4.907	5.643
	95% CI	(-4.8,12.9)	(-5.8,13.4)	(-10.8,11.3)
	Pr >  t			0.9671
Week 120	n	28	16	
	LS Mean	3.895	1.212	2.683
	SEM	4.422	5.365	5.974



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-4.8,12.6)	(-9.3,11.7)	(-9.0,14.4)
	Pr >  t			0.6533
	n	20	8	
	LS Mean	4.050	2.238	1.812
	SEM	4.905	6.943	7.717
Week 144	95% CI	(-5.6,13.7)	(-11.4,15.9)	(-13.3,16.9)
	Pr >  t			0.8143
	n	15	5	
	LS Mean	6.162	2.256	3.906
	SEM	5.395	8.464	9.389
Week 156	95% CI	(-4.4,16.7)	(-14.3,18.9)	(-14.5,22.3)
	Pr >  t			0.6775
	n	10	3	
	LS Mean	2.873	4.749	-1.876
	SEM	6.293	10.62	11.82
Week 168	95% CI	(-9.5,15.2)	(-16.1,25.6)	(-25.1,21.3)
	Pr >  t			0.8739
	n	4	2	
	LS Mean	18.480	-10.61	29.087
	SEM	9.274	12.82	15.42
Week 180	95% CI	( 0.3,36.7)	(-35.8,14.5)	(-1.2,59.3)
	Pr >  t			0.0595
	n	1	1	
	LS Mean	48.445	11.471	36.975
	SEM	17.83	17.84	24.97
Week 192	95% CI	( 13.5,83.4)	(-23.5,46.5)	(-12.0,86.0)
	Pr >  t			0.1389
	n	1	1	
	LS Mean	48.445	-21.86	70.305
	SEM	17.83	17.84	24.97
	95% CI	( 13.5,83.4)	(-56.9,13.1)	( 21.3, 119)
	Pr >  t			0.0049

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	-7.167	-11.87	4.700		
			SEM	9.121	9.406	4.342		
			95% CI	(-25.3,10.9)	(-30.5, 6.8)	( -3.8,13.2)		
					Pr >  t			0.2798
		Week 16	n	59	49			
			LS Mean	-7.768	-4.647	-3.121		
			SEM	9.165	9.503	4.665		
			95% CI	(-25.9,10.4)	(-23.5,14.2)	(-12.3, 6.0)		
					Pr >  t			0.5038
		Week 24	n	54	41			
			LS Mean	-3.302	-6.004	2.702		
			SEM	9.194	9.594	4.926		
			95% CI	(-21.5,14.9)	(-25.0,13.0)	( -7.0,12.4)		
					Pr >  t			0.5836
		Week 32	n	48	37			
			LS Mean	-7.508	-9.395	1.887		
			SEM	9.233	9.647	5.125		
			95% CI	(-25.8,10.8)	(-28.5, 9.7)	( -8.2,12.0)		
					Pr >  t			0.7129
		Week 40	n	43	33			
			LS Mean	-7.462	-8.763	1.301		
			SEM	9.276	9.711	5.337		
			95% CI	(-25.8,10.9)	(-28.0,10.5)	( -9.2,11.8)		
			Pr >  t			0.8074		
Week 48	n	41	28					
	LS Mean	-4.578	-8.725	4.146				
	SEM	9.297	9.813	5.570				
	95% CI	(-23.0,13.8)	(-28.2,10.7)	( -6.8,15.1)				
			Pr >  t			0.4569		
Week 56	n	35	22					
	LS Mean	-3.987	-7.456	3.469				
	SEM	9.370	9.999	6.021				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.5,14.6)	(-27.2,12.3)	( -8.4,15.3)
		Pr >  t			0.5647
	Week 64	n	26	23	
		LS Mean	-12.89	-10.26	-2.627
		SEM	9.541	9.963	6.258
		95% CI	(-31.8, 6.0)	(-30.0, 9.5)	(-14.9, 9.7)
		Pr >  t			0.6748
	Week 72	n	28	18	
		LS Mean	-5.835	-7.709	1.874
		SEM	9.496	10.18	6.526
		95% CI	(-24.6,13.0)	(-27.8,12.4)	(-10.9,14.7)
		Pr >  t			0.7741
	Week 84	n	22	18	
		LS Mean	-8.679	-5.776	-2.903
		SEM	9.724	10.18	6.787
		95% CI	(-27.9,10.6)	(-25.9,14.4)	(-16.2,10.4)
		Pr >  t			0.6689
	Week 96	n	21	13	
		LS Mean	-10.41	-2.801	-7.613
		SEM	9.697	10.55	7.390
		95% CI	(-29.6, 8.8)	(-23.6,18.0)	(-22.1, 6.9)
		Pr >  t			0.3032
	Week 108	n	17	12	
		LS Mean	-6.600	-4.869	-1.731
		SEM	9.966	10.66	7.796
		95% CI	(-26.3,13.1)	(-25.9,16.2)	(-17.0,13.6)
		Pr >  t			0.8243
	Week 120	n	18	11	
		LS Mean	-8.058	-3.978	-4.080
		SEM	9.826	10.79	7.899
		95% CI	(-27.5,11.4)	(-25.3,17.3)	(-19.6,11.4)
		Pr >  t			0.6056
	Week 132	n	13	5	
		LS Mean	-3.440	-7.188	3.748
		SEM	10.28	12.44	10.41
		95% CI	(-23.7,16.9)	(-31.7,17.3)	(-16.7,24.2)
		Pr >  t			0.7189
	Week 144	n	12	3	
		LS Mean	0.524	-6.389	6.912
		SEM	10.28	14.21	12.56

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.8,20.8)	(-34.3,21.5)	(-17.7,31.6)
		Pr >  t			0.5823
	Week 156	n	7	2	
		LS Mean	-2.199	-3.287	1.088
		SEM	11.35	16.13	15.39
		95% CI	(-24.6,20.2)	(-35.0,28.4)	(-29.1,31.3)
		Pr >  t			0.9436
	Week 168	n	3	1	
		LS Mean	16.689	-32.09	48.781
		SEM	13.97	20.86	21.88
		95% CI	(-10.8,44.1)	(-73.0, 8.9)	( 5.8,91.7)
		Pr >  t			0.0261
	Week 180	n	1	1	
		LS Mean	40.707	1.238	39.469
		SEM	20.71	20.86	26.69
		95% CI	( 0.1,81.4)	(-39.7,42.2)	(-12.9,91.9)
		Pr >  t			0.1396
	Week 192	n	1	1	
		LS Mean	40.707	-32.09	72.799
		SEM	20.71	20.86	26.69
		95% CI	( 0.1,81.4)	(-73.0, 8.9)	( 20.4, 125)
		Pr >  t			0.0065
Yes	Week 8	n	73	80	
		LS Mean	4.852	9.817	-4.965
		SEM	4.732	4.807	3.623
		95% CI	( -4.5,14.2)	( 0.3,19.3)	(-12.1, 2.2)
		Pr >  t			0.1716
	Week 16	n	65	58	
		LS Mean	2.036	10.745	-8.708
		SEM	4.866	5.030	3.934
		95% CI	( -7.5,11.6)	( 0.8,20.7)	(-16.4,-1.0)
		Pr >  t			0.0275
	Week 24	n	51	40	
		LS Mean	5.317	9.923	-4.606
		SEM	4.983	5.312	4.394
		95% CI	( -4.5,15.1)	( -0.5,20.4)	(-13.2, 4.0)
		Pr >  t			0.2950
	Week 32	n	38	36	
		LS Mean	2.972	6.498	-3.526
		SEM	5.247	5.401	4.713

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.4,13.3)	(-4.1,17.1)	(-12.8, 5.7)
		Pr >  t			0.4548
	Week 40	n	32	29	
		LS Mean	5.058	2.622	2.436
		SEM	5.396	5.583	5.066
		95% CI	(-5.6,15.7)	(-8.4,13.6)	(-7.5,12.4)
		Pr >  t			0.6308
	Week 48	n	28	23	
		LS Mean	8.270	10.623	-2.354
		SEM	5.509	5.812	5.425
		95% CI	(-2.6,19.1)	(-0.8,22.1)	(-13.0, 8.3)
		Pr >  t			0.6645
	Week 56	n	24	23	
		LS Mean	2.695	11.710	-9.016
		SEM	5.663	5.811	5.576
		95% CI	(-8.4,13.8)	( 0.3,23.1)	(-20.0, 1.9)
		Pr >  t			0.1064
	Week 64	n	21	19	
		LS Mean	3.934	3.170	0.764
		SEM	5.809	6.024	5.940
		95% CI	(-7.5,15.4)	(-8.7,15.0)	(-10.9,12.4)
		Pr >  t			0.8977
	Week 72	n	20	17	
		LS Mean	0.898	11.084	-10.19
		SEM	5.869	6.159	6.135
		95% CI	(-10.6,12.4)	(-1.0,23.2)	(-22.2, 1.9)
		Pr >  t			0.0972
	Week 84	n	18	15	
		LS Mean	9.960	6.446	3.514
		SEM	5.980	6.330	6.415
		95% CI	(-1.8,21.7)	(-6.0,18.9)	(-9.1,16.1)
		Pr >  t			0.5840
	Week 96	n	14	11	
		LS Mean	4.944	9.678	-4.735
		SEM	6.332	6.825	7.202
		95% CI	(-7.5,17.4)	(-3.7,23.1)	(-18.9, 9.4)
		Pr >  t			0.5111
	Week 108	n	9	9	
		LS Mean	10.928	6.879	4.049
		SEM	7.108	7.205	8.228

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.0,24.9)	(-7.3,21.0)	(-12.1,20.2)
		Pr >  t			0.6228
	Week 120	n	10	5	
		LS Mean	13.289	-4.957	18.246
		SEM	6.925	8.680	9.409
		95% CI	(-0.3,26.9)	(-22.0,12.1)	(-0.2,36.7)
		Pr >  t			0.0529
	Week 132	n	7	3	
		LS Mean	4.849	6.018	-1.168
		SEM	7.670	10.48	11.58
		95% CI	(-10.2,19.9)	(-14.6,26.6)	(-23.9,21.6)
		Pr >  t			0.9197
	Week 144	n	3	2	
		LS Mean	-2.176	5.262	-7.438
		SEM	10.40	12.38	15.07
		95% CI	(-22.6,18.2)	(-19.0,29.6)	(-37.0,22.2)
		Pr >  t			0.6217
	Week 156	n	3	1	
		LS Mean	-2.498	5.979	-8.477
		SEM	10.42	16.84	18.90
		95% CI	(-22.9,18.0)	(-27.1,39.0)	(-45.6,28.6)
		Pr >  t			0.6539
	Week 168	n	1	1	
		LS Mean	1.498	5.979	-4.481
		SEM	16.82	16.84	23.06
		95% CI	(-31.5,34.5)	(-27.1,39.0)	(-49.8,40.8)
		Pr >  t			0.8460

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	9.415	19.608	-10.19
			SEM	8.305	9.293	8.050
			95% CI	(-7.3,26.2)	( 0.8,38.4)	(-26.3, 5.9)
		Pr >  t			0.2101	
		Week 16	n	14	17	
			LS Mean	0.999	28.525	-27.53
			SEM	8.432	9.587	8.637
			95% CI	(-16.0,18.0)	( 9.2,47.9)	(-44.7, -10)
		Pr >  t			0.0021	
		Week 24	n	14	11	
			LS Mean	15.285	26.564	-11.28
			SEM	8.432	10.08	9.205
			95% CI	(-1.7,32.3)	( 6.3,46.8)	(-29.6, 7.0)
		Pr >  t			0.2236	
		Week 32	n	10	10	
			LS Mean	6.013	15.292	-9.278
			SEM	9.319	10.25	9.783
			95% CI	(-12.6,24.6)	(-5.3,35.8)	(-28.7,10.1)
		Pr >  t			0.3450	
		Week 40	n	8	10	
			LS Mean	1.359	19.650	-18.29
			SEM	9.720	10.25	10.15
			95% CI	(-18.0,20.7)	(-0.9,40.2)	(-38.4, 1.8)
		Pr >  t			0.0740	
		Week 48	n	7	11	
			LS Mean	9.194	22.125	-12.93
			SEM	9.980	10.12	10.28
			95% CI	(-10.6,29.0)	( 1.8,42.4)	(-33.3, 7.4)
		Pr >  t			0.2110	
		Week 56	n	6	9	
			LS Mean	2.389	14.999	-12.61
			SEM	10.29	10.41	10.91



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.0,22.8)	(-5.8,35.8)	(-34.2, 9.0)
		Pr >  t			0.2498
	Week 64	n	5	8	
		LS Mean	0.784	13.729	-12.95
		SEM	10.73	10.60	11.51
		95% CI	(-20.5,22.1)	(-7.5,34.9)	(-35.7, 9.8)
		Pr >  t			0.2624
	Week 72	n	7	7	
		LS Mean	2.836	10.738	-7.901
		SEM	9.949	10.84	11.02
		95% CI	(-16.9,22.6)	(-10.9,32.4)	(-29.7,13.9)
		Pr >  t			0.4747
	Week 84	n	7	7	
		LS Mean	7.598	15.499	-7.901
		SEM	9.949	10.84	11.02
		95% CI	(-12.2,27.4)	(-6.2,37.1)	(-29.7,13.9)
		Pr >  t			0.4747
	Week 96	n	5	6	
		LS Mean	1.600	32.491	-30.89
		SEM	10.73	11.16	12.02
		95% CI	(-19.7,22.9)	(10.3,54.7)	(-54.6,-7.2)
		Pr >  t			0.0110
	Week 108	n	4	6	
		LS Mean	-4.946	21.379	-26.33
		SEM	11.38	11.16	12.60
		95% CI	(-27.5,17.6)	(-0.9,43.6)	(-51.2,-1.5)
		Pr >  t			0.0381
	Week 120	n	4	4	
		LS Mean	12.680	1.584	11.095
		SEM	11.38	12.18	13.52
		95% CI	(-9.8,35.2)	(-22.6,25.8)	(-15.6,37.8)
		Pr >  t			0.4129
	Week 132	n	3	1	
		LS Mean	2.325	35.274	-32.95
		SEM	12.35	18.87	20.33
		95% CI	(-22.1,26.7)	(-1.9,72.5)	(-73.0, 7.1)
		Pr >  t			0.1067
	Week 144	n	1	1	
		LS Mean	66.769	12.206	54.563
		SEM	18.36	18.91	24.50

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	( 30.6, 103)	(-25.1,49.5)	( 6.2, 103)
		Pr >  t			0.0271
		n	35	37	
	Week 16	LS Mean	34.851	31.762	3.089
		SEM	10.59	11.16	4.943
		95% CI	( 14.0,55.7)	( 9.8,53.7)	( -6.6,12.8)
	Week 24	Pr >  t			0.5326
		n	34	30	
		LS Mean	33.550	37.164	-3.614
	Week 32	SEM	11.04	11.28	5.204
		95% CI	( 11.8,55.3)	( 15.0,59.4)	(-13.9, 6.6)
		Pr >  t			0.4879
	Week 40	n	32	23	
		LS Mean	31.179	36.508	-5.329
		SEM	11.06	11.45	5.651
	Week 48	95% CI	( 9.4,53.0)	( 14.0,59.1)	(-16.4, 5.8)
		Pr >  t			0.3464
		n	21	22	
	Week 56	LS Mean	31.647	30.664	0.983
		SEM	11.33	11.49	6.244
		95% CI	( 9.4,53.9)	( 8.0,53.3)	(-11.3,13.3)
	Week 64	Pr >  t			0.8750
		n	20	20	
		LS Mean	40.472	28.755	11.717
Week 8	SEM	11.37	11.56	6.454	
	95% CI	( 18.1,62.8)	( 6.0,51.5)	( -1.0,24.4)	
	Pr >  t			0.0703	
Week 16	n	19	12		
	LS Mean	27.874	30.017	-2.143	
	SEM	11.40	12.06	7.380	
Week 24	95% CI	( 5.4,50.3)	( 6.3,53.8)	(-16.7,12.4)	
	Pr >  t			0.7716	
	n	16	8		
Week 32	LS Mean	33.920	32.101	1.818	
	SEM	11.56	12.66	8.508	
	95% CI	( 11.2,56.7)	( 7.2,57.0)	(-14.9,18.5)	
Week 40	Pr >  t			0.8309	
	n	12	11		
	LS Mean	33.289	32.894	0.394	
Week 48	SEM	11.86	12.18	8.225	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 9.9,56.6)	( 8.9,56.9)	(-15.8,16.6)
		Pr >  t			0.9618
	Week 72	n	13	7	
		LS Mean	29.310	32.793	-3.483
		SEM	11.78	12.91	9.154
		95% CI	( 6.1,52.5)	( 7.4,58.2)	(-21.5,14.5)
		Pr >  t			0.7038
	Week 84	n	12	6	
		LS Mean	32.111	36.621	-4.510
		SEM	11.86	13.23	9.713
		95% CI	( 8.8,55.4)	( 10.6,62.6)	(-23.6,14.6)
		Pr >  t			0.6427
	Week 96	n	7	6	
		LS Mean	27.616	31.974	-4.357
		SEM	12.68	13.23	10.71
		95% CI	( 2.7,52.6)	( 6.0,58.0)	(-25.4,16.7)
		Pr >  t			0.6842
	Week 108	n	5	3	
		LS Mean	49.037	43.764	5.273
		SEM	13.42	15.21	13.81
		95% CI	( 22.7,75.4)	( 13.8,73.7)	(-21.9,32.4)
		Pr >  t			0.7027
	Week 120	n	8	3	
		LS Mean	36.066	32.650	3.415
		SEM	12.46	15.21	12.85
		95% CI	( 11.5,60.6)	( 2.7,62.6)	(-21.9,28.7)
		Pr >  t			0.7905
	Week 132	n	2	1	
		LS Mean	19.934	34.927	-14.99
		SEM	16.75	21.33	22.67
		95% CI	(-13.0,52.9)	( -7.0,76.9)	(-59.6,29.6)
		Pr >  t			0.5089
	Week 144	n	2		
		LS Mean	31.400		
		SEM	16.77		
		95% CI	( -1.6,64.4)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	31.400		
		SEM	16.77		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-1.6,64.4)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	-1.988	0.040	-2.029
		SEM	4.161	4.311	4.078
		95% CI	(-10.2, 6.2)	(-8.5, 8.5)	(-10.1, 6.0)
		Pr >  t			0.6193
	Week 16	n	70	52	
		LS Mean	-2.355	1.628	-3.983
		SEM	4.272	4.544	4.355
		95% CI	(-10.8, 6.1)	(-7.3,10.6)	(-12.5, 4.6)
		Pr >  t			0.3611
	Week 24	n	54	40	
		LS Mean	3.051	0.972	2.078
		SEM	4.451	4.810	4.765
		95% CI	(-5.7,11.8)	(-8.5,10.4)	(-7.3,11.4)
		Pr >  t			0.6629
	Week 32	n	50	36	
		LS Mean	0.188	0.541	-0.352
		SEM	4.525	4.906	4.918
		95% CI	(-8.7, 9.1)	(-9.1,10.2)	(-10.0, 9.3)
		Pr >  t			0.9429
	Week 40	n	42	28	
		LS Mean	-1.867	-1.509	-0.358
		SEM	4.658	5.185	5.301
		95% CI	(-11.0, 7.3)	(-11.7, 8.7)	(-10.8,10.1)
		Pr >  t			0.9462
	Week 48	n	38	24	
		LS Mean	8.021	1.470	6.550
		SEM	4.743	5.364	5.553
		95% CI	(-1.3,17.4)	(-9.1,12.0)	(-4.4,17.5)
		Pr >  t			0.2386
	Week 56	n	33	24	
		LS Mean	2.875	5.328	-2.453
		SEM	4.871	5.368	5.670
		95% CI	(-6.7,12.5)	(-5.2,15.9)	(-13.6, 8.7)
		Pr >  t			0.6654
	Week 64	n	27	19	
		LS Mean	-4.248	-4.166	-0.082
		SEM	5.075	5.679	6.140

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.2, 5.7)	(-15.3, 7.0)	(-12.1,12.0)
		Pr >  t			0.9894
	Week 72	n	26	17	
		LS Mean	2.280	5.828	-3.548
		SEM	5.117	5.842	6.324
		95% CI	(-7.8,12.3)	(-5.6,17.3)	(-16.0, 8.9)
		Pr >  t			0.5750
	Week 84	n	18	16	
		LS Mean	6.405	2.219	4.186
		SEM	5.621	5.939	6.803
		95% CI	(-4.6,17.4)	(-9.4,13.9)	(-9.2,17.5)
		Pr >  t			0.5385
	Week 96	n	20	10	
		LS Mean	0.827	2.930	-2.103
		SEM	5.461	6.825	7.481
		95% CI	(-9.9,11.6)	(-10.5,16.3)	(-16.8,12.6)
		Pr >  t			0.7787
	Week 108	n	14	10	
		LS Mean	3.553	1.996	1.557
		SEM	6.035	6.826	7.902
		95% CI	(-8.3,15.4)	(-11.4,15.4)	(-14.0,17.1)
		Pr >  t			0.8439
	Week 120	n	14	7	
		LS Mean	4.192	2.875	1.317
		SEM	6.015	7.708	8.674
		95% CI	(-7.6,16.0)	(-12.3,18.0)	(-15.7,18.3)
		Pr >  t			0.8793
	Week 132	n	12	5	
		LS Mean	3.151	-5.685	8.836
		SEM	6.319	8.743	9.789
		95% CI	(-9.3,15.6)	(-22.8,11.5)	(-10.4,28.1)
		Pr >  t			0.3670
	Week 144	n	11	4	
		LS Mean	-1.593	1.908	-3.501
		SEM	6.472	9.555	10.63
		95% CI	(-14.3,11.1)	(-16.8,20.7)	(-24.4,17.4)
		Pr >  t			0.7419
	Week 156	n	8	3	
		LS Mean	2.253	2.959	-0.706
		SEM	7.227	10.77	12.15

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.9,16.4)	(-18.2,24.1)	(-24.6,23.1)
		Pr >  t			0.9537
	Week 168	n	4	2	
		LS Mean	17.446	-12.46	29.909
		SEM	9.445	12.85	15.29
		95% CI	(-1.1,36.0)	(-37.7,12.8)	(-0.1,59.9)
		Pr >  t			0.0509
	Week 180	n	1	1	
		LS Mean	46.660	9.744	36.916
		SEM	17.62	17.67	24.54
		95% CI	(12.1,81.3)	(-24.9,44.4)	(-11.3,85.1)
		Pr >  t			0.1329
	Week 192	n	1	1	
		LS Mean	46.660	-23.59	70.246
		SEM	17.62	17.67	24.54
		95% CI	(12.1,81.3)	(-58.3,11.1)	(22.1,118)
		Pr >  t			0.0043

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64	
			LS Mean	-1.988	0.040	-2.029
			SEM	4.161	4.311	4.078
			95% CI	(-10.2, 6.2)	(-8.5, 8.5)	(-10.1, 6.0)
		Pr >  t			0.6193	
		Week 16	n	70	52	
			LS Mean	-2.355	1.628	-3.983
			SEM	4.272	4.544	4.355
			95% CI	(-10.8, 6.1)	(-7.3, 10.6)	(-12.5, 4.6)
		Pr >  t			0.3611	
		Week 24	n	54	40	
			LS Mean	3.051	0.972	2.078
			SEM	4.451	4.810	4.765
			95% CI	(-5.7, 11.8)	(-8.5, 10.4)	(-7.3, 11.4)
		Pr >  t			0.6629	
		Week 32	n	50	36	
			LS Mean	0.188	0.541	-0.352
			SEM	4.525	4.906	4.918
			95% CI	(-8.7, 9.1)	(-9.1, 10.2)	(-10.0, 9.3)
		Pr >  t			0.9429	
		Week 40	n	42	28	
			LS Mean	-1.867	-1.509	-0.358
			SEM	4.658	5.185	5.301
			95% CI	(-11.0, 7.3)	(-11.7, 8.7)	(-10.8, 10.1)
		Pr >  t			0.9462	
		Week 48	n	38	24	
			LS Mean	8.021	1.470	6.550
			SEM	4.743	5.364	5.553
			95% CI	(-1.3, 17.4)	(-9.1, 12.0)	(-4.4, 17.5)
		Pr >  t			0.2386	
		Week 56	n	33	24	
			LS Mean	2.875	5.328	-2.453
			SEM	4.871	5.368	5.670

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-6.7,12.5)	(-5.2,15.9)	(-13.6, 8.7)
	Pr >  t			0.6654
Week 64	n	27	19	
	LS Mean	-4.248	-4.166	-0.082
	SEM	5.075	5.679	6.140
	95% CI	(-14.2, 5.7)	(-15.3, 7.0)	(-12.1,12.0)
	Pr >  t			0.9894
Week 72	n	26	17	
	LS Mean	2.280	5.828	-3.548
	SEM	5.117	5.842	6.324
	95% CI	(-7.8,12.3)	(-5.6,17.3)	(-16.0, 8.9)
	Pr >  t			0.5750
Week 84	n	18	16	
	LS Mean	6.405	2.219	4.186
	SEM	5.621	5.939	6.803
	95% CI	(-4.6,17.4)	(-9.4,13.9)	(-9.2,17.5)
	Pr >  t			0.5385
Week 96	n	20	10	
	LS Mean	0.827	2.930	-2.103
	SEM	5.461	6.825	7.481
	95% CI	(-9.9,11.6)	(-10.5,16.3)	(-16.8,12.6)
	Pr >  t			0.7787
Week 108	n	14	10	
	LS Mean	3.553	1.996	1.557
	SEM	6.035	6.826	7.902
	95% CI	(-8.3,15.4)	(-11.4,15.4)	(-14.0,17.1)
	Pr >  t			0.8439
Week 120	n	14	7	
	LS Mean	4.192	2.875	1.317
	SEM	6.015	7.708	8.674
	95% CI	(-7.6,16.0)	(-12.3,18.0)	(-15.7,18.3)
	Pr >  t			0.8793
Week 132	n	12	5	
	LS Mean	3.151	-5.685	8.836
	SEM	6.319	8.743	9.789
	95% CI	(-9.3,15.6)	(-22.8,11.5)	(-10.4,28.1)
	Pr >  t			0.3670
Week 144	n	11	4	
	LS Mean	-1.593	1.908	-3.501
	SEM	6.472	9.555	10.63



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.3,11.1)	(-16.8,20.7)	(-24.4,17.4)
		Pr >  t			0.7419
	Week 156	n	8	3	
		LS Mean	2.253	2.959	-0.706
		SEM	7.227	10.77	12.15
		95% CI	(-11.9,16.4)	(-18.2,24.1)	(-24.6,23.1)
		Pr >  t			0.9537
	Week 168	n	4	2	
		LS Mean	17.446	-12.46	29.909
		SEM	9.445	12.85	15.29
		95% CI	(-1.1,36.0)	(-37.7,12.8)	(-0.1,59.9)
		Pr >  t			0.0509
	Week 180	n	1	1	
		LS Mean	46.660	9.744	36.916
		SEM	17.62	17.67	24.54
		95% CI	( 12.1,81.3)	(-24.9,44.4)	(-11.3,85.1)
		Pr >  t			0.1329
	Week 192	n	1	1	
		LS Mean	46.660	-23.59	70.246
		SEM	17.62	17.67	24.54
		95% CI	( 12.1,81.3)	(-58.3,11.1)	( 22.1, 118)
		Pr >  t			0.0043
Exon 9	Week 8	n	53	64	
		LS Mean	16.037	16.615	-0.578
		SEM	5.788	6.230	4.191
		95% CI	( 4.6,27.5)	( 4.3,28.9)	(-8.8, 7.7)
		Pr >  t			0.8904
	Week 16	n	48	48	
		LS Mean	11.415	23.624	-12.21
		SEM	5.945	6.404	4.521
		95% CI	(-0.3,23.1)	( 11.0,36.3)	(-21.1,-3.3)
		Pr >  t			0.0073
	Week 24	n	46	36	
		LS Mean	13.998	22.083	-8.085
		SEM	5.967	6.604	4.847
		95% CI	( 2.2,25.8)	( 9.1,35.1)	(-17.6, 1.4)
		Pr >  t			0.0961
	Week 32	n	31	33	
		LS Mean	11.383	15.211	-3.828
		SEM	6.415	6.680	5.314

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( -1.3,24.0)	( 2.0,28.4)	(-14.3, 6.6)
		Pr >  t			0.4717
	Week 40	n	28	30	
		LS Mean	16.242	14.577	1.665
		SEM	6.509	6.760	5.527
		95% CI	( 3.4,29.1)	( 1.2,27.9)	( -9.2,12.5)
		Pr >  t			0.7633
	Week 48	n	26	23	
		LS Mean	9.546	17.035	-7.489
		SEM	6.578	7.016	5.916
		95% CI	( -3.4,22.5)	( 3.2,30.9)	(-19.1, 4.1)
		Pr >  t			0.2061
	Week 56	n	22	17	
		LS Mean	12.149	14.706	-2.557
		SEM	6.752	7.377	6.525
		95% CI	( -1.1,25.4)	( 0.2,29.2)	(-15.4,10.3)
		Pr >  t			0.6953
	Week 64	n	17	19	
		LS Mean	10.907	14.783	-3.876
		SEM	7.071	7.237	6.700
		95% CI	( -3.0,24.8)	( 0.5,29.0)	(-17.0, 9.3)
		Pr >  t			0.5632
	Week 72	n	20	14	
		LS Mean	8.777	12.894	-4.117
		SEM	6.869	7.661	6.956
		95% CI	( -4.7,22.3)	( -2.2,28.0)	(-17.8, 9.5)
		Pr >  t			0.5541
	Week 84	n	19	13	
		LS Mean	12.392	16.984	-4.592
		SEM	6.923	7.778	7.147
		95% CI	( -1.2,26.0)	( 1.7,32.3)	(-18.6, 9.4)
		Pr >  t			0.5208
	Week 96	n	12	12	
		LS Mean	7.089	23.416	-16.33
		SEM	7.612	7.915	7.953
		95% CI	( -7.9,22.1)	( 7.8,39.0)	(-31.9,-0.7)
		Pr >  t			0.0405
	Week 108	n	9	9	
		LS Mean	16.261	22.194	-5.933
		SEM	8.181	8.466	9.016

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.2,32.3)	(-23.6,11.8)
		Pr >  t		0.5107
	Week 120	n	12	7
		LS Mean	16.471	6.955
		SEM	7.631	9.063
		95% CI	( 1.5,31.5)	(-10.9,24.8)
		Pr >  t		0.2960
	Week 132	n	5	2
		LS Mean	4.500	26.228
		SEM	9.770	14.02
		95% CI	(-14.7,23.7)	(-1.3,53.8)
		Pr >  t		0.1567
	Week 144	n	3	1
		LS Mean	32.229	10.702
		SEM	11.78	18.94
		95% CI	( 9.1,55.4)	(-26.5,47.9)
		Pr >  t		0.3054
	Week 156	n	2	
		LS Mean	12.803	
		SEM	13.88	
		95% CI	(-14.5,40.1)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-28: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Appetitverlust“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
PTEN Loss of Expression (L)	No	Week 8	n	137	130	
			LS Mean	15.670	4.803	10.867
			SEM	3.372	3.437	3.014
			95% CI	( 9.0,22.3)	( -2.0,11.6)	( 4.9,16.8)
			Pr >  t			0.0003
		Week 16	n	119	97	
			LS Mean	15.443	2.996	12.447
			SEM	3.452	3.616	3.252
			95% CI	( 8.7,22.2)	( -4.1,10.1)	( 6.1,18.8)
			Pr >  t			0.0001
		Week 24	n	100	75	
			LS Mean	10.988	4.928	6.059
			SEM	3.534	3.771	3.491
			95% CI	( 4.0,17.9)	( -2.5,12.3)	( -0.8,12.9)
			Pr >  t			0.0830
		Week 32	n	82	69	
			LS Mean	9.956	3.255	6.701
			SEM	3.656	3.833	3.647
			95% CI	( 2.8,17.1)	( -4.3,10.8)	( -0.5,13.9)
			Pr >  t			0.0665
Week 40	n	73	58			
	LS Mean	8.815	4.949	3.866		
	SEM	3.719	3.950	3.824		
	95% CI	( 1.5,16.1)	( -2.8,12.7)	( -3.6,11.4)		
	Pr >  t			0.3122		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48		n	66	48	
		LS Mean	7.039	4.297	2.742
		SEM	3.776	4.085	4.017
		95% CI	(-0.4,14.5)	(-3.7,12.3)	(-5.1,10.6)
		Pr >  t			0.4950
Week 56		n	56	43	
		LS Mean	5.894	2.987	2.907
		SEM	3.877	4.172	4.202
		95% CI	(-1.7,13.5)	(-5.2,11.2)	(-5.3,11.2)
		Pr >  t			0.4892
Week 64		n	45	41	
		LS Mean	8.194	5.666	2.527
		SEM	4.031	4.212	4.386
		95% CI	( 0.3,16.1)	(-2.6,13.9)	(-6.1,11.1)
		Pr >  t			0.5646
Week 72		n	46	34	
		LS Mean	6.248	3.839	2.409
		SEM	4.016	4.380	4.533
		95% CI	(-1.6,14.1)	(-4.8,12.4)	(-6.5,11.3)
		Pr >  t			0.5952
Week 84		n	37	32	
		LS Mean	6.834	7.087	-0.253
		SEM	4.207	4.439	4.749
		95% CI	(-1.4,15.1)	(-1.6,15.8)	(-9.6, 9.1)
		Pr >  t			0.9575
Week 96		n	33	23	
		LS Mean	7.320	6.805	0.516
		SEM	4.310	4.811	5.189
		95% CI	(-1.1,15.8)	(-2.6,16.2)	(-9.7,10.7)
		Pr >  t			0.9209
Week 108		n	24	20	
		LS Mean	3.922	5.282	-1.360
		SEM	4.669	4.999	5.651
		95% CI	(-5.2,13.1)	(-4.5,15.1)	(-12.4, 9.7)
		Pr >  t			0.8098
Week 120		n	25	16	
		LS Mean	8.280	3.888	4.392
		SEM	4.615	5.337	5.915
		95% CI	(-0.8,17.3)	(-6.6,14.4)	(-7.2,16.0)
		Pr >  t			0.4579

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 132	n	19	8	
		LS Mean	4.181	9.046	-4.865
		SEM	4.982	6.758	7.460
		95% CI	(-5.6,14.0)	(-4.2,22.3)	(-19.5, 9.8)
		Pr >  t			0.5144
	Week 144	n	14	5	
		LS Mean	18.832	1.922	16.909
		SEM	5.466	8.151	9.032
		95% CI	( 8.1,29.6)	(-14.1,17.9)	(-0.8,34.6)
		Pr >  t			0.0614
	Week 156	n	10	3	
		LS Mean	1.521	2.896	-1.374
		SEM	6.152	10.14	11.22
		95% CI	(-10.5,13.6)	(-17.0,22.8)	(-23.4,20.6)
		Pr >  t			0.9025
	Week 168	n	4	2	
		LS Mean	-0.241	2.200	-2.440
		SEM	8.884	12.19	14.58
		95% CI	(-17.7,17.2)	(-21.7,26.1)	(-31.0,26.2)
		Pr >  t			0.8671
	Week 180	n	1	1	
		LS Mean	6.721	0.201	6.520
		SEM	16.86	16.88	23.54
		95% CI	(-26.4,39.8)	(-32.9,33.3)	(-39.7,52.7)
		Pr >  t			0.7819
	Week 192	n	1	1	
		LS Mean	40.061	0.201	39.860
		SEM	16.86	16.88	23.54
		95% CI	( 7.0,73.1)	(-32.9,33.3)	(-6.3,86.0)
		Pr >  t			0.0907
Yes	Week 8	n	5	9	
		LS Mean	27.343	-0.034	27.377
		SEM	10.87	7.835	13.44
		95% CI	( 5.3,49.4)	(-15.8,15.8)	( 0.2,54.6)
		Pr >  t			0.0486
	Week 16	n	5	9	
		LS Mean	20.677	-3.834	24.511
		SEM	10.87	8.035	13.59
		95% CI	(-1.4,42.7)	(-20.1,12.4)	(-3.0,52.0)
		Pr >  t			0.0792

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	n		5	5	
	LS Mean		27.343	-13.69	41.034
	SEM		10.87	10.75	15.39
	95% CI		( 5.3,49.4)	(-35.3, 7.9)	( 10.0,72.1)
	Pr >  t				0.0108
Week 32	n		4	3	
	LS Mean		1.742	-13.34	15.078
	SEM		11.94	13.53	18.17
	95% CI		(-22.4,25.9)	(-40.5,13.8)	(-21.4,51.6)
	Pr >  t				0.4107
Week 40	n		2	3	
	LS Mean		-9.513	-13.26	3.744
	SEM		16.06	13.37	20.82
	95% CI		(-41.8,22.7)	(-40.1,13.6)	(-38.1,45.6)
	Pr >  t				0.8580
Week 48	n		3	2	
	LS Mean		0.136	4.029	-3.893
	SEM		13.51	16.25	20.92
	95% CI		(-27.1,27.3)	(-28.6,36.7)	(-45.9,38.1)
	Pr >  t				0.8531
Week 56	n		3	1	
	LS Mean		-10.97	18.830	-29.80
	SEM		13.51	22.49	26.39
	95% CI		(-38.2,16.2)	(-26.4,64.0)	(-82.8,23.2)
	Pr >  t				0.2641
Week 64	n		2		
	LS Mean		-9.513		
	SEM		16.06		
	95% CI		(-41.8,22.7)		
	Pr >  t				
Week 72	n		2		
	LS Mean		11.992		
	SEM		16.04		
	95% CI		(-20.2,44.2)		
	Pr >  t				
Week 84	n		3		
	LS Mean		-10.97		
	SEM		13.51		
	95% CI		(-38.2,16.2)		
	Pr >  t				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 96	n	2		
		LS Mean	23.822		
		SEM	16.06		
		95% CI	(-8.4,56.1)		
		Pr >  t			
	Week 108	n	2		
		LS Mean	14.598		
		SEM	16.15		
		95% CI	(-17.8,47.0)		
		Pr >  t			
	Week 120	n	3		
		LS Mean	0.136		
		SEM	13.51		
		95% CI	(-27.1,27.3)		
		Pr >  t			
	Week 132	n	1		
		LS Mean	-23.58		
		SEM	22.10		
		95% CI	(-68.0,20.8)		
		Pr >  t			
	Week 144	n	1		
		LS Mean	9.752		
		SEM	22.10		
		95% CI	(-34.6,54.2)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	15.692	5.313	10.379		
			SEM	3.357	3.416	3.122		
			95% CI	( 9.1,22.3)	( -1.4,12.0)	( 4.2,16.5)		
					Pr >  t			0.0009
		Week 16	n	111	91			
			LS Mean	16.595	3.064	13.531		
			SEM	3.440	3.620	3.372		
			95% CI	( 9.8,23.4)	( -4.1,10.2)	( 6.9,20.2)		
					Pr >  t			<.0001
		Week 24	n	96	70			
			LS Mean	12.484	4.501	7.982		
			SEM	3.522	3.803	3.629		
			95% CI	( 5.6,19.4)	( -3.0,12.0)	( 0.9,15.1)		
					Pr >  t			0.0282
		Week 32	n	77	61			
			LS Mean	9.885	3.137	6.748		
			SEM	3.677	3.912	3.853		
			95% CI	( 2.7,17.1)	( -4.5,10.8)	( -0.8,14.3)		
					Pr >  t			0.0802
		Week 40	n	69	52			
			LS Mean	8.675	4.918	3.757		
			SEM	3.746	4.047	4.043		
			95% CI	( 1.3,16.0)	( -3.0,12.9)	( -4.2,11.7)		
			Pr >  t			0.3530		
Week 48	n	62	41					
	LS Mean	6.115	4.197	1.919				
	SEM	3.815	4.252	4.311				
	95% CI	( -1.4,13.6)	( -4.2,12.5)	( -6.5,10.4)				
			Pr >  t			0.6564		
Week 56	n	53	35					
	LS Mean	4.775	2.947	1.828				
	SEM	3.927	4.408	4.565				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-2.9,12.5)	(-5.7,11.6)	(-7.1,10.8)
		Pr >  t			0.6890
	Week 64	n	44	33	
		LS Mean	7.469	4.268	3.201
		SEM	4.075	4.473	4.756
		95% CI	(-0.5,15.5)	(-4.5,13.0)	(-6.1,12.5)
		Pr >  t			0.5010
	Week 72	n	45	28	
		LS Mean	5.630	2.821	2.809
		SEM	4.058	4.659	4.916
		95% CI	(-2.3,13.6)	(-6.3,12.0)	(-6.8,12.5)
		Pr >  t			0.5679
	Week 84	n	39	27	
		LS Mean	5.493	7.872	-2.378
		SEM	4.199	4.705	5.065
		95% CI	(-2.7,13.7)	(-1.4,17.1)	(-12.3, 7.6)
		Pr >  t			0.6387
	Week 96	n	34	19	
		LS Mean	8.389	7.792	0.596
		SEM	4.330	5.195	5.630
		95% CI	(-0.1,16.9)	(-2.4,18.0)	(-10.4,11.6)
		Pr >  t			0.9157
	Week 108	n	26	17	
		LS Mean	4.673	7.909	-3.236
		SEM	4.650	5.379	6.037
		95% CI	(-4.5,13.8)	(-2.6,18.5)	(-15.1, 8.6)
		Pr >  t			0.5920
	Week 120	n	27	11	
		LS Mean	6.628	5.047	1.580
		SEM	4.596	6.233	6.776
		95% CI	(-2.4,15.6)	(-7.2,17.3)	(-11.7,14.9)
		Pr >  t			0.8156
	Week 132	n	20	6	
		LS Mean	2.684	10.629	-7.945
		SEM	5.014	7.876	8.548
		95% CI	(-7.2,12.5)	(-4.8,26.1)	(-24.7, 8.8)
		Pr >  t			0.3528
	Week 144	n	15	4	
		LS Mean	18.138	1.475	16.663
		SEM	5.487	9.363	10.19

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 7.4,28.9)	(-16.9,19.8)	( -3.3,36.6)
		Pr >  t			0.1022
	Week 156	n	10	2	
		LS Mean	1.282	2.372	-1.089
		SEM	6.357	12.80	13.79
		95% CI	(-11.2,13.8)	(-22.7,27.5)	(-28.1,26.0)
		Pr >  t			0.9370
	Week 168	n	4	2	
		LS Mean	-0.544	2.372	-2.916
		SEM	9.274	12.80	15.35
		95% CI	(-18.7,17.6)	(-22.7,27.5)	(-33.0,27.2)
		Pr >  t			0.8494
	Week 180	n	1	1	
		LS Mean	6.449	0.433	6.015
		SEM	17.72	17.75	24.80
		95% CI	(-28.3,41.2)	(-34.4,35.3)	(-42.6,54.7)
		Pr >  t			0.8084
	Week 192	n	1	1	
		LS Mean	39.789	0.433	39.355
		SEM	17.72	17.75	24.80
		95% CI	( 5.0,74.5)	(-34.4,35.3)	( -9.3,88.0)
		Pr >  t			0.1127
>= 75 Years	Week 8	n	17	19	
		LS Mean	14.180	-2.864	17.044
		SEM	6.202	5.485	8.283
		95% CI	( 1.6,26.7)	(-14.0, 8.2)	( 0.3,33.8)
		Pr >  t			0.0464
	Week 16	n	13	16	
		LS Mean	4.635	-1.623	6.258
		SEM	6.479	5.675	8.601
		95% CI	( -8.4,17.7)	(-13.1, 9.8)	(-11.1,23.6)
		Pr >  t			0.4707
	Week 24	n	9	11	
		LS Mean	1.669	-2.964	4.632
		SEM	6.874	6.044	9.141
		95% CI	(-12.1,15.4)	(-15.1, 9.1)	(-13.7,22.9)
		Pr >  t			0.6143
	Week 32	n	9	12	
		LS Mean	3.118	-3.656	6.773
		SEM	6.874	5.975	9.094

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.7,16.9)	(-15.6, 8.3)	(-11.5,25.0)
		Pr >  t			0.4596
	Week 40	n	6	10	
		LS Mean	-1.128	-4.220	3.092
		SEM	7.395	6.142	9.598
		95% CI	(-15.9,13.6)	(-16.5, 8.1)	(-16.1,22.3)
		Pr >  t			0.7484
	Week 48	n	7	10	
		LS Mean	7.650	0.117	7.533
		SEM	7.186	6.156	9.445
		95% CI	(-6.7,22.0)	(-12.2,12.4)	(-11.3,26.4)
		Pr >  t			0.4282
	Week 56	n	6	10	
		LS Mean	2.645	0.079	2.566
		SEM	7.388	6.160	9.599
		95% CI	(-12.1,17.4)	(-12.2,12.4)	(-16.6,21.7)
		Pr >  t			0.7901
	Week 64	n	3	9	
		LS Mean	2.689	4.731	-2.042
		SEM	8.679	6.274	10.69
		95% CI	(-14.5,19.9)	(-7.8,17.3)	(-23.3,19.2)
		Pr >  t			0.8489
	Week 72	n	3	7	
		LS Mean	13.799	1.780	12.019
		SEM	8.679	6.584	10.87
		95% CI	(-3.4,31.0)	(-11.3,14.9)	(-9.6,33.6)
		Pr >  t			0.2717
	Week 84	n	1	6	
		LS Mean	-2.227	2.256	-4.482
		SEM	12.49	6.797	14.20
		95% CI	(-26.9,22.4)	(-11.3,15.8)	(-32.5,23.6)
		Pr >  t			0.7527
	Week 96	n	1	5	
		LS Mean	-2.227	-3.845	1.619
		SEM	12.49	7.090	14.35
		95% CI	(-26.9,22.4)	(-17.9,10.2)	(-26.7,30.0)
		Pr >  t			0.9103
	Week 108	n		4	
		LS Mean		-4.532	
		SEM		7.499	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-19.4,10.3)
		Pr >  t		
	Week 120	n	1	5
		LS Mean	26.987	-3.845
		SEM	12.51	7.090
		95% CI	( 2.3,51.7)	(-17.9,10.2)
		Pr >  t		( 2.5,59.2)
	Week 132	n		2
		LS Mean		-1.348
		SEM		9.224
		95% CI		(-19.6,16.9)
		Pr >  t		
	Week 144	n		1
		LS Mean		-1.518
		SEM		11.96
		95% CI		(-25.1,22.1)
		Pr >  t		
	Week 156	n		1
		LS Mean		-1.518
		SEM		11.96
		95% CI		(-25.1,22.1)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	12.695	-2.814	15.509		
			SEM	5.804	5.538	5.019		
			95% CI	( 1.2,24.2)	(-13.8, 8.2)	( 5.6,25.4)		
					Pr >  t			0.0024
		Week 16	n	30	30			
			LS Mean	15.276	-2.654	17.929		
			SEM	5.856	5.801	5.288		
			95% CI	( 3.6,26.9)	(-14.2, 8.9)	( 7.5,28.4)		
					Pr >  t			0.0009
		Week 24	n	21	26			
			LS Mean	3.981	-0.156	4.137		
			SEM	6.151	5.908	5.758		
			95% CI	( -8.2,16.2)	(-11.9,11.6)	( -7.2,15.5)		
					Pr >  t			0.4734
		Week 32	n	19	24			
			LS Mean	8.994	-4.022	13.016		
			SEM	6.247	5.983	5.951		
			95% CI	( -3.4,21.4)	(-15.9, 7.8)	( 1.3,24.7)		
					Pr >  t			0.0298
		Week 40	n	16	19			
			LS Mean	4.432	-1.616	6.048		
			SEM	6.427	6.272	6.377		
			95% CI	( -8.3,17.2)	(-14.0,10.8)	( -6.5,18.6)		
			Pr >  t			0.3439		
Week 48	n	16	18					
	LS Mean	2.348	-1.662	4.010				
	SEM	6.427	6.326	6.429				
	95% CI	(-10.4,15.1)	(-14.2,10.9)	( -8.7,16.7)				
			Pr >  t			0.5334		
Week 56	n	12	14					
	LS Mean	3.491	-3.450	6.941				
	SEM	6.782	6.615	7.072				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.9,16.9)	(-7.0,20.9)
		Pr >  t		0.3272
	Week 64	n	12	11
		LS Mean	9.047	-0.954
		SEM	6.782	6.955
		95% CI	(-4.4,22.5)	(-14.7,12.8)
		Pr >  t		(-4.5,24.5) 0.1769
	Week 72	n	10	9
		LS Mean	-3.341	-1.085
		SEM	7.054	7.282
		95% CI	(-17.3,10.6)	(-15.4,13.3)
		Pr >  t		(-17.9,13.4) 0.7769
	Week 84	n	8	8
		LS Mean	6.582	-0.667
		SEM	7.512	7.500
		95% CI	(-8.2,21.4)	(-15.5,14.1)
		Pr >  t		(-9.5,24.0) 0.3941
	Week 96	n	6	6
		LS Mean	5.748	-0.135
		SEM	8.124	8.119
		95% CI	(-10.3,21.8)	(-16.1,15.9)
		Pr >  t		(-12.9,24.7) 0.5390
	Week 108	n	4	5
		LS Mean	8.762	-5.867
		SEM	9.216	8.583
		95% CI	(-9.4,26.9)	(-22.8,11.0)
		Pr >  t		(-6.8,36.0) 0.1793
	Week 120	n	4	4
		LS Mean	17.094	2.859
		SEM	9.216	9.231
		95% CI	(-1.0,35.2)	(-15.3,21.0)
		Pr >  t		(-8.2,36.6) 0.2123
	Week 132	n	3	2
		LS Mean	22.249	-1.312
		SEM	10.18	11.87
		95% CI	( 2.2,42.3)	(-24.6,22.0)
		Pr >  t		(-4.5,51.7) 0.1000
	Week 144	n	3	1
		LS Mean	33.362	-1.990
		SEM	10.18	15.89
				35.352 17.77

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 13.3,53.4)	(-33.2,29.3)	( 0.4,70.3)
		Pr >  t			0.0474
	Week 156	n	2	1	
		LS Mean	2.784	-1.990	4.774
		SEM	11.86	15.89	18.78
		95% CI	(-20.5,26.1)	(-33.2,29.3)	(-32.2,41.7)
		Pr >  t			0.7995
	Week 168	n	1		
		LS Mean	8.613		
		SEM	15.87		
		95% CI	(-22.6,39.8)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	17.707	9.669	8.039
		SEM	13.33	12.62	8.389
		95% CI	(-9.1,44.5)	(-15.6,34.9)	(-8.9,24.9)
		Pr >  t			0.3430
	Week 16	n	15	14	
		LS Mean	15.579	7.567	8.013
		SEM	13.35	11.87	8.818
		95% CI	(-11.3,42.5)	(-16.3,31.5)	(-9.7,25.7)
		Pr >  t			0.3678
	Week 24	n	12	11	
		LS Mean	8.322	15.241	-6.919
		SEM	13.67	13.03	9.609
		95% CI	(-19.1,35.8)	(-10.8,41.3)	(-26.1,12.3)
		Pr >  t			0.4741
	Week 32	n	8	9	
		LS Mean	10.180	8.648	1.532
		SEM	14.22	13.33	10.77
		95% CI	(-18.3,38.7)	(-17.9,35.2)	(-19.9,22.9)
		Pr >  t			0.8872
	Week 40	n	6	7	
		LS Mean	12.731	9.212	3.519
		SEM	14.77	13.74	11.86
		95% CI	(-16.8,42.2)	(-18.1,36.6)	(-20.0,27.0)
		Pr >  t			0.7672
	Week 48	n	4	6	
		LS Mean	12.310	12.515	-0.205
		SEM	15.70	14.03	13.31



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-19.0,43.6)	(-15.4,40.4)	(-26.5,26.1)
		Pr >  t			0.9877
	Week 56	n	4	6	
		LS Mean	3.795	12.177	-8.383
		SEM	15.68	14.05	13.33
		95% CI	(-27.4,35.0)	(-15.8,40.1)	(-34.7,18.0)
		Pr >  t			0.5304
	Week 64	n	4	4	
		LS Mean	3.115	15.457	-12.34
		SEM	15.71	15.00	14.33
		95% CI	(-28.2,34.4)	(-14.3,45.2)	(-40.7,16.0)
		Pr >  t			0.3904
	Week 72	n	4	4	
		LS Mean	3.115	15.457	-12.34
		SEM	15.71	15.00	14.33
		95% CI	(-28.2,34.4)	(-14.3,45.2)	(-40.7,16.0)
		Pr >  t			0.3904
	Week 84	n	4	4	
		LS Mean	3.978	15.457	-11.48
		SEM	15.70	15.00	14.35
		95% CI	(-27.3,35.2)	(-14.3,45.2)	(-39.8,16.9)
		Pr >  t			0.4250
	Week 96	n	3	2	
		LS Mean	1.359	8.348	-6.989
		SEM	16.55	17.52	17.71
		95% CI	(-31.5,34.2)	(-26.3,43.0)	(-42.0,28.0)
		Pr >  t			0.6937
	Week 108	n	3	3	
		LS Mean	1.359	19.622	-18.26
		SEM	16.55	15.90	16.12
		95% CI	(-31.5,34.2)	(-11.9,51.1)	(-50.1,13.6)
		Pr >  t			0.2592
	Week 120	n	2	1	
		LS Mean	-0.822	38.531	-39.35
		SEM	18.12	21.62	23.01
		95% CI	(-36.7,35.1)	(-4.2,81.3)	(-84.9, 6.2)
		Pr >  t			0.0897
	Week 132	n	2	1	
		LS Mean	18.931	38.531	-19.60
		SEM	18.10	21.62	23.02

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.9,54.8)	(-4.2,81.3)	(-65.1,25.9)
		Pr >  t			0.3961
	Week 156	n	1		
		LS Mean	-1.189		
		SEM	22.13		
		95% CI	(-44.9,42.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-1.189		
		SEM	22.13		
		95% CI	(-44.9,42.6)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	17.350	7.850	9.499
		SEM	4.206	4.431	3.916
		95% CI	( 9.1,25.6)	( -0.9,16.6)	( 1.8,17.2)
		Pr >  t			0.0158
	Week 16	n	79	61	
		LS Mean	16.755	4.607	12.148
		SEM	4.332	4.740	4.283
		95% CI	( 8.2,25.3)	( -4.7,13.9)	( 3.7,20.6)
		Pr >  t			0.0048
	Week 24	n	71	43	
		LS Mean	15.855	4.223	11.632
		SEM	4.406	5.005	4.641
		95% CI	( 7.2,24.5)	( -5.6,14.1)	( 2.5,20.8)
		Pr >  t			0.0125
	Week 32	n	59	39	
		LS Mean	10.334	4.894	5.440
		SEM	4.565	5.114	4.841
		95% CI	( 1.4,19.3)	( -5.2,14.9)	( -4.1,14.9)
		Pr >  t			0.2616
	Week 40	n	52	35	
		LS Mean	9.904	5.823	4.081
		SEM	4.650	5.212	5.025
		95% CI	( 0.8,19.1)	( -4.4,16.1)	( -5.8,13.9)
		Pr >  t			0.4170
	Week 48	n	48	26	
		LS Mean	8.533	6.674	1.859
		SEM	4.707	5.516	5.388

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-0.7,17.8)	(-4.2,17.5)	(-8.7,12.4)
		Pr >  t			0.7302
	Week 56	n	42	24	
		LS Mean	5.707	4.582	1.125
		SEM	4.805	5.610	5.572
		95% CI	(-3.7,15.2)	(-6.4,15.6)	(-9.8,12.1)
		Pr >  t			0.8400
	Week 64	n	30	26	
		LS Mean	8.108	6.353	1.755
		SEM	5.102	5.519	5.747
		95% CI	(-1.9,18.1)	(-4.5,17.2)	(-9.5,13.0)
		Pr >  t			0.7602
	Week 72	n	34	21	
		LS Mean	10.337	3.226	7.110
		SEM	4.986	5.775	5.893
		95% CI	( 0.5,20.1)	(-8.1,14.6)	(-4.5,18.7)
		Pr >  t			0.2279
	Week 84	n	28	20	
		LS Mean	6.113	11.633	-5.521
		SEM	5.184	5.837	6.115
		95% CI	(-4.1,16.3)	( 0.2,23.1)	(-17.5, 6.5)
		Pr >  t			0.3669
	Week 96	n	26	15	
		LS Mean	10.458	6.144	4.314
		SEM	5.256	6.265	6.591
		95% CI	( 0.1,20.8)	(-6.2,18.4)	(-8.6,17.2)
		Pr >  t			0.5129
	Week 108	n	19	12	
		LS Mean	5.356	8.552	-3.196
		SEM	5.668	6.666	7.277
		95% CI	(-5.8,16.5)	(-4.5,21.6)	(-17.5,11.1)
		Pr >  t			0.6606
	Week 120	n	22	10	
		LS Mean	7.339	-0.386	7.725
		SEM	5.461	7.039	7.478
		95% CI	(-3.4,18.1)	(-14.2,13.4)	(-6.9,22.4)
		Pr >  t			0.3019
	Week 132	n	15	4	
		LS Mean	-2.444	7.005	-9.449
		SEM	6.030	9.765	10.40

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.3, 9.4)	(-12.2,26.2)	(-29.9,11.0)
		Pr >  t			0.3638
	Week 144	n	12	4	
		LS Mean	15.364	2.209	13.155
		SEM	6.423	9.771	10.65
		95% CI	( 2.8,28.0)	(-17.0,21.4)	( -7.7,34.0)
		Pr >  t			0.2169
	Week 156	n	7	2	
		LS Mean	2.143	3.129	-0.986
		SEM	7.715	13.08	14.39
		95% CI	(-13.0,17.3)	(-22.5,28.8)	(-29.2,27.3)
		Pr >  t			0.9454
	Week 168	n	2	2	
		LS Mean	-3.881	3.129	-7.010
		SEM	12.94	13.08	17.75
		95% CI	(-29.3,21.5)	(-22.5,28.8)	(-41.8,27.8)
		Pr >  t			0.6930
	Week 180	n	1	1	
		LS Mean	6.912	1.021	5.890
		SEM	17.86	17.94	24.84
		95% CI	(-28.1,42.0)	(-34.2,36.2)	(-42.9,54.6)
		Pr >  t			0.8126
	Week 192	n	1	1	
		LS Mean	40.252	1.021	39.230
		SEM	17.86	17.94	24.84
		95% CI	( 5.2,75.3)	(-34.2,36.2)	( -9.5,88.0)
		Pr >  t			0.1146

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	11.231	0.527	10.703	
		SEM	3.961	3.873	3.135	
		95% CI	( 3.4,19.0)	( -7.1, 8.2)	( 4.5,16.9)	
			Pr >  t			0.0007
	Week 16	n	88	71		
		LS Mean	9.181	0.699	8.482	
		SEM	4.036	4.128	3.359	
		95% CI	( 1.2,17.1)	( -7.4, 8.8)	( 1.9,15.1)	
			Pr >  t			0.0119
	Week 24	n	75	54		
		LS Mean	7.986	0.026	7.960	
		SEM	4.102	4.280	3.642	
		95% CI	( -0.1,16.1)	( -8.4, 8.4)	( 0.8,15.1)	
			Pr >  t			0.0292
	Week 32	n	62	52		
		LS Mean	6.634	-3.046	9.680	
		SEM	4.214	4.306	3.784	
		95% CI	( -1.7,14.9)	( -11.5, 5.4)	( 2.2,17.1)	
			Pr >  t			0.0107
	Week 40	n	51	46		
		LS Mean	5.911	-2.264	8.175	
		SEM	4.324	4.407	3.999	
		95% CI	( -2.6,14.4)	( -10.9, 6.4)	( 0.3,16.0)	
		Pr >  t			0.0413	
Week 48	n	50	37			
	LS Mean	5.594	-0.997	6.591		
	SEM	4.336	4.566	4.186		
	95% CI	( -2.9,14.1)	( -10.0, 8.0)	( -1.6,14.8)		
		Pr >  t			0.1158	
Week 56	n	43	33			
	LS Mean	2.261	-1.544	3.805		
	SEM	4.433	4.661	4.390		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.5,11.0)	(-10.7, 7.6)	(-4.8,12.4)
		Pr >  t			0.3863
	Week 64	n	35	33	
		LS Mean	6.516	2.009	4.507
		SEM	4.583	4.661	4.545
		95% CI	(-2.5,15.5)	(-7.1,11.2)	(-4.4,13.4)
		Pr >  t			0.3216
	Week 72	n	35	31	
		LS Mean	5.787	-1.415	7.202
		SEM	4.583	4.714	4.600
		95% CI	(-3.2,14.8)	(-10.7, 7.8)	(-1.8,16.2)
		Pr >  t			0.1178
	Week 84	n	31	29	
		LS Mean	5.568	3.287	2.281
		SEM	4.695	4.774	4.762
		95% CI	(-3.7,14.8)	(-6.1,12.7)	(-7.1,11.6)
		Pr >  t			0.6321
	Week 96	n	27	22	
		LS Mean	4.472	2.432	2.040
		SEM	4.810	5.060	5.168
		95% CI	(-5.0,13.9)	(-7.5,12.4)	(-8.1,12.2)
		Pr >  t			0.6931
	Week 108	n	19	20	
		LS Mean	2.207	0.752	1.455
		SEM	5.217	5.174	5.642
		95% CI	(-8.0,12.5)	(-9.4,10.9)	(-9.6,12.5)
		Pr >  t			0.7965
	Week 120	n	20	15	
		LS Mean	8.490	-2.464	10.954
		SEM	5.134	5.567	5.948
		95% CI	(-1.6,18.6)	(-13.4, 8.5)	(-0.7,22.6)
		Pr >  t			0.0658
	Week 132	n	15	7	
		LS Mean	4.542	1.556	2.986
		SEM	5.542	7.074	7.657
		95% CI	(-6.3,15.4)	(-12.3,15.4)	(-12.0,18.0)
		Pr >  t			0.6967
	Week 144	n	10	5	
		LS Mean	19.730	-2.887	22.616
		SEM	6.222	8.027	9.019

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( -7.5,31.9)	(-18.6,12.9)	( -4.9,40.3)
		Pr >  t			0.0123
	Week 156	n	6	3	
		LS Mean	-1.677	-1.942	0.265
		SEM	7.468	9.878	11.45
		95% CI	(-16.3,13.0)	(-21.3,17.4)	(-22.2,22.7)
		Pr >  t			0.9815
	Week 168	n	3	2	
		LS Mean	-5.341	-2.612	-2.728
		SEM	9.865	11.79	14.64
		95% CI	(-24.7,14.0)	(-25.8,20.5)	(-31.5,26.0)
		Pr >  t			0.8522
	Week 180	n	1	1	
		LS Mean	4.444	-4.598	9.042
		SEM	16.22	16.22	22.45
		95% CI	(-27.4,36.3)	(-36.4,27.2)	(-35.0,53.1)
		Pr >  t			0.6872
	Week 192	n	1	1	
		LS Mean	37.784	-4.598	42.382
		SEM	16.22	16.22	22.45
		95% CI	( -6.0,69.6)	(-36.4,27.2)	( -1.7,86.4)
		Pr >  t			0.0593
1	Week 8	n	43	50	
		LS Mean	21.805	6.919	14.886
		SEM	6.274	6.512	6.308
		95% CI	( 9.4,34.2)	( -6.0,19.8)	( 2.4,27.4)
		Pr >  t			0.0197
	Week 16	n	35	35	
		LS Mean	25.817	0.884	24.933
		SEM	6.516	6.724	6.858
		95% CI	( 12.9,38.7)	(-12.4,14.2)	( 11.4,38.5)
		Pr >  t			0.0004
	Week 24	n	29	26	
		LS Mean	14.672	5.975	8.698
		SEM	6.734	7.131	7.353
		95% CI	( 1.4,28.0)	( -8.1,20.1)	( -5.8,23.2)
		Pr >  t			0.2382
	Week 32	n	23	21	
		LS Mean	9.900	9.263	0.638
		SEM	7.059	7.447	7.836

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-4.0,23.8)	(-5.4,24.0)	(-14.8,16.1)
		Pr >  t			0.9352
		n	23	16	
		LS Mean	5.481	13.233	-7.751
		SEM	7.070	7.824	8.201
Week 48		95% CI	(-8.5,19.4)	(-2.2,28.7)	(-23.9, 8.4)
		Pr >  t			0.3454
		n	18	14	
		LS Mean	-0.439	9.840	-10.28
		SEM	7.376	8.046	8.689
Week 56		95% CI	(-15.0,14.1)	(-6.0,25.7)	(-27.4, 6.8)
		Pr >  t			0.2377
		n	15	12	
		LS Mean	1.630	7.608	-5.978
		SEM	7.656	8.319	9.190
Week 64		95% CI	(-13.5,16.7)	(-8.8,24.0)	(-24.1,12.1)
		Pr >  t			0.5158
		n	11	9	
		LS Mean	0.831	4.588	-3.757
		SEM	8.200	8.926	10.18
Week 72		95% CI	(-15.3,17.0)	(-13.0,22.2)	(-23.8,16.3)
		Pr >  t			0.7124
		n	12	4	
		LS Mean	-0.912	11.364	-12.28
		SEM	8.051	11.45	12.35
Week 84		95% CI	(-16.8,14.9)	(-11.1,33.9)	(-36.6,12.0)
		Pr >  t			0.3209
		n	8	4	
		LS Mean	-6.765	11.364	-18.13
		SEM	8.965	11.45	12.95
Week 96		95% CI	(-24.4,10.9)	(-11.1,33.9)	(-43.6, 7.3)
		Pr >  t			0.1623
		n	8	2	
		LS Mean	9.901	5.225	4.676
		SEM	8.965	14.87	16.05
Week 108		95% CI	(-7.7,27.5)	(-24.0,34.5)	(-26.9,36.2)
		Pr >  t			0.7710
		n	6	1	
	LS Mean	2.710	36.961	-34.25	
	SEM	9.767	20.02	21.26	



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.5,21.9)	(-2.4,76.3)	(-76.1, 7.6)
		Pr >  t			0.1080
	Week 120	n	8	1	
		LS Mean	-4.434	36.961	-41.39
		SEM	8.990	20.02	20.91
		95% CI	(-22.1,13.3)	(-2.4,76.3)	(-82.5,-0.3)
		Pr >  t			0.0485
	Week 132	n	5	1	
		LS Mean	-12.85	36.961	-49.81
		SEM	10.36	20.02	21.54
		95% CI	(-33.2, 7.5)	(-2.4,76.3)	(-92.2,-7.5)
		Pr >  t			0.0213
	Week 144	n	5		
		LS Mean	7.145		
		SEM	10.36		
		95% CI	(-13.2,27.5)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	-1.514		
		SEM	11.17		
		95% CI	(-23.5,20.4)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	4.093		
		SEM	19.68		
		95% CI	(-34.6,42.8)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	20.457	5.965	14.492		
			SEM	4.799	4.781	3.817		
			95% CI	( 11.0,29.9)	( -3.5,15.4)	( 7.0,22.0)		
					Pr >  t			0.0002
		Week 16	n	79	68			
			LS Mean	16.853	4.148	12.705		
			SEM	4.844	5.002	4.111		
			95% CI	( 7.3,26.4)	( -5.7,14.0)	( 4.6,20.8)		
					Pr >  t			0.0021
		Week 24	n	64	55			
			LS Mean	13.122	4.103	9.019		
			SEM	4.969	5.172	4.402		
			95% CI	( 3.3,22.9)	( -6.1,14.3)	( 0.4,17.7)		
					Pr >  t			0.0410
		Week 32	n	49	53			
			LS Mean	14.219	3.461	10.757		
			SEM	5.171	5.199	4.617		
			95% CI	( 4.0,24.4)	( -6.8,13.7)	( 1.7,19.8)		
					Pr >  t			0.0202
		Week 40	n	44	45			
			LS Mean	11.550	6.574	4.977		
			SEM	5.245	5.305	4.817		
			95% CI	( 1.2,21.9)	( -3.9,17.0)	( -4.5,14.4)		
					Pr >  t			0.3020
		Week 48	n	41	36			
			LS Mean	10.201	6.027	4.174		
			SEM	5.294	5.471	5.052		
95% CI	( -0.2,20.6)		( -4.7,16.8)	( -5.7,14.1)				
			Pr >  t			0.4091		
Week 56	n	33	32					
	LS Mean	6.895	4.825	2.070				
	SEM	5.462	5.572	5.339				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-3.8,17.6)	(-6.1,15.8)	(-8.4,12.6)
	Pr >  t			0.6983
	n	27	31	
	LS Mean	10.315	6.405	3.911
	SEM	5.646	5.602	5.560
Week 72	95% CI	(-0.8,21.4)	(-4.6,17.4)	(-7.0,14.8)
	Pr >  t			0.4820
	n	26	26	
	LS Mean	8.215	4.990	3.225
	SEM	5.682	5.773	5.767
Week 84	95% CI	(-3.0,19.4)	(-6.4,16.3)	(-8.1,14.5)
	Pr >  t			0.5761
	n	22	23	
	LS Mean	8.314	8.233	0.081
	SEM	5.884	5.902	6.077
Week 96	95% CI	(-3.2,19.9)	(-3.4,19.8)	(-11.8,12.0)
	Pr >  t			0.9894
	n	18	18	
	LS Mean	9.391	9.060	0.331
	SEM	6.140	6.206	6.608
Week 108	95% CI	(-2.7,21.5)	(-3.1,21.3)	(-12.6,13.3)
	Pr >  t			0.9600
	n	14	14	
	LS Mean	10.184	6.490	3.694
	SEM	6.522	6.582	7.299
Week 120	95% CI	(-2.6,23.0)	(-6.4,19.4)	(-10.6,18.0)
	Pr >  t			0.6129
	n	12	12	
	LS Mean	4.733	7.086	-2.354
	SEM	6.783	6.849	7.768
Week 132	95% CI	(-8.6,18.1)	(-6.4,20.5)	(-17.6,12.9)
	Pr >  t			0.7620
	n	9	5	
	LS Mean	-1.707	11.524	-13.23
	SEM	7.365	9.022	10.15
Week 144	95% CI	(-16.2,12.7)	(-6.2,29.2)	(-33.2, 6.7)
	Pr >  t			0.1928
	n	7	4	
	LS Mean	7.596	3.718	3.878
	SEM	7.977	9.819	11.29

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.1,23.3)	(-15.5,23.0)	(-18.3,26.0)
		Pr >  t			0.7313
	Week 156	n	4	2	
		LS Mean	1.862	5.684	-3.822
		SEM	9.753	13.04	15.25
		95% CI	(-17.3,21.0)	(-19.9,31.3)	(-33.7,26.1)
		Pr >  t			0.8021
	Week 168	n	2	1	
		LS Mean	-3.017	5.634	-8.651
		SEM	12.98	17.81	21.29
		95% CI	(-28.5,22.5)	(-29.3,40.6)	(-50.4,33.1)
		Pr >  t			0.6845
Yes	Week 8	n	53	48	
		LS Mean	9.277	2.536	6.742
		SEM	4.312	4.531	4.370
		95% CI	( 0.8,17.8)	(-6.4,11.5)	(-1.9,15.4)
		Pr >  t			0.1243
	Week 16	n	45	39	
		LS Mean	14.182	0.304	13.878
		SEM	4.529	4.746	4.685
		95% CI	( 5.2,23.1)	(-9.1, 9.7)	( 4.7,23.1)
		Pr >  t			0.0033
	Week 24	n	41	26	
		LS Mean	9.838	4.019	5.819
		SEM	4.599	5.123	5.179
		95% CI	( 0.8,18.9)	(-6.1,14.1)	(-4.4,16.0)
		Pr >  t			0.2620
	Week 32	n	37	20	
		LS Mean	3.225	1.262	1.962
		SEM	4.717	5.491	5.583
		95% CI	(-6.1,12.5)	(-9.5,12.1)	(-9.0,12.9)
		Pr >  t			0.7254
	Week 40	n	31	17	
		LS Mean	3.472	-1.691	5.163
		SEM	4.874	5.771	5.946
		95% CI	(-6.1,13.1)	(-13.0, 9.7)	(-6.5,16.8)
		Pr >  t			0.3857
	Week 48	n	28	15	
		LS Mean	1.403	0.481	0.922
		SEM	4.972	5.961	6.214

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-8.4,11.2)	(-11.2,12.2)	(-11.3,13.1)
	Pr >  t			0.8821
Week 56	n	26	13	
	LS Mean	1.947	-0.018	1.965
	SEM	5.047	6.198	6.506
	95% CI	(-8.0,11.9)	(-12.2,12.2)	(-10.8,14.7)
	Pr >  t			0.7627
Week 64	n	20	11	
	LS Mean	2.975	3.168	-0.194
	SEM	5.345	6.503	7.025
	95% CI	(-7.5,13.5)	(-9.6,16.0)	(-14.0,13.6)
	Pr >  t			0.9780
Week 72	n	22	9	
	LS Mean	3.411	0.520	2.891
	SEM	5.235	6.913	7.326
	95% CI	(-6.9,13.7)	(-13.1,14.1)	(-11.5,17.3)
	Pr >  t			0.6933
Week 84	n	18	10	
	LS Mean	0.906	6.771	-5.865
	SEM	5.501	6.694	7.307
	95% CI	(-9.9,11.7)	(-6.4,19.9)	(-20.2, 8.5)
	Pr >  t			0.4225
Week 96	n	17	6	
	LS Mean	5.804	-0.754	6.558
	SEM	5.561	7.920	8.497
	95% CI	(-5.1,16.7)	(-16.3,14.8)	(-10.1,23.2)
	Pr >  t			0.4405
Week 108	n	12	7	
	LS Mean	-2.950	6.244	-9.194
	SEM	6.141	7.505	8.507
	95% CI	(-15.0, 9.1)	(-8.5,21.0)	(-25.9, 7.5)
	Pr >  t			0.2802
Week 120	n	16	4	
	LS Mean	7.531	-5.053	12.584
	SEM	5.655	9.223	9.777
	95% CI	(-3.6,18.7)	(-23.2,13.1)	(-6.6,31.8)
	Pr >  t			0.1985
Week 132	n	11	3	
	LS Mean	4.358	4.088	0.269
	SEM	6.303	10.36	11.20

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.0,16.7)	(-16.3,24.4)	(-21.7,22.3)
		Pr >  t			0.9808
	Week 144	n	8	1	
		LS Mean	25.535	-3.632	29.167
		SEM	6.952	16.87	17.66
		95% CI	(11.9,39.2)	(-36.8,29.5)	(-5.5,63.9)
		Pr >  t			0.0992
	Week 156	n	6	1	
		LS Mean	-1.157	-3.632	2.475
		SEM	7.737	16.87	17.97
		95% CI	(-16.4,14.0)	(-36.8,29.5)	(-32.8,37.8)
		Pr >  t			0.8905
	Week 168	n	2	1	
		LS Mean	0.507	-3.632	4.138
		SEM	12.18	16.87	20.28
		95% CI	(-23.4,24.4)	(-36.8,29.5)	(-35.7,44.0)
		Pr >  t			0.8384
	Week 180	n	1	1	
		LS Mean	4.652	-3.632	8.284
		SEM	16.73	16.87	23.30
		95% CI	(-28.2,37.5)	(-36.8,29.5)	(-37.5,54.1)
		Pr >  t			0.7223
	Week 192	n	1	1	
		LS Mean	37.992	-3.632	41.624
		SEM	16.73	16.87	23.30
		95% CI	(5.1,70.9)	(-36.8,29.5)	(-4.1,87.4)
		Pr >  t			0.0746

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Estrogen Receptor Status (L)	Negative	LS Mean				
		SEM				
		95% CI	( , )			
		Pr >  t				
		Week 8	n	2		
		Week 16	n	2		
		Week 24	n	1		
		Week 32	n	1		
		Week 40	n	1		
		Week 48	n	1		
		Week 56	n	1		
		Week 72	n	1		
		Week 84	n	1		
		Week 96	n	1		
	Positive	Week 8	n	140	140	
			LS Mean	16.211	4.444	11.767
			SEM	3.298	3.336	2.904
			95% CI	( 9.7,22.7)	( -2.1,11.0)	( 6.1,17.5)
			Pr >  t			<.0001
		Week 16	n	122	107	
			LS Mean	15.775	2.464	13.311
			SEM	3.378	3.501	3.127
			95% CI	( 9.1,22.4)	( -4.4, 9.3)	( 7.2,19.5)
			Pr >  t			<.0001
Week 24	n	104	81			
	LS Mean	11.751	3.573	8.179		
	SEM	3.457	3.662	3.373		
	95% CI	( 5.0,18.5)	( -3.6,10.8)	( 1.6,14.8)		
	Pr >  t			0.0155		
Week 32	n	85	73			
	LS Mean	9.487	2.268	7.219		
	SEM	3.583	3.735	3.545		
	95% CI	( 2.4,16.5)	( -5.1, 9.6)	( 0.3,14.2)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.0420
Week 40	n	74	62	
	LS Mean	8.109	3.707	4.402
	SEM	3.659	3.846	3.729
	95% CI	( 0.9,15.3)	( -3.8,11.3)	( -2.9,11.7)
	Pr >  t			0.2381
Week 48	n	68	51	
	LS Mean	6.496	3.830	2.666
	SEM	3.709	3.985	3.920
	95% CI	( -0.8,13.8)	( -4.0,11.7)	( -5.0,10.4)
	Pr >  t			0.4966
Week 56	n	58	45	
	LS Mean	4.738	2.835	1.903
	SEM	3.809	4.084	4.117
	95% CI	( -2.7,12.2)	( -5.2,10.9)	( -6.2,10.0)
	Pr >  t			0.6440
Week 64	n	47	42	
	LS Mean	7.208	4.850	2.358
	SEM	3.959	4.144	4.316
	95% CI	( -0.6,15.0)	( -3.3,13.0)	( -6.1,10.8)
	Pr >  t			0.5850
Week 72	n	47	35	
	LS Mean	6.152	3.052	3.100
	SEM	3.961	4.311	4.478
	95% CI	( -1.6,13.9)	( -5.4,11.5)	( -5.7,11.9)
	Pr >  t			0.4888
Week 84	n	39	33	
	LS Mean	5.180	7.218	-2.038
	SEM	4.129	4.370	4.672
	95% CI	( -2.9,13.3)	( -1.4,15.8)	( -11.2, 7.1)
	Pr >  t			0.6627
Week 96	n	34	24	
	LS Mean	8.048	5.857	2.191
	SEM	4.254	4.735	5.125
	95% CI	( -0.3,16.4)	( -3.4,15.1)	( -7.9,12.2)
	Pr >  t			0.6690
Week 108	n	26	21	
	LS Mean	4.523	5.974	-1.451
	SEM	4.560	4.915	5.535
	95% CI	( -4.4,13.5)	( -3.7,15.6)	( -12.3, 9.4)



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.7932
Week 120	n	28	16	
	LS Mean	7.236	3.298	3.938
	SEM	4.466	5.337	5.845
	95% CI	(-1.5,16.0)	(-7.2,13.8)	(-7.5,15.4)
	Pr >  t			0.5006
Week 132	n	20	8	
	LS Mean	2.541	8.488	-5.947
	SEM	4.908	6.808	7.492
	95% CI	(-7.1,12.2)	(-4.9,21.8)	(-20.6, 8.7)
	Pr >  t			0.4274
Week 144	n	15	5	
	LS Mean	18.014	1.329	16.686
	SEM	5.361	8.241	9.080
	95% CI	( 7.5,28.5)	(-14.8,17.5)	(-1.1,34.5)
	Pr >  t			0.0663
Week 156	n	10	3	
	LS Mean	1.150	2.297	-1.146
	SEM	6.195	10.29	11.40
	95% CI	(-11.0,13.3)	(-17.9,22.5)	(-23.5,21.2)
	Pr >  t			0.9199
Week 168	n	4	2	
	LS Mean	-0.622	1.606	-2.228
	SEM	9.004	12.38	14.83
	95% CI	(-18.3,17.0)	(-22.7,25.9)	(-31.3,26.9)
	Pr >  t			0.8806
Week 180	n	1	1	
	LS Mean	6.390	-0.376	6.766
	SEM	17.16	17.17	23.98
	95% CI	(-27.3,40.0)	(-34.1,33.3)	(-40.3,53.8)
	Pr >  t			0.7779
Week 192	n	1	1	
	LS Mean	39.730	-0.376	40.106
	SEM	17.16	17.17	23.98
	95% CI	( 6.1,73.4)	(-34.1,33.3)	(-6.9,87.1)
	Pr >  t			0.0947

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	17.660	7.308	10.353
			SEM	3.463	3.575	3.338
			95% CI	( 10.8,24.5)	( 0.3,14.3)	( 3.8,16.9)
		Pr >  t			0.0021	
		Week 16	n	90	75	
			LS Mean	17.327	3.493	13.834
			SEM	3.551	3.755	3.597
			95% CI	( 10.3,24.3)	( -3.9,10.9)	( 6.8,20.9)
		Pr >  t			0.0001	
		Week 24	n	79	62	
			LS Mean	12.020	4.810	7.210
			SEM	3.637	3.907	3.809
			95% CI	( 4.9,19.2)	( -2.9,12.5)	( -0.3,14.7)
		Pr >  t			0.0589	
		Week 32	n	70	56	
			LS Mean	8.901	4.139	4.761
			SEM	3.745	3.996	3.958
			95% CI	( 1.5,16.3)	( -3.7,12.0)	( -3.0,12.5)
		Pr >  t			0.2294	
		Week 40	n	61	46	
			LS Mean	8.210	5.319	2.891
			SEM	3.832	4.160	4.189
			95% CI	( 0.7,15.7)	( -2.9,13.5)	( -5.3,11.1)
		Pr >  t			0.4903	
		Week 48	n	56	38	
			LS Mean	7.749	3.565	4.185
			SEM	3.890	4.329	4.410
95% CI	( 0.1,15.4)		( -4.9,12.1)	( -4.5,12.8)		
Pr >  t			0.3429			
Week 56	n	49	33			
	LS Mean	6.318	4.985	1.333		
	SEM	3.986	4.466	4.632		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.5,14.2)	(-3.8,13.8)	(-7.8,10.4)
		Pr >  t			0.7735
	Week 64	n	37	29	
		LS Mean	8.876	9.210	-0.334
		SEM	4.219	4.609	4.968
		95% CI	(0.6,17.2)	(0.2,18.3)	(-10.1, 9.4)
		Pr >  t			0.9465
	Week 72	n	40	25	
		LS Mean	8.120	5.719	2.401
		SEM	4.150	4.782	5.071
		95% CI	(-0.0,16.3)	(-3.7,15.1)	(-7.6,12.4)
		Pr >  t			0.6360
	Week 84	n	32	23	
		LS Mean	6.172	8.907	-2.735
		SEM	4.379	4.890	5.347
		95% CI	(-2.4,14.8)	(-0.7,18.5)	(-13.2, 7.8)
		Pr >  t			0.6091
	Week 96	n	29	17	
		LS Mean	8.962	8.089	0.873
		SEM	4.477	5.331	5.835
		95% CI	(0.2,17.8)	(-2.4,18.6)	(-10.6,12.3)
		Pr >  t			0.8810
	Week 108	n	22	15	
		LS Mean	5.564	5.473	0.090
		SEM	4.830	5.542	6.287
		95% CI	(-3.9,15.0)	(-5.4,16.3)	(-12.2,12.4)
		Pr >  t			0.9886
	Week 120	n	23	13	
		LS Mean	8.802	6.084	2.718
		SEM	4.762	5.808	6.478
		95% CI	(-0.5,18.1)	(-5.3,17.5)	(-10.0,15.4)
		Pr >  t			0.6749
	Week 132	n	17	5	
		LS Mean	4.956	13.054	-8.098
		SEM	5.210	8.305	9.033
		95% CI	(-5.3,15.2)	(-3.2,29.3)	(-25.8, 9.6)
		Pr >  t			0.3701
	Week 144	n	14	3	
		LS Mean	19.421	1.473	17.948
		SEM	5.533	10.36	11.11

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 8.6,30.3)	(-18.9,21.8)	( -3.9,39.8)
		Pr >  t			0.1066
	Week 156	n	9	2	
		LS Mean	0.834	3.345	-2.511
		SEM	6.489	12.44	13.50
		95% CI	(-11.9,13.6)	(-21.1,27.7)	(-29.0,24.0)
		Pr >  t			0.8524
	Week 168	n	4	1	
		LS Mean	0.505	1.241	-0.735
		SEM	9.035	17.24	19.08
		95% CI	(-17.2,18.2)	(-32.6,35.1)	(-38.2,36.7)
		Pr >  t			0.9693
	Week 180	n	1	1	
		LS Mean	7.651	1.241	6.410
		SEM	17.18	17.24	24.03
		95% CI	(-26.1,41.4)	(-32.6,35.1)	(-40.8,53.6)
		Pr >  t			0.7897
	Week 192	n	1	1	
		LS Mean	40.991	1.241	39.750
		SEM	17.18	17.24	24.03
		95% CI	( 7.3,74.7)	(-32.6,35.1)	( -7.4,86.9)
		Pr >  t			0.0984
>= 3	Week 8	n	37	45	
		LS Mean	6.530	-7.034	13.563
		SEM	10.19	10.09	5.782
		95% CI	(-13.6,26.7)	(-27.0,12.9)	( 2.1,25.0)
		Pr >  t			0.0204
	Week 16	n	34	32	
		LS Mean	5.520	-4.999	10.520
		SEM	10.42	10.46	6.216
		95% CI	(-15.1,26.1)	(-25.7,15.7)	( -1.8,22.8)
		Pr >  t			0.0925
	Week 24	n	26	19	
		LS Mean	5.823	-3.665	9.488
		SEM	10.58	10.82	7.083
		95% CI	(-15.1,26.7)	(-25.0,17.7)	( -4.5,23.4)
		Pr >  t			0.1817
	Week 32	n	16	17	
		LS Mean	8.338	-7.047	15.385
		SEM	10.96	10.94	7.803

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.3,30.0)	(-28.6,14.5)	( 0.0,30.7)
		Pr >  t			0.0496
	Week 40	n	14	16	
		LS Mean	4.243	-4.986	9.229
		SEM	11.10	10.99	8.071
		95% CI	(-17.7,26.2)	(-26.7,16.7)	( -6.7,25.1)
		Pr >  t			0.2538
	Week 48	n	13	13	
		LS Mean	-2.209	0.566	-2.775
		SEM	11.18	11.20	8.451
		95% CI	(-24.3,19.9)	(-21.5,22.7)	(-19.4,13.9)
		Pr >  t			0.7429
	Week 56	n	10	12	
		LS Mean	-5.362	-7.262	1.900
		SEM	11.50	11.29	8.980
		95% CI	(-28.1,17.3)	(-29.5,15.0)	(-15.8,19.6)
		Pr >  t			0.8326
	Week 64	n	10	13	
		LS Mean	-2.985	-9.844	6.859
		SEM	11.51	11.21	8.875
		95% CI	(-25.7,19.7)	(-32.0,12.3)	(-10.6,24.3)
		Pr >  t			0.4402
	Week 72	n	8	10	
		LS Mean	-6.123	-8.037	1.913
		SEM	11.83	11.52	9.665
		95% CI	(-29.4,17.2)	(-30.8,14.7)	(-17.1,20.9)
		Pr >  t			0.8432
	Week 84	n	8	10	
		LS Mean	-2.063	-1.500	-0.563
		SEM	11.83	11.51	9.665
		95% CI	(-25.4,21.3)	(-24.2,21.2)	(-19.6,18.4)
		Pr >  t			0.9536
	Week 96	n	6	7	
		LS Mean	0.968	-4.196	5.164
		SEM	12.36	12.07	10.90
		95% CI	(-23.4,25.3)	(-28.0,19.6)	(-16.3,26.6)
		Pr >  t			0.6361
	Week 108	n	4	6	
		LS Mean	-3.504	2.668	-6.171
		SEM	13.32	12.35	12.27

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-29.7,22.7)	(-21.7,27.0)	(-30.3,18.0)
		Pr >  t			0.6154
	Week 120	n	5	3	
		LS Mean	-3.128	-10.06	6.931
		SEM	12.75	14.20	13.60
		95% CI	(-28.2,22.0)	(-38.0,17.9)	(-19.8,33.7)
		Pr >  t			0.6107
	Week 132	n	3	3	
		LS Mean	-13.23	-5.056	-8.171
		SEM	14.20	14.20	14.98
		95% CI	(-41.2,14.7)	(-33.0,22.9)	(-37.6,21.3)
		Pr >  t			0.5858
	Week 144	n	1	2	
		LS Mean	4.943	-5.291	10.234
		SEM	19.94	15.84	21.66
		95% CI	(-34.3,44.1)	(-36.4,25.9)	(-32.4,52.8)
		Pr >  t			0.6369
	Week 156	n	1	1	
		LS Mean	4.943	-5.053	9.995
		SEM	19.94	19.95	24.81
		95% CI	(-34.3,44.1)	(-44.3,34.2)	(-38.8,58.8)
		Pr >  t			0.6874
	Week 168	n		1	
		LS Mean		-5.053	
		SEM		19.95	
		95% CI		(-44.3,34.2)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	4.685	-2.081	6.766
			SEM	8.678	9.422	8.201
			95% CI	(-12.9,22.3)	(-21.3,17.1)	(-9.7,23.2)
			Pr >  t			0.4130
		Week 16	n	14	17	
			LS Mean	2.476	1.866	0.610
			SEM	8.789	9.780	8.794
			95% CI	(-15.3,20.3)	(-18.0,21.7)	(-17.0,18.2)
			Pr >  t			0.9449
		Week 24	n	14	11	
			LS Mean	2.476	-10.93	13.411
			SEM	8.789	10.32	9.380
			95% CI	(-15.3,20.3)	(-31.7, 9.9)	(-5.3,32.1)
			Pr >  t			0.1567
		Week 32	n	10	10	
			LS Mean	-3.903	-2.960	-0.943
			SEM	9.589	10.48	9.945
			95% CI	(-23.1,15.3)	(-24.0,18.1)	(-20.7,18.8)
			Pr >  t			0.9246
		Week 40	n	8	10	
			LS Mean	-1.715	-8.241	6.527
			SEM	9.955	10.47	10.29
			95% CI	(-21.6,18.2)	(-29.3,12.8)	(-13.9,26.9)
			Pr >  t			0.5272
		Week 48	n	7	11	
			LS Mean	-3.993	-1.532	-2.462
			SEM	10.20	10.35	10.42
95% CI	(-24.3,16.4)		(-22.4,19.3)	(-23.1,18.2)		
	Pr >  t			0.8137		
Week 56	n	6	9			
	LS Mean	0.277	-2.714	2.991		
	SEM	10.52	10.63	11.01		



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.7,21.2)	(-24.1,18.6)	(-18.8,24.8)
		Pr >  t			0.7864
	Week 64	n	5	8	
		LS Mean	-8.174	-2.365	-5.809
		SEM	10.93	10.82	11.58
		95% CI	(-29.9,13.5)	(-24.1,19.3)	(-28.7,17.1)
		Pr >  t			0.6166
	Week 72	n	7	7	
		LS Mean	-4.694	-1.501	-3.193
		SEM	10.20	11.05	11.12
		95% CI	(-25.0,15.7)	(-23.6,20.6)	(-25.2,18.8)
		Pr >  t			0.7745
	Week 84	n	7	7	
		LS Mean	-4.694	17.546	-22.24
		SEM	10.20	11.05	11.12
		95% CI	(-25.0,15.7)	(-4.6,39.7)	(-44.2,-0.2)
		Pr >  t			0.0476
	Week 96	n	5	6	
		LS Mean	0.562	-1.565	2.127
		SEM	10.93	11.34	12.07
		95% CI	(-21.2,22.3)	(-24.2,21.1)	(-21.7,26.0)
		Pr >  t			0.8604
	Week 108	n	4	6	
		LS Mean	-11.36	3.988	-15.35
		SEM	11.53	11.34	12.62
		95% CI	(-34.2,11.5)	(-18.7,26.6)	(-40.3, 9.6)
		Pr >  t			0.2257
	Week 120	n	4	4	
		LS Mean	5.213	-8.625	13.838
		SEM	11.54	12.31	13.50
		95% CI	(-17.7,28.1)	(-33.1,15.8)	(-12.8,40.5)
		Pr >  t			0.3068
	Week 132	n	3	1	
		LS Mean	-7.226	3.627	-10.85
		SEM	12.46	18.69	20.05
		95% CI	(-31.9,17.4)	(-33.2,40.5)	(-50.4,28.7)
		Pr >  t			0.5889
	Week 144	n	1	1	
		LS Mean	94.952	-10.08	105.03
		SEM	18.20	18.76	24.09

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	( 59.1, 131)	(-47.1,26.9)	( 57.5, 153)
		Pr >  t			<.0001
		n	35	37	
	Week 16	LS Mean	-2.871	-19.71	16.837
		SEM	11.15	11.72	5.134
		95% CI	(-24.9,19.1)	(-42.8, 3.4)	( 6.7,27.0)
	Week 24	Pr >  t			0.0012
		n	34	30	
		LS Mean	-7.235	-24.69	17.458
	Week 32	SEM	11.54	11.84	5.377
		95% CI	(-30.0,15.5)	(-48.0,-1.3)	( 6.9,28.1)
		Pr >  t			0.0013
	Week 40	n	32	23	
		LS Mean	-5.188	-17.25	12.065
		SEM	11.58	11.98	5.781
	Week 48	95% CI	(-28.0,17.6)	(-40.9, 6.4)	( 0.7,23.4)
		Pr >  t			0.0379
		n	21	22	
	Week 56	LS Mean	-19.67	-17.28	-2.393
		SEM	11.82	12.01	6.325
		95% CI	(-43.0, 3.6)	(-41.0, 6.4)	(-14.8,10.1)
	Week 64	Pr >  t			0.7054
		n	20	20	
		LS Mean	-13.40	-16.03	2.638
Week 8	SEM	11.85	12.08	6.513	
	95% CI	(-36.7,10.0)	(-39.8, 7.8)	(-10.2,15.5)	
	Pr >  t			0.6857	
Week 16	n	19	12		
	LS Mean	-19.08	-15.20	-3.878	
	SEM	11.88	12.53	7.368	
Week 24	95% CI	(-42.5, 4.3)	(-39.9, 9.5)	(-18.4,10.6)	
	Pr >  t			0.5990	
	n	16	8		
Week 32	LS Mean	-16.83	-21.05	4.211	
	SEM	12.02	13.06	8.433	
	95% CI	(-40.5, 6.9)	(-46.8, 4.7)	(-12.4,20.8)	
Week 40	Pr >  t			0.6178	
	n	12	11		
	LS Mean	-23.46	-16.76	-6.706	
Week 48	SEM	12.30	12.64	8.173	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-47.7, 0.8)	(-41.7, 8.1)	(-22.8, 9.4)	
	Pr >  t			0.4124	
	n	13	7		
	LS Mean	-12.59	-16.39	3.800	
	SEM	12.24	13.27	9.041	
Week 84	95% CI	(-36.7,11.5)	(-42.5, 9.7)	(-14.0,21.6)	
	Pr >  t			0.6745	
	n	12	6		
	LS Mean	-12.15	-21.24	9.093	
	SEM	12.30	13.57	9.548	
Week 96	95% CI	(-36.4,12.1)	(-48.0, 5.5)	( -9.7,27.9)	
	Pr >  t			0.3415	
	n	7	6		
	LS Mean	-20.96	-9.851	-11.11	
	SEM	13.03	13.56	10.49	
Week 108	95% CI	(-46.6, 4.7)	(-36.5,16.8)	(-31.7, 9.5)	
	Pr >  t			0.2902	
	n	5	3		
	LS Mean	-20.93	-18.96	-1.976	
	SEM	13.70	15.38	13.44	
Week 120	95% CI	(-47.9, 6.0)	(-49.2,11.3)	(-28.4,24.4)	
	Pr >  t			0.8832	
	n	8	3		
	LS Mean	-19.98	-18.96	-1.024	
	SEM	12.86	15.38	12.55	
Week 132	95% CI	(-45.3, 5.3)	(-49.2,11.3)	(-25.7,23.6)	
	Pr >  t			0.9350	
	n	2	1		
	LS Mean	-1.268	-16.85	15.586	
	SEM	16.75	21.08	21.92	
Week 144	95% CI	(-34.2,31.7)	(-58.3,24.6)	(-27.5,58.7)	
	Pr >  t			0.4775	
	n	2			
	LS Mean	-14.57			
	SEM	16.78			
Week 156	95% CI	(-47.6,18.4)			
	Pr >  t				
	n	2			
	LS Mean	-14.57			
	SEM	16.78			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-47.6,18.4)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	18.921	6.367	12.553
		SEM	4.467	4.613	4.336
		95% CI	( 10.1,27.7)	( -2.7,15.5)	( 4.0,21.1)
		Pr >  t			0.0041
	Week 16	n	70	52	
		LS Mean	19.890	3.690	16.200
		SEM	4.559	4.821	4.589
		95% CI	( 10.9,28.9)	( -5.8,13.2)	( 7.2,25.2)
		Pr >  t			0.0005
	Week 24	n	54	40	
		LS Mean	12.093	4.608	7.485
		SEM	4.716	5.054	4.952
		95% CI	( 2.8,21.4)	( -5.3,14.6)	( -2.3,17.2)
		Pr >  t			0.1316
	Week 32	n	50	36	
		LS Mean	16.345	2.374	13.971
		SEM	4.780	5.136	5.085
		95% CI	( 6.9,25.8)	( -7.7,12.5)	( 4.0,24.0)
		Pr >  t			0.0063
	Week 40	n	42	28	
		LS Mean	12.443	4.899	7.544
		SEM	4.894	5.374	5.414
		95% CI	( 2.8,22.1)	( -5.7,15.5)	( -3.1,18.2)
		Pr >  t			0.1642
	Week 48	n	38	24	
		LS Mean	11.166	4.011	7.156
		SEM	4.966	5.530	5.634
		95% CI	( 1.4,20.9)	( -6.9,14.9)	( -3.9,18.2)
		Pr >  t			0.2046
	Week 56	n	33	24	
		LS Mean	7.913	3.872	4.041
		SEM	5.074	5.533	5.735
		95% CI	( -2.1,17.9)	( -7.0,14.8)	( -7.2,15.3)
		Pr >  t			0.4813
	Week 64	n	27	19	
		LS Mean	14.266	5.837	8.429
		SEM	5.249	5.803	6.147

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 3.9,24.6)	( -5.6,17.2)	( -3.6,20.5)
		Pr >  t			0.1708
	Week 72	n	26	17	
		LS Mean	8.158	4.065	4.093
		SEM	5.286	5.945	6.313
		95% CI	( -2.2,18.6)	( -7.6,15.7)	( -8.3,16.5)
		Pr >  t			0.5169
	Week 84	n	18	16	
		LS Mean	7.160	3.958	3.202
		SEM	5.725	6.029	6.744
		95% CI	( -4.1,18.4)	( -7.9,15.8)	( -10.0,16.4)
		Pr >  t			0.6350
	Week 96	n	20	10	
		LS Mean	10.185	5.084	5.101
		SEM	5.584	6.814	7.354
		95% CI	( -0.8,21.2)	( -8.3,18.5)	( -9.3,19.5)
		Pr >  t			0.4881
	Week 108	n	14	10	
		LS Mean	8.151	5.358	2.792
		SEM	6.090	6.815	7.738
		95% CI	( -3.8,20.1)	( -8.0,18.7)	( -12.4,18.0)
		Pr >  t			0.7183
	Week 120	n	14	7	
		LS Mean	13.435	6.829	6.606
		SEM	6.071	7.606	8.440
		95% CI	( 1.5,25.4)	( -8.1,21.8)	( -10.0,23.2)
		Pr >  t			0.4341
	Week 132	n	12	5	
		LS Mean	1.939	8.394	-6.455
		SEM	6.339	8.545	9.462
		95% CI	( -10.5,14.4)	( -8.4,25.2)	( -25.0,12.1)
		Pr >  t			0.4953
	Week 144	n	11	4	
		LS Mean	15.899	3.396	12.504
		SEM	6.477	9.286	10.23
		95% CI	( 3.2,28.6)	( -14.8,21.6)	( -7.6,32.6)
		Pr >  t			0.2221
	Week 156	n	8	3	
		LS Mean	2.304	3.002	-0.699
		SEM	7.151	10.40	11.65

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168	95% CI	(-11.7,16.3)	(-17.4,23.4)	(-23.6,22.2)
	Pr >  t			0.9522
	n	4	2	
	LS Mean	2.474	2.247	0.227
	SEM	9.164	12.33	14.57
Week 180	95% CI	(-15.5,20.5)	(-22.0,26.4)	(-28.4,28.8)
	Pr >  t			0.9876
	n	1	1	
	LS Mean	9.333	0.382	8.951
	SEM	16.76	16.82	23.24
Week 192	95% CI	(-23.6,42.2)	(-32.6,33.4)	(-36.7,54.6)
	Pr >  t			0.7002
	n	1	1	
	LS Mean	42.673	0.382	42.291
	SEM	16.76	16.82	23.24
	95% CI	( 9.8,75.6)	(-32.6,33.4)	( -3.3,87.9)
	Pr >  t			0.0692

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	18.921	6.367	12.553		
			SEM	4.467	4.613	4.336		
			95% CI	( 10.1,27.7)	( -2.7,15.5)	( 4.0,21.1)		
					Pr >  t			0.0041
		Week 16	n	70	52			
			LS Mean	19.890	3.690	16.200		
			SEM	4.559	4.821	4.589		
			95% CI	( 10.9,28.9)	( -5.8,13.2)	( 7.2,25.2)		
					Pr >  t			0.0005
		Week 24	n	54	40			
			LS Mean	12.093	4.608	7.485		
			SEM	4.716	5.054	4.952		
			95% CI	( 2.8,21.4)	( -5.3,14.6)	( -2.3,17.2)		
					Pr >  t			0.1316
		Week 32	n	50	36			
			LS Mean	16.345	2.374	13.971		
			SEM	4.780	5.136	5.085		
			95% CI	( 6.9,25.8)	( -7.7,12.5)	( 4.0,24.0)		
					Pr >  t			0.0063
		Week 40	n	42	28			
			LS Mean	12.443	4.899	7.544		
			SEM	4.894	5.374	5.414		
			95% CI	( 2.8,22.1)	( -5.7,15.5)	( -3.1,18.2)		
					Pr >  t			0.1642
		Week 48	n	38	24			
			LS Mean	11.166	4.011	7.156		
			SEM	4.966	5.530	5.634		
95% CI	( 1.4,20.9)		( -6.9,14.9)	( -3.9,18.2)				
			Pr >  t			0.2046		
Week 56	n	33	24					
	LS Mean	7.913	3.872	4.041				
	SEM	5.074	5.533	5.735				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-2.1,17.9)	(-7.0,14.8)	(-7.2,15.3)
	Pr >  t			0.4813
	n	27	19	
	LS Mean	14.266	5.837	8.429
	SEM	5.249	5.803	6.147
Week 72	95% CI	(-3.9,24.6)	(-5.6,17.2)	(-3.6,20.5)
	Pr >  t			0.1708
	n	26	17	
	LS Mean	8.158	4.065	4.093
	SEM	5.286	5.945	6.313
Week 84	95% CI	(-2.2,18.6)	(-7.6,15.7)	(-8.3,16.5)
	Pr >  t			0.5169
	n	18	16	
	LS Mean	7.160	3.958	3.202
	SEM	5.725	6.029	6.744
Week 96	95% CI	(-4.1,18.4)	(-7.9,15.8)	(-10.0,16.4)
	Pr >  t			0.6350
	n	20	10	
	LS Mean	10.185	5.084	5.101
	SEM	5.584	6.814	7.354
Week 108	95% CI	(-0.8,21.2)	(-8.3,18.5)	(-9.3,19.5)
	Pr >  t			0.4881
	n	14	10	
	LS Mean	8.151	5.358	2.792
	SEM	6.090	6.815	7.738
Week 120	95% CI	(-3.8,20.1)	(-8.0,18.7)	(-12.4,18.0)
	Pr >  t			0.7183
	n	14	7	
	LS Mean	13.435	6.829	6.606
	SEM	6.071	7.606	8.440
Week 132	95% CI	(-1.5,25.4)	(-8.1,21.8)	(-10.0,23.2)
	Pr >  t			0.4341
	n	12	5	
	LS Mean	1.939	8.394	-6.455
	SEM	6.339	8.545	9.462
Week 144	95% CI	(-10.5,14.4)	(-8.4,25.2)	(-25.0,12.1)
	Pr >  t			0.4953
	n	11	4	
Week 144	LS Mean	15.899	3.396	12.504
	SEM	6.477	9.286	10.23



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	( 3.2,28.6)	(-14.8,21.6)	( -7.6,32.6)
		Pr >  t			0.2221
		n	8	3	
		LS Mean	2.304	3.002	-0.699
	Week 168	SEM	7.151	10.40	11.65
		95% CI	(-11.7,16.3)	(-17.4,23.4)	(-23.6,22.2)
		Pr >  t			0.9522
		n	4	2	
	Week 180	LS Mean	2.474	2.247	0.227
		SEM	9.164	12.33	14.57
		95% CI	(-15.5,20.5)	(-22.0,26.4)	(-28.4,28.8)
		Pr >  t			0.9876
Week 192	n	1	1		
	LS Mean	9.333	0.382	8.951	
	SEM	16.76	16.82	23.24	
	95% CI	(-23.6,42.2)	(-32.6,33.4)	(-36.7,54.6)	
Week 8	Pr >  t			0.7002	
	n	1	1		
	LS Mean	42.673	0.382	42.291	
	SEM	16.76	16.82	23.24	
Week 16	95% CI	( 9.8,75.6)	(-32.6,33.4)	( -3.3,87.9)	
	Pr >  t			0.0692	
	n	53	64		
	LS Mean	3.884	-9.029	12.912	
Week 24	SEM	5.821	6.226	4.156	
	95% CI	( -7.6,15.4)	(-21.3, 3.3)	( 4.7,21.1)	
	Pr >  t			0.0021	
	n	48	48		
Week 32	LS Mean	0.631	-11.09	11.718	
	SEM	5.973	6.394	4.480	
	95% CI	(-11.2,12.4)	(-23.7, 1.5)	( 2.9,20.5)	
	Pr >  t			0.0093	
Week 8	n	46	36		
	LS Mean	2.021	-10.80	12.820	
	SEM	5.996	6.590	4.795	
	95% CI	( -9.8,13.9)	(-23.8, 2.2)	( 3.4,22.2)	
Week 16	Pr >  t			0.0078	
	n	31	33		
	LS Mean	-10.15	-8.408	-1.740	
	SEM	6.423	6.662	5.248	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-22.8, 2.5)	(-21.6, 4.7)	(-12.1, 8.6)
		Pr >  t			0.7404
	Week 40	n	28	30	
		LS Mean	-5.173	-9.043	3.869
		SEM	6.514	6.738	5.453
		95% CI	(-18.0, 7.7)	(-22.3, 4.3)	(-6.8, 14.6)
		Pr >  t			0.4783
	Week 48	n	26	23	
		LS Mean	-10.08	-6.496	-3.589
		SEM	6.581	6.984	5.833
		95% CI	(-23.1, 2.9)	(-20.3, 7.3)	(-15.0, 7.9)
		Pr >  t			0.5387
	Week 56	n	22	17	
		LS Mean	-7.184	-10.04	2.858
		SEM	6.747	7.335	6.427
		95% CI	(-20.5, 6.1)	(-24.5, 4.4)	(-9.8, 15.5)
		Pr >  t			0.6567
	Week 64	n	17	19	
		LS Mean	-14.41	-7.587	-6.823
		SEM	7.053	7.199	6.598
		95% CI	(-28.3, -0.5)	(-21.8, 6.6)	(-19.8, 6.1)
		Pr >  t			0.3015
	Week 72	n	20	14	
		LS Mean	-5.674	-7.216	1.542
		SEM	6.860	7.609	6.845
		95% CI	(-19.2, 7.8)	(-22.2, 7.8)	(-11.9, 15.0)
		Pr >  t			0.8219
	Week 84	n	19	13	
		LS Mean	-5.600	1.014	-6.614
		SEM	6.913	7.722	7.028
		95% CI	(-19.2, 8.0)	(-14.2, 16.2)	(-20.4, 7.2)
		Pr >  t			0.3471
	Week 96	n	12	12	
		LS Mean	-9.048	-3.832	-5.216
		SEM	7.575	7.853	7.812
		95% CI	(-23.9, 5.8)	(-19.3, 11.6)	(-20.6, 10.1)
		Pr >  t			0.5045
	Week 108	n	9	9	
		LS Mean	-13.98	-4.549	-9.436
		SEM	8.123	8.389	8.852

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-30.0, 2.0)	(-21.0, 11.9)	(-26.8, 7.9)
		Pr >  t			0.2868
	Week 120	n	12	7	
		LS Mean	-7.355	-12.35	4.993
		SEM	7.591	8.962	8.934
		95% CI	(-22.3, 7.6)	(-30.0, 5.3)	(-12.6, 22.5)
		Pr >  t			0.5764
	Week 132	n	5	2	
		LS Mean	-4.576	-4.457	-0.119
		SEM	9.659	13.78	15.01
		95% CI	(-23.5, 14.4)	(-31.5, 22.6)	(-29.6, 29.4)
		Pr >  t			0.9937
	Week 144	n	3	1	
		LS Mean	26.053	-16.03	42.079
		SEM	11.60	18.59	20.54
		95% CI	( 3.3, 48.8)	(-52.5, 20.5)	( 1.7, 82.4)
		Pr >  t			0.0410
	Week 156	n	2		
		LS Mean	-4.267		
		SEM	13.65		
		95% CI	(-31.1, 22.5)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-29: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Obstipation“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv			
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-5.981	-0.409	-5.572		
			SEM	2.894	3.026	2.937		
			95% CI	(-11.7,-0.3)	( -6.4, 5.5)	(-11.3, 0.2)		
							Pr >  t	0.0586
		Week 16	n	70	52			
			LS Mean	-8.290	-2.837	-5.453		
			SEM	2.970	3.296	3.208		
			95% CI	(-14.1,-2.4)	( -9.3, 3.6)	(-11.8, 0.9)		
							Pr >  t	0.0899
		Week 24	n	61	37			
			LS Mean	-6.231	-4.372	-1.859		
			SEM	3.058	3.586	3.543		
			95% CI	(-12.3,-0.2)	(-11.4, 2.7)	( -8.8, 5.1)		
							Pr >  t	0.6000
		Week 32	n	48	33			
			LS Mean	-7.625	-5.582	-2.043		
			SEM	3.238	3.685	3.772		
			95% CI	(-14.0,-1.3)	(-12.8, 1.7)	( -9.5, 5.4)		
							Pr >  t	0.5882
		Week 40	n	42	31			
			LS Mean	-8.633	-0.929	-7.704		
			SEM	3.329	3.741	3.908		
			95% CI	(-15.2,-2.1)	( -8.3, 6.4)	(-15.4,-0.0)		
					Pr >  t	0.0491		
Week 48	n	40	25					
	LS Mean	-4.700	-4.387	-0.313				
	SEM	3.364	3.942	4.131				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.3, 1.9)	(-12.1, 3.4)	(-8.4, 7.8)
		Pr >  t			0.9397
	Week 56	n	35	20	
		LS Mean	-9.678	-9.411	-0.267
		SEM	3.464	4.190	4.451
		95% CI	(-16.5,-2.9)	(-17.6,-1.2)	(-9.0, 8.5)
		Pr >  t			0.9521
	Week 64	n	29	18	
		LS Mean	-6.111	-2.175	-3.935
		SEM	3.620	4.322	4.696
		95% CI	(-13.2, 1.0)	(-10.7, 6.3)	(-13.2, 5.3)
		Pr >  t			0.4023
	Week 72	n	28	18	
		LS Mean	-10.28	3.645	-13.93
		SEM	3.653	4.318	4.720
		95% CI	(-17.5,-3.1)	(-4.8,12.1)	(-23.2,-4.7)
		Pr >  t			0.0033
	Week 84	n	27	17	
		LS Mean	-7.558	-4.028	-3.530
		SEM	3.709	4.393	4.814
		95% CI	(-14.8,-0.3)	(-12.7, 4.6)	(-13.0, 5.9)
		Pr >  t			0.4637
	Week 96	n	23	14	
		LS Mean	-3.071	-1.705	-1.365
		SEM	3.861	4.660	5.180
		95% CI	(-10.7, 4.5)	(-10.9, 7.4)	(-11.5, 8.8)
		Pr >  t			0.7922
	Week 108	n	19	12	
		LS Mean	-7.517	-9.310	1.793
		SEM	4.094	4.898	5.555
		95% CI	(-15.6, 0.5)	(-18.9, 0.3)	(-9.1,12.7)
		Pr >  t			0.7470
	Week 120	n	18	8	
		LS Mean	-6.333	-8.950	2.617
		SEM	4.146	5.651	6.272
		95% CI	(-14.5, 1.8)	(-20.0, 2.1)	(-9.7,14.9)
		Pr >  t			0.6765
	Week 132	n	11	4	
		LS Mean	-11.05	-9.366	-1.683
		SEM	4.896	7.450	8.342

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.7,-1.4)	(-24.0, 5.3)	(-18.1,14.7)
		Pr >  t			0.8402
	Week 144	n	11	4	
		LS Mean	8.703	-7.270	15.972
		SEM	4.880	7.456	8.349
		95% CI	(-0.9,18.3)	(-21.9, 7.4)	(-0.4,32.4)
		Pr >  t			0.0561
	Week 156	n	5	2	
		LS Mean	-12.42	-8.352	-4.070
		SEM	6.671	10.12	11.71
		95% CI	(-25.5, 0.7)	(-28.2,11.5)	(-27.1,18.9)
		Pr >  t			0.7282
	Week 168	n	1	2	
		LS Mean	-25.10	-8.352	-16.74
		SEM	13.91	10.12	16.91
		95% CI	(-52.4, 2.2)	(-28.2,11.5)	(-49.9,16.5)
		Pr >  t			0.3225
	Week 180	n		1	
		LS Mean		-9.679	
		SEM		13.99	
		95% CI		(-37.1,17.8)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-9.679	
		SEM		13.99	
		95% CI		(-37.1,17.8)	
		Pr >  t			
	>= 65 Years	n	63	71	
		LS Mean	-6.376	-3.184	-3.192
		SEM	4.263	4.238	3.228
		95% CI	(-14.8, 2.0)	(-11.5, 5.2)	(-9.5, 3.2)
		Pr >  t			0.3234
	Week 16	n	54	55	
		LS Mean	-11.58	-6.169	-5.413
		SEM	4.413	4.340	3.524
		95% CI	(-20.3,-2.9)	(-14.7, 2.4)	(-12.3, 1.5)
		Pr >  t			0.1253
	Week 24	n	44	44	
		LS Mean	-8.463	-3.915	-4.547
		SEM	4.542	4.469	3.861

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169			
Week 32	95% CI		(-17.4, 0.5)	(-12.7, 4.9)	(-12.1, 3.0)
	Pr >  t				0.2395
	n	38		40	
	LS Mean	-8.062		-3.567	-4.496
	SEM	4.694		4.583	4.063
Week 40	95% CI		(-17.3, 1.2)	(-12.6, 5.5)	(-12.5, 3.5)
	Pr >  t				0.2690
	n	33		31	
	LS Mean	-9.240		-5.809	-3.431
	SEM	4.808		4.825	4.408
Week 48	95% CI		(-18.7, 0.2)	(-15.3, 3.7)	(-12.1, 5.2)
	Pr >  t				0.4366
	n	29		26	
	LS Mean	-11.45		-5.173	-6.275
	SEM	4.915		4.992	4.700
Week 56	95% CI		(-21.1,-1.8)	(-15.0, 4.6)	(-15.5, 3.0)
	Pr >  t				0.1823
	n	24		25	
	LS Mean	-10.88		-2.583	-8.298
	SEM	5.091		5.027	4.927
Week 64	95% CI		(-20.9,-0.9)	(-12.5, 7.3)	(-18.0, 1.4)
	Pr >  t				0.0926
	n	18		24	
	LS Mean	-8.467		-9.237	0.770
	SEM	5.418		5.071	5.305
Week 72	95% CI		(-19.1, 2.2)	(-19.2, 0.7)	(-9.6,11.2)
	Pr >  t				0.8846
	n	20		17	
	LS Mean	-10.97		-5.210	-5.765
	SEM	5.296		5.473	5.572
Week 84	95% CI		(-21.4,-0.6)	(-16.0, 5.5)	(-16.7, 5.2)
	Pr >  t				0.3012
	n	13		16	
	LS Mean	-11.24		-8.257	-2.980
	SEM	5.873		5.551	6.195
Week 96	95% CI		(-22.8, 0.3)	(-19.2, 2.7)	(-15.1, 9.2)
	Pr >  t				0.6307
	n	12		10	
	LS Mean	-11.53		-1.753	-9.773
	SEM	6.008		6.322	7.007

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	95% CI	(-23.3, 0.3)	(-14.2,10.7)	(-23.5, 4.0)
	Pr >  t			0.1635
	n	7	9	
	LS Mean	-5.316	-4.913	-0.403
	SEM	7.087	6.528	8.121
Week 120	95% CI	(-19.2, 8.6)	(-17.7, 7.9)	(-16.3,15.5)
	Pr >  t			0.9605
	n	10	8	
	LS Mean	-8.481	-12.30	3.823
	SEM	6.346	6.783	7.699
Week 132	95% CI	(-20.9, 4.0)	(-25.6, 1.0)	(-11.3,18.9)
	Pr >  t			0.6197
	n	9	4	
	LS Mean	-10.07	-3.597	-6.470
	SEM	6.537	8.701	9.558
Week 144	95% CI	(-22.9, 2.8)	(-20.7,13.5)	(-25.2,12.3)
	Pr >  t			0.4987
	n	4	1	
	LS Mean	-11.42	-6.286	-5.136
	SEM	8.697	15.91	17.37
Week 156	95% CI	(-28.5, 5.7)	(-37.5,24.9)	(-39.2,29.0)
	Pr >  t			0.7676
	n	5	1	
	LS Mean	-11.02	-6.286	-4.736
	SEM	7.993	15.91	17.03
Week 168	95% CI	(-26.7, 4.7)	(-37.5,24.9)	(-38.2,28.7)
	Pr >  t			0.7810
	n	3		
	LS Mean	-8.309		
	SEM	9.770		
Week 180	95% CI	(-27.5,10.9)		
	Pr >  t			
	n	1		
	LS Mean	-16.11		
	SEM	15.90		
Week 192	95% CI	(-47.3,15.1)		
	Pr >  t			
	n	1		
Week 192	LS Mean	-16.11		
	SEM	15.90		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI Pr >  t		(-47.3,15.1)

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	-6.790	-6.928	0.138		
			SEM	4.693	4.457	4.053		
			95% CI	(-16.1, 2.5)	(-15.8, 1.9)	(-7.9, 8.1)		
					Pr >  t		0.9728	
		Week 16	n	30	30			
			LS Mean	-9.334	-8.241	-1.092		
			SEM	4.736	4.688	4.272		
			95% CI	(-18.7, 0.1)	(-17.5, 1.0)	(-9.5, 7.3)		
					Pr >  t		0.7984	
		Week 24	n	21	26			
			LS Mean	-9.970	-11.73	1.760		
			SEM	5.027	4.787	4.716		
			95% CI	(-19.9,-0.0)	(-21.2,-2.3)	(-7.5,11.0)		
					Pr >  t		0.7093	
		Week 32	n	19	24			
			LS Mean	-8.670	-9.923	1.253		
			SEM	5.114	4.855	4.892		
			95% CI	(-18.8, 1.4)	(-19.5,-0.3)	(-8.4,10.9)		
					Pr >  t		0.7981	
		Week 40	n	16	19			
			LS Mean	-12.55	-8.043	-4.506		
			SEM	5.289	5.131	5.291		
			95% CI	(-23.0,-2.1)	(-18.2, 2.1)	(-14.9, 5.9)		
					Pr >  t		0.3951	
		Week 48	n	16	18			
			LS Mean	-14.63	-13.53	-1.100		
			SEM	5.289	5.183	5.343		
95% CI	(-25.1,-4.2)		(-23.8,-3.3)	(-11.6, 9.4)				
			Pr >  t		0.8370			
Week 56	n	12	14					
	LS Mean	-11.78	-14.04	2.264				
	SEM	5.618	5.458	5.946				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-22.9,-0.7)	(-24.8,-3.3)	(-9.4,14.0)
		Pr >  t			0.7037
	Week 64	n	12	11	
		LS Mean	-14.56	-13.84	-0.717
		SEM	5.618	5.777	6.240
		95% CI	(-25.6,-3.5)	(-25.2,-2.4)	(-13.0,11.6)
		Pr >  t			0.9086
	Week 72	n	10	9	
		LS Mean	-6.151	-13.49	7.343
		SEM	5.864	6.084	6.755
		95% CI	(-17.7, 5.4)	(-25.5,-1.5)	(-5.9,20.6)
		Pr >  t			0.2777
	Week 84	n	8	8	
		LS Mean	-5.633	-5.181	-0.451
		SEM	6.291	6.288	7.255
		95% CI	(-18.0, 6.8)	(-17.6, 7.2)	(-14.7,13.8)
		Pr >  t			0.9504
	Week 96	n	6	6	
		LS Mean	-3.492	-12.63	9.136
		SEM	6.854	6.856	8.215
		95% CI	(-17.0,10.0)	(-26.1, 0.9)	(-7.0,25.3)
		Pr >  t			0.2668
	Week 108	n	4	5	
		LS Mean	-7.493	-12.89	5.397
		SEM	7.853	7.279	9.389
		95% CI	(-22.9, 8.0)	(-27.2, 1.4)	(-13.1,23.9)
		Pr >  t			0.5658
	Week 120	n	4	4	
		LS Mean	-7.493	-19.72	12.231
		SEM	7.853	7.869	9.852
		95% CI	(-22.9, 8.0)	(-35.2,-4.2)	(-7.1,31.6)
		Pr >  t			0.2152
	Week 132	n	3	2	
		LS Mean	-5.951	-13.63	7.682
		SEM	8.732	10.25	12.44
		95% CI	(-23.1,11.2)	(-33.8, 6.5)	(-16.8,32.2)
		Pr >  t			0.5374
	Week 144	n	3	1	
		LS Mean	-5.951	-11.86	5.906
		SEM	8.732	13.86	15.55

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-23.1,11.2)	(-39.1,15.4)	(-24.7,36.5)
		Pr >  t			0.7043
	Week 156	n	2	1	
		LS Mean	-4.258	-11.86	7.599
		SEM	10.25	13.86	16.45
		95% CI	(-24.4,15.9)	(-39.1,15.4)	(-24.8,40.0)
		Pr >  t			0.6444
	Week 168	n	1		
		LS Mean	2.444		
		SEM	13.84		
		95% CI	(-24.8,29.7)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	4.055	28.030	-23.97
		SEM	11.06	10.66	6.880
		95% CI	(-18.0,26.2)	( 6.8,49.3)	(-37.7, -10)
		Pr >  t			0.0009
	Week 16	n	15	14	
		LS Mean	3.772	17.206	-13.43
		SEM	11.09	9.971	7.301
		95% CI	(-18.4,25.9)	( -2.7,37.1)	(-28.0, 1.1)
		Pr >  t			0.0701
	Week 24	n	12	11	
		LS Mean	4.206	23.990	-19.78
		SEM	11.37	11.02	8.023
		95% CI	(-18.5,26.9)	( 2.1,45.9)	(-35.7,-3.8)
		Pr >  t			0.0157
	Week 32	n	8	9	
		LS Mean	8.806	30.834	-22.03
		SEM	11.91	11.30	9.085
		95% CI	(-14.9,32.5)	( 8.4,53.3)	(-40.0,-4.0)
		Pr >  t			0.0170
	Week 40	n	6	7	
		LS Mean	16.876	25.197	-8.321
		SEM	12.39	11.66	10.07
		95% CI	( -7.8,41.5)	( 2.1,48.3)	(-28.2,11.6)
		Pr >  t			0.4100
	Week 48	n	4	6	
		LS Mean	7.370	21.392	-14.02
		SEM	13.24	11.92	11.38

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-18.9,33.6)	(-2.3,45.0)	(-36.5, 8.5)
		Pr >  t			0.2198
	Week 56	n	4	6	
		LS Mean	8.002	20.116	-12.11
		SEM	13.23	11.95	11.37
		95% CI	(-18.3,34.3)	(-3.6,43.8)	(-34.6,10.4)
		Pr >  t			0.2884
	Week 64	n	4	4	
		LS Mean	16.305	20.404	-4.099
		SEM	13.26	12.80	12.27
		95% CI	(-10.0,42.6)	(-5.0,45.8)	(-28.4,20.2)
		Pr >  t			0.7388
	Week 72	n	4	4	
		LS Mean	7.972	20.404	-12.43
		SEM	13.26	12.80	12.27
		95% CI	(-18.3,34.3)	(-5.0,45.8)	(-36.7,11.8)
		Pr >  t			0.3127
	Week 84	n	4	4	
		LS Mean	7.370	12.071	-4.702
		SEM	13.24	12.80	12.27
		95% CI	(-18.9,33.6)	(-13.3,37.4)	(-29.0,19.5)
		Pr >  t			0.7021
	Week 96	n	3	2	
		LS Mean	7.615	26.973	-19.36
		SEM	14.03	15.05	15.33
		95% CI	(-20.2,35.4)	(-2.8,56.7)	(-49.7,10.9)
		Pr >  t			0.2086
	Week 108	n	3	3	
		LS Mean	7.615	7.337	0.278
		SEM	14.03	13.60	13.92
		95% CI	(-20.2,35.4)	(-19.6,34.3)	(-27.2,27.8)
		Pr >  t			0.9841
	Week 120	n	2	1	
		LS Mean	7.654	0.599	7.056
		SEM	15.46	18.70	20.03
		95% CI	(-22.9,38.2)	(-36.4,37.6)	(-32.6,46.7)
		Pr >  t			0.7252
	Week 132	n	2	1	
		LS Mean	8.228	0.599	7.629
		SEM	15.44	18.70	20.03

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.3,38.8)	(-36.4,37.6)	(-32.0,47.3)
		Pr >  t			0.7039
	Week 156	n	1		
		LS Mean	8.919		
		SEM	19.08		
		95% CI	(-28.8,46.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	8.919		
		SEM	19.08		
		95% CI	(-28.8,46.6)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	-4.469	-0.637	-3.832
		SEM	2.778	2.932	2.712
		95% CI	(-9.9, 1.0)	(-6.4, 5.1)	(-9.2, 1.5)
		Pr >  t			0.1582
	Week 16	n	79	61	
		LS Mean	-9.116	-3.414	-5.703
		SEM	2.896	3.214	3.039
		95% CI	(-14.8,-3.4)	(-9.7, 2.9)	(-11.7, 0.3)
		Pr >  t			0.0611
	Week 24	n	71	43	
		LS Mean	-5.482	-2.604	-2.878
		SEM	2.969	3.466	3.363
		95% CI	(-11.3, 0.4)	(-9.4, 4.2)	(-9.5, 3.7)
		Pr >  t			0.3924
	Week 32	n	59	39	
		LS Mean	-7.136	-5.850	-1.286
		SEM	3.129	3.572	3.546
		95% CI	(-13.3,-1.0)	(-12.9, 1.2)	(-8.2, 5.7)
		Pr >  t			0.7169
	Week 40	n	52	35	
		LS Mean	-8.057	-2.110	-5.948
		SEM	3.213	3.668	3.715
		95% CI	(-14.4,-1.7)	(-9.3, 5.1)	(-13.2, 1.3)
		Pr >  t			0.1097
	Week 48	n	48	26	
		LS Mean	-5.032	-1.392	-3.639
		SEM	3.269	3.961	4.049

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.5, 1.4)	(-9.2, 6.4)	(-11.6, 4.3)
		Pr >  t			0.3691
	Week 56	n	42	24	
		LS Mean	-9.179	-3.848	-5.331
		SEM	3.366	4.052	4.220
		95% CI	(-15.8,-2.6)	(-11.8, 4.1)	(-13.6, 2.9)
		Pr >  t			0.2067
	Week 64	n	30	26	
		LS Mean	-4.198	-4.019	-0.180
		SEM	3.656	3.965	4.380
		95% CI	(-11.4, 3.0)	(-11.8, 3.8)	(-8.8, 8.4)
		Pr >  t			0.9673
	Week 72	n	34	21	
		LS Mean	-11.58	3.125	-14.71
		SEM	3.542	4.209	4.511
		95% CI	(-18.5,-4.6)	(-5.1,11.4)	(-23.6,-5.9)
		Pr >  t			0.0012
	Week 84	n	28	20	
		LS Mean	-9.388	-4.322	-5.065
		SEM	3.737	4.269	4.715
		95% CI	(-16.7,-2.0)	(-12.7, 4.1)	(-14.3, 4.2)
		Pr >  t			0.2830
	Week 96	n	26	15	
		LS Mean	-5.690	1.199	-6.889
		SEM	3.804	4.672	5.141
		95% CI	(-13.2, 1.8)	(-8.0,10.4)	(-17.0, 3.2)
		Pr >  t			0.1805
	Week 108	n	19	12	
		LS Mean	-6.198	-6.640	0.442
		SEM	4.197	5.042	5.747
		95% CI	(-14.4, 2.0)	(-16.5, 3.3)	(-10.8,11.7)
		Pr >  t			0.9387
	Week 120	n	22	10	
		LS Mean	-6.307	-7.023	0.716
		SEM	3.998	5.383	5.923
		95% CI	(-14.2, 1.5)	(-17.6, 3.5)	(-10.9,12.3)
		Pr >  t			0.9038
	Week 132	n	15	4	
		LS Mean	-10.91	-8.572	-2.341
		SEM	4.535	7.797	8.448

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.8,-2.0)	(-23.9, 6.7)	(-18.9,14.2)
		Pr >  t			0.7818
	Week 144	n	12	4	
		LS Mean	5.918	-6.414	12.331
		SEM	4.891	7.803	8.662
		95% CI	(-3.7,15.5)	(-21.7, 8.9)	(-4.7,29.3)
		Pr >  t			0.1549
	Week 156	n	7	2	
		LS Mean	-13.17	-7.454	-5.720
		SEM	6.056	10.66	11.84
		95% CI	(-25.1,-1.3)	(-28.4,13.5)	(-29.0,17.5)
		Pr >  t			0.6293
	Week 168	n	2	2	
		LS Mean	-19.46	-7.454	-12.00
		SEM	10.57	10.66	14.68
		95% CI	(-40.2, 1.3)	(-28.4,13.5)	(-40.8,16.8)
		Pr >  t			0.4136
	Week 180	n	1	1	
		LS Mean	-13.87	-8.696	-5.175
		SEM	14.74	14.78	20.63
		95% CI	(-42.8,15.1)	(-37.7,20.3)	(-45.7,35.3)
		Pr >  t			0.8020
	Week 192	n	1	1	
		LS Mean	-13.87	-8.696	-5.175
		SEM	14.74	14.78	20.63
		95% CI	(-42.8,15.1)	(-37.7,20.3)	(-45.7,35.3)
		Pr >  t			0.8020

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Geographic Region 1 (L)	Asia	Week 8	n	30	35	
			LS Mean	-7.393	-6.368	-1.025
			SEM	4.739	4.463	4.151
			95% CI	(-16.8, 2.0)	(-15.2, 2.5)	(-9.2, 7.2)
			Pr >  t			0.8053
		Week 16	n	28	29	
			LS Mean	-8.959	-7.614	-1.345
			SEM	4.788	4.707	4.385
			95% CI	(-18.5, 0.5)	(-16.9, 1.7)	(-10.0, 7.3)
			Pr >  t			0.7593
		Week 24	n	21	25	
			LS Mean	-10.09	-11.22	1.127
			SEM	5.034	4.813	4.783
			95% CI	(-20.1,-0.1)	(-20.7,-1.7)	(-8.3,10.6)
			Pr >  t			0.8140
		Week 32	n	19	23	
			LS Mean	-8.776	-9.317	0.541
			SEM	5.122	4.888	4.965
			95% CI	(-18.9, 1.4)	(-19.0, 0.4)	(-9.2,10.3)
			Pr >  t			0.9133
		Week 40	n	16	18	
			LS Mean	-12.66	-7.300	-5.364
			SEM	5.300	5.191	5.384
			95% CI	(-23.1,-2.2)	(-17.6, 3.0)	(-16.0, 5.2)
			Pr >  t			0.3200
		Week 48	n	16	17	
			LS Mean	-14.75	-13.11	-1.640
			SEM	5.300	5.249	5.443
95% CI	(-25.2,-4.3)		(-23.5,-2.7)	(-12.4, 9.1)		
	Pr >  t			0.7634		
Week 56	n	12	14			
	LS Mean	-11.89	-13.62	1.725		
	SEM	5.633	5.469	5.992		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-23.0,-0.8)	(-24.4,-2.8)	(-10.1,13.5)
	Pr >  t			0.7736
	n	12	11	
	LS Mean	-14.67	-13.41	-1.256
	SEM	5.633	5.793	6.290
Week 72	95% CI	(-25.8,-3.5)	(-24.8,-2.0)	(-13.6,11.1)
	Pr >  t			0.8418
	n	10	8	
	LS Mean	-6.240	-13.10	6.855
	SEM	5.881	6.312	6.996
Week 84	95% CI	(-17.8, 5.4)	(-25.5,-0.7)	(-6.9,20.6)
	Pr >  t			0.3278
	n	8	8	
	LS Mean	-5.718	-4.763	-0.955
	SEM	6.313	6.312	7.313
Week 96	95% CI	(-18.2, 6.7)	(-17.2, 7.7)	(-15.3,13.4)
	Pr >  t			0.8962
	n	6	6	
	LS Mean	-3.576	-12.21	8.632
	SEM	6.883	6.887	8.282
Week 108	95% CI	(-17.1,10.0)	(-25.8, 1.3)	(-7.7,24.9)
	Pr >  t			0.2980
	n	4	5	
	LS Mean	-7.613	-12.47	4.856
	SEM	7.895	7.315	9.466
Week 120	95% CI	(-23.1, 7.9)	(-26.9, 1.9)	(-13.8,23.5)
	Pr >  t			0.6082
	n	4	4	
	LS Mean	-7.613	-19.31	11.694
	SEM	7.895	7.912	9.932
Week 132	95% CI	(-23.1, 7.9)	(-34.9,-3.7)	(-7.8,31.2)
	Pr >  t			0.2398
	n	3	2	
	LS Mean	-6.067	-13.23	7.158
	SEM	8.783	10.32	12.55
Week 144	95% CI	(-23.3,11.2)	(-33.5, 7.1)	(-17.5,31.8)
	Pr >  t			0.5687
	n	3	1	
	LS Mean	-6.067	-11.38	5.309
	SEM	8.783	13.96	15.68

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Europe	Week 156	95% CI	(-23.3,11.2)	(-38.8,16.1)	(-25.5,36.2)
		Pr >  t			0.7351
		n	2	1	
		LS Mean	-4.364	-11.38	7.012
		SEM	10.32	13.96	16.59
	Week 168	95% CI	(-24.7,15.9)	(-38.8,16.1)	(-25.6,39.6)
		Pr >  t			0.6728
		n	1		
		LS Mean	2.361		
		SEM	13.94		
	Week 8	95% CI	(-25.1,29.8)		
		Pr >  t			
		n	66	68	
		LS Mean	-1.916	3.589	-5.505
		SEM	5.831	5.822	3.271
	Week 16	95% CI	(-13.5, 9.6)	(-7.9,15.1)	(-11.9, 0.9)
		Pr >  t			0.0934
		n	58	48	
		LS Mean	-7.234	0.284	-7.518
		SEM	5.873	5.942	3.631
	Week 24	95% CI	(-18.9, 4.4)	(-11.5,12.0)	(-14.7,-0.4)
		Pr >  t			0.0391
		n	51	36	
		LS Mean	-4.765	4.284	-9.049
SEM		5.918	6.067	3.946	
Week 32	95% CI	(-16.5, 6.9)	(-7.7,16.3)	(-16.8,-1.3)	
	Pr >  t			0.0223	
	n	43	30		
	LS Mean	-5.049	-2.140	-2.909	
	SEM	6.048	6.247	4.219	
Week 40	95% CI	(-17.0, 6.9)	(-14.5,10.2)	(-11.2, 5.4)	
	Pr >  t			0.4908	
	n	37	25		
	LS Mean	-3.700	3.994	-7.695	
	SEM	6.119	6.368	4.494	
Week 48	95% CI	(-15.8, 8.4)	(-8.6,16.6)	(-16.5, 1.1)	
	Pr >  t			0.0874	
	n	33	21		
	LS Mean	-5.271	6.377	-11.65	
	SEM	6.180	6.501	4.760	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-17.5, 6.9)	(-6.4,19.2)	(-21.0,-2.3)
	Pr >  t			0.0147
	n	29	20	
	LS Mean	-5.312	-1.490	-3.822
	SEM	6.252	6.543	4.913
Week 64	95% CI	(-17.7, 7.0)	(-14.4,11.4)	(-13.5, 5.8)
	Pr >  t			0.4369
	n	23	20	
	LS Mean	-2.695	0.359	-3.054
	SEM	6.403	6.545	5.106
Week 72	95% CI	(-15.3, 9.9)	(-12.5,13.3)	(-13.1, 7.0)
	Pr >  t			0.5500
	n	25	19	
	LS Mean	-8.163	0.579	-8.742
	SEM	6.347	6.586	5.090
Week 84	95% CI	(-20.7, 4.4)	(-12.4,13.6)	(-18.7, 1.3)
	Pr >  t			0.0864
	n	22	17	
	LS Mean	-8.309	-0.413	-7.896
	SEM	6.438	6.686	5.330
Week 96	95% CI	(-21.0, 4.4)	(-13.6,12.8)	(-18.4, 2.6)
	Pr >  t			0.1389
	n	20	13	
	LS Mean	-3.225	5.194	-8.419
	SEM	6.512	6.968	5.764
Week 108	95% CI	(-16.1, 9.6)	(-8.5,18.9)	(-19.7, 2.9)
	Pr >  t			0.1445
	n	15	11	
	LS Mean	-1.184	-0.846	-0.338
	SEM	6.779	7.179	6.304
Week 120	95% CI	(-14.5,12.2)	(-15.0,13.3)	(-12.7,12.0)
	Pr >  t			0.9573
	n	16	8	
	LS Mean	-2.456	-1.226	-1.230
	SEM	6.717	7.664	6.790
Week 132	95% CI	(-15.7,10.8)	(-16.3,13.8)	(-14.6,12.1)
	Pr >  t			0.8563
	n	12	3	
	LS Mean	-7.903	-1.806	-6.097
	SEM	7.029	10.11	9.695

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-21.7, 5.9)	(-21.7,18.1)	(-25.1,12.9)
		Pr >  t			0.5296
	Week 144	n	7	4	
		LS Mean	19.909	-1.850	21.759
		SEM	7.862	9.219	9.437
		95% CI	( 4.5,35.4)	(-20.0,16.3)	( 3.2,40.3)
		Pr >  t			0.0214
	Week 156	n	5	2	
		LS Mean	-10.42	-2.772	-7.649
		SEM	8.584	11.70	12.37
		95% CI	(-27.3, 6.4)	(-25.7,20.2)	(-31.9,16.6)
		Pr >  t			0.5364
	Week 168	n	2	2	
		LS Mean	-13.62	-2.772	-10.85
		SEM	11.66	11.70	14.67
		95% CI	(-36.5, 9.3)	(-25.7,20.2)	(-39.7,18.0)
		Pr >  t			0.4599
	Week 180	n		1	
		LS Mean		-3.835	
		SEM		15.50	
		95% CI		(-34.3,26.6)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-3.835	
		SEM		15.50	
		95% CI		(-34.3,26.6)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	-1.358	4.860	-6.218
		SEM	6.024	5.865	8.581
		95% CI	(-13.4,10.6)	( -6.8,16.5)	(-23.3,10.9)
		Pr >  t			0.4710
	Week 16	n	13	12	
		LS Mean	-8.699	0.638	-9.338
		SEM	6.176	6.057	8.752
		95% CI	(-21.0, 3.6)	(-11.4,12.7)	(-26.8, 8.1)
		Pr >  t			0.2893
	Week 24	n	12	10	
		LS Mean	-3.317	-4.809	1.492
		SEM	6.344	6.548	9.202

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-15.9, 9.3)	(-17.8, 8.2)	(-16.8,19.8)
	Pr >  t			0.8716
	n	9	10	
	LS Mean	4.868	5.190	-0.322
	SEM	7.068	6.548	9.713
Week 40	95% CI	(-9.2,18.9)	(-7.8,18.2)	(-19.6,19.0)
	Pr >  t			0.9736
	n	7	10	
	LS Mean	-6.047	-1.475	-4.572
	SEM	7.764	6.548	10.23
Week 48	95% CI	(-21.4, 9.3)	(-14.5,11.5)	(-24.8,15.7)
	Pr >  t			0.6557
	n	7	7	
	LS Mean	8.239	-4.967	13.205
	SEM	7.764	7.572	10.91
Week 56	95% CI	(-7.1,23.6)	(-20.0,10.0)	(-8.4,34.8)
	Pr >  t			0.2286
	n	6	7	
	LS Mean	-6.677	2.856	-9.533
	SEM	8.274	7.568	11.30
Week 64	95% CI	(-23.1, 9.7)	(-12.1,17.8)	(-31.9,12.8)
	Pr >  t			0.4004
	n	4	7	
	LS Mean	16.493	2.286	14.207
	SEM	9.740	7.558	12.36
Week 72	95% CI	(-2.8,35.7)	(-12.7,17.2)	(-10.2,38.6)
	Pr >  t			0.2523
	n	4	4	
	LS Mean	-8.507	31.756	-40.26
	SEM	9.740	9.605	13.74
Week 84	95% CI	(-27.8,10.7)	(12.8,50.7)	(-67.4, -13)
	Pr >  t			0.0039
	n	4	5	
	LS Mean	1.691	-2.164	3.856
	SEM	9.730	8.713	13.13
Week 96	95% CI	(-17.5,20.9)	(-19.4,15.1)	(-22.1,29.8)
	Pr >  t			0.7694
	n	3	2	
Week 96	LS Mean	11.866	21.578	-9.712
	SEM	11.02	13.08	17.16

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-9.9,33.6)	(-4.3,47.4)	(-43.6,24.2)
		Pr >  t			0.5722
		n	2	3	
		LS Mean	-23.26	-16.88	-6.378
		SEM	13.24	10.96	17.31
	Week 120	95% CI	(-49.4, 2.9)	(-38.5, 4.8)	(-40.6,27.8)
		Pr >  t			0.7131
		n	2	2	
		LS Mean	6.245	-14.34	20.586
		SEM	13.18	13.15	18.70
	Week 132	95% CI	(-19.8,32.3)	(-40.3,11.6)	(-16.4,57.5)
		Pr >  t			0.2726
		n	1	2	
		LS Mean	12.277	-14.34	26.618
		SEM	18.21	13.15	22.50
	Week 8	95% CI	(-23.7,48.3)	(-40.3,11.6)	(-17.8,71.1)
		Pr >  t			0.2387
		n	16	19	
		LS Mean	-6.284	2.716	-9.000
		SEM	5.065	4.873	6.091
	Week 16	95% CI	(-16.5, 3.9)	(-7.1,12.5)	(-21.2, 3.2)
		Pr >  t			0.1456
		n	12	14	
		LS Mean	-1.761	-1.157	-0.604
		SEM	5.454	5.273	6.634
	Week 24	95% CI	(-12.7, 9.2)	(-11.7, 9.4)	(-13.9,12.6)
		Pr >  t			0.9277
		n	12	8	
LS Mean		0.030	1.689	-1.659	
SEM		5.460	6.206	7.340	
Week 32	95% CI	(-10.9,11.0)	(-10.6,14.0)	(-16.3,12.9)	
	Pr >  t			0.8217	
	n	9	7		
	LS Mean	-8.163	6.539	-14.70	
	SEM	5.857	6.427	7.801	
Week 40	95% CI	(-19.8, 3.5)	(-6.2,19.3)	(-30.2, 0.8)	
	Pr >  t			0.0624	
	n	9	7		
	LS Mean	-6.075	-7.747	1.672	
	SEM	5.876	6.427	7.824	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-17.8, 5.6)	(-20.5, 5.0)	(-13.9,17.2)
	Pr >  t			0.8312
	n	8	5	
	LS Mean	-2.038	-2.703	0.665
	SEM	6.049	7.054	8.465
Week 56	95% CI	(-14.1,10.0)	(-16.7,11.3)	(-16.1,17.4)
	Pr >  t			0.9375
	n	7	3	
	LS Mean	-8.428	18.260	-26.69
	SEM	6.250	8.276	9.642
Week 64	95% CI	(-20.9, 4.0)	(-1.9,34.6)	(-45.8,-7.6)
	Pr >  t			0.0065
	n	5	3	
	LS Mean	-9.826	-3.960	-5.866
	SEM	6.855	8.276	10.05
Week 72	95% CI	(-23.4, 3.8)	(-20.3,12.4)	(-25.7,14.0)
	Pr >  t			0.5605
	n	5	3	
	LS Mean	-7.556	19.568	-27.12
	SEM	6.832	8.275	10.03
Week 84	95% CI	(-21.1, 6.0)	(-3.2,35.9)	(-47.0,-7.3)
	Pr >  t			0.0077
	n	2	2	
	LS Mean	-5.726	-21.11	15.387
	SEM	9.383	9.562	12.83
Week 96	95% CI	(-24.3,12.8)	(-40.0,-2.2)	(-10.0,40.7)
	Pr >  t			0.2324
	n	3	2	
	LS Mean	-9.098	-4.443	-4.656
	SEM	8.028	9.562	11.91
Week 108	95% CI	(-25.0, 6.8)	(-23.3,14.5)	(-28.2,18.9)
	Pr >  t			0.6964
	n	1	2	
	LS Mean	-6.344	12.222	-18.57
	SEM	12.41	9.562	15.18
Week 120	95% CI	(-30.9,18.2)	(-6.7,31.1)	(-48.6,11.5)
	Pr >  t			0.2235
	n	3	2	
	LS Mean	-9.098	-4.443	-4.656
	SEM	8.028	9.562	11.91



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-25.0, 6.8)	(-23.3,14.5)	(-28.2,18.9)
		Pr >  t			0.6964
	Week 132	n	1	1	
		LS Mean	-14.63	30.759	-45.39
		SEM	12.41	12.57	17.24
		95% CI	(-39.2, 9.9)	(-5.9,55.6)	(-79.5, -11)
		Pr >  t			0.0095
	Week 144	n	2		
		LS Mean	-10.48		
		SEM	9.306		
		95% CI	(-28.9, 7.9)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	-14.63		
		SEM	12.41		
		95% CI	(-39.2, 9.9)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-14.63		
		SEM	12.41		
		95% CI	(-39.2, 9.9)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-14.63		
		SEM	12.41		
		95% CI	(-39.2, 9.9)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-14.63		
		SEM	12.41		
		95% CI	(-39.2, 9.9)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	-2.538	-0.361	-2.177
		SEM	4.764	7.379	8.115
		95% CI	(-12.3, 7.2)	(-15.3,14.6)	(-18.6,14.3)
		Pr >  t			0.7899
	Week 16	n	13	4	
		LS Mean	-7.081	8.286	-15.37
		SEM	5.155	8.449	9.019

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-17.5, 3.4)	(-8.7,25.3)	(-33.5, 2.8)
	Pr >  t			0.0955
	n	9	2	
	LS Mean	1.682	21.788	-20.11
	SEM	5.853	11.03	11.64
Week 32	95% CI	(-10.1,13.4)	(-0.2,43.8)	(-43.3, 3.1)
	Pr >  t			0.0885
	n	6	3	
	LS Mean	-6.732	14.644	-21.38
	SEM	6.784	9.489	10.69
Week 40	95% CI	(-20.3, 6.8)	(-4.4,33.6)	(-42.8, 0.0)
	Pr >  t			0.0501
	n	6	2	
	LS Mean	-5.931	28.161	-34.09
	SEM	6.871	11.03	12.12
Week 48	95% CI	(-19.6, 7.8)	(-6.2,50.2)	(-58.3,-9.9)
	Pr >  t			0.0064
	n	5	1	
	LS Mean	3.325	0.356	2.969
	SEM	7.322	14.74	15.81
Week 56	95% CI	(-11.3,17.9)	(-29.0,29.7)	(-28.5,34.4)
	Pr >  t			0.8515
	n	5	1	
	LS Mean	-10.01	0.356	-10.36
	SEM	7.322	14.74	15.81
Week 64	95% CI	(-24.6, 4.6)	(-29.0,29.7)	(-41.8,21.1)
	Pr >  t			0.5140
	n	3	1	
	LS Mean	-0.503	0.356	-0.859
	SEM	8.777	14.74	16.54
Week 72	95% CI	(-18.0,17.0)	(-29.0,29.7)	(-33.8,32.1)
	Pr >  t			0.9587
	n	4	1	
	LS Mean	-11.11	0.356	-11.47
	SEM	7.914	14.74	16.11
Week 84	95% CI	(-26.9, 4.6)	(-29.0,29.7)	(-43.5,20.6)
	Pr >  t			0.4784
	n	4	1	
Week 84	LS Mean	-2.782	0.356	-3.138
	SEM	7.914	14.74	16.11

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-18.5,13.0)	(-29.0,29.7)	(-35.2,28.9)
	Pr >  t			0.8460
	n	3	1	
	LS Mean	-11.61	0.356	-11.97
	SEM	8.777	14.74	16.54
Week 108	95% CI	(-29.1, 5.9)	(-29.0,29.7)	(-44.9,20.9)
	Pr >  t			0.4714
	n	4		
	LS Mean	-2.782		
	SEM	7.914		
Week 120	95% CI	(-18.5,13.0)		
	Pr >  t			
	n	3		
	LS Mean	-11.61		
	SEM	8.777		
Week 132	95% CI	(-29.1, 5.9)		
	Pr >  t			
	n	3		
	LS Mean	-11.61		
	SEM	8.777		
Week 144	95% CI	(-29.1, 5.9)		
	Pr >  t			
	n	3		
	LS Mean	-7.263		
	SEM	8.782		
Week 156	95% CI	(-24.7,10.2)		
	Pr >  t			
	n	2		
	LS Mean	-7.760		
	SEM	10.22		
	95% CI	(-28.1,12.6)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	-6.054	-3.575	-2.479	
		SEM	3.203	3.133	2.598	
		95% CI	(-12.4, 0.2)	(-9.7, 2.6)	(-7.6, 2.6)	
			Pr >  t			0.3403
	Week 16	n	88	71		
		LS Mean	-9.116	-4.573	-4.543	
		SEM	3.274	3.370	2.802	
		95% CI	(-15.6,-2.7)	(-11.2, 2.1)	(-10.0, 1.0)	
			Pr >  t			0.1054
	Week 24	n	75	54		
		LS Mean	-5.720	-5.365	-0.355	
		SEM	3.337	3.516	3.066	
		95% CI	(-12.3, 0.8)	(-12.3, 1.5)	(-6.4, 5.7)	
			Pr >  t			0.9078
	Week 32	n	62	52		
		LS Mean	-5.562	-5.231	-0.331	
		SEM	3.446	3.540	3.198	
		95% CI	(-12.3, 1.2)	(-12.2, 1.7)	(-6.6, 5.9)	
			Pr >  t			0.9176
	Week 40	n	51	46		
		LS Mean	-8.647	-2.542	-6.105	
		SEM	3.553	3.639	3.401	
		95% CI	(-15.6,-1.7)	(-9.7, 4.6)	(-12.8, 0.6)	
		Pr >  t			0.0729	
Week 48	n	50	37			
	LS Mean	-4.431	-4.997	0.566		
	SEM	3.565	3.793	3.576		
	95% CI	(-11.4, 2.6)	(-12.4, 2.5)	(-6.5, 7.6)		
		Pr >  t			0.8744	
Week 56	n	43	33			
	LS Mean	-8.057	-5.833	-2.224		
	SEM	3.659	3.885	3.768		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-15.2,-0.9)	(-13.5, 1.8)	(-9.6, 5.2)
		Pr >  t			0.5551
	Week 64	n	35	33	
		LS Mean	-3.709	-6.864	3.155
		SEM	3.804	3.885	3.913
		95% CI	(-11.2, 3.8)	(-14.5, 0.8)	(-4.5,10.8)
		Pr >  t			0.4203
	Week 72	n	35	31	
		LS Mean	-10.14	-1.197	-8.942
		SEM	3.805	3.937	3.965
		95% CI	(-17.6,-2.7)	(-8.9, 6.5)	(-16.7,-1.2)
		Pr >  t			0.0243
	Week 84	n	31	29	
		LS Mean	-7.681	-5.031	-2.650
		SEM	3.914	3.995	4.115
		95% CI	(-15.4, 0.0)	(-12.9, 2.8)	(-10.7, 5.4)
		Pr >  t			0.5198
	Week 96	n	27	22	
		LS Mean	-2.707	-3.643	0.935
		SEM	4.023	4.269	4.493
		95% CI	(-10.6, 5.2)	(-12.0, 4.7)	(-7.9, 9.8)
		Pr >  t			0.8351
	Week 108	n	19	20	
		LS Mean	-7.314	-6.949	-0.365
		SEM	4.414	4.376	4.930
		95% CI	(-16.0, 1.4)	(-15.5, 1.6)	(-10.0, 9.3)
		Pr >  t			0.9410
	Week 120	n	20	15	
		LS Mean	-4.609	-9.994	5.386
		SEM	4.333	4.749	5.212
		95% CI	(-13.1, 3.9)	(-19.3,-0.7)	(-4.8,15.6)
		Pr >  t			0.3016
	Week 132	n	15	7	
		LS Mean	-7.580	-4.133	-3.448
		SEM	4.723	6.159	6.776
		95% CI	(-16.8, 1.7)	(-16.2, 8.0)	(-16.7, 9.8)
		Pr >  t			0.6110
	Week 144	n	10	5	
		LS Mean	6.665	-7.551	14.217
		SEM	5.359	7.038	8.016

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.9,17.2)	(-21.4, 6.3)	(-1.5,29.9)
		Pr >  t			0.0764
	Week 156	n	6	3	
		LS Mean	-11.72	-7.866	-3.854
		SEM	6.520	8.734	10.22
		95% CI	(-24.5, 1.1)	(-25.0, 9.3)	(-23.9,16.2)
		Pr >  t			0.7062
	Week 168	n	3	2	
		LS Mean	-14.97	-8.875	-6.091
		SEM	8.719	10.48	13.09
		95% CI	(-32.1, 2.1)	(-29.4,11.7)	(-31.8,19.6)
		Pr >  t			0.6419
	Week 180	n	1	1	
		LS Mean	-12.96	-10.12	-2.848
		SEM	14.48	14.48	20.13
		95% CI	(-41.4,15.5)	(-38.5,18.3)	(-42.3,36.6)
		Pr >  t			0.8875
	Week 192	n	1	1	
		LS Mean	-12.96	-10.12	-2.848
		SEM	14.48	14.48	20.13
		95% CI	(-41.4,15.5)	(-38.5,18.3)	(-42.3,36.6)
		Pr >  t			0.8875
1	Week 8	n	43	50	
		LS Mean	-5.873	3.639	-9.513
		SEM	3.911	4.064	4.082
		95% CI	(-13.6, 1.9)	(-4.4,11.7)	(-17.6,-1.5)
		Pr >  t			0.0209
	Week 16	n	35	35	
		LS Mean	-10.82	-2.009	-8.810
		SEM	4.143	4.272	4.588
		95% CI	(-19.0,-2.6)	(-10.5, 6.4)	(-17.9, 0.2)
		Pr >  t			0.0561
	Week 24	n	29	26	
		LS Mean	-10.17	1.331	-11.50
		SEM	4.354	4.651	5.026
		95% CI	(-18.8,-1.6)	(-7.8,10.5)	(-21.4,-1.6)
		Pr >  t			0.0229
	Week 32	n	23	21	
		LS Mean	-12.91	-0.172	-12.74
		SEM	4.672	4.959	5.466

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-22.1,-3.7)	(-9.9, 9.6)	(-23.5,-2.0)
	Pr >  t			0.0204
	n	23	16	
	LS Mean	-9.104	-3.798	-5.306
	SEM	4.686	5.322	5.810
Week 48	95% CI	(-18.3, 0.1)	(-14.3, 6.7)	(-16.7, 6.1)
	Pr >  t			0.3617
	n	18	14	
	LS Mean	-15.37	-1.951	-13.42
	SEM	4.982	5.530	6.251
Week 56	95% CI	(-25.2,-5.6)	(-12.8, 8.9)	(-25.7,-1.1)
	Pr >  t			0.0324
	n	15	12	
	LS Mean	-15.95	-2.234	-13.72
	SEM	5.252	5.784	6.703
Week 64	95% CI	(-26.3,-5.6)	(-13.6, 9.1)	(-26.9,-0.5)
	Pr >  t			0.0413
	n	11	9	
	LS Mean	-16.83	-1.008	-15.82
	SEM	5.761	6.345	7.581
Week 72	95% CI	(-28.2,-5.5)	(-13.5,11.5)	(-30.7,-0.9)
	Pr >  t			0.0375
	n	12	4	
	LS Mean	-11.21	4.231	-15.44
	SEM	5.618	8.588	9.450
Week 84	95% CI	(-22.3,-0.2)	(-12.7,21.1)	(-34.0, 3.1)
	Pr >  t			0.1030
	n	8	4	
	LS Mean	-12.13	-12.43	0.308
	SEM	6.466	8.588	9.959
Week 96	95% CI	(-24.8, 0.6)	(-29.3, 4.4)	(-19.3,19.9)
	Pr >  t			0.9753
	n	8	2	
	LS Mean	-16.29	16.680	-32.97
	SEM	6.466	11.52	12.57
Week 108	95% CI	(-29.0,-3.6)	(-6.0,39.3)	(-57.7,-8.3)
	Pr >  t			0.0091
	n	6	1	
	LS Mean	-6.235	-21.72	15.481
	SEM	7.186	15.81	16.88



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.4, 7.9)	(-17.7,48.7)
		Pr >  t		0.3597
	Week 120	n	8	1
		LS Mean	-13.84	-21.72
		SEM	6.480	15.81
		95% CI	(-26.6,-1.1)	(-52.8, 9.4)
		Pr >  t		(-24.8,40.5)
	Week 132	n	5	1
		LS Mean	-18.51	-21.72
		SEM	7.706	15.81
		95% CI	(-33.7,-3.4)	(-52.8, 9.4)
		Pr >  t		(-30.4,36.9)
	Week 144	n	5	
		LS Mean	-5.179	
		SEM	7.706	
		95% CI	(-20.3,10.0)	
		Pr >  t		0.8515
	Week 156	n	4	
		LS Mean	-12.73	
		SEM	8.418	
		95% CI	(-29.3, 3.8)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	-1.061	
		SEM	15.59	
		95% CI	(-31.7,29.6)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	-5.050	-9.056	4.006		
			SEM	4.983	5.848	6.058		
			95% CI	(-15.1, 5.0)	(-20.8, 2.7)	(-8.1,16.1)		
					Pr >  t			0.5110
		Week 16	n	17	10			
			LS Mean	-8.234	-6.311	-1.923		
			SEM	5.330	6.717	6.963		
			95% CI	(-18.9, 2.5)	(-19.7, 7.1)	(-15.8,11.9)		
					Pr >  t			0.7832
		Week 24	n	9	5			
			LS Mean	-6.150	10.200	-16.35		
			SEM	6.106	8.082	8.943		
			95% CI	(-18.3, 6.0)	(-5.9,26.3)	(-34.1, 1.4)		
					Pr >  t			0.0703
		Week 32	n	8	4			
			LS Mean	-9.767	7.329	-17.10		
			SEM	6.308	8.662	9.644		
			95% CI	(-22.3, 2.8)	(-9.9,24.5)	(-36.2, 2.0)		
					Pr >  t			0.0790
		Week 40	n	5	4			
			LS Mean	-9.739	-9.338	-0.400		
			SEM	7.204	8.662	10.33		
			95% CI	(-24.0, 4.6)	(-26.5, 7.8)	(-20.9,20.1)		
					Pr >  t			0.9692
		Week 48	n	5	3			
			LS Mean	-9.739	-3.535	-6.204		
			SEM	7.204	9.465	11.01		
95% CI	(-24.0, 4.6)		(-22.3,15.2)	(-28.0,15.6)				
			Pr >  t			0.5743		
Week 56	n	4	3					
	LS Mean	-10.17	7.575	-17.74				
	SEM	7.734	9.465	11.40				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-25.5, 5.2)	(-11.2,26.3)	(-40.3, 4.8)
		Pr >  t			0.1223
		n	4	3	
		LS Mean	-10.17	7.575	-17.74
		SEM	7.734	9.465	11.40
Week 72		95% CI	(-25.5, 5.2)	(-11.2,26.3)	(-40.3, 4.8)
		Pr >  t			0.1223
		n	4	3	
		LS Mean	-10.17	18.685	-28.85
		SEM	7.734	9.465	11.40
Week 84		95% CI	(-25.5, 5.2)	(-0.1,37.4)	(-51.4,-6.3)
		Pr >  t			0.0127
		n	2	3	
		LS Mean	-9.799	-14.65	4.849
		SEM	10.13	9.465	13.04
Week 96		95% CI	(-29.9,10.3)	(-33.4, 4.1)	(-21.0,30.7)
		Pr >  t			0.7107
		n	1	3	
		LS Mean	-7.719	7.575	-15.29
		SEM	13.46	9.465	15.95
Week 108		95% CI	(-34.4,19.0)	(-11.2,26.3)	(-46.9,16.4)
		Pr >  t			0.3400
		n		2	
		LS Mean		16.578	
		SEM		10.80	
Week 120		95% CI		(-4.8,38.0)	
		Pr >  t			
		n	1	1	
		LS Mean	-7.719	-1.511	-6.208
		SEM	13.46	14.04	19.03
Week 132		95% CI	(-34.4,19.0)	(-29.3,26.3)	(-44.0,31.6)
		Pr >  t			0.7450
		n		1	
		LS Mean		31.819	
		SEM		14.04	
Week 144		95% CI		( 4.0,59.7)	
		Pr >  t			
		n	1		
		LS Mean	-7.719		
		SEM	13.46		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-34.4,19.0)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-5.094	0.335	-5.428
		SEM	2.953	2.945	2.550
		95% CI	(-10.9, 0.7)	(-5.5, 6.1)	(-10.4,-0.4)
		Pr >  t			0.0337
	Week 16	n	83	81	
		LS Mean	-8.225	-2.961	-5.264
		SEM	3.045	3.113	2.799
		95% CI	(-14.2,-2.2)	(-9.1, 3.2)	(-10.8, 0.2)
		Pr >  t			0.0605
	Week 24	n	75	62	
		LS Mean	-4.423	-4.376	-0.046
		SEM	3.115	3.289	3.025
		95% CI	(-10.5, 1.7)	(-10.8, 2.1)	(-6.0, 5.9)
		Pr >  t			0.9878
	Week 32	n	59	56	
		LS Mean	-4.816	-2.561	-2.254
		SEM	3.310	3.351	3.237
		95% CI	(-11.3, 1.7)	(-9.1, 4.0)	(-8.6, 4.1)
		Pr >  t			0.4864
	Week 40	n	52	48	
		LS Mean	-7.018	0.026	-7.044
		SEM	3.390	3.473	3.424
		95% CI	(-13.7,-0.4)	(-6.8, 6.8)	(-13.8,-0.3)
		Pr >  t			0.0400
	Week 48	n	47	37	
		LS Mean	-2.962	-2.778	-0.185
		SEM	3.459	3.673	3.691
		95% CI	(-9.8, 3.8)	(-10.0, 4.4)	(-7.4, 7.1)
		Pr >  t			0.9601
	Week 56	n	41	31	
		LS Mean	-8.085	-4.885	-3.200
		SEM	3.560	3.832	3.944
		95% CI	(-15.1,-1.1)	(-12.4, 2.6)	(-10.9, 4.5)
		Pr >  t			0.4173
	Week 64	n	32	28	
		LS Mean	-3.645	-4.598	0.953
		SEM	3.769	3.935	4.228

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-11.0, 3.8)	(-12.3, 3.1)	(-7.3, 9.2)	
	Pr >  t			0.8217	
	n	29	22		
	LS Mean	-9.955	1.968	-11.92	
	SEM	3.866	4.202	4.560	
Week 84	95% CI	(-17.5,-2.4)	(-6.3,10.2)	(-20.9,-3.0)	
	Pr >  t			0.0090	
	n	26	21		
	LS Mean	-9.928	-4.498	-5.429	
	SEM	3.975	4.258	4.704	
Week 96	95% CI	(-17.7,-2.1)	(-12.9, 3.9)	(-14.7, 3.8)	
	Pr >  t			0.2487	
	n	23	14		
	LS Mean	-4.566	-0.459	-4.106	
	SEM	4.113	4.836	5.338	
Week 108	95% CI	(-12.6, 3.5)	(-9.9, 9.0)	(-14.6, 6.4)	
	Pr >  t			0.4418	
	n	18	13		
	LS Mean	-6.523	-11.33	4.804	
	SEM	4.425	4.959	5.688	
Week 120	95% CI	(-15.2, 2.2)	(-21.1,-1.6)	(-6.4,16.0)	
	Pr >  t			0.3985	
	n	19	10		
	LS Mean	-5.332	-10.82	5.488	
	SEM	4.355	5.445	6.065	
Week 132	95% CI	(-13.9, 3.2)	(-21.5,-0.1)	(-6.4,17.4)	
	Pr >  t			0.3657	
	n	13	4		
	LS Mean	-10.23	-13.77	3.544	
	SEM	4.920	7.887	8.636	
Week 144	95% CI	(-19.9,-0.6)	(-29.2, 1.7)	(-13.4,20.5)	
	Pr >  t			0.6816	
	n	8	1		
	LS Mean	11.313	-9.853	21.166	
	SEM	5.887	15.00	15.74	
Week 156	95% CI	(-0.2,22.9)	(-39.3,19.6)	(-9.7,52.1)	
	Pr >  t			0.1790	
	n	5	1		
	LS Mean	-11.94	-9.853	-2.083	
	SEM	7.136	15.00	16.25	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-25.9, 2.1)	(-39.3,19.6)	(-34.0,29.8)
		Pr >  t			0.8980
		n	3	1	
	Week 180	LS Mean	-14.58	-9.853	-4.727
		SEM	8.924	15.00	17.11
		95% CI	(-32.1, 2.9)	(-39.3,19.6)	(-38.3,28.8)
	Week 180	Pr >  t			0.7824
		n	1	1	
		LS Mean	-12.30	-9.853	-2.449
	Week 192	SEM	14.94	15.00	20.88
		95% CI	(-41.6,17.0)	(-39.3,19.6)	(-43.4,38.5)
		Pr >  t			0.9067
	Week 192	n	1	1	
		LS Mean	-12.30	-9.853	-2.449
		SEM	14.94	15.00	20.88
	Week 8	95% CI	(-41.6,17.0)	(-39.3,19.6)	(-43.4,38.5)
		Pr >  t			0.9067
		n	17	16	
	Week 16	LS Mean	-8.413	4.083	-12.50
		SEM	4.377	4.510	6.206
		95% CI	(-17.1, 0.3)	( -4.9,13.0)	(-24.8,-0.2)
	Week 16	Pr >  t			0.0470
		n	18	14	
		LS Mean	-8.920	-1.990	-6.930
	Week 24	SEM	4.288	4.737	6.338
		95% CI	(-17.4,-0.4)	(-11.4, 7.4)	(-19.5, 5.7)
		Pr >  t			0.2770
	Week 24	n	16	13	
LS Mean		-10.57	-1.912	-8.659	
SEM		4.487	4.852	6.555	
Week 32	95% CI	(-19.5,-1.7)	(-11.5, 7.7)	(-21.7, 4.3)	
	Pr >  t			0.1894	
	n	15	13		
Week 32	LS Mean	-7.436	-7.701	0.265	
	SEM	4.574	4.862	6.625	
	95% CI	(-16.5, 1.6)	(-17.3, 1.9)	(-12.9,13.4)	
Week 40	Pr >  t			0.9681	
	n	14	10		
	LS Mean	-7.520	-8.345	0.825	
		SEM	4.698	5.300	7.037

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	95% CI	(-16.8, 1.8)	(-18.8, 2.1)	(-13.1,14.7)	
	Pr >  t			0.9069	
	n	14	11		
	LS Mean	-14.66	-4.995	-9.667	
	SEM	4.698	5.146	6.920	
Week 56	95% CI	(-24.0,-5.4)	(-15.2, 5.2)	(-23.4, 4.0)	
	Pr >  t			0.1650	
	n	11	11		
	LS Mean	-7.981	-4.996	-2.984	
	SEM	5.062	5.146	7.174	
Week 64	95% CI	(-18.0, 2.0)	(-15.2, 5.2)	(-17.2,11.2)	
	Pr >  t			0.6781	
	n	8	11		
	LS Mean	-14.43	-8.026	-6.406	
	SEM	5.635	5.146	7.595	
Week 72	95% CI	(-25.6,-3.3)	(-18.2, 2.2)	(-21.4, 8.6)	
	Pr >  t			0.4003	
	n	11	10		
	LS Mean	-11.01	-7.343	-3.669	
	SEM	5.062	5.313	7.294	
Week 84	95% CI	(-21.0,-1.0)	(-17.8, 3.2)	(-18.1,10.8)	
	Pr >  t			0.6158	
	n	9	9		
	LS Mean	-2.783	-1.553	-1.229	
	SEM	5.412	5.500	7.683	
Week 96	95% CI	(-13.5, 7.9)	(-12.4, 9.3)	(-16.4,13.9)	
	Pr >  t			0.8731	
	n	8	7		
	LS Mean	-6.111	-3.906	-2.205	
	SEM	5.642	5.994	8.205	
Week 108	95% CI	(-17.2, 5.0)	(-15.7, 7.9)	(-18.4,14.0)	
	Pr >  t			0.7884	
	n	7	6		
	LS Mean	-4.809	-2.827	-1.982	
	SEM	5.916	6.347	8.650	
Week 120	95% CI	(-16.5, 6.9)	(-15.3, 9.7)	(-19.0,15.1)	
	Pr >  t			0.8190	
	n	6	5		
	LS Mean	-9.584	-8.569	-1.016	
	SEM	6.271	6.808	9.222	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-21.9, 2.8)	(-22.0, 4.8)	(-19.2,17.2)
	Pr >  t			0.9124
	n	5	3	
	LS Mean	-9.712	-5.871	-3.840
	SEM	6.725	8.349	10.70
Week 144	95% CI	(-23.0, 3.5)	(-22.3,10.6)	(-24.9,17.2)
	Pr >  t			0.7199
	n	5	4	
	LS Mean	-3.046	-6.420	3.375
	SEM	6.725	7.425	9.990
Week 156	95% CI	(-16.3,10.2)	(-21.0, 8.2)	(-16.3,23.1)
	Pr >  t			0.7358
	n	4	2	
	LS Mean	-9.701	-6.223	-3.478
	SEM	7.343	9.946	12.35
Week 168	95% CI	(-24.2, 4.8)	(-25.8,13.4)	(-27.8,20.8)
	Pr >  t			0.7784
	n	1	1	
	LS Mean	2.549	-7.291	9.840
	SEM	13.61	13.66	19.28
	95% CI	(-24.2,29.3)	(-34.2,19.6)	(-28.1,47.8)
	Pr >  t			0.6102

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	-6.968	-1.456	-5.511		
			SEM	7.103	7.284	2.881		
			95% CI	(-21.0, 7.0)	(-15.8,12.9)	(-11.2, 0.2)		
					Pr >  t			0.0564
		Week 16	n	69	55			
			LS Mean	-8.254	-4.350	-3.904		
			SEM	7.113	7.365	3.111		
			95% CI	(-22.3, 5.8)	(-18.9,10.2)	(-10.0, 2.2)		
					Pr >  t			0.2101
		Week 24	n	54	46			
			LS Mean	-9.157	-0.941	-8.216		
			SEM	7.150	7.417	3.379		
			95% CI	(-23.3, 4.9)	(-15.6,13.7)	(-14.9,-1.6)		
					Pr >  t			0.0153
		Week 32	n	49	41			
			LS Mean	-8.014	-7.118	-0.896		
			SEM	7.257	7.454	3.522		
			95% CI	(-22.3, 6.3)	(-21.8, 7.6)	(-7.8, 6.0)		
					Pr >  t			0.7993
		Week 40	n	40	33			
			LS Mean	-9.429	-9.020	-0.409		
			SEM	7.323	7.536	3.820		
			95% CI	(-23.9, 5.0)	(-23.9, 5.8)	(-7.9, 7.1)		
					Pr >  t			0.9148
		Week 48	n	38	28			
			LS Mean	-9.079	-6.807	-2.272		
			SEM	7.340	7.608	3.996		
95% CI	(-23.6, 5.4)		(-21.8, 8.2)	(-10.1, 5.6)				
			Pr >  t			0.5699		
Week 56	n	32	28					
	LS Mean	-9.447	-5.456	-3.991				
	SEM	7.409	7.609	4.119				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-24.1, 5.2)	(-20.5, 9.5)	(-12.1, 4.1)
	Pr >  t			0.3328
	n	23	26	
	LS Mean	-10.16	-7.904	-2.254
	SEM	7.568	7.645	4.460
Week 72	95% CI	(-25.1, 4.8)	(-23.0, 7.2)	(-11.0, 6.5)
	Pr >  t			0.6135
	n	27	25	
	LS Mean	-11.12	-0.817	-10.30
	SEM	7.484	7.664	4.354
Week 84	95% CI	(-25.9, 3.6)	(-15.9, 14.3)	(-18.8, -1.8)
	Pr >  t			0.0182
	n	23	22	
	LS Mean	-7.737	-5.397	-2.340
	SEM	7.566	7.733	4.611
Week 96	95% CI	(-22.6, 7.2)	(-20.6, 9.8)	(-11.4, 6.7)
	Pr >  t			0.6119
	n	20	16	
	LS Mean	-5.458	-4.525	-0.933
	SEM	7.649	7.943	5.080
Week 108	95% CI	(-20.5, 9.6)	(-20.2, 11.1)	(-10.9, 9.0)
	Pr >  t			0.8543
	n	20	14	
	LS Mean	-5.463	-5.628	0.165
	SEM	7.650	8.049	5.247
Week 120	95% CI	(-20.5, 9.6)	(-21.5, 10.2)	(-10.1, 10.5)
	Pr >  t			0.9749
	n	17	11	
	LS Mean	-4.462	-10.83	6.365
	SEM	7.758	8.275	5.738
Week 132	95% CI	(-19.7, 10.8)	(-27.1, 5.5)	(-4.9, 17.6)
	Pr >  t			0.2676
	n	13	6	
	LS Mean	-8.037	-4.588	-3.448
	SEM	7.977	9.096	7.115
Week 144	95% CI	(-23.7, 7.7)	(-22.5, 13.3)	(-17.4, 10.5)
	Pr >  t			0.6280
	n	10	5	
	LS Mean	9.327	-7.855	17.182
	SEM	8.242	9.442	7.832

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.9,25.5)	(-26.4,10.7)	(-1.8,32.6)
		Pr >  t			0.0285
	Week 156	n	7	3	
		LS Mean	-11.25	-8.154	-3.095
		SEM	8.718	10.69	9.718
		95% CI	(-28.4, 5.9)	(-29.1,12.8)	(-22.2,16.0)
		Pr >  t			0.7502
	Week 168	n	3	2	
		LS Mean	-10.06	-9.173	-0.886
		SEM	10.57	12.06	12.71
		95% CI	(-30.8,10.7)	(-32.9,14.5)	(-25.8,24.1)
		Pr >  t			0.9444
	Week 180	n		1	
		LS Mean		-10.44	
		SEM		15.46	
		95% CI		(-40.8,19.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-10.44	
		SEM		15.46	
		95% CI		(-40.8,19.9)	
		Pr >  t			
Second Line	Week 8	n	66	67	
		LS Mean	-3.493	0.264	-3.757
		SEM	2.950	2.960	3.283
		95% CI	(-9.3, 2.3)	(-5.6, 6.1)	(-10.2, 2.7)
		Pr >  t			0.2534
	Week 16	n	54	52	
		LS Mean	-10.27	-2.686	-7.582
		SEM	3.145	3.233	3.627
		95% CI	(-16.5,-4.1)	(-9.1, 3.7)	(-14.7,-0.4)
		Pr >  t			0.0373
	Week 24	n	49	35	
		LS Mean	-4.049	-5.963	1.914
		SEM	3.247	3.630	4.041
		95% CI	(-10.4, 2.3)	(-13.1, 1.2)	(-6.0, 9.9)
		Pr >  t			0.6359
	Week 32	n	36	32	
		LS Mean	-5.892	1.281	-7.173
		SEM	3.560	3.743	4.360

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-12.9, 1.1)	(-6.1, 8.6)	(-15.7, 1.4)
	Pr >  t			0.1005
	n	33	29	
Week 48	LS Mean	-6.271	5.054	-11.32
	SEM	3.647	3.879	4.530
	95% CI	(-13.4, 0.9)	(-2.6, 12.7)	(-20.2, -2.4)
Week 56	Pr >  t			0.0127
	n	29	23	
	LS Mean	-4.641	-0.174	-4.467
Week 64	SEM	3.786	4.159	4.881
	95% CI	(-12.1, 2.8)	(-8.3, 8.0)	(-14.1, 5.1)
	Pr >  t			0.3605
Week 72	n	25	17	
	LS Mean	-9.318	-3.604	-5.715
	SEM	3.953	4.590	5.386
Week 84	95% CI	(-17.1, -1.5)	(-12.6, 5.4)	(-16.3, 4.9)
	Pr >  t			0.2891
	n	22	16	
Week 96	LS Mean	-1.705	-0.978	-0.727
	SEM	4.115	4.688	5.590
	95% CI	(-9.8, 6.4)	(-10.2, 8.2)	(-11.7, 10.2)
Week 108	Pr >  t			0.8965
	n	20	10	
	LS Mean	-8.367	1.062	-9.430
Week 108	SEM	4.244	5.575	6.439
	95% CI	(-16.7, -0.0)	(-9.9, 12.0)	(-22.1, 3.2)
	Pr >  t			0.1435
Week 108	n	16	11	
	LS Mean	-9.029	-5.690	-3.339
	SEM	4.603	5.374	6.499
Week 108	95% CI	(-18.1, 0.0)	(-16.2, 4.9)	(-16.1, 9.4)
	Pr >  t			0.6076
	n	15	8	
Week 108	LS Mean	-5.574	5.002	-10.58
	SEM	4.700	6.082	7.169
	95% CI	(-14.8, 3.7)	(-6.9, 16.9)	(-24.7, 3.5)
Week 108	Pr >  t			0.1406
	n	6	7	
	LS Mean	-11.17	-10.08	-1.084
	SEM	6.768	6.422	8.899

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-24.5, 2.1)	(-22.7, 2.5)	(-18.6,16.4)
	Pr >  t			0.9031
	n	11	5	
	LS Mean	-10.22	-8.979	-1.239
	SEM	5.285	7.400	8.661
Week 132	95% CI	(-20.6, 0.2)	(-23.5, 5.6)	(-18.2,15.8)
	Pr >  t			0.8863
	n	7	2	
	LS Mean	-13.57	-11.26	-2.311
	SEM	6.342	11.20	12.56
Week 144	95% CI	(-26.0,-1.1)	(-33.3,10.7)	(-27.0,22.3)
	Pr >  t			0.8540
	n	5		
	LS Mean	-7.880		
	SEM	7.299		
Week 156	95% CI	(-22.2, 6.5)		
	Pr >  t			
	n	3		
	LS Mean	-9.835		
	SEM	9.213		
Week 168	95% CI	(-27.9, 8.3)		
	Pr >  t			
	n	1		
	LS Mean	-13.96		
	SEM	15.52		
Week 180	95% CI	(-44.4,16.5)		
	Pr >  t			
	n	1		
	LS Mean	-13.96		
	SEM	15.52		
Week 192	95% CI	(-44.4,16.5)		
	Pr >  t			
	n	1		
	LS Mean	-13.96		
	SEM	15.52		
	95% CI	(-44.4,16.5)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-8.836	-0.732	-8.104		
			SEM	4.622	4.510	3.477		
			95% CI	(-17.9, 0.3)	(-9.6, 8.2)	(-14.9, -1.3)		
					Pr >  t			0.0204
		Week 16	n	60	51			
			LS Mean	-9.025	-2.814	-6.211		
			SEM	4.718	4.770	3.728		
			95% CI	(-18.3, 0.3)	(-12.2, 6.6)	(-13.5, 1.1)		
					Pr >  t			0.0966
		Week 24	n	51	42			
			LS Mean	-5.732	-0.257	-5.476		
			SEM	4.798	4.887	3.989		
			95% CI	(-15.2, 3.7)	(-9.9, 9.4)	(-13.3, 2.4)		
					Pr >  t			0.1705
		Week 32	n	46	36			
			LS Mean	-6.780	-3.688	-3.092		
			SEM	4.896	5.040	4.193		
			95% CI	(-16.4, 2.9)	(-13.6, 6.2)	(-11.3, 5.1)		
					Pr >  t			0.4613
		Week 40	n	40	33			
			LS Mean	-9.559	-0.258	-9.300		
			SEM	4.987	5.105	4.372		
			95% CI	(-19.4, 0.3)	(-10.3, 9.8)	(-17.9, -0.7)		
					Pr >  t			0.0339
		Week 48	n	37	28			
			LS Mean	-6.524	-1.526	-4.998		
			SEM	5.036	5.238	4.579		
95% CI	(-16.4, 3.4)		(-11.8, 8.8)	(-14.0, 4.0)				
			Pr >  t			0.2755		
Week 56	n	33	23					
	LS Mean	-8.034	-1.080	-6.954				
	SEM	5.117	5.417	4.870				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-18.1, 2.0)	(-11.7, 9.6)	(-16.5, 2.6)
	Pr >  t			0.1538
	n	26	20	
	LS Mean	-6.145	-3.478	-2.667
	SEM	5.306	5.563	5.224
Week 72	95% CI	(-16.6, 4.3)	(-14.4, 7.5)	(-12.9, 7.6)
	Pr >  t			0.6098
	n	28	17	
	LS Mean	-11.31	5.492	-16.80
	SEM	5.245	5.749	5.362
Week 84	95% CI	(-21.6,-1.0)	(-5.8,16.8)	(-27.3,-6.3)
	Pr >  t			0.0018
	n	23	17	
	LS Mean	-7.246	0.390	-7.636
	SEM	5.416	5.750	5.532
Week 96	95% CI	(-17.9, 3.4)	(-10.9,11.7)	(-18.5, 3.2)
	Pr >  t			0.1679
	n	23	11	
	LS Mean	-7.947	-0.987	-6.960
	SEM	5.419	6.376	6.183
Week 108	95% CI	(-18.6, 2.7)	(-13.5,11.5)	(-19.1, 5.2)
	Pr >  t			0.2606
	n	15	13	
	LS Mean	-4.276	-3.448	-0.827
	SEM	5.902	6.114	6.355
Week 120	95% CI	(-15.9, 7.3)	(-15.5, 8.6)	(-13.3,11.6)
	Pr >  t			0.8965
	n	16	9	
	LS Mean	-2.138	-8.937	6.799
	SEM	5.825	6.743	6.893
Week 132	95% CI	(-13.6, 9.3)	(-22.2, 4.3)	(-6.7,20.3)
	Pr >  t			0.3242
	n	14	5	
	LS Mean	-10.05	0.021	-10.07
	SEM	5.997	8.138	8.382
Week 144	95% CI	(-21.8, 1.7)	(-16.0,16.0)	(-26.5, 6.4)
	Pr >  t			0.2298
	n	8	3	
	LS Mean	2.358	-4.615	6.973
	SEM	6.963	9.859	10.67



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-11.3,16.0)	(-24.0,14.7)	(-14.0,27.9)
		Pr >  t			0.5136
		n	7	2	
	Week 168	LS Mean	-10.48	-5.714	-4.770
		SEM	7.251	11.66	12.52
		95% CI	(-24.7, 3.8)	(-28.6,17.2)	(-29.3,19.8)
	Week 180	Pr >  t			0.7032
		n	4	2	
		LS Mean	-10.95	-5.714	-5.232
	Week 192	SEM	8.796	11.66	13.47
		95% CI	(-28.2, 6.3)	(-28.6,17.2)	(-31.7,21.2)
		Pr >  t			0.6978
	Week 8	n	1	1	
		LS Mean	-13.78	-7.061	-6.722
		SEM	15.84	15.85	21.69
	Week 16	95% CI	(-44.9,17.3)	(-38.2,24.0)	(-49.3,35.9)
		Pr >  t			0.7567
		n	1	1	
	Week 24	LS Mean	-13.78	-7.061	-6.722
		SEM	15.84	15.85	21.69
		95% CI	(-44.9,17.3)	(-38.2,24.0)	(-49.3,35.9)
	Week 32	Pr >  t			0.7567
		n	18	17	
		LS Mean	1.104	3.434	-2.330
Week 8	SEM	3.360	3.507	4.843	
	95% CI	(-5.5, 7.8)	(-3.5,10.4)	(-11.9, 7.3)	
	Pr >  t			0.6313	
Week 16	n	17	11		
	LS Mean	-6.387	-1.894	-4.493	
	SEM	3.469	4.300	5.514	
Week 24	95% CI	(-13.3, 0.5)	(-10.4, 6.6)	(-15.4, 6.4)	
	Pr >  t			0.4166	
	n	15	5		
Week 32	LS Mean	-5.183	5.232	-10.41	
	SEM	3.690	6.339	7.333	
	95% CI	(-12.5, 2.1)	(-7.3,17.8)	(-24.9, 4.1)	
Week 8	Pr >  t			0.1575	
	n	13	5		
	LS Mean	-1.925	-8.102	6.177	
		SEM	3.950	6.339	7.478

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-9.7, 5.9)	(-20.6, 4.4)	(-8.6,20.9)	
	Pr >  t			0.4101	
	n	11	5		
	LS Mean	-5.445	-8.102	2.656	
	SEM	4.275	6.339	7.655	
Week 48	95% CI	(-13.9, 3.0)	(-20.6, 4.4)	(-12.5,17.8)	
	Pr >  t			0.7291	
	n	11	2		
	LS Mean	5.037	-7.168	12.205	
	SEM	4.283	9.796	10.70	
Week 56	95% CI	(-3.4,13.5)	(-26.5,12.2)	(-8.9,33.3)	
	Pr >  t			0.2555	
	n	8	2		
	LS Mean	-8.003	-7.168	-0.834	
	SEM	4.960	9.796	10.99	
Week 64	95% CI	(-17.8, 1.8)	(-26.5,12.2)	(-22.5,20.8)	
	Pr >  t			0.9396	
	n	7	3		
	LS Mean	-3.316	-6.495	3.179	
	SEM	5.269	8.089	9.659	
Week 72	95% CI	(-13.7, 7.1)	(-22.5, 9.5)	(-15.9,22.2)	
	Pr >  t			0.7424	
	n	7	3		
	LS Mean	-5.887	-6.495	0.608	
	SEM	5.279	8.089	9.662	
Week 84	95% CI	(-16.3, 4.5)	(-22.5, 9.5)	(-18.5,19.7)	
	Pr >  t			0.9499	
	n	7	2		
	LS Mean	-1.126	-7.168	6.042	
	SEM	5.279	9.796	11.13	
Week 96	95% CI	(-11.5, 9.3)	(-26.5,12.2)	(-15.9,28.0)	
	Pr >  t			0.5880	
	n	6	3		
	LS Mean	0.070	-6.495	6.565	
	SEM	5.666	8.089	9.879	
Week 108	95% CI	(-11.1,11.3)	(-22.5, 9.5)	(-12.9,26.1)	
	Pr >  t			0.5072	
	n	7	2		
	LS Mean	-5.887	-5.330	-0.557	
	SEM	5.279	9.784	11.12	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	N=169	N=172	
No Prior Use	Week 120	Pr >  t	(-16.3, 4.5)	(-24.6,14.0)	(-22.5,21.4)
		n	6	1	0.9601
		LS Mean	-5.485	-5.148	-0.337
	Week 132	SEM	5.666	13.70	14.82
		95% CI	(-16.7, 5.7)	(-32.2,21.9)	(-29.6,28.9)
		Pr >  t			0.9819
	Week 144	n	4		
		LS Mean	2.565		
		SEM	6.856		
	Week 156	95% CI	(-11.0,16.1)		
		Pr >  t			
		n	5		
	Week 8	LS Mean	13.726		
		SEM	6.176		
		95% CI	( 1.5,25.9)		
Week 16	Pr >  t				
	n	3			
	LS Mean	-6.906			
Week 24	SEM	7.875			
	95% CI	(-22.5, 8.6)			
	Pr >  t				
Week 32	n	59	57		
	LS Mean	-3.481	-1.406	-2.075	
	SEM	2.920	3.073	3.180	
Week 16	95% CI	( -9.2, 2.3)	( -7.5, 4.7)	( -8.3, 4.2)	
	Pr >  t			0.5147	
	n	47	44		
Week 24	LS Mean	-9.687	-4.340	-5.347	
	SEM	3.086	3.293	3.542	
	95% CI	(-15.8,-3.6)	(-10.8, 2.2)	(-12.3, 1.6)	
Week 32	Pr >  t			0.1320	
	n	39	34		
	LS Mean	-7.473	-7.615	0.142	
Week 8	SEM	3.253	3.546	3.889	
	95% CI	(-13.9,-1.1)	(-14.6,-0.6)	( -7.5, 7.8)	
	Pr >  t			0.9710	
Week 16	n	27	32		
	LS Mean	-9.353	-2.217	-7.136	
	SEM	3.635	3.600	4.232	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Placebo qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
		95% CI	N=169		N=172					
Week 40		Pr >  t								
		n	24		24					0.0924
		LS Mean	-6.604		-3.587					-3.017
		SEM	3.760		3.904					4.582
		95% CI	(-14.0, 0.8)		(-11.3, 4.1)					(-12.0, 6.0)
Week 48		Pr >  t								0.5106
		n	21		21					
		LS Mean	-12.90		-6.118					-6.787
		SEM	3.912		4.056					4.843
		95% CI	(-20.6,-5.2)		(-14.1, 1.9)					(-16.3, 2.7)
Week 56		Pr >  t								0.1617
		n	18		20					
		LS Mean	-13.18		-8.095					-5.088
		SEM	4.099		4.118					5.054
		95% CI	(-21.2,-5.1)		(-16.2, 0.0)					(-15.0, 4.8)
Week 64		Pr >  t								0.3145
		n	14		19					
		LS Mean	-8.230		-6.544					-1.686
		SEM	4.450		4.183					5.400
		95% CI	(-17.0, 0.5)		(-14.8, 1.7)					(-12.3, 8.9)
Week 72		Pr >  t								0.7549
		n	13		15					
		LS Mean	-9.007		-4.203					-4.804
		SEM	4.567		4.498					5.742
		95% CI	(-18.0,-0.0)		(-13.0, 4.6)					(-16.1, 6.5)
Week 84		Pr >  t								0.4032
		n	10		14					
		LS Mean	-15.08		-11.20					-3.879
		SEM	5.062		4.597					6.188
		95% CI	(-25.0,-5.1)		(-20.2,-2.2)					(-16.0, 8.3)
Week 96		Pr >  t								0.5310
		n	6		10					
		LS Mean	0.437		0.655					-0.218
		SEM	6.167		5.158					7.519
		95% CI	(-11.7,12.6)		(-9.5,10.8)					(-15.0,14.6)
Week 108		Pr >  t								0.9769
		n	4		6					
		LS Mean	-11.97		-12.08					0.109
	SEM	7.360		6.266					9.221	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-26.4, 2.5)	(-24.4, 0.2)	(-18.0,18.2)
	Pr >  t			0.9906
	n	6	6	
	LS Mean	-17.73	-10.88	-6.856
	SEM	6.169	6.269	8.322
Week 132	95% CI	(-29.9,-5.6)	(-23.2, 1.4)	(-23.2, 9.5)
	Pr >  t			0.4104
	n	2	3	
	LS Mean	-26.47	-13.50	-12.97
	SEM	10.05	8.389	12.76
Week 144	95% CI	(-46.2,-6.7)	(-30.0, 3.0)	(-38.1,12.1)
	Pr >  t			0.3098
	n	2	2	
	LS Mean	-7.518	-8.213	0.695
	SEM	10.01	10.10	13.96
Week 156	95% CI	(-27.2,12.1)	(-28.1,11.6)	(-26.7,28.1)
	Pr >  t			0.9603
	n		1	
	LS Mean		-7.085	
	SEM		13.95	
	95% CI		(-34.5,20.3)	
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-5.111	-1.616	-3.495
		SEM	7.031	7.260	3.280
		95% CI	(-19.0, 8.8)	(-16.0,12.7)	( -9.9, 3.0)
		Pr >  t			0.2874
	Week 16	n	51	41	
		LS Mean	-6.656	-3.629	-3.027
		SEM	7.054	7.384	3.606
		95% CI	(-20.6, 7.3)	(-18.2,11.0)	(-10.1, 4.1)
		Pr >  t			0.4019
	Week 24	n	38	33	
		LS Mean	-7.265	1.015	-8.279
		SEM	7.120	7.473	4.000
		95% CI	(-21.3, 6.8)	(-13.8,15.8)	(-16.1,-0.4)
		Pr >  t			0.0391
	Week 32	n	34	28	
		LS Mean	-7.035	-5.270	-1.765
		SEM	7.286	7.548	4.231
		95% CI	(-21.4, 7.4)	(-20.2, 9.6)	(-10.1, 6.5)
		Pr >  t			0.6767
	Week 40	n	26	23	
		LS Mean	-9.256	-7.700	-1.556
		SEM	7.423	7.658	4.639
		95% CI	(-23.9, 5.4)	(-22.8, 7.4)	(-10.7, 7.6)
	Pr >  t			0.7374	
Week 48	n	24	17		
	LS Mean	-4.628	-6.252	1.624	
	SEM	7.467	7.863	5.040	
	95% CI	(-19.4,10.1)	(-21.8, 9.3)	( -8.3,11.5)	
	Pr >  t			0.7475	
Week 56	n	21	17		
	LS Mean	-9.068	-3.967	-5.101	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	7.549	7.865	5.163
		95% CI	(-24.0, 5.8)	(-19.5, 11.6)	(-15.2, 5.0)
		Pr >  t			0.3236
	Week 64	n	15	15	
		LS Mean	-6.767	-5.963	-0.804
		SEM	7.801	7.966	5.670
		95% CI	(-22.2, 8.6)	(-21.7, 9.8)	(-11.9, 10.3)
		Pr >  t			0.8873
	Week 72	n	16	15	
		LS Mean	-10.19	5.435	-15.63
		SEM	7.747	7.966	5.597
		95% CI	(-25.5, 5.1)	(-10.3, 21.2)	(-26.6, -4.6)
		Pr >  t			0.0054
	Week 84	n	14	13	
		LS Mean	-9.887	-6.210	-3.678
		SEM	7.859	8.092	5.930
		95% CI	(-25.4, 5.6)	(-22.2, 9.7)	(-15.3, 8.0)
		Pr >  t			0.5354
	Week 96	n	12	9	
		LS Mean	-4.008	-3.212	-0.795
		SEM	8.013	8.504	6.666
		95% CI	(-19.8, 11.8)	(-20.0, 13.5)	(-13.9, 12.3)
		Pr >  t			0.9051
	Week 108	n	13	8	
		LS Mean	-4.719	-5.944	1.225
		SEM	7.932	8.664	6.779
		95% CI	(-20.4, 10.9)	(-23.0, 11.1)	(-12.1, 14.5)
		Pr >  t			0.8566
	Week 120	n	11	6	
		LS Mean	-0.589	-10.83	10.241
		SEM	8.104	9.127	7.550
		95% CI	(-16.6, 15.4)	(-28.8, 7.1)	(-4.6, 25.1)
		Pr >  t			0.1755
	Week 132	n	8	3	
		LS Mean	-5.936	-1.236	-4.699
		SEM	8.512	10.78	9.828
		95% CI	(-22.7, 10.8)	(-22.4, 19.9)	(-24.0, 14.6)
		Pr >  t			0.6327
	Week 144	n	5	1	
		LS Mean	22.617	-9.834	32.451

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	9.335	15.73	15.58
		95% CI	(-4.3,41.0)	(-40.7,21.1)	(-1.8,63.1)
		Pr >  t			0.0377
	Week 168	n	3	1	
		LS Mean	-13.45	-9.834	-3.615
		SEM	10.65	15.73	16.40
	Week 180	95% CI	(-34.4, 7.5)	(-40.7,21.1)	(-35.8,28.6)
		Pr >  t			0.8256
		n	2	1	
	Week 192	LS Mean	-15.40	-9.834	-5.561
		SEM	12.08	15.73	17.37
		95% CI	(-39.1, 8.3)	(-40.7,21.1)	(-39.7,28.6)
	Week 8	Pr >  t			0.7489
		n		1	
		LS Mean		-9.834	
	Week 16	SEM		15.73	
		95% CI		(-40.7,21.1)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-9.834	
		SEM		15.73	
	Week 32	95% CI		(-40.7,21.1)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	-8.413	4.083	-12.50	
	SEM	4.377	4.510	6.206	
	95% CI	(-17.1, 0.3)	(-4.9,13.0)	(-24.8,-0.2)	
Week 16	Pr >  t			0.0470	
	n	18	14		
	LS Mean	-8.920	-1.990	-6.930	
Week 24	SEM	4.288	4.737	6.338	
	95% CI	(-17.4,-0.4)	(-11.4, 7.4)	(-19.5, 5.7)	
	Pr >  t			0.2770	
Week 32	n	16	13		
	LS Mean	-10.57	-1.912	-8.659	
	SEM	4.487	4.852	6.555	
Week 32	95% CI	(-19.5,-1.7)	(-11.5, 7.7)	(-21.7, 4.3)	
	Pr >  t			0.1894	
	n	15	13		
	LS Mean	-7.436	-7.701	0.265	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	SEM	4.574	4.862	6.625	
	95% CI	(-16.5, 1.6)	(-17.3, 1.9)	(-12.9,13.4)	
	Pr >  t			0.9681	
	n	14	10		
	LS Mean	-7.520	-8.345	0.825	
Week 48	SEM	4.698	5.300	7.037	
	95% CI	(-16.8, 1.8)	(-18.8, 2.1)	(-13.1,14.7)	
	Pr >  t			0.9069	
	n	14	11		
	LS Mean	-14.66	-4.995	-9.667	
Week 56	SEM	4.698	5.146	6.920	
	95% CI	(-24.0,-5.4)	(-15.2, 5.2)	(-23.4, 4.0)	
	Pr >  t			0.1650	
	n	11	11		
	LS Mean	-7.981	-4.996	-2.984	
Week 64	SEM	5.062	5.146	7.174	
	95% CI	(-18.0, 2.0)	(-15.2, 5.2)	(-17.2,11.2)	
	Pr >  t			0.6781	
	n	8	11		
	LS Mean	-14.43	-8.026	-6.406	
Week 72	SEM	5.635	5.146	7.595	
	95% CI	(-25.6,-3.3)	(-18.2, 2.2)	(-21.4, 8.6)	
	Pr >  t			0.4003	
	n	11	10		
	LS Mean	-11.01	-7.343	-3.669	
Week 84	SEM	5.062	5.313	7.294	
	95% CI	(-21.0,-1.0)	(-17.8, 3.2)	(-18.1,10.8)	
	Pr >  t			0.6158	
	n	9	9		
	LS Mean	-2.783	-1.553	-1.229	
Week 96	SEM	5.412	5.500	7.683	
	95% CI	(-13.5, 7.9)	(-12.4, 9.3)	(-16.4,13.9)	
	Pr >  t			0.8731	
	n	8	7		
	LS Mean	-6.111	-3.906	-2.205	
Week 108	SEM	5.642	5.994	8.205	
	95% CI	(-17.2, 5.0)	(-15.7, 7.9)	(-18.4,14.0)	
	Pr >  t			0.7884	
	n	7	6		
	LS Mean	-4.809	-2.827	-1.982	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.916	6.347	8.650
		95% CI	(-16.5, 6.9)	(-15.3, 9.7)	(-19.0,15.1)
		Pr >  t			0.8190
	Week 120	n	6	5	
		LS Mean	-9.584	-8.569	-1.016
		SEM	6.271	6.808	9.222
		95% CI	(-21.9, 2.8)	(-22.0, 4.8)	(-19.2,17.2)
		Pr >  t			0.9124
	Week 132	n	5	3	
		LS Mean	-9.712	-5.871	-3.840
		SEM	6.725	8.349	10.70
		95% CI	(-23.0, 3.5)	(-22.3,10.6)	(-24.9,17.2)
		Pr >  t			0.7199
	Week 144	n	5	4	
		LS Mean	-3.046	-6.420	3.375
		SEM	6.725	7.425	9.990
		95% CI	(-16.3,10.2)	(-21.0, 8.2)	(-16.3,23.1)
		Pr >  t			0.7358
	Week 156	n	4	2	
		LS Mean	-9.701	-6.223	-3.478
		SEM	7.343	9.946	12.35
		95% CI	(-24.2, 4.8)	(-25.8,13.4)	(-27.8,20.8)
		Pr >  t			0.7784
	Week 168	n	1	1	
		LS Mean	2.549	-7.291	9.840
		SEM	13.61	13.66	19.28
		95% CI	(-24.2,29.3)	(-34.2,19.6)	(-28.1,47.8)
		Pr >  t			0.6102
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-4.301	0.370	-4.670
		SEM	4.555	4.404	4.877
		95% CI	(-13.5, 4.9)	( -8.5, 9.3)	(-14.4, 5.1)
		Pr >  t			0.3422
	Week 16	n	15	17	
		LS Mean	-7.082	-3.422	-3.660
		SEM	4.798	4.621	5.112
		95% CI	(-16.7, 2.6)	(-12.7, 5.9)	(-13.9, 6.5)
		Pr >  t			0.4765
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	-3.851	3.965	-7.817
	SEM	4.876	5.063	5.581
	95% CI	(-13.6, 5.9)	(-6.2, 14.1)	(-18.9, 3.3)
	Pr >  t			0.1650
	n	12	9	
Week 40	LS Mean	-10.26	4.061	-14.32
	SEM	5.071	5.299	5.934
	95% CI	(-20.4, -0.1)	(-6.5, 14.6)	(-26.1, -2.6)
	Pr >  t			0.0176
	n	11	7	
Week 48	LS Mean	-6.796	14.308	-21.10
	SEM	5.173	5.741	6.346
	95% CI	(-17.1, 3.5)	(2.9, 25.7)	(-33.7, -8.5)
	Pr >  t			0.0012
	n	8	6	
Week 56	LS Mean	-4.647	-6.503	1.855
	SEM	5.518	5.959	6.862
	95% CI	(-15.6, 6.3)	(-18.3, 5.3)	(-11.7, 15.4)
	Pr >  t			0.7873
	n	7	5	
Week 64	LS Mean	-4.391	-7.854	3.463
	SEM	5.697	6.264	7.275
	95% CI	(-15.7, 6.9)	(-20.3, 4.5)	(-10.9, 17.8)
	Pr >  t			0.6348
	n	5	3	
Week 72	LS Mean	-8.619	-4.294	-4.325
	SEM	6.223	7.351	8.600
	95% CI	(-20.9, 3.7)	(-18.8, 10.2)	(-21.3, 12.7)
	Pr >  t			0.6157
	n	5	2	
Week 84	LS Mean	-12.14	-6.073	-6.070
	SEM	6.286	8.530	9.631
	95% CI	(-24.6, 0.3)	(-22.9, 10.8)	(-25.1, 12.9)
	Pr >  t			0.5293
	n	4	2	
Week 96	LS Mean	-7.140	-6.073	-1.066
	SEM	6.634	8.530	9.900
	95% CI	(-20.3, 6.0)	(-22.9, 10.8)	(-20.6, 18.5)
	Pr >  t			0.9143
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	LS Mean	-9.160	-6.073	-3.086
	SEM	6.645	8.530	9.905
	95% CI	(-22.3, 4.0)	(-22.9,10.8)	(-22.6,16.5)
	Pr >  t			0.7557
	n	1	2	
Week 120	LS Mean	-7.421	-13.91	6.491
	SEM	11.11	8.545	13.31
	95% CI	(-29.4,14.5)	(-30.8, 3.0)	(-19.8,32.8)
	Pr >  t			0.6265
	n	5	1	
Week 132	LS Mean	-5.478	-6.234	0.756
	SEM	6.286	11.23	12.07
	95% CI	(-17.9, 7.0)	(-28.4,15.9)	(-23.1,24.6)
	Pr >  t			0.9501
	n	3	1	
Week 144	LS Mean	-9.797	-6.234	-3.563
	SEM	7.293	11.23	12.65
	95% CI	(-24.2, 4.6)	(-28.4,15.9)	(-28.6,21.4)
	Pr >  t			0.7786
	n	3		
Week 156	LS Mean	-9.797		
	SEM	7.293		
	95% CI	(-24.2, 4.6)		
	Pr >  t			
	n	3		
Week 168	LS Mean	-14.37		
	SEM	11.11		
	95% CI	(-36.3, 7.6)		
	Pr >  t			
	n	1		
Week 180	LS Mean	-14.37		
	SEM	11.11		
	95% CI	(-36.3, 7.6)		
	Pr >  t			
	n	1		
Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	-14.37		
		SEM	11.11		
		95% CI	(-36.3, 7.6)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	-0.534	2.040	-2.574
		SEM	3.750	3.774	4.213
		95% CI	(-8.0, 6.9)	(-5.4, 9.5)	(-10.9, 5.7)
		Pr >  t			0.5418
	Week 16	n	30	29	
		LS Mean	-8.389	2.292	-10.68
		SEM	3.931	4.207	4.753
		95% CI	(-16.2,-0.6)	(-6.0,10.6)	(-20.0,-1.3)
		Pr >  t			0.0256
	Week 24	n	26	20	
		LS Mean	-4.086	-7.256	3.170
		SEM	4.144	4.768	5.340
		95% CI	(-12.3, 4.1)	(-16.7, 2.1)	(-7.3,13.7)
		Pr >  t			0.5532
	Week 32	n	18	20	
		LS Mean	-4.838	2.743	-7.580
		SEM	4.676	4.768	5.747
		95% CI	(-14.1, 4.4)	(-6.7,12.1)	(-18.9, 3.7)
		Pr >  t			0.1882
	Week 40	n	18	19	
		LS Mean	-4.484	3.003	-7.487
		SEM	4.675	4.841	5.806
		95% CI	(-13.7, 4.7)	(-6.5,12.5)	(-18.9, 3.9)
		Pr >  t			0.1981
	Week 48	n	16	14	
		LS Mean	-8.981	-0.145	-8.835
		SEM	4.850	5.304	6.341
		95% CI	(-18.5, 0.6)	(-10.6,10.3)	(-21.3, 3.6)
		Pr >  t			0.1644
	Week 56	n	14	10	
		LS Mean	-11.35	1.935	-13.29
		SEM	5.068	5.941	7.053
		95% CI	(-21.3,-1.4)	(-9.8,13.6)	(-27.2, 0.6)
		Pr >  t			0.0604

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n		13	11	
	LS Mean		-4.058	0.310	-4.368
	SEM		5.199	5.754	6.995
	95% CI		(-14.3, 6.2)	(-11.0,11.6)	(-18.1, 9.4)
	Pr >  t				0.5327
Week 72	n		10	6	
	LS Mean		-5.796	8.850	-14.65
	SEM		5.698	7.197	8.560
	95% CI		(-17.0, 5.4)	(-5.3,23.0)	(-31.5, 2.2)
	Pr >  t				0.0879
Week 84	n		8	7	
	LS Mean		-10.21	-2.668	-7.537
	SEM		6.278	6.780	8.574
	95% CI		(-22.6, 2.1)	(-16.0,10.7)	(-24.4, 9.3)
	Pr >  t				0.3800
Week 96	n		6	5	
	LS Mean		0.215	13.367	-13.15
	SEM		7.002	7.740	9.890
	95% CI		(-13.6,14.0)	(-1.9,28.6)	(-32.6, 6.3)
	Pr >  t				0.1844
Week 108	n		2	4	
	LS Mean		-4.440	-6.942	2.502
	SEM		11.40	8.486	13.79
	95% CI		(-26.9,18.0)	(-23.6, 9.7)	(-24.6,29.6)
	Pr >  t				0.8561
Week 120	n		4	4	
	LS Mean		-12.61	-6.942	-5.671
	SEM		8.301	8.486	11.41
	95% CI		(-28.9, 3.7)	(-23.6, 9.7)	(-28.1,16.8)
	Pr >  t				0.6195
Week 132	n		3	1	
	LS Mean		-12.73	-13.74	1.011
	SEM		9.475	15.89	18.17
	95% CI		(-31.4, 5.9)	(-45.0,17.5)	(-34.7,36.8)
	Pr >  t				0.9557
Week 144	n		2		
	LS Mean		-4.159		
	SEM		11.32		
	95% CI		(-26.4,18.1)		
	Pr >  t				

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-30: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Diarrhoe“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-28i**  
 Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score  
 in subgroups i  
 (Full Analysis Set, PIK3CA mutant cohort)

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Presence of Lung Metastases (L)	No	Week 8	n	98	84	
			LS Mean	17.393	3.586	13.808
			SEM	3.110	3.291	3.176
			95% CI	( 11.3,23.5)	( -2.9,10.1)	( 7.6,20.0)
		Pr >  t			<.0001	
	Week 16	n	86	68		
		LS Mean	16.215	5.812	10.403	
		SEM	3.202	3.461	3.434	
		95% CI	( 9.9,22.5)	( -1.0,12.6)	( 3.7,17.1)	
		Pr >  t			0.0026	
	Week 24	n	73	48		
		LS Mean	17.831	1.700	16.131	
		SEM	3.316	3.777	3.840	
		95% CI	( 11.3,24.4)	( -5.7, 9.1)	( 8.6,23.7)	
		Pr >  t			<.0001	
	Week 32	n	60	43		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	14.253	-0.670	14.923
		SEM	3.506	3.902	4.069
		95% CI	( 7.4,21.1)	( -8.3, 7.0)	( 6.9,22.9)
		Pr >  t			0.0003
	Week 40	n	50	38	
		LS Mean	15.975	2.450	13.525
		SEM	3.649	4.047	4.314
		95% CI	( 8.8,23.1)	( -5.5,10.4)	( 5.1,22.0)
		Pr >  t			0.0018
	Week 48	n	48	31	
		LS Mean	15.521	0.703	14.818
		SEM	3.686	4.272	4.557
		95% CI	( 8.3,22.8)	( -7.7, 9.1)	( 5.9,23.8)
		Pr >  t			0.0012
	Week 56	n	41	25	
		LS Mean	14.373	1.422	12.951
		SEM	3.829	4.549	4.933
		95% CI	( 6.9,21.9)	( -7.5,10.4)	( 3.3,22.6)
		Pr >  t			0.0088
	Week 64	n	30	24	
		LS Mean	11.635	2.398	9.237
		SEM	4.161	4.607	5.252
		95% CI	( 3.5,19.8)	( -6.6,11.4)	( -1.1,19.5)
		Pr >  t			0.0789
	Week 72	n	32	19	
		LS Mean	12.424	4.330	8.094
		SEM	4.088	4.958	5.507
		95% CI	( 4.4,20.5)	( -5.4,14.1)	( -2.7,18.9)
		Pr >  t			0.1419
	Week 84	n	26	19	
		LS Mean	17.417	5.235	12.182
		SEM	4.367	4.959	5.700
		95% CI	( 8.8,26.0)	( -4.5,15.0)	( 1.0,23.4)
		Pr >  t			0.0328
	Week 96	n	23	14	
		LS Mean	17.036	-3.700	20.737
		SEM	4.524	5.502	6.301
		95% CI	( 8.2,25.9)	(-14.5, 7.1)	( 8.4,33.1)
		Pr >  t			0.0010
	Week 108	n	19	13	



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	10.574	0.218	10.356
		SEM	4.832	5.650	6.640
		95% CI	( 1.1,20.1)	(-10.9,11.3)	( -2.7,23.4)
		Pr >  t			0.1192
	Week 120	n	19	11	
		LS Mean	13.679	3.555	10.123
		SEM	4.816	6.012	6.951
		95% CI	( 4.2,23.1)	( -8.2,15.4)	( -3.5,23.8)
		Pr >  t			0.1456
	Week 132	n	15	5	
		LS Mean	13.282	1.346	11.936
		SEM	5.244	8.277	9.213
		95% CI	( 3.0,23.6)	(-14.9,17.6)	( -6.1,30.0)
		Pr >  t			0.1954
	Week 144	n	12	3	
		LS Mean	15.661	-0.750	16.412
		SEM	5.679	10.41	11.38
		95% CI	( 4.5,26.8)	(-21.2,19.7)	( -5.9,38.8)
		Pr >  t			0.1497
	Week 156	n	7	2	
		LS Mean	14.060	1.556	12.505
		SEM	7.077	12.54	14.01
		95% CI	( 0.2,27.9)	(-23.1,26.2)	(-15.0,40.0)
		Pr >  t			0.3723
	Week 168	n	3	1	
		LS Mean	27.393	1.474	25.919
		SEM	10.30	17.46	20.00
		95% CI	( 7.2,47.6)	(-32.8,35.7)	(-13.3,65.2)
		Pr >  t			0.1953
	Week 180	n	1	1	
		LS Mean	52.716	1.474	51.242
		SEM	17.41	17.46	24.43
		95% CI	( 18.6,86.9)	(-32.8,35.7)	( 3.3,99.2)
		Pr >  t			0.0362
	Week 192	n	1	1	
		LS Mean	86.046	1.474	84.572
		SEM	17.41	17.46	24.43
		95% CI	( 51.9, 120)	(-32.8,35.7)	( 36.6, 133)
		Pr >  t			0.0006
Yes	Week 8	n	44	56	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	2.920	-2.607	5.528
	SEM	5.218	4.972	3.292
	95% CI	(-7.3,13.2)	(-12.4, 7.2)	(-0.9,12.0)
	Pr >  t			0.0941
Week 16	n	38	39	
	LS Mean	4.874	-4.236	9.111
	SEM	5.421	5.364	3.669
	95% CI	(-5.8,15.5)	(-14.8, 6.3)	( 1.9,16.3)
	Pr >  t			0.0135
Week 24	n	32	33	
	LS Mean	5.577	-3.016	8.594
	SEM	5.523	5.454	3.951
	95% CI	(-5.3,16.4)	(-13.7, 7.7)	( 0.8,16.4)
	Pr >  t			0.0302
Week 32	n	26	30	
	LS Mean	9.670	-2.976	12.645
	SEM	5.661	5.519	4.225
	95% CI	(-1.5,20.8)	(-13.8, 7.9)	( 4.3,20.9)
	Pr >  t			0.0029
Week 40	n	25	24	
	LS Mean	8.604	-3.253	11.858
	SEM	5.692	5.674	4.465
	95% CI	(-2.6,19.8)	(-14.4, 7.9)	( 3.1,20.6)
	Pr >  t			0.0082
Week 48	n	21	20	
	LS Mean	3.064	0.684	2.380
	SEM	5.821	5.823	4.812
	95% CI	(-8.4,14.5)	(-10.8,12.1)	(-7.1,11.8)
	Pr >  t			0.6211
Week 56	n	18	20	
	LS Mean	11.456	-4.556	16.012
	SEM	5.956	5.822	4.975
	95% CI	(-0.3,23.2)	(-16.0, 6.9)	( 6.2,25.8)
	Pr >  t			0.0014
Week 64	n	17	18	
	LS Mean	12.375	-6.702	19.077
	SEM	6.014	5.919	5.152
	95% CI	( 0.6,24.2)	(-18.3, 4.9)	( 9.0,29.2)
	Pr >  t			0.0002
Week 72	n	16	16	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	4.904	-3.605	8.509
	SEM	6.076	6.034	5.353
	95% CI	(-7.0,16.8)	(-15.5, 8.3)	(-2.0,19.0)
	Pr >  t			0.1125
Week 84	n	14	14	
	LS Mean	8.784	-6.555	15.339
	SEM	6.212	6.176	5.666
	95% CI	(-3.4,21.0)	(-18.7, 5.6)	( 4.2,26.5)
	Pr >  t			0.0070
Week 96	n	12	10	
	LS Mean	16.564	-6.396	22.961
	SEM	6.400	6.611	6.328
	95% CI	( 4.0,29.1)	(-19.4, 6.6)	( 10.5,35.4)
	Pr >  t			0.0003
Week 108	n	7	8	
	LS Mean	5.235	-6.572	11.807
	SEM	7.240	6.970	7.507
	95% CI	(-9.0,19.5)	(-20.3, 7.1)	(-2.9,26.6)
	Pr >  t			0.1163
Week 120	n	9	5	
	LS Mean	0.129	-7.857	7.986
	SEM	6.817	7.941	8.055
	95% CI	(-13.3,13.5)	(-23.5, 7.7)	(-7.8,23.8)
	Pr >  t			0.3219
Week 132	n	5	3	
	LS Mean	-8.110	-5.266	-2.844
	SEM	7.962	9.404	10.35
	95% CI	(-23.8, 7.5)	(-23.7,13.2)	(-23.2,17.5)
	Pr >  t			0.7836
Week 144	n	3	2	
	LS Mean	-6.198	-4.517	-1.681
	SEM	9.417	10.97	12.82
	95% CI	(-24.7,12.3)	(-26.1,17.0)	(-26.9,23.5)
	Pr >  t			0.8957
Week 156	n	3	1	
	LS Mean	16.086	-4.472	20.557
	SEM	9.426	14.68	16.12
	95% CI	(-2.4,34.6)	(-33.3,24.4)	(-11.1,52.2)
	Pr >  t			0.2027
Week 168	n	1	1	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	-3.667	-4.472	0.805
	SEM	14.72	14.68	19.69
	95% CI	(-32.6,25.3)	(-33.3,24.4)	(-37.9,39.5)
	Pr >  t			0.9674

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	9.977	0.928	9.050		
			SEM	3.018	3.000	2.678		
			95% CI	( 4.0,15.9)	( -5.0, 6.8)	( 3.8,14.3)		
					Pr >  t			0.0008
		Week 16	n	92	77			
			LS Mean	9.048	0.933	8.115		
			SEM	3.069	3.210	2.906		
			95% CI	( 3.0,15.1)	( -5.4, 7.2)	( 2.4,13.8)		
					Pr >  t			0.0054
		Week 24	n	83	66			
			LS Mean	10.750	-1.092	11.843		
			SEM	3.139	3.300	3.072		
			95% CI	( 4.6,16.9)	( -7.6, 5.4)	( 5.8,17.9)		
					Pr >  t			0.0001
		Week 32	n	72	60			
			LS Mean	12.648	-2.794	15.442		
			SEM	3.233	3.384	3.225		
			95% CI	( 6.3,19.0)	( -9.4, 3.9)	( 9.1,21.8)		
					Pr >  t			<.0001
		Week 40	n	64	51			
			LS Mean	11.569	0.485	11.083		
			SEM	3.303	3.518	3.418		
			95% CI	( 5.1,18.1)	( -6.4, 7.4)	( 4.4,17.8)		
			Pr >  t			0.0012		
Week 48	n	58	45					
	LS Mean	9.682	-1.438	11.120				
	SEM	3.365	3.616	3.580				
	95% CI	( 3.1,16.3)	( -8.5, 5.7)	( 4.1,18.1)				
			Pr >  t			0.0019		
Week 56	n	49	38					
	LS Mean	11.464	-1.762	13.226				
	SEM	3.482	3.763	3.840				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 4.6,18.3)	( -9.2, 5.6)	( 5.7,20.8)
	Pr >  t			0.0006
	n	39	37	
	LS Mean	10.662	-1.277	11.939
	SEM	3.665	3.789	4.036
Week 72	95% CI	( 3.5,17.9)	( -8.7, 6.2)	( 4.0,19.9)
	Pr >  t			0.0032
	n	41	32	
	LS Mean	7.584	1.228	6.357
	SEM	3.624	3.930	4.131
Week 84	95% CI	( 0.5,14.7)	( -6.5, 8.9)	( -1.7,14.5)
	Pr >  t			0.1241
	n	33	29	
	LS Mean	12.910	0.883	12.028
	SEM	3.847	4.035	4.404
Week 96	95% CI	( 5.4,20.5)	( -7.0, 8.8)	( 3.4,20.7)
	Pr >  t			0.0064
	n	31	21	
	LS Mean	15.879	-4.962	20.841
	SEM	3.899	4.430	4.822
Week 108	95% CI	( 8.2,23.5)	( -13.7, 3.7)	( 11.4,30.3)
	Pr >  t			<.0001
	n	23	18	
	LS Mean	7.215	-2.194	9.409
	SEM	4.260	4.653	5.302
Week 120	95% CI	( -1.1,15.6)	( -11.3, 6.9)	( -1.0,19.8)
	Pr >  t			0.0762
	n	25	15	
	LS Mean	9.697	-0.003	9.700
	SEM	4.143	4.945	5.483
Week 132	95% CI	( 1.6,17.8)	( -9.7, 9.7)	( -1.1,20.5)
	Pr >  t			0.0771
	n	17	8	
	LS Mean	7.026	-1.673	8.699
	SEM	4.689	6.249	7.025
Week 144	95% CI	( -2.2,16.2)	( -13.9,10.6)	( -5.1,22.5)
	Pr >  t			0.2158
	n	15	5	
	LS Mean	8.683	-2.597	11.280
	SEM	4.872	7.609	8.376

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.9,18.2)	(-17.5,12.3)	(-5.2,27.7)
		Pr >  t			0.1783
	Week 156	n	10	3	
		LS Mean	12.923	-1.299	14.221
		SEM	5.681	9.543	10.57
		95% CI	( 1.8,24.1)	(-20.0,17.4)	( -6.5,35.0)
		Pr >  t			0.1786
	Week 168	n	4	2	
		LS Mean	17.479	-1.335	18.814
		SEM	8.344	11.52	13.80
		95% CI	( 1.1,33.8)	(-23.9,21.3)	( -8.3,45.9)
		Pr >  t			0.1732
	Week 180	n	1	1	
		LS Mean	48.385	-1.370	49.755
		SEM	16.01	16.02	22.39
		95% CI	( 17.0,79.8)	(-32.8,30.1)	( 5.8,93.7)
		Pr >  t			0.0264
	Week 192	n	1	1	
		LS Mean	81.715	-1.370	83.085
		SEM	16.01	16.02	22.39
		95% CI	( 50.3, 113)	(-32.8,30.1)	( 39.2, 127)
		Pr >  t			0.0002
Yes	Week 8	n	38	42	
		LS Mean	21.950	3.517	18.433
		SEM	5.094	5.385	5.065
		95% CI	( 11.9,32.0)	( -7.1,14.2)	( 8.4,28.4)
		Pr >  t			0.0004
	Week 16	n	32	30	
		LS Mean	24.315	6.265	18.049
		SEM	5.461	5.683	5.655
		95% CI	( 13.5,35.1)	( -5.0,17.5)	( 6.9,29.2)
		Pr >  t			0.0017
	Week 24	n	22	15	
		LS Mean	25.468	4.965	20.503
		SEM	5.848	6.772	7.041
		95% CI	( 13.9,37.0)	( -8.4,18.3)	( 6.6,34.4)
		Pr >  t			0.0039
	Week 32	n	14	13	
		LS Mean	9.438	5.160	4.278
		SEM	6.705	7.030	7.871

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-3.8,22.6)	(-8.7,19.0)	(-11.2,19.8)
	Pr >  t			0.5872
	n	11	11	
	LS Mean	20.631	-0.685	21.316
	SEM	7.145	7.354	8.529
Week 48	95% CI	( 6.6,34.7)	(-15.2,13.8)	( 4.5,38.1)
	Pr >  t			0.0130
	n	11	6	
	LS Mean	17.601	15.150	2.451
	SEM	7.145	8.845	9.844
Week 56	95% CI	( 3.5,31.7)	(-2.3,32.6)	(-16.9,21.8)
	Pr >  t			0.8036
	n	10	7	
	LS Mean	19.080	3.262	15.818
	SEM	7.345	8.410	9.608
Week 64	95% CI	( 4.6,33.5)	(-13.3,19.8)	(-3.1,34.7)
	Pr >  t			0.1008
	n	8	5	
	LS Mean	15.964	-3.306	19.270
	SEM	7.854	9.414	10.86
Week 72	95% CI	( 0.5,31.4)	(-21.8,15.2)	(-2.1,40.7)
	Pr >  t			0.0771
	n	7	3	
	LS Mean	18.941	-4.544	23.485
	SEM	8.198	11.38	12.82
Week 84	95% CI	( 2.8,35.1)	(-26.9,17.9)	(-1.8,48.7)
	Pr >  t			0.0680
	n	7	4	
	LS Mean	18.941	-5.087	24.028
	SEM	8.198	10.20	11.79
Week 96	95% CI	( 2.8,35.1)	(-25.2,15.0)	( 0.8,47.2)
	Pr >  t			0.0425
	n	4	3	
	LS Mean	16.735	-4.544	21.278
	SEM	9.980	11.38	14.02
Week 108	95% CI	(-2.9,36.4)	(-26.9,17.9)	(-6.3,48.9)
	Pr >  t			0.1305
	n	3	3	
Week 108	LS Mean	12.435	-4.172	16.607
	SEM	11.16	11.37	14.88



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.5,34.4)	(-26.6,18.2)	(-12.7,45.9)
		Pr >  t			0.2655
	Week 120	n	3	1	
		LS Mean	-3.794	-13.88	10.090
		SEM	11.16	18.14	20.52
		95% CI	(-25.8,18.2)	(-49.6,21.9)	(-30.4,50.5)
		Pr >  t			0.6235
	Week 132	n	3		
		LS Mean	4.149		
		SEM	11.16		
		95% CI	(-17.8,26.1)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	14.075	2.654	11.422		
			SEM	2.620	2.677	2.445		
			95% CI	( 8.9,19.2)	( -2.6, 7.9)	( 6.6,16.2)		
					Pr >  t			<.0001
		Week 16	n	119	97			
			LS Mean	13.914	3.783	10.131		
			SEM	2.706	2.868	2.694		
			95% CI	( 8.6,19.2)	( -1.8, 9.4)	( 4.8,15.4)		
					Pr >  t			0.0002
		Week 24	n	100	75			
			LS Mean	15.173	1.333	13.840		
			SEM	2.798	3.038	2.948		
			95% CI	( 9.7,20.7)	( -4.6, 7.3)	( 8.1,19.6)		
					Pr >  t			<.0001
		Week 32	n	82	69			
			LS Mean	13.338	-0.134	13.472		
			SEM	2.940	3.109	3.113		
			95% CI	( 7.6,19.1)	( -6.2, 6.0)	( 7.4,19.6)		
					Pr >  t			<.0001
		Week 40	n	73	58			
			LS Mean	14.325	1.687	12.638		
			SEM	3.010	3.242	3.302		
			95% CI	( 8.4,20.2)	( -4.7, 8.1)	( 6.2,19.1)		
					Pr >  t			0.0001
		Week 48	n	66	48			
			LS Mean	11.849	2.104	9.746		
			SEM	3.074	3.392	3.506		
95% CI	( 5.8,17.9)		( -4.6, 8.8)	( 2.9,16.6)				
			Pr >  t			0.0055		
Week 56	n	56	43					
	LS Mean	12.947	-0.368	13.315				
	SEM	3.188	3.490	3.703				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 6.7,19.2)	( -7.2, 6.5)	( 6.1,20.6)
	Pr >  t			0.0003
	n	45	41	
	LS Mean	12.803	-0.854	13.657
	SEM	3.361	3.535	3.897
Week 72	95% CI	( 6.2,19.4)	( -7.8, 6.1)	( 6.0,21.3)
	Pr >  t			0.0005
	n	46	34	
	LS Mean	9.832	2.403	7.429
	SEM	3.345	3.720	4.051
Week 84	95% CI	( 3.3,16.4)	( -4.9, 9.7)	( -0.5,15.4)
	Pr >  t			0.0669
	n	37	32	
	LS Mean	15.616	1.733	13.882
	SEM	3.560	3.785	4.276
Week 96	95% CI	( 8.6,22.6)	( -5.7, 9.2)	( 5.5,22.3)
	Pr >  t			0.0012
	n	33	23	
	LS Mean	16.919	-3.576	20.495
	SEM	3.671	4.189	4.731
Week 108	95% CI	( 9.7,24.1)	( -11.8, 4.6)	( 11.2,29.8)
	Pr >  t			<.0001
	n	24	20	
	LS Mean	9.647	-1.181	10.828
	SEM	4.064	4.390	5.203
Week 120	95% CI	( 1.7,17.6)	( -9.8, 7.4)	( 0.6,21.0)
	Pr >  t			0.0376
	n	25	16	
	LS Mean	8.474	0.639	7.835
	SEM	4.003	4.749	5.471
Week 132	95% CI	( 0.6,16.3)	( -8.7,10.0)	( -2.9,18.6)
	Pr >  t			0.1523
	n	19	8	
	LS Mean	8.014	-0.016	8.030
	SEM	4.399	6.221	7.024
Week 144	95% CI	( -0.6,16.6)	( -12.2,12.2)	( -5.7,21.8)
	Pr >  t			0.2531
	n	14	5	
	LS Mean	11.140	-0.965	12.105
	SEM	4.906	7.628	8.584

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.5,20.8)	(-15.9,14.0)	( -4.7,28.9)
		Pr >  t			0.1587
	Week 156	n	10	3	
		LS Mean	15.107	0.398	14.709
		SEM	5.621	9.616	10.74
		95% CI	( 4.1,26.1)	(-18.5,19.3)	( -6.4,35.8)
		Pr >  t			0.1710
	Week 168	n	4	2	
		LS Mean	19.525	0.407	19.118
		SEM	8.378	11.64	14.03
		95% CI	( 3.1,36.0)	(-22.4,23.2)	( -8.4,46.6)
		Pr >  t			0.1732
	Week 180	n	1	1	
		LS Mean	50.164	0.266	49.898
		SEM	16.22	16.23	22.76
		95% CI	( 18.3,82.0)	(-31.6,32.1)	( 5.3,94.5)
		Pr >  t			0.0285
	Week 192	n	1	1	
		LS Mean	83.494	0.266	83.228
		SEM	16.22	16.23	22.76
		95% CI	( 51.7, 115)	(-31.6,32.1)	( 38.6, 128)
		Pr >  t			0.0003
Yes	Week 8	n	5	9	
		LS Mean	13.118	-1.040	14.158
		SEM	9.106	6.638	11.43
		95% CI	( -5.3,31.5)	(-14.4,12.3)	( -8.9,37.2)
		Pr >  t			0.2222
	Week 16	n	5	9	
		LS Mean	13.118	-1.072	14.190
		SEM	9.106	6.671	11.48
		95% CI	( -5.3,31.5)	(-14.5,12.4)	( -9.0,37.3)
		Pr >  t			0.2231
	Week 24	n	5	5	
		LS Mean	13.118	-1.038	14.156
		SEM	9.106	8.669	12.68
		95% CI	( -5.3,31.5)	(-18.5,16.4)	(-11.4,39.7)
		Pr >  t			0.2702
	Week 32	n	4	3	
		LS Mean	24.465	-1.109	25.574
		SEM	9.978	11.01	14.99

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 4.4,44.6)	( -4.5,55.7)
		Pr >  t		0.0942
	Week 40	n	2	3
		LS Mean	21.822	-0.744
		SEM	13.39	11.04
		95% CI	( -5.1,48.7)	( -22.9,21.4)
		Pr >  t		( -12.2,57.3)
	Week 48	n	3	2
		LS Mean	31.188	-0.433
		SEM	11.27	13.46
		95% CI	( 8.5,53.8)	( -27.5,26.6)
		Pr >  t		( -3.3,66.5)
	Week 56	n	3	1
		LS Mean	42.301	31.964
		SEM	11.27	18.67
		95% CI	( 19.6,65.0)	( -5.5,69.5)
		Pr >  t		( -33.8,54.4)
	Week 64	n	2	
		LS Mean	21.822	
		SEM	13.39	
		95% CI	( -5.1,48.7)	
		Pr >  t		0.6399
	Week 72	n	2	
		LS Mean	39.580	
		SEM	13.39	
		95% CI	( 12.7,66.5)	
		Pr >  t		
	Week 84	n	3	
		LS Mean	20.078	
		SEM	11.27	
		95% CI	( -2.6,42.7)	
		Pr >  t		
	Week 96	n	2	
		LS Mean	38.487	
		SEM	13.39	
		95% CI	( 11.6,65.4)	
		Pr >  t		
	Week 108	n	2	
		LS Mean	15.503	
		SEM	13.50	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-11.6,42.6)
		Pr >  t		
	Week 120	n	3	
		LS Mean	31.191	
		SEM	11.27	
		95% CI		( - 8.5,53.8)
		Pr >  t		
	Week 132	n	1	
		LS Mean	14.415	
		SEM	18.47	
		95% CI		(-22.7,51.5)
		Pr >  t		
	Week 144	n	1	
		LS Mean	14.415	
		SEM	18.47	
		95% CI		(-22.7,51.5)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	8.961	-1.246	10.206		
			SEM	4.455	4.218	3.961		
					95% CI	( 0.1,17.8)	( -9.6, 7.1)	( 2.4,18.0)
					Pr >  t			0.0107
				Week 16	n	30	30	
					LS Mean	11.706	-1.079	12.785
					SEM	4.501	4.465	4.185
					95% CI	( 2.8,20.6)	( -9.9, 7.8)	( 4.5,21.0)
					Pr >  t			0.0025
				Week 24	n	21	26	
					LS Mean	7.524	-2.194	9.718
					SEM	4.805	4.568	4.654
					95% CI	( -2.0,17.0)	( -11.2, 6.9)	( 0.6,18.9)
					Pr >  t			0.0378
				Week 32	n	19	24	
					LS Mean	12.799	-3.562	16.361
					SEM	4.903	4.641	4.840
					95% CI	( 3.1,22.5)	( -12.8, 5.6)	( 6.8,25.9)
					Pr >  t			0.0008
				Week 40	n	16	19	
					LS Mean	6.673	-0.401	7.074
					SEM	5.092	4.941	5.267
					95% CI	( -3.4,16.7)	( -10.2, 9.4)	( -3.3,17.4)
			Pr >  t			0.1802		
		Week 48	n	16	18			
			LS Mean	4.590	-2.170	6.760		
			SEM	5.092	4.998	5.322		
			95% CI	( -5.5,14.7)	( -12.0, 7.7)	( -3.7,17.2)		
			Pr >  t			0.2050		
		Week 56	n	12	14			
			LS Mean	11.950	-4.544	16.494		
			SEM	5.463	5.297	5.967		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.2,22.7)	(-15.0, 5.9)	( 4.8,28.2)
		Pr >  t			0.0060
	Week 64	n	12	11	
		LS Mean	14.728	-4.858	19.585
		SEM	5.463	5.644	6.280
		95% CI	( 3.9,25.5)	(-16.0, 6.3)	( 7.2,31.9)
		Pr >  t			0.0020
	Week 72	n	10	9	
		LS Mean	8.859	-3.853	12.712
		SEM	5.735	5.979	6.825
		95% CI	( -2.5,20.2)	(-15.6, 7.9)	( -0.7,26.1)
		Pr >  t			0.0633
	Week 84	n	8	8	
		LS Mean	12.592	-4.121	16.713
		SEM	6.203	6.201	7.351
		95% CI	( 0.4,24.8)	(-16.3, 8.1)	( 2.3,31.2)
		Pr >  t			0.0236
	Week 96	n	6	6	
		LS Mean	16.434	-4.589	21.023
		SEM	6.808	6.812	8.362
		95% CI	( 3.0,29.8)	(-18.0, 8.8)	( 4.6,37.5)
		Pr >  t			0.0124
	Week 108	n	4	5	
		LS Mean	12.020	-4.991	17.011
		SEM	7.873	7.264	9.591
		95% CI	( -3.5,27.5)	(-19.3, 9.3)	( -1.8,35.9)
		Pr >  t			0.0769
	Week 120	n	4	4	
		LS Mean	12.020	11.118	0.902
		SEM	7.873	7.891	10.08
		95% CI	( -3.5,27.5)	( -4.4,26.6)	(-18.9,20.7)
		Pr >  t			0.9287
	Week 132	n	3	2	
		LS Mean	3.275	-3.185	6.460
		SEM	8.804	10.41	12.76
		95% CI	(-14.0,20.6)	(-23.7,17.3)	(-18.6,31.6)
		Pr >  t			0.6131
	Week 144	n	3	1	
		LS Mean	3.275	-2.366	5.641
		SEM	8.804	14.18	15.99



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.0,20.6)	(-30.3,25.5)	(-25.8,37.1)
		Pr >  t			0.7245
	Week 156	n	2	1	
		LS Mean	4.517	-2.366	6.883
		SEM	10.41	14.18	16.92
		95% CI	(-15.9,25.0)	(-30.3,25.5)	(-26.4,40.2)
		Pr >  t			0.6845
	Week 168	n	1		
		LS Mean	6.174		
		SEM	14.16		
		95% CI	(-21.7,34.0)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	10.363	-2.721	13.084
		SEM	10.17	10.01	6.232
		95% CI	(-9.8,30.5)	(-22.5,17.1)	( 0.7,25.4)
		Pr >  t			0.0382
	Week 16	n	15	14	
		LS Mean	0.488	0.751	-0.263
		SEM	10.23	9.281	6.770
		95% CI	(-19.8,20.8)	(-17.7,19.2)	(-13.7,13.2)
		Pr >  t			0.9690
	Week 24	n	12	11	
		LS Mean	10.889	-4.274	15.163
		SEM	10.46	10.44	7.461
		95% CI	(-9.9,31.6)	(-24.9,16.4)	( 0.4,29.9)
		Pr >  t			0.0443
	Week 32	n	8	9	
		LS Mean	3.078	-7.815	10.893
		SEM	11.03	10.72	8.598
		95% CI	(-18.8,24.9)	(-29.0,13.4)	(-6.1,27.9)
		Pr >  t			0.2074
	Week 40	n	6	7	
		LS Mean	17.377	-8.122	25.499
		SEM	11.56	11.10	9.699
		95% CI	(-5.5,40.3)	(-30.1,13.8)	( 6.3,44.7)
		Pr >  t			0.0095
	Week 48	n	4	6	
		LS Mean	10.412	-8.427	18.839
		SEM	12.50	11.38	11.12

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.3,35.1)	(-30.9,14.1)	(-3.1,40.8)
		Pr >  t			0.0922
	Week 56	n	4	6	
		LS Mean	6.795	2.217	4.579
		SEM	12.49	11.41	11.09
		95% CI	(-17.9,31.5)	(-20.4,24.8)	(-17.3,26.5)
		Pr >  t			0.6803
	Week 64	n	4	4	
		LS Mean	-4.341	-9.126	4.785
		SEM	12.51	12.33	12.02
		95% CI	(-29.1,20.4)	(-33.5,15.2)	(-19.0,28.6)
		Pr >  t			0.6913
	Week 72	n	4	4	
		LS Mean	3.992	-0.793	4.785
		SEM	12.51	12.33	12.02
		95% CI	(-20.7,28.7)	(-25.2,23.6)	(-19.0,28.6)
		Pr >  t			0.6913
	Week 84	n	4	4	
		LS Mean	2.080	-9.126	11.205
		SEM	12.50	12.33	12.08
		95% CI	(-22.7,26.8)	(-33.5,15.2)	(-12.7,35.1)
		Pr >  t			0.3552
	Week 96	n	3	2	
		LS Mean	12.746	-6.667	19.413
		SEM	13.35	14.73	15.23
		95% CI	(-13.7,39.2)	(-35.8,22.5)	(-10.7,49.5)
		Pr >  t			0.2046
	Week 108	n	3	3	
		LS Mean	1.633	-7.235	8.868
		SEM	13.35	13.20	13.74
		95% CI	(-24.8,28.0)	(-33.3,18.8)	(-18.3,36.0)
		Pr >  t			0.5198
	Week 120	n	2	1	
		LS Mean	0.899	-7.627	8.526
		SEM	14.91	18.59	20.12
		95% CI	(-28.6,30.4)	(-44.4,29.1)	(-31.3,48.3)
		Pr >  t			0.6724
	Week 132	n	2	1	
		LS Mean	-1.617	-7.627	6.009
		SEM	14.87	18.59	20.08

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-31.0,27.8)	(-44.4,29.1)	(-33.7,45.7)
		Pr >  t			0.7652
	Week 156	n	1		
		LS Mean	-6.334		
		SEM	18.76		
		95% CI	(-43.4,30.7)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-6.334		
		SEM	18.76		
		95% CI	(-43.4,30.7)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	15.745	3.712	12.033
		SEM	3.364	3.539	3.262
		95% CI	( 9.1,22.4)	( -3.2,10.7)	( 5.6,18.4)
		Pr >  t			0.0002
	Week 16	n	79	61	
		LS Mean	16.322	4.578	11.744
		SEM	3.508	3.869	3.654
		95% CI	( 9.4,23.2)	( -3.0,12.2)	( 4.6,18.9)
		Pr >  t			0.0014
	Week 24	n	71	43	
		LS Mean	17.536	2.608	14.927
		SEM	3.592	4.169	4.038
		95% CI	( 10.5,24.6)	( -5.6,10.8)	( 7.0,22.9)
		Pr >  t			0.0002
	Week 32	n	59	39	
		LS Mean	15.253	1.736	13.517
		SEM	3.780	4.296	4.256
		95% CI	( 7.8,22.7)	( -6.7,10.2)	( 5.2,21.9)
		Pr >  t			0.0016
	Week 40	n	52	35	
		LS Mean	16.723	3.110	13.613
		SEM	3.876	4.409	4.454
		95% CI	( 9.1,24.3)	( -5.6,11.8)	( 4.9,22.4)
		Pr >  t			0.0023
	Week 48	n	48	26	
		LS Mean	15.631	5.350	10.280
		SEM	3.941	4.757	4.850

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 7.9,23.4)	( -4.0,14.7)	( 0.8,19.8)
		Pr >  t			0.0343
	Week 56	n	42	24	
		LS Mean	15.987	0.950	15.036
		SEM	4.056	4.863	5.051
		95% CI	( 8.0,24.0)	( -8.6,10.5)	( 5.1,24.9)
		Pr >  t			0.0030
	Week 64	n	30	26	
		LS Mean	14.570	2.705	11.865
		SEM	4.398	4.760	5.241
		95% CI	( 5.9,23.2)	( -6.6,12.1)	( 1.6,22.2)
		Pr >  t			0.0238
	Week 72	n	34	21	
		LS Mean	12.456	4.733	7.723
		SEM	4.264	5.050	5.397
		95% CI	( 4.1,20.8)	( -5.2,14.6)	( -2.9,18.3)
		Pr >  t			0.1528
	Week 84	n	28	20	
		LS Mean	18.333	5.331	13.001
		SEM	4.493	5.121	5.637
		95% CI	( 9.5,27.2)	( -4.7,15.4)	( 1.9,24.1)
		Pr >  t			0.0213
	Week 96	n	26	15	
		LS Mean	19.258	-3.385	22.643
		SEM	4.572	5.598	6.144
		95% CI	( 10.3,28.2)	( -14.4, 7.6)	( 10.6,34.7)
		Pr >  t			0.0002
	Week 108	n	19	12	
		LS Mean	10.436	0.520	9.916
		SEM	5.038	6.038	6.868
		95% CI	( 0.5,20.3)	( -11.3,12.4)	( -3.6,23.4)
		Pr >  t			0.1491
	Week 120	n	22	10	
		LS Mean	11.329	-2.941	14.270
		SEM	4.803	6.444	7.077
		95% CI	( 1.9,20.8)	( -15.6, 9.7)	( 0.4,28.2)
		Pr >  t			0.0440
	Week 132	n	15	4	
		LS Mean	10.868	2.084	8.784
		SEM	5.439	9.319	10.09

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.2,21.5)	(-16.2,20.4)	(-11.0,28.6)
		Pr >  t			0.3842
	Week 144	n	12	4	
		LS Mean	14.617	0.195	14.422
		SEM	5.863	9.324	10.34
		95% CI	( 3.1,26.1)	(-18.1,18.5)	( -5.9,34.7)
		Pr >  t			0.1634
	Week 156	n	7	2	
		LS Mean	21.666	1.922	19.743
		SEM	7.246	12.73	14.14
		95% CI	( 7.4,35.9)	(-23.1,26.9)	( -8.0,47.5)
		Pr >  t			0.1629
	Week 168	n	2	2	
		LS Mean	35.739	1.922	33.817
		SEM	12.62	12.73	17.51
		95% CI	( 11.0,60.5)	(-23.1,26.9)	( -0.6,68.2)
		Pr >  t			0.0538
	Week 180	n	1	1	
		LS Mean	53.636	1.682	51.953
		SEM	17.59	17.64	24.61
		95% CI	( 19.1,88.2)	(-32.9,36.3)	( 3.6, 100)
		Pr >  t			0.0351
	Week 192	n	1	1	
		LS Mean	86.966	1.682	85.283
		SEM	17.59	17.64	24.61
		95% CI	( 52.4, 121)	(-32.9,36.3)	( 37.0, 134)
		Pr >  t			0.0006

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Geographic Region 1 (L)	Asia	Week 8	n	30	35	
			LS Mean	5.391	-1.176	6.567
			SEM	3.913	3.675	3.696
			95% CI	(-2.4,13.1)	(-8.4, 6.1)	(-0.7,13.8)
			Pr >  t			0.0767
		Week 16	n	28	29	
			LS Mean	10.608	-1.027	11.635
			SEM	3.967	3.931	3.927
			95% CI	( 2.8,18.5)	(-8.8, 6.7)	( 3.9,19.4)
			Pr >  t			0.0033
		Week 24	n	21	25	
			LS Mean	6.809	-2.121	8.930
			SEM	4.233	4.047	4.340
			95% CI	(-1.6,15.2)	(-10.1, 5.9)	( 0.4,17.5)
			Pr >  t			0.0405
		Week 32	n	19	23	
			LS Mean	11.936	-3.523	15.459
			SEM	4.336	4.129	4.532
			95% CI	( 3.4,20.5)	(-11.7, 4.6)	( 6.5,24.4)
			Pr >  t			0.0007
		Week 40	n	16	18	
			LS Mean	5.703	-0.167	5.870
			SEM	4.536	4.473	4.981
			95% CI	(-3.2,14.7)	(-9.0, 8.7)	(-3.9,15.7)
			Pr >  t			0.2395
		Week 48	n	16	17	
			LS Mean	3.620	-1.993	5.613
			SEM	4.536	4.539	5.043
95% CI	(-5.3,12.6)		(-10.9, 7.0)	(-4.3,15.5)		
	Pr >  t			0.2665		
Week 56	n	12	14			
	LS Mean	11.133	-4.219	15.353		
	SEM	4.928	4.785	5.635		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 1.4,20.8)	(-13.6, 5.2)	( 4.3,26.4)
	Pr >  t			0.0068
	n	12	11	
	LS Mean	13.911	-4.555	18.465
	SEM	4.928	5.150	5.951
Week 72	95% CI	( 4.2,23.6)	(-14.7, 5.6)	( 6.8,30.2)
	Pr >  t			0.0021
	n	10	8	
	LS Mean	7.961	-4.010	11.971
	SEM	5.214	5.730	6.698
Week 84	95% CI	( -2.3,18.2)	(-15.3, 7.3)	( -1.2,25.1)
	Pr >  t			0.0747
	n	8	8	
	LS Mean	11.583	-4.010	15.594
	SEM	5.710	5.730	7.028
Week 96	95% CI	( 0.3,22.8)	(-15.3, 7.3)	( 1.8,29.4)
	Pr >  t			0.0271
	n	6	6	
	LS Mean	15.486	-4.496	19.982
	SEM	6.336	6.360	8.039
Week 108	95% CI	( 3.0,28.0)	(-17.0, 8.0)	( 4.2,35.8)
	Pr >  t			0.0134
	n	4	5	
	LS Mean	10.761	-4.972	15.732
	SEM	7.427	6.824	9.264
Week 120	95% CI	( -3.8,25.4)	(-18.4, 8.4)	( -2.5,34.0)
	Pr >  t			0.0903
	n	4	4	
	LS Mean	10.761	11.029	-0.269
	SEM	7.427	7.464	9.747
Week 132	95% CI	( -3.8,25.4)	( -3.6,25.7)	(-19.4,18.9)
	Pr >  t			0.9780
	n	3	2	
	LS Mean	2.003	-3.010	5.013
	SEM	8.371	10.00	12.41
Week 144	95% CI	(-14.5,18.5)	(-22.7,16.7)	(-19.4,29.4)
	Pr >  t			0.6865
	n	3	1	
	LS Mean	2.003	-2.514	4.517
	SEM	8.371	13.76	15.60

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Europe	Week 156	95% CI	(-14.5,18.5)	(-29.6,24.6)	(-26.2,35.2)
		Pr >  t			0.7723
		n	2	1	
	Week 168	LS Mean	3.073	-2.514	5.587
		SEM	9.986	13.76	16.52
		95% CI	(-16.6,22.7)	(-29.6,24.6)	(-26.9,38.1)
	Week 8	Pr >  t			0.7354
		n	1		
		LS Mean	4.384		
	Week 16	SEM	13.73		
		95% CI	(-22.6,31.4)		
		Pr >  t			
	Week 24	n	66	68	
		LS Mean	17.580	6.542	11.038
		SEM	6.764	6.757	3.849
	Week 32	95% CI	( 4.2,30.9)	( -6.8,19.9)	( 3.5,18.6)
		Pr >  t			0.0044
		n	58	48	
	Week 40	LS Mean	15.724	9.228	6.496
		SEM	6.823	6.871	4.292
		95% CI	( 2.3,29.2)	( -4.3,22.8)	( -1.9,14.9)
	Week 48	Pr >  t			0.1308
		n	51	36	
		LS Mean	21.429	6.475	14.954
Week 8	SEM	6.881	7.035	4.698	
	95% CI	( 7.9,35.0)	( -7.4,20.3)	( 5.7,24.2)	
	Pr >  t			0.0015	
Week 16	n	43	30		
	LS Mean	24.457	3.404	21.053	
	SEM	7.048	7.274	5.045	
Week 24	95% CI	( 10.6,38.4)	(-10.9,17.7)	( 11.1,31.0)	
	Pr >  t			<.0001	
	n	37	25		
Week 32	LS Mean	20.496	4.372	16.124	
	SEM	7.133	7.433	5.391	
	95% CI	( 6.4,34.6)	(-10.3,19.0)	( 5.5,26.7)	
Week 40	Pr >  t			0.0029	
	n	33	21		
	LS Mean	23.037	8.624	14.414	
Week 48	SEM	7.208	7.609	5.725	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	( 8.8,37.2)	( -6.4,23.6)	( 3.2,25.7)
	Pr >  t			0.0120
	n	29	20	
	LS Mean	17.169	4.923	12.246
	SEM	7.300	7.663	5.917
Week 64	95% CI	( 2.8,31.6)	( -10.2,20.0)	( 0.6,23.9)
	Pr >  t			0.0389
	n	23	20	
	LS Mean	19.894	5.714	14.180
	SEM	7.501	7.661	6.165
Week 72	95% CI	( 5.1,34.7)	( -9.4,20.8)	( 2.1,26.3)
	Pr >  t			0.0217
	n	25	19	
	LS Mean	17.498	9.285	8.213
	SEM	7.426	7.716	6.142
Week 84	95% CI	( 2.9,32.1)	( -5.9,24.5)	( -3.8,20.3)
	Pr >  t			0.1816
	n	22	17	
	LS Mean	20.701	8.776	11.925
	SEM	7.545	7.847	6.445
Week 96	95% CI	( 5.8,35.6)	( -6.7,24.2)	( -0.7,24.6)
	Pr >  t			0.0647
	n	20	13	
	LS Mean	26.162	-0.925	27.088
	SEM	7.643	8.215	6.996
Week 108	95% CI	( 11.1,41.2)	( -17.1,15.2)	( 13.4,40.8)
	Pr >  t			0.0001
	n	15	11	
	LS Mean	14.764	3.368	11.396
	SEM	7.995	8.489	7.678
Week 120	95% CI	( -1.0,30.5)	( -13.3,20.1)	( -3.7,26.5)
	Pr >  t			0.1381
	n	16	8	
	LS Mean	13.387	-1.277	14.664
	SEM	7.911	9.118	8.287
Week 132	95% CI	( -2.2,29.0)	( -19.2,16.6)	( -1.6,30.9)
	Pr >  t			0.0772
	n	12	3	
	LS Mean	13.375	4.976	8.400
	SEM	8.315	12.25	11.93

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.0,29.7)	(-19.1,29.0)	(-15.0,31.8)
		Pr >  t			0.4816
	Week 144	n	7	4	
		LS Mean	9.145	3.157	5.989
		SEM	9.393	11.11	11.61
		95% CI	(-9.3,27.6)	(-18.7,25.0)	(-16.8,28.8)
		Pr >  t			0.6060
	Week 156	n	5	2	
		LS Mean	26.126	4.898	21.228
		SEM	10.32	14.26	15.26
		95% CI	( 5.9,46.4)	(-23.1,32.9)	(-8.7,51.2)
		Pr >  t			0.1647
	Week 168	n	2	2	
		LS Mean	14.207	4.898	9.309
		SEM	14.22	14.26	18.13
		95% CI	(-13.7,42.1)	(-23.1,32.9)	(-26.3,44.9)
		Pr >  t			0.6079
	Week 180	n		1	
		LS Mean		4.518	
		SEM		19.03	
		95% CI		(-32.8,41.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		4.518	
		SEM		19.03	
		95% CI		(-32.8,41.9)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	11.757	-3.571	15.329
		SEM	4.107	4.202	5.887
		95% CI	( 3.6,19.9)	(-11.9, 4.7)	( 3.7,27.0)
		Pr >  t			0.0103
	Week 16	n	13	12	
		LS Mean	12.959	2.107	10.852
		SEM	4.245	4.369	6.091
		95% CI	( 4.6,21.4)	(-6.5,10.7)	(-1.2,22.9)
		Pr >  t			0.0771
	Week 24	n	12	10	
		LS Mean	5.544	-0.274	5.818
		SEM	4.402	4.779	6.498

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-3.2,14.3)	(-9.7, 9.2)	(-7.0,18.7)
	Pr >  t			0.3722
	n	9	10	
	LS Mean	0.678	-0.274	0.952
	SEM	5.058	4.779	6.959
Week 40	95% CI	(-9.3,10.7)	(-9.7, 9.2)	(-12.8,14.7)
	Pr >  t			0.8914
	n	7	10	
	LS Mean	20.642	-3.607	24.248
	SEM	5.694	4.779	7.435
Week 48	95% CI	( 9.4,31.9)	(-13.1, 5.8)	( 9.6,38.9)
	Pr >  t			0.0014
	n	7	7	
	LS Mean	11.118	-2.640	13.758
	SEM	5.694	5.681	8.024
Week 56	95% CI	(-0.1,22.4)	(-13.9, 8.6)	(-2.1,29.6)
	Pr >  t			0.0885
	n	6	7	
	LS Mean	12.609	1.504	11.105
	SEM	6.148	5.671	8.356
Week 64	95% CI	( 0.5,24.8)	(-9.7,12.7)	(-5.4,27.6)
	Pr >  t			0.1859
	n	4	7	
	LS Mean	2.815	-3.068	5.882
	SEM	7.455	5.679	9.360
Week 72	95% CI	(-11.9,17.5)	(-14.3, 8.2)	(-12.6,24.4)
	Pr >  t			0.5307
	n	4	4	
	LS Mean	11.150	-2.623	13.773
	SEM	7.455	7.444	10.53
Week 84	95% CI	(-3.6,25.9)	(-17.3,12.1)	(-7.0,34.6)
	Pr >  t			0.1928
	n	4	5	
	LS Mean	9.581	-3.770	13.351
	SEM	7.455	6.673	9.993
Week 96	95% CI	(-5.1,24.3)	(-17.0, 9.4)	(-6.4,33.1)
	Pr >  t			0.1835
	n	3	2	
	LS Mean	5.761	-3.691	9.452
	SEM	8.573	10.43	13.51

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-11.2,22.7)	(-24.3,16.9)	(-17.2,36.1)
		Pr >  t			0.4852
		n	2	3	
	Week 120	LS Mean	-3.476	-3.466	-0.010
		SEM	10.43	8.548	13.48
		95% CI	(-24.1,17.1)	(-20.4,13.4)	(-26.6,26.6)
	Week 120	Pr >  t			0.9994
		n	2	2	
		LS Mean	-7.560	-2.515	-5.045
	Week 132	SEM	10.43	10.42	14.73
		95% CI	(-28.2,13.1)	(-23.1,18.1)	(-34.2,24.1)
		Pr >  t			0.7325
	Week 132	n	1	2	
		LS Mean	1.201	-2.515	3.717
		SEM	14.67	10.42	17.97
	Week 8	95% CI	(-27.8,30.2)	(-23.1,18.1)	(-31.8,39.2)
		Pr >  t			0.8364
		n	16	19	
	Week 8	LS Mean	10.926	-5.041	15.967
		SEM	4.912	4.935	6.214
		95% CI	( 1.1,20.7)	(-14.9, 4.8)	( 3.6,28.4)
	Week 16	Pr >  t			0.0124
		n	12	14	
		LS Mean	15.863	-7.650	23.513
Week 16	SEM	5.465	5.466	6.990	
	95% CI	( 5.0,26.7)	(-18.5, 3.2)	( 9.6,37.4)	
	Pr >  t			0.0012	
Week 24	n	12	8		
	LS Mean	16.413	-8.598	25.011	
	SEM	5.451	6.668	7.854	
Week 24	95% CI	( 5.6,27.3)	(-21.8, 4.6)	( 9.4,40.6)	
	Pr >  t			0.0019	
	n	9	7		
Week 32	LS Mean	-0.930	-8.629	7.698	
	SEM	6.058	6.955	8.539	
	95% CI	(-13.0,11.1)	(-22.4, 5.1)	( -9.2,24.6)	
Week 32	Pr >  t			0.3692	
	n	9	7		
	LS Mean	13.086	0.894	12.191	
Week 40	SEM	6.054	6.955	8.504	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	( 1.1,25.1)	(-12.9,14.7)	( -4.7,29.0)
	Pr >  t			0.1544
	n	8	5	
	LS Mean	-2.156	-6.486	4.330
	SEM	6.296	7.771	9.352
Week 56	95% CI	(-14.6,10.3)	(-21.9, 8.9)	(-14.2,22.8)
	Pr >  t			0.6441
	n	7	3	
	LS Mean	22.535	-6.457	28.992
	SEM	6.577	9.365	10.90
Week 64	95% CI	( 9.5,35.6)	(-25.0,12.1)	( 7.5,50.5)
	Pr >  t			0.0087
	n	5	3	
	LS Mean	1.655	-6.457	8.112
	SEM	7.378	9.365	11.37
Week 72	95% CI	(-12.9,16.3)	(-25.0,12.1)	(-14.4,30.6)
	Pr >  t			0.4766
	n	5	3	
	LS Mean	0.096	-6.621	6.717
	SEM	7.366	9.356	11.37
Week 84	95% CI	(-14.5,14.7)	(-25.1,11.9)	(-15.8,29.2)
	Pr >  t			0.5558
	n	2	2	
	LS Mean	19.082	-6.533	25.615
	SEM	10.70	11.00	14.88
Week 96	95% CI	( -2.1,40.2)	(-28.3,15.2)	( -3.8,55.0)
	Pr >  t			0.0875
	n	3	2	
	LS Mean	14.450	-6.533	20.983
	SEM	8.942	11.00	13.74
Week 108	95% CI	( -3.2,32.1)	(-28.3,15.2)	( -6.2,48.1)
	Pr >  t			0.1289
	n	1	2	
	LS Mean	12.915	-6.533	19.448
	SEM	14.52	11.00	17.84
Week 120	95% CI	(-15.8,41.6)	(-28.3,15.2)	(-15.8,54.7)
	Pr >  t			0.2776
	n	3	2	
	LS Mean	25.563	-6.533	32.097
	SEM	8.942	11.00	13.74

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 7.9,43.2)	( -28.3,15.2)	( 4.9,59.3)
		Pr >  t			0.0209
	Week 132	n	1	1	
		LS Mean	18.824	-6.390	25.214
		SEM	14.52	14.76	20.38
		95% CI	( -9.9,47.6)	(-35.6,22.8)	(-15.1,65.5)
		Pr >  t			0.2183
	Week 144	n	2		
		LS Mean	31.888		
		SEM	10.59		
		95% CI	( 10.9,52.8)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	18.824		
		SEM	14.52		
		95% CI	( -9.9,47.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	52.164		
		SEM	14.52		
		95% CI	( 23.4,80.9)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	52.164		
		SEM	14.52		
		95% CI	( 23.4,80.9)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	85.494		
		SEM	14.52		
		95% CI	( 56.8, 114)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	29.161	30.026	-0.866
		SEM	7.492	11.62	12.74
		95% CI	( 13.6,44.7)	( 6.0,54.0)	(-27.2,25.4)
		Pr >  t			0.9464
	Week 16	n	13	4	
		LS Mean	19.420	13.394	6.026
		SEM	7.896	12.69	13.69

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	( 3.2,35.6)	(-12.5,39.3)	(-21.9,34.0)
	Pr >  t			0.6629
	n	9	2	
	LS Mean	20.474	3.316	17.158
	SEM	8.544	15.11	16.23
Week 32	95% CI	( 3.1,37.8)	(-27.0,33.7)	(-15.5,49.8)
	Pr >  t			0.2956
	n	6	3	
	LS Mean	-0.303	16.261	-16.56
	SEM	9.398	13.61	15.27
Week 40	95% CI	(-19.2,18.6)	(-11.3,43.8)	(-47.4,14.3)
	Pr >  t			0.2846
	n	6	2	
	LS Mean	11.118	11.583	-0.465
	SEM	9.503	15.11	16.66
Week 48	95% CI	( -8.0,30.2)	(-18.8,41.9)	(-33.9,33.0)
	Pr >  t			0.9778
	n	5	1	
	LS Mean	10.281	8.822	1.459
	SEM	9.936	18.92	20.43
Week 56	95% CI	( -9.7,30.2)	(-28.9,46.5)	(-39.3,42.2)
	Pr >  t			0.9432
	n	5	1	
	LS Mean	10.281	8.822	1.459
	SEM	9.936	18.92	20.43
Week 64	95% CI	( -9.7,30.2)	(-28.9,46.5)	(-39.3,42.2)
	Pr >  t			0.9432
	n	3	1	
	LS Mean	9.385	8.822	0.564
	SEM	11.40	18.92	21.18
Week 72	95% CI	(-13.4,32.1)	(-28.9,46.5)	(-41.6,42.8)
	Pr >  t			0.9788
	n	4	1	
	LS Mean	9.132	8.822	0.310
	SEM	10.53	18.92	20.73
Week 84	95% CI	(-11.9,30.2)	(-28.9,46.5)	(-41.0,41.6)
	Pr >  t			0.9881
	n	4	1	
	LS Mean	17.464	8.822	8.642
	SEM	10.53	18.92	20.73

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-3.6,38.5)	(-28.9,46.5)	(-32.7,50.0)
	Pr >  t			0.6780
	n	3	1	
	LS Mean	9.385	8.822	0.564
	SEM	11.40	18.92	21.18
Week 108	95% CI	(-13.4,32.1)	(-28.9,46.5)	(-41.6,42.8)
	Pr >  t			0.9788
	n	4		
	LS Mean	9.132		
	SEM	10.53		
Week 120	95% CI	(-11.9,30.2)		
	Pr >  t			
	n	3		
	LS Mean	9.385		
	SEM	11.40		
Week 132	95% CI	(-13.4,32.1)		
	Pr >  t			
	n	3		
	LS Mean	9.385		
	SEM	11.40		
Week 144	95% CI	(-13.4,32.1)		
	Pr >  t			
	n	3		
	LS Mean	20.783		
	SEM	11.41		
Week 156	95% CI	(-2.0,43.5)		
	Pr >  t			
	n	2		
	LS Mean	9.854		
	SEM	12.90		
	95% CI	(-15.8,35.5)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status (L) Primary resistant		Week 8	n	21	16		
			LS Mean	11.589	-3.436	15.026	
			SEM	7.131	8.292	8.540	
			95% CI	(-2.8,26.0)	(-20.2,13.3)	(-2.1,32.2)	
				Pr >  t			0.0847
		Week 16	n	17	10		
			LS Mean	5.548	1.042	4.506	
			SEM	7.566	9.398	9.661	
			95% CI	(-9.7,20.8)	(-17.8,19.9)	(-14.8,23.8)	
				Pr >  t			0.6425
		Week 24	n	9	5		
			LS Mean	13.244	-2.964	16.207	
			SEM	8.507	11.06	12.12	
			95% CI	(-3.7,30.2)	(-25.0,19.0)	(-7.8,40.3)	
				Pr >  t			0.1842
		Week 32	n	8	4		
			LS Mean	7.346	-3.078	10.424	
			SEM	8.728	11.78	12.98	
			95% CI	(-10.1,24.8)	(-26.5,20.3)	(-15.3,36.1)	
				Pr >  t			0.4236
		Week 40	n	5	4		
			LS Mean	18.926	-3.078	22.004	
			SEM	9.860	11.78	13.86	
			95% CI	(-0.7,38.5)	(-26.5,20.3)	(-5.5,49.5)	
		Pr >  t			0.1153		
Week 48	n	5	3				
	LS Mean	18.926	-3.162	22.088			
	SEM	9.860	12.77	14.72			
	95% CI	(-0.7,38.5)	(-28.5,22.2)	(-7.1,51.2)			
		Pr >  t			0.1362		
Week 56	n	4	3				
	LS Mean	20.946	-3.162	24.108			
	SEM	10.51	12.77	15.20			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	95% CI	( 0.1,41.8)	(-28.5,22.2)	( -6.0,54.2)	
	Pr >  t			0.1155	
	n	4	3		
	LS Mean	4.278	7.948	-3.670	
	SEM	10.51	12.77	15.20	
Week 72	95% CI	(-16.6,25.1)	(-17.4,33.3)	(-33.8,26.4)	
	Pr >  t			0.8096	
	n	4	3		
	LS Mean	20.946	-3.162	24.108	
	SEM	10.51	12.77	15.20	
Week 84	95% CI	( 0.1,41.8)	(-28.5,22.2)	( -6.0,54.2)	
	Pr >  t			0.1155	
	n	2	3		
	LS Mean	19.583	-3.162	22.745	
	SEM	13.51	12.77	17.28	
Week 96	95% CI	( -7.2,46.3)	(-28.5,22.2)	(-11.5,57.0)	
	Pr >  t			0.1908	
	n	1	3		
	LS Mean	12.600	-3.162	15.762	
	SEM	17.72	12.77	20.96	
Week 108	95% CI	(-22.5,47.7)	(-28.5,22.2)	(-25.8,57.3)	
	Pr >  t			0.4538	
	n		2		
	LS Mean		-3.478		
	SEM		14.43		
Week 120	95% CI		(-32.1,25.1)		
	Pr >  t				
	n	1	1		
	LS Mean	12.600	-2.158	14.758	
	SEM	17.72	18.51	24.87	
Week 132	95% CI	(-22.5,47.7)	(-38.8,34.5)	(-34.6,64.1)	
	Pr >  t			0.5544	
	n		1		
	LS Mean		-2.158		
	SEM		18.51		
Week 144	95% CI		(-38.8,34.5)		
	Pr >  t				
	n	1			
	LS Mean	12.600			
	SEM	17.72			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.5,47.7)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	14.738	4.971	9.768
		SEM	3.192	3.185	2.771
		95% CI	( 8.5,21.0)	( -1.3,11.2)	( 4.3,15.2)
		Pr >  t			0.0005
	Week 16	n	83	81	
		LS Mean	16.488	5.212	11.276
		SEM	3.297	3.368	3.049
		95% CI	( 10.0,23.0)	( -1.4,11.8)	( 5.3,17.3)
		Pr >  t			0.0002
	Week 24	n	75	62	
		LS Mean	18.386	3.661	14.726
		SEM	3.377	3.566	3.302
		95% CI	( 11.8,25.0)	( -3.3,10.7)	( 8.2,21.2)
		Pr >  t			<.0001
	Week 32	n	59	56	
		LS Mean	17.484	1.913	15.572
		SEM	3.596	3.636	3.539
		95% CI	( 10.4,24.5)	( -5.2, 9.1)	( 8.6,22.5)
		Pr >  t			<.0001
	Week 40	n	52	48	
		LS Mean	18.854	4.178	14.676
		SEM	3.685	3.775	3.748
		95% CI	( 11.6,26.1)	( -3.2,11.6)	( 7.3,22.0)
		Pr >  t			<.0001
	Week 48	n	47	37	
		LS Mean	13.966	5.003	8.962
		SEM	3.763	4.001	4.047
		95% CI	( 6.6,21.4)	( -2.9,12.9)	( 1.0,16.9)
		Pr >  t			0.0270
	Week 56	n	41	31	
		LS Mean	14.577	2.679	11.898
		SEM	3.877	4.180	4.329
		95% CI	( 7.0,22.2)	( -5.5,10.9)	( 3.4,20.4)
		Pr >  t			0.0061
	Week 64	n	32	28	
		LS Mean	16.744	0.940	15.804
		SEM	4.112	4.295	4.647

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	( 8.7,24.8)	( -7.5, 9.4)	( 6.7,24.9)	
	Pr >  t			0.0007	
	n	29	22		
	LS Mean	16.427	4.440	11.987	
	SEM	4.222	4.596	5.018	
Week 84	95% CI	( 8.1,24.7)	( -4.6,13.5)	( 2.1,21.8)	
	Pr >  t			0.0171	
	n	26	21		
	LS Mean	18.297	1.740	16.556	
	SEM	4.346	4.659	5.180	
Week 96	95% CI	( 9.8,26.8)	( -7.4,10.9)	( 6.4,26.7)	
	Pr >  t			0.0014	
	n	23	14		
	LS Mean	20.517	-3.317	23.835	
	SEM	4.500	5.308	5.887	
Week 108	95% CI	( 11.7,29.3)	(-13.7, 7.1)	( 12.3,35.4)	
	Pr >  t			<.0001	
	n	18	13		
	LS Mean	16.641	0.622	16.019	
	SEM	4.851	5.447	6.278	
Week 120	95% CI	( 7.1,26.2)	(-10.1,11.3)	( 3.7,28.3)	
	Pr >  t			0.0109	
	n	19	10		
	LS Mean	16.732	3.687	13.046	
	SEM	4.772	5.991	6.698	
Week 132	95% CI	( 7.4,26.1)	( -8.1,15.4)	( -0.1,26.2)	
	Pr >  t			0.0517	
	n	13	4		
	LS Mean	14.776	1.425	13.350	
	SEM	5.405	8.715	9.560	
Week 144	95% CI	( 4.2,25.4)	(-15.7,18.5)	( -5.4,32.1)	
	Pr >  t			0.1629	
	n	8	1		
	LS Mean	21.497	2.259	19.238	
	SEM	6.487	16.62	17.45	
Week 156	95% CI	( 8.8,34.2)	(-30.4,34.9)	(-15.0,53.5)	
	Pr >  t			0.2705	
	n	5	1		
	LS Mean	19.903	2.259	17.644	
	SEM	7.881	16.62	18.01	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	( 4.4,35.4)	(-30.4,34.9)	(-17.7,53.0)
		Pr >  t			0.3276
		n	3	1	
	Week 180	LS Mean	27.220	2.259	24.961
		SEM	9.871	16.62	18.97
		95% CI	( 7.9,46.6)	(-30.4,34.9)	(-12.3,62.2)
	Week 180	Pr >  t			0.1885
		n	1	1	
		LS Mean	54.845	2.259	52.586
	Week 192	SEM	16.56	16.62	23.16
		95% CI	( 22.4,87.3)	(-30.4,34.9)	( 7.1,98.0)
		Pr >  t			0.0234
	Week 192	n	1	1	
		LS Mean	88.175	2.259	85.916
		SEM	16.56	16.62	23.16
	Week 8	95% CI	( 55.7, 121)	(-30.4,34.9)	( 40.5, 131)
		Pr >  t			0.0002
		n	17	16	
	Week 8	LS Mean	17.484	-0.377	17.861
		SEM	4.064	4.147	5.766
		95% CI	( 9.5,25.5)	( -8.6, 7.8)	( 6.5,29.3)
	Week 16	Pr >  t			0.0023
		n	18	14	
		LS Mean	8.956	0.103	8.853
Week 16	SEM	3.978	4.399	5.916	
	95% CI	( 1.1,16.8)	( -8.6, 8.8)	( -2.8,20.5)	
	Pr >  t			0.1365	
Week 24	n	16	13		
	LS Mean	8.317	-2.318	10.635	
	SEM	4.198	4.540	6.165	
Week 24	95% CI	( 0.0,16.6)	(-11.3, 6.6)	( -1.5,22.8)	
	Pr >  t			0.0863	
	n	15	13		
Week 32	LS Mean	9.712	-2.567	12.279	
	SEM	4.308	4.545	6.243	
	95% CI	( 1.2,18.2)	(-11.5, 6.4)	( -0.0,24.6)	
Week 32	Pr >  t			0.0508	
	n	14	10		
	LS Mean	4.774	-2.888	7.662	
Week 40	SEM	4.432	5.084	6.720	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	95% CI	(-4.0,13.5)	(-12.9, 7.1)	(-5.6,20.9)	
	Pr >  t			0.2557	
	n	14	11		
	LS Mean	11.915	-2.784	14.699	
	SEM	4.432	4.890	6.572	
Week 56	95% CI	( 3.2,20.7)	(-12.4, 6.9)	( 1.7,27.7)	
	Pr >  t			0.0265	
	n	11	11		
	LS Mean	13.164	-2.784	15.948	
	SEM	4.879	4.890	6.885	
Week 64	95% CI	( 3.5,22.8)	(-12.4, 6.9)	( 2.4,29.5)	
	Pr >  t			0.0215	
	n	8	11		
	LS Mean	0.554	-2.784	3.338	
	SEM	5.565	4.890	7.392	
Week 72	95% CI	(-10.4,11.5)	(-12.4, 6.9)	(-11.2,17.9)	
	Pr >  t			0.6520	
	n	11	10		
	LS Mean	-1.987	0.425	-2.412	
	SEM	4.879	5.093	7.025	
Week 84	95% CI	(-11.6, 7.6)	(-9.6,10.5)	(-16.3,11.4)	
	Pr >  t			0.7317	
	n	9	9		
	LS Mean	12.148	4.405	7.744	
	SEM	5.293	5.324	7.487	
Week 96	95% CI	( 1.7,22.6)	(-6.1,14.9)	(-7.0,22.5)	
	Pr >  t			0.3021	
	n	8	7		
	LS Mean	18.631	-3.367	21.998	
	SEM	5.572	5.925	8.117	
Week 108	95% CI	( 7.7,29.6)	(-15.0, 8.3)	( 6.0,38.0)	
	Pr >  t			0.0072	
	n	7	6		
	LS Mean	-5.214	-3.367	-1.847	
	SEM	5.903	6.348	8.650	
Week 120	95% CI	(-16.8, 6.4)	(-15.9, 9.1)	(-18.9,15.2)	
	Pr >  t			0.8311	
	n	6	5		
	LS Mean	-5.021	-3.851	-1.170	
	SEM	6.324	6.895	9.324	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-17.5, 7.4)	(-17.4, 9.7)	(-19.5,17.2)
	Pr >  t			0.9003
	n	5	3	
	LS Mean	-5.414	-1.779	-3.635
	SEM	6.857	8.695	11.06
Week 144	95% CI	(-18.9, 8.1)	(-18.9,15.3)	(-25.4,18.1)
	Pr >  t			0.7426
	n	5	4	
	LS Mean	-5.414	-3.463	-1.951
	SEM	6.857	7.620	10.23
Week 156	95% CI	(-18.9, 8.1)	(-18.5,11.5)	(-22.1,18.2)
	Pr >  t			0.8489
	n	4	2	
	LS Mean	9.785	-1.710	11.495
	SEM	7.582	10.52	12.96
Week 168	95% CI	(-5.1,24.7)	(-22.4,19.0)	(-14.0,37.0)
	Pr >  t			0.3759
	n	1	1	
	LS Mean	2.748	-1.435	4.183
	SEM	14.67	14.69	20.76
	95% CI	(-26.1,31.6)	(-30.4,27.5)	(-36.7,45.1)
	Pr >  t			0.8405

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73	
			LS Mean	24.942	10.383	14.559
		SEM	8.581	8.777	3.400	
		95% CI	( 8.0,41.9)	( -7.0,27.7)	( 7.9,21.2)	
		Pr >  t			<.0001	
		Week 16	n	69	55	
			LS Mean	22.748	11.539	11.210
			SEM	8.595	8.856	3.671
			95% CI	( 5.8,39.7)	( -6.0,29.0)	( 4.0,18.4)
		Week 24	n	54	46	
			LS Mean	21.910	8.172	13.738
			SEM	8.638	8.916	3.983
			95% CI	( 4.8,39.0)	( -9.4,25.8)	( 5.9,21.6)
		Week 32	n	49	41	
			LS Mean	23.235	6.492	16.743
			SEM	8.764	8.959	4.150
			95% CI	( 5.9,40.5)	(-11.2,24.2)	( 8.6,24.9)
		Week 40	n	40	33	
			LS Mean	24.097	9.051	15.046
			SEM	8.827	9.054	4.493
			95% CI	( 6.7,41.5)	( -8.8,26.9)	( 6.2,23.9)
		Week 48	n	38	28	
			LS Mean	22.540	7.604	14.935
			SEM	8.848	9.138	4.696
			95% CI	( 5.1,40.0)	(-10.4,25.6)	( 5.7,24.2)
		Week 56	n	32	28	
			LS Mean	23.940	8.643	15.297

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	8.922	9.139	4.839
	95% CI	( 6.3,41.5)	( -9.4,26.7)	( 5.8,24.8)
	Pr >  t			0.0016
	n	23	26	
	LS Mean	21.166	8.313	12.853
Week 72	SEM	9.099	9.181	5.234
	95% CI	( 3.2,39.1)	( -9.8,26.4)	( 2.6,23.1)
	Pr >  t			0.0143
	n	27	25	
	LS Mean	18.136	10.980	7.156
Week 84	SEM	9.008	9.202	5.111
	95% CI	( 0.4,35.9)	( -7.2,29.1)	( -2.9,17.2)
	Pr >  t			0.1619
	n	23	22	
	LS Mean	26.002	10.573	15.430
Week 96	SEM	9.099	9.282	5.409
	95% CI	( 8.1,43.9)	( -7.7,28.9)	( 4.8,26.0)
	Pr >  t			0.0044
	n	20	16	
	LS Mean	29.156	6.108	23.048
Week 108	SEM	9.193	9.524	5.954
	95% CI	( 11.0,47.3)	( -12.7,24.9)	( 11.4,34.7)
	Pr >  t			0.0001
	n	20	14	
	LS Mean	18.489	8.388	10.100
Week 120	SEM	9.193	9.643	6.150
	95% CI	( 0.4,36.6)	( -10.6,27.4)	( -2.0,22.2)
	Pr >  t			0.1008
	n	17	11	
	LS Mean	18.086	11.382	6.703
Week 132	SEM	9.317	9.903	6.721
	95% CI	( -0.3,36.5)	( -8.1,30.9)	( -6.5,19.9)
	Pr >  t			0.3188
	n	13	6	
	LS Mean	13.775	8.386	5.389
Week 144	SEM	9.562	10.83	8.324
	95% CI	( -5.1,32.6)	( -12.9,29.7)	( -10.9,21.7)
	Pr >  t			0.5176
	n	10	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Second Line	Week 156	LS Mean	13.733	7.292	6.441
		SEM	9.866	11.22	9.159
		95% CI	( -5.7,33.2)	(-14.8,29.4)	(-11.5,24.4)
		Pr >  t			0.4821
		n	7	3	
	Week 168	LS Mean	26.086	8.627	17.459
		SEM	10.41	12.65	11.36
		95% CI	( 5.6,46.6)	(-16.2,33.5)	( -4.8,39.8)
		Pr >  t			0.1246
		n	3	2	
	Week 180	LS Mean	17.736	8.569	9.168
		SEM	12.53	14.24	14.85
		95% CI	( -6.9,42.4)	(-19.4,36.5)	(-20.0,38.3)
		Pr >  t			0.5371
		n		1	
	Week 192	LS Mean		8.604	
		SEM		18.17	
		95% CI		(-27.1,44.3)	
		Pr >  t			
		n		1	
	Week 8	LS Mean		8.604	
		SEM		18.17	
		95% CI		(-27.1,44.3)	
		Pr >  t			
n			1		
Week 16	LS Mean	11.523	2.662	8.861	
	SEM	2.912	2.924	3.281	
	95% CI	( 5.8,17.3)	( -3.1, 8.4)	( 2.4,15.3)	
	Pr >  t			0.0072	
	n	66	67		
Week 24	LS Mean	13.062	3.377	9.685	
	SEM	3.112	3.213	3.639	
	95% CI	( 6.9,19.2)	( -2.9, 9.7)	( 2.5,16.8)	
	Pr >  t			0.0080	
	n	54	52		
Week 24	LS Mean	16.557	2.802	13.754	
	SEM	3.221	3.631	4.077	
	95% CI	( 10.2,22.9)	( -4.3, 9.9)	( 5.7,21.8)	
	Pr >  t			0.0008	
	n	49	35		

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172	
Week 32	n	36	32	
	LS Mean	12.285	1.867	10.419
	SEM	3.559	3.754	4.413
	95% CI	( 5.3,19.3)	( -5.5, 9.2)	( 1.8,19.1)
	Pr >  t			0.0185
Week 40	n	33	29	
	LS Mean	12.301	2.431	9.870
	SEM	3.654	3.900	4.594
	95% CI	( 5.1,19.5)	( -5.2,10.1)	( 0.8,18.9)
	Pr >  t			0.0321
Week 48	n	29	23	
	LS Mean	8.159	5.351	2.808
	SEM	3.803	4.200	4.966
	95% CI	( 0.7,15.6)	( -2.9,13.6)	( -6.9,12.6)
	Pr >  t			0.5720
Week 56	n	25	17	
	LS Mean	11.383	0.080	11.303
	SEM	3.984	4.660	5.503
	95% CI	( 3.6,19.2)	( -9.1, 9.2)	( 0.5,22.1)
	Pr >  t			0.0404
Week 64	n	22	16	
	LS Mean	13.386	-0.196	13.582
	SEM	4.157	4.767	5.719
	95% CI	( 5.2,21.6)	( -9.6, 9.2)	( 2.4,24.8)
	Pr >  t			0.0178
Week 72	n	20	10	
	LS Mean	10.835	0.815	10.020
	SEM	4.295	5.709	6.617
	95% CI	( 2.4,19.3)	(-10.4,12.0)	( -3.0,23.0)
	Pr >  t			0.1304
Week 84	n	16	11	
	LS Mean	12.546	0.227	12.320
	SEM	4.682	5.496	6.681
	95% CI	( 3.4,21.7)	(-10.6,11.0)	( -0.8,25.4)
	Pr >  t			0.0656
Week 96	n	15	8	
	LS Mean	13.920	-6.120	20.039
	SEM	4.783	6.247	7.387
	95% CI	( 4.5,23.3)	(-18.4, 6.1)	( 5.5,34.5)

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
		Pr >  t		0.0068
	Week 108	n	6	7
		LS Mean	8.189	-3.893
		SEM	6.977	6.605
		95% CI	(-5.5,21.9)	(-16.9, 9.1)
		Pr >  t		(-6.0,30.2)
	Week 120	n	11	5
		LS Mean	10.884	-4.722
		SEM	5.404	7.636
		95% CI	( 0.3,21.5)	(-19.7,10.3)
		Pr >  t		(-2.0,33.2)
	Week 132	n	7	2
		LS Mean	13.515	-0.647
		SEM	6.527	11.62
		95% CI	( 0.7,26.3)	(-23.5,22.2)
		Pr >  t		(-11.4,39.8)
	Week 144	n	5	
		LS Mean	23.319	
		SEM	7.535	
		95% CI	( 8.5,38.1)	
		Pr >  t		0.2779
	Week 156	n	3	
		LS Mean	10.547	
		SEM	9.548	
		95% CI	(-8.2,29.3)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	52.689	
		SEM	16.15	
		95% CI	( 21.0,84.4)	
		Pr >  t		
	Week 180	n	1	
		LS Mean	52.689	
		SEM	16.15	
		95% CI	( 21.0,84.4)	
		Pr >  t		
	Week 192	n	1	
		LS Mean	86.019	
		SEM	16.15	

Subgroup	Time Window	95% CI Pr >  t	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
			( 54.3, 118)		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	9.436	-3.463	12.899		
			SEM	4.160	4.061	3.202		
			95% CI	( 1.2,17.6)	(-11.5, 4.5)	( 6.6,19.2)		
					Pr >  t			<.0001
		Week 16	n	60	51			
			LS Mean	8.242	-0.749	8.991		
			SEM	4.258	4.320	3.445		
			95% CI	( -0.1,16.6)	( -9.2, 7.8)	( 2.2,15.8)		
					Pr >  t			0.0094
		Week 24	n	51	42			
			LS Mean	8.449	-3.672	12.120		
			SEM	4.342	4.436	3.710		
			95% CI	( -0.1,17.0)	(-12.4, 5.1)	( 4.8,19.4)		
					Pr >  t			0.0012
		Week 32	n	46	36			
			LS Mean	9.918	-2.938	12.857		
			SEM	4.446	4.598	3.918		
			95% CI	( 1.2,18.7)	(-12.0, 6.1)	( 5.2,20.6)		
					Pr >  t			0.0011
		Week 40	n	40	33			
			LS Mean	12.409	-4.362	16.771		
			SEM	4.540	4.668	4.102		
			95% CI	( 3.5,21.3)	(-13.5, 4.8)	( 8.7,24.8)		
			Pr >  t			<.0001		
Week 48	n	37	28					
	LS Mean	9.298	-1.613	10.911				
	SEM	4.592	4.805	4.313				
	95% CI	( 0.3,18.3)	(-11.1, 7.8)	( 2.4,19.4)				
			Pr >  t			0.0116		
Week 56	n	33	23					
	LS Mean	6.170	-5.650	11.819				
	SEM	4.678	4.993	4.610				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 64	95% CI	(-3.0,15.4)	(-15.5, 4.2)	( 2.8,20.9)
	Pr >  t			0.0106
	n	26	20	
	LS Mean	5.809	-6.089	11.898
	SEM	4.876	5.145	4.970
Week 72	95% CI	(-3.8,15.4)	(-16.2, 4.0)	( 2.1,21.7)
	Pr >  t			0.0169
	n	28	17	
	LS Mean	4.820	-5.979	10.799
	SEM	4.811	5.339	5.109
Week 84	95% CI	(-4.6,14.3)	(-16.5, 4.5)	( 0.8,20.8)
	Pr >  t			0.0348
	n	23	17	
	LS Mean	8.186	-6.478	14.664
	SEM	4.990	5.341	5.281
Week 96	95% CI	(-1.6,18.0)	(-17.0, 4.0)	( 4.3,25.0)
	Pr >  t			0.0056
	n	23	11	
	LS Mean	11.900	-7.007	18.907
	SEM	4.994	5.989	5.938
Week 108	95% CI	( 2.1,21.7)	(-18.8, 4.8)	( 7.3,30.6)
	Pr >  t			0.0015
	n	15	13	
	LS Mean	3.682	-6.546	10.228
	SEM	5.499	5.717	6.111
Week 120	95% CI	(-7.1,14.5)	(-17.8, 4.7)	(-1.8,22.2)
	Pr >  t			0.0946
	n	16	9	
	LS Mean	2.769	0.329	2.440
	SEM	5.415	6.362	6.651
Week 132	95% CI	(-7.9,13.4)	(-12.2,12.8)	(-10.6,15.5)
	Pr >  t			0.7139
	n	14	5	
	LS Mean	6.428	-4.204	10.632
	SEM	5.595	7.779	8.137
Week 144	95% CI	(-4.6,17.4)	(-19.5,11.1)	(-5.3,26.6)
	Pr >  t			0.1917
	n	8	3	
	LS Mean	7.646	-4.265	11.911
	SEM	6.587	9.516	10.41



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-5.3,20.6)	(-22.9,14.4)	(-8.5,32.3)
		Pr >  t			0.2528
		n	7	2	
	Week 168	LS Mean	17.157	-4.381	21.538
		SEM	6.882	11.31	12.24
		95% CI	( 3.6,30.7)	(-26.6,17.8)	(-2.5,45.6)
	Week 180	Pr >  t			0.0788
		n	4	2	
		LS Mean	15.301	-4.381	19.682
	Week 192	SEM	8.447	11.31	13.18
		95% CI	(-1.3,31.9)	(-26.6,17.8)	(-6.2,45.6)
		Pr >  t			0.1358
	Week 8	n	1	1	
		LS Mean	46.343	-4.131	50.474
		SEM	15.47	15.47	21.28
	Week 16	95% CI	( 16.0,76.7)	(-34.5,26.2)	( 8.7,92.3)
		Pr >  t			0.0180
		n	1	1	
	Week 24	LS Mean	79.673	-4.131	83.804
		SEM	15.47	15.47	21.28
		95% CI	( 49.3, 110)	(-34.5,26.2)	( 42.0, 126)
	Week 32	Pr >  t			<.0001
		n	18	17	
		LS Mean	18.849	-0.521	19.370
Week 8	SEM	5.811	6.066	8.403	
	95% CI	( 7.3,30.4)	(-12.6,11.5)	( 2.7,36.1)	
	Pr >  t			0.0236	
Week 16	n	17	11		
	LS Mean	21.423	3.097	18.326	
	SEM	5.964	7.346	9.483	
Week 24	95% CI	( 9.6,33.3)	(-11.5,17.7)	(-0.5,37.1)	
	Pr >  t			0.0561	
	n	15	5		
Week 32	LS Mean	18.849	-6.254	25.103	
	SEM	6.278	10.28	12.07	
	95% CI	( 6.4,31.3)	(-26.6,14.1)	( 1.2,49.0)	
Week 8	Pr >  t			0.0394	
	n	13	5		
	LS Mean	9.662	-6.254	15.917	
Week 16	SEM	6.631	10.28	12.26	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-3.5,22.8)	(-26.6,14.1)	(-8.3,40.1)	
	Pr >  t			0.1962	
	n	11	5		
	LS Mean	14.715	0.412	14.304	
	SEM	7.067	10.28	12.50	
Week 48	95% CI	(0.7,28.7)	(-19.9,20.7)	(-10.4,39.0)	
	Pr >  t			0.2544	
	n	11	2		
	LS Mean	13.753	-3.781	17.534	
	SEM	7.072	15.08	16.67	
Week 56	95% CI	(-0.2,27.7)	(-33.5,26.0)	(-15.4,50.4)	
	Pr >  t			0.2943	
	n	8	2		
	LS Mean	19.235	-3.781	23.016	
	SEM	7.972	15.08	17.07	
Week 64	95% CI	(3.5,35.0)	(-33.5,26.0)	(-10.7,56.7)	
	Pr >  t			0.1792	
	n	7	3		
	LS Mean	7.898	13.265	-5.367	
	SEM	8.400	12.70	15.24	
Week 72	95% CI	(-8.7,24.5)	(-11.8,38.3)	(-35.5,24.7)	
	Pr >  t			0.7252	
	n	7	3		
	LS Mean	6.139	2.155	3.984	
	SEM	8.425	12.70	15.26	
Week 84	95% CI	(-10.5,22.8)	(-22.9,27.2)	(-26.1,34.1)	
	Pr >  t			0.7943	
	n	7	2		
	LS Mean	25.187	-3.781	28.967	
	SEM	8.425	15.08	17.29	
Week 96	95% CI	(8.5,41.8)	(-33.5,26.0)	(-5.2,63.1)	
	Pr >  t			0.0956	
	n	6	3		
	LS Mean	28.121	-8.955	37.076	
	SEM	8.954	12.70	15.56	
Week 108	95% CI	(10.4,45.8)	(-34.0,16.1)	(6.4,67.8)	
	Pr >  t			0.0183	
	n	7	2		
	LS Mean	10.901	5.346	5.555	
	SEM	8.425	15.05	17.26	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-5.7,27.5)	(-24.4,35.0)	(-28.5,39.6)
		Pr >  t			0.7479
		n	6	1	
	Week 132	LS Mean	0.343	-19.30	19.646
		SEM	8.954	20.62	22.49
		95% CI	(-17.3,18.0)	(-60.0,21.4)	(-24.7,64.0)
	Week 144	Pr >  t			0.3835
		n	4		
		LS Mean	2.975		
	Week 156	SEM	10.58		
		95% CI	(-17.9,23.9)		
		Pr >  t			
	Week 8	n	5		
		LS Mean	10.564		
		SEM	9.638		
Week 16	95% CI	(-8.5,29.6)			
	Pr >  t				
	n	3			
Week 24	LS Mean	0.844			
	SEM	12.00			
	95% CI	(-22.8,24.5)			
Week 32	Pr >  t				
	n	59	57		
	LS Mean	14.011	6.928	7.083	
Week 16	SEM	3.447	3.611	3.783	
	95% CI	( 7.2,20.8)	(-0.2,14.0)	(-0.4,14.5)	
	Pr >  t			0.0621	
Week 24	n	47	44		
	LS Mean	13.963	4.920	9.043	
	SEM	3.659	3.871	4.215	
Week 32	95% CI	( 6.8,21.2)	(-2.7,12.5)	( 0.8,17.3)	
	Pr >  t			0.0326	
	n	39	34		
Week 8	LS Mean	17.905	4.921	12.983	
	SEM	3.865	4.183	4.642	
	95% CI	( 10.3,25.5)	(-3.3,13.2)	( 3.9,22.1)	
Week 16	Pr >  t			0.0054	
	n	27	32		
	LS Mean	15.994	0.730	15.265	
Week 24	SEM	4.332	4.249	5.063	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	( 7.5,24.5)	( -7.6, 9.1)	( 5.3,25.2)	
	Pr >  t			0.0027	
	n	24	24		
	LS Mean	12.037	5.361	6.676	
	SEM	4.474	4.622	5.476	
Week 48	95% CI	( 3.2,20.8)	( -3.7,14.4)	( -4.1,17.4)	
	Pr >  t			0.2233	
	n	21	21		
	LS Mean	11.667	3.481	8.186	
	SEM	4.656	4.808	5.786	
Week 56	95% CI	( 2.5,20.8)	( -6.0,12.9)	( -3.2,19.6)	
	Pr >  t			0.1577	
	n	18	20		
	LS Mean	20.720	4.546	16.174	
	SEM	4.881	4.880	6.037	
Week 64	95% CI	( 11.1,30.3)	( -5.0,14.1)	( 4.3,28.0)	
	Pr >  t			0.0076	
	n	14	19		
	LS Mean	23.116	1.385	21.731	
	SEM	5.304	4.958	6.452	
Week 72	95% CI	( 12.7,33.5)	( -8.4,11.1)	( 9.1,34.4)	
	Pr >  t			0.0008	
	n	13	15		
	LS Mean	19.136	8.483	10.653	
	SEM	5.446	5.343	6.866	
Week 84	95% CI	( 8.4,29.8)	( -2.0,19.0)	( -2.8,24.1)	
	Pr >  t			0.1213	
	n	10	14		
	LS Mean	17.157	8.783	8.373	
	SEM	6.047	5.464	7.403	
Week 96	95% CI	( 5.3,29.0)	( -2.0,19.5)	( -6.2,22.9)	
	Pr >  t			0.2585	
	n	6	10		
	LS Mean	15.226	-1.252	16.478	
	SEM	7.383	6.145	9.013	
Week 108	95% CI	( 0.7,29.7)	( -13.3,10.8)	( -1.2,34.2)	
	Pr >  t			0.0681	
	n	4	6		
	LS Mean	15.793	-0.362	16.155	
	SEM	8.825	7.489	11.06	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-1.5,33.1)	(-15.1,14.3)	(-5.6,37.9)
	Pr >  t			0.1448
	n	6	6	
	LS Mean	30.734	-0.525	31.259
	SEM	7.386	7.493	9.981
Week 132	95% CI	(16.2,45.2)	(-15.2,14.2)	(11.7,50.9)
	Pr >  t			0.0018
	n	2	3	
	LS Mean	1.417	1.657	-0.239
	SEM	12.07	10.06	15.34
Week 144	95% CI	(-22.3,25.1)	(-18.1,21.4)	(-30.4,29.9)
	Pr >  t			0.9876
	n	2	2	
	LS Mean	12.476	-0.839	13.315
	SEM	12.02	12.12	16.78
Week 156	95% CI	(-11.1,36.1)	(-24.6,23.0)	(-19.6,46.3)
	Pr >  t			0.4277
	n		1	
	LS Mean		2.699	
	SEM		16.76	
	95% CI		(-30.2,35.6)	
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	24.508	11.131	13.376
		SEM	9.330	9.639	4.129
		95% CI	( 6.0,43.0)	( -8.0,30.2)	( 5.2,21.5)
		Pr >  t			0.0014
	Week 16	n	51	41	
		LS Mean	24.235	12.442	11.793
		SEM	9.352	9.755	4.526
		95% CI	( 5.7,42.8)	( -6.9,31.8)	( 2.9,20.7)
		Pr >  t			0.0096
	Week 24	n	38	33	
		LS Mean	23.139	8.795	14.343
		SEM	9.426	9.856	4.988
		95% CI	( 4.5,41.8)	(-10.7,28.3)	( 4.5,24.2)
		Pr >  t			0.0043
	Week 32	n	34	28	
		LS Mean	24.956	6.399	18.558
		SEM	9.619	9.936	5.259
		95% CI	( 5.9,44.0)	(-13.3,26.1)	( 8.2,28.9)
		Pr >  t			0.0005
	Week 40	n	26	23	
		LS Mean	29.004	10.267	18.737
		SEM	9.752	10.06	5.738
		95% CI	( 9.7,48.3)	( -9.6,30.2)	( 7.5,30.0)
		Pr >  t			0.0012
	Week 48	n	24	17	
		LS Mean	22.621	8.099	14.523
		SEM	9.803	10.29	6.210
95% CI		( 3.2,42.0)	(-12.2,28.4)	( 2.3,26.7)	
	Pr >  t			0.0197	
Week 56	n	21	17		
	LS Mean	24.454	9.800	14.655	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	9.892	10.29	6.356
	95% CI	( 4.9,44.0)	(-10.5,30.1)	( 2.2,27.1)
	Pr >  t			0.0215
Week 64	n	15	15	
	LS Mean	26.918	9.326	17.592
	SEM	10.17	10.41	6.952
	95% CI	( 6.8,47.0)	(-11.2,29.9)	( 3.9,31.2)
	Pr >  t			0.0117
Week 72	n	16	15	
	LS Mean	24.820	11.538	13.282
	SEM	10.11	10.41	6.866
	95% CI	( 4.8,44.8)	( -9.0,32.1)	( -0.2,26.8)
	Pr >  t			0.0536
Week 84	n	14	13	
	LS Mean	28.237	8.109	20.128
	SEM	10.24	10.55	7.260
	95% CI	( 8.0,48.5)	(-12.7,28.9)	( 5.9,34.4)
	Pr >  t			0.0057
Week 96	n	12	9	
	LS Mean	29.181	6.009	23.173
	SEM	10.41	11.01	8.129
	95% CI	( 8.6,49.7)	(-15.7,27.7)	( 7.2,39.1)
	Pr >  t			0.0045
Week 108	n	13	8	
	LS Mean	26.193	9.894	16.299
	SEM	10.32	11.19	8.264
	95% CI	( 5.8,46.6)	(-12.2,32.0)	( 0.1,32.5)
	Pr >  t			0.0490
Week 120	n	11	6	
	LS Mean	25.461	15.716	9.746
	SEM	10.51	11.71	9.178
	95% CI	( 4.7,46.2)	( -7.4,38.8)	( -8.3,27.8)
	Pr >  t			0.2887
Week 132	n	8	3	
	LS Mean	19.382	8.792	10.590
	SEM	10.96	13.57	11.89
	95% CI	( -2.2,41.0)	(-17.9,35.5)	(-12.8,33.9)
	Pr >  t			0.3735
Week 144	n	5	1	
	LS Mean	21.018	9.431	11.587

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	11.89	19.34	18.77
		95% CI	(-2.4,44.4)	(-28.6,47.4)	(-25.3,48.5)
		Pr >  t			0.5374
		n	3	1	
		LS Mean	31.038	9.431	21.608
	Week 168	SEM	13.39	19.34	19.76
		95% CI	(4.7,57.4)	(-28.6,47.4)	(-17.2,60.4)
		Pr >  t			0.2747
		n	2	1	
		LS Mean	20.539	9.431	11.108
	Week 180	SEM	15.04	19.34	20.91
		95% CI	(-9.0,50.1)	(-28.6,47.4)	(-30.0,52.2)
		Pr >  t			0.5955
		n		1	
		LS Mean		9.431	
	Week 192	SEM		19.34	
		95% CI		(-28.6,47.4)	
		Pr >  t			
		n		1	
		LS Mean		9.431	
	Week 8	SEM		19.34	
		95% CI		(-28.6,47.4)	
		Pr >  t			
		n	17	16	
LS Mean		17.484	-0.377	17.861	
Week 16	SEM	4.064	4.147	5.766	
	95% CI	(9.5,25.5)	(-8.6, 7.8)	(6.5,29.3)	
	Pr >  t			0.0023	
	n	18	14		
	LS Mean	8.956	0.103	8.853	
Week 24	SEM	3.978	4.399	5.916	
	95% CI	(1.1,16.8)	(-8.6, 8.8)	(-2.8,20.5)	
	Pr >  t			0.1365	
	n	16	13		
	LS Mean	8.317	-2.318	10.635	
Week 32	SEM	4.198	4.540	6.165	
	95% CI	(0.0,16.6)	(-11.3, 6.6)	(-1.5,22.8)	
	Pr >  t			0.0863	
	n	15	13		
	LS Mean	9.712	-2.567	12.279	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	4.308	4.545	6.243
	95% CI	( 1.2,18.2)	(-11.5, 6.4)	( -0.0,24.6)
	Pr >  t			0.0508
Week 40	n	14	10	
	LS Mean	4.774	-2.888	7.662
	SEM	4.432	5.084	6.720
	95% CI	( -4.0,13.5)	(-12.9, 7.1)	( -5.6,20.9)
	Pr >  t			0.2557
Week 48	n	14	11	
	LS Mean	11.915	-2.784	14.699
	SEM	4.432	4.890	6.572
	95% CI	( 3.2,20.7)	(-12.4, 6.9)	( 1.7,27.7)
	Pr >  t			0.0265
Week 56	n	11	11	
	LS Mean	13.164	-2.784	15.948
	SEM	4.879	4.890	6.885
	95% CI	( 3.5,22.8)	(-12.4, 6.9)	( 2.4,29.5)
	Pr >  t			0.0215
Week 64	n	8	11	
	LS Mean	0.554	-2.784	3.338
	SEM	5.565	4.890	7.392
	95% CI	(-10.4,11.5)	(-12.4, 6.9)	(-11.2,17.9)
	Pr >  t			0.6520
Week 72	n	11	10	
	LS Mean	-1.987	0.425	-2.412
	SEM	4.879	5.093	7.025
	95% CI	(-11.6, 7.6)	( -9.6,10.5)	(-16.3,11.4)
	Pr >  t			0.7317
Week 84	n	9	9	
	LS Mean	12.148	4.405	7.744
	SEM	5.293	5.324	7.487
	95% CI	( 1.7,22.6)	( -6.1,14.9)	( -7.0,22.5)
	Pr >  t			0.3021
Week 96	n	8	7	
	LS Mean	18.631	-3.367	21.998
	SEM	5.572	5.925	8.117
	95% CI	( 7.7,29.6)	(-15.0, 8.3)	( 6.0,38.0)
	Pr >  t			0.0072
Week 108	n	7	6	
	LS Mean	-5.214	-3.367	-1.847

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.903	6.348	8.650
		95% CI	(-16.8, 6.4)	(-15.9, 9.1)	(-18.9,15.2)
		Pr >  t			0.8311
	Week 120	n	6	5	
		LS Mean	-5.021	-3.851	-1.170
		SEM	6.324	6.895	9.324
		95% CI	(-17.5, 7.4)	(-17.4, 9.7)	(-19.5,17.2)
		Pr >  t			0.9003
	Week 132	n	5	3	
		LS Mean	-5.414	-1.779	-3.635
		SEM	6.857	8.695	11.06
		95% CI	(-18.9, 8.1)	(-18.9,15.3)	(-25.4,18.1)
		Pr >  t			0.7426
	Week 144	n	5	4	
		LS Mean	-5.414	-3.463	-1.951
		SEM	6.857	7.620	10.23
		95% CI	(-18.9, 8.1)	(-18.5,11.5)	(-22.1,18.2)
		Pr >  t			0.8489
	Week 156	n	4	2	
		LS Mean	9.785	-1.710	11.495
		SEM	7.582	10.52	12.96
		95% CI	(-5.1,24.7)	(-22.4,19.0)	(-14.0,37.0)
		Pr >  t			0.3759
	Week 168	n	1	1	
		LS Mean	2.748	-1.435	4.183
		SEM	14.67	14.69	20.76
		95% CI	(-26.1,31.6)	(-30.4,27.5)	(-36.7,45.1)
		Pr >  t			0.8405
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	10.809	-3.668	14.477
		SEM	5.829	5.369	6.694
		95% CI	(-0.8,22.4)	(-14.3, 7.0)	(-1.2,27.8)
		Pr >  t			0.0329
	Week 16	n	15	17	
		LS Mean	9.551	-3.024	12.575
		SEM	6.216	5.710	7.046
		95% CI	(-2.8,21.9)	(-14.4, 8.3)	(-1.4,26.5)
		Pr >  t			0.0771
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	19.496	-7.713	27.209
	SEM	6.337	6.395	7.794
	95% CI	( 6.9,32.1)	(-20.4, 5.0)	( 11.8,42.6)
	Pr >  t			0.0007
	n	12	9	
Week 40	LS Mean	13.134	-5.163	18.296
	SEM	6.690	6.888	8.391
	95% CI	( -0.1,26.4)	(-18.8, 8.5)	( 1.7,34.9)
	Pr >  t			0.0309
	n	11	7	
Week 48	LS Mean	13.157	-2.863	16.020
	SEM	6.893	7.627	9.038
	95% CI	( -0.5,26.8)	(-17.9,12.2)	( -1.8,33.9)
	Pr >  t			0.0783
	n	8	6	
Week 56	LS Mean	12.687	-8.056	20.743
	SEM	7.531	8.045	9.885
	95% CI	( -2.2,27.6)	(-23.9, 7.8)	( 1.2,40.3)
	Pr >  t			0.0374
	n	7	5	
Week 64	LS Mean	10.333	-8.501	18.835
	SEM	7.834	8.555	10.56
	95% CI	( -5.2,25.8)	(-25.4, 8.4)	( -2.0,39.7)
	Pr >  t			0.0763
	n	5	3	
Week 72	LS Mean	11.482	-8.430	19.912
	SEM	8.727	10.41	12.68
	95% CI	( -5.8,28.7)	(-29.0,12.1)	( -5.1,44.9)
	Pr >  t			0.1182
	n	5	2	
Week 84	LS Mean	16.522	-9.600	26.122
	SEM	8.753	12.32	14.32
	95% CI	( -0.8,33.8)	(-33.9,14.7)	( -2.1,54.4)
	Pr >  t			0.0699
	n	4	2	
Week 96	LS Mean	15.151	-9.600	24.752
	SEM	9.404	12.32	14.74
	95% CI	( -3.4,33.7)	(-33.9,14.7)	( -4.4,53.9)
	Pr >  t			0.0951
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	LS Mean	22.924	-9.600	32.524
	SEM	9.428	12.32	14.75
	95% CI	( 4.3,41.5)	(-33.9,14.7)	( 3.4,61.6)
	Pr >  t			0.0288
	n	1	2	
Week 120	LS Mean	12.318	-9.569	21.886
	SEM	16.62	12.26	20.09
	95% CI	(-20.5,45.1)	(-33.8,14.6)	(-17.8,61.6)
	Pr >  t			0.2776
	n	5	1	
Week 132	LS Mean	16.522	-9.523	26.044
	SEM	8.753	16.62	18.15
	95% CI	( -0.8,33.8)	(-42.3,23.3)	( -9.8,61.9)
	Pr >  t			0.1533
	n	3	1	
Week 144	LS Mean	24.519	-9.523	34.042
	SEM	10.50	16.62	19.06
	95% CI	( 3.8,45.2)	(-42.3,23.3)	( -3.6,71.7)
	Pr >  t			0.0760
	n	3		
Week 156	LS Mean	35.632		
	SEM	10.50		
	95% CI	( 14.9,56.4)		
	Pr >  t			
	n	3		
Week 168	LS Mean	13.409		
	SEM	10.50		
	95% CI	( -7.3,34.1)		
	Pr >  t			
	n	1		
Week 180	LS Mean	54.993		
	SEM	16.60		
	95% CI	( 22.2,87.8)		
	Pr >  t			
	n	1		
Week 192	LS Mean	54.993		
	SEM	16.60		
	95% CI	( 22.2,87.8)		
	Pr >  t			
	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	88.323		
		SEM	16.60		
		95% CI	( 55.5, 121)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	14.244	8.081	6.162
		SEM	3.711	3.717	4.255
		95% CI	( 6.9,21.6)	( 0.7,15.4)	( -2.2,14.5)
		Pr >  t			0.1487
	Week 16	n	30	29	
		LS Mean	15.998	8.247	7.750
		SEM	3.933	4.177	4.830
		95% CI	( 8.2,23.8)	( 0.0,16.5)	( -1.8,17.3)
		Pr >  t			0.1097
	Week 24	n	26	20	
		LS Mean	18.537	10.074	8.463
		SEM	4.169	4.796	5.474
		95% CI	( 10.3,26.8)	( 0.6,19.5)	( -2.3,19.2)
		Pr >  t			0.1231
	Week 32	n	18	20	
		LS Mean	14.268	8.408	5.860
		SEM	4.739	4.796	5.900
		95% CI	( 4.9,23.6)	( -1.0,17.9)	( -5.7,17.5)
		Pr >  t			0.3213
	Week 40	n	18	19	
		LS Mean	8.467	8.458	0.009
		SEM	4.737	4.880	5.966
		95% CI	( -0.9,17.8)	( -1.2,18.1)	( -11.7,11.7)
		Pr >  t			0.9987
	Week 48	n	16	14	
		LS Mean	8.063	15.629	-7.566
		SEM	4.933	5.405	6.559
		95% CI	( -1.6,17.8)	( 5.0,26.3)	( -20.5, 5.3)
		Pr >  t			0.2495
	Week 56	n	14	10	
		LS Mean	14.691	4.573	10.117
		SEM	5.174	6.111	7.339
		95% CI	( 4.5,24.9)	( -7.4,16.6)	( -4.3,24.6)
		Pr >  t			0.1689

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	17.783	4.116	13.666
		SEM	5.320	5.898	7.272
		95% CI	( 7.3,28.2)	( -7.5,15.7)	( -0.6,28.0)
		Pr >  t			0.0610
Week 72		n	10	6	
		LS Mean	11.366	10.324	1.042
		SEM	5.873	7.494	8.986
		95% CI	( -0.2,22.9)	( -4.4,25.1)	(-16.6,18.7)
		Pr >  t			0.9078
Week 84		n	8	7	
		LS Mean	14.881	8.949	5.931
		SEM	6.519	7.033	8.997
		95% CI	( 2.1,27.7)	( -4.9,22.8)	(-11.8,23.6)
		Pr >  t			0.5101
Week 96		n	6	5	
		LS Mean	14.538	-2.206	16.744
		SEM	7.308	8.083	10.42
		95% CI	( 0.2,28.9)	(-18.1,13.7)	( -3.8,37.2)
		Pr >  t			0.1090
Week 108		n	2	4	
		LS Mean	8.820	0.739	8.081
		SEM	12.09	8.904	14.64
		95% CI	(-15.0,32.6)	(-16.8,18.2)	(-20.7,36.9)
		Pr >  t			0.5813
Week 120		n	4	4	
		LS Mean	6.320	0.739	5.581
		SEM	8.726	8.904	12.07
		95% CI	(-10.8,23.5)	(-16.8,18.2)	(-18.2,29.3)
		Pr >  t			0.6442
Week 132		n	3	1	
		LS Mean	8.109	6.315	1.794
		SEM	10.01	16.91	19.36
		95% CI	(-11.6,27.8)	(-27.0,39.6)	(-36.3,39.9)
		Pr >  t			0.9262
Week 144		n	2		
		LS Mean	8.148		
		SEM	12.00		
		95% CI	(-15.4,31.7)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Estrogen Receptor Status (L)	Negative	LS Mean				
		SEM				
		95% CI	( , )			
		Pr >  t				
		Week 8	n	2		
		Week 16	n	2		
		Week 24	n	1		
		Week 32	n	1		
		Week 40	n	1		
		Week 48	n	1		
		Week 56	n	1		
		Week 72	n	1		
		Week 84	n	1		
		Week 96	n	1		
	Positive	Week 8	n	140	140	
			LS Mean	14.263	2.329	11.934
			SEM	2.593	2.627	2.378
		Week 16	95% CI	( 9.2,19.4)	( -2.8, 7.5)	( 7.3,16.6)
			Pr >  t			<.0001
			n	122	107	
		Week 24	LS Mean	14.110	3.283	10.827
			SEM	2.677	2.796	2.604
			95% CI	( 8.9,19.4)	( -2.2, 8.8)	( 5.7,15.9)
		Week 32	Pr >  t			<.0001
			n	104	81	
			LS Mean	15.319	1.128	14.190
Week 32	SEM	2.763	2.969	2.857		
	95% CI	( 9.9,20.7)	( -4.7, 7.0)	( 8.6,19.8)		
	Pr >  t			<.0001		
Week 32	n	85	73			
	LS Mean	14.109	-0.250	14.359		
	SEM	2.904	3.049	3.036		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	( 8.4,19.8)	( -6.2, 5.7)	( 8.4,20.3)
		Pr >  t			<.0001
	Week 40	n	74	62	
		LS Mean	14.978	1.450	13.528
		SEM	2.987	3.173	3.227
		95% CI	( 9.1,20.8)	( -4.8, 7.7)	( 7.2,19.9)
		Pr >  t			<.0001
	Week 48	n	68	51	
		LS Mean	12.922	1.925	10.997
		SEM	3.040	3.323	3.424
		95% CI	( 7.0,18.9)	( -4.6, 8.4)	( 4.3,17.7)
		Pr >  t			0.0013
	Week 56	n	58	45	
		LS Mean	14.680	0.239	14.441
		SEM	3.150	3.430	3.627
		95% CI	( 8.5,20.9)	( -6.5, 7.0)	( 7.3,21.6)
		Pr >  t			<.0001
	Week 64	n	47	42	
		LS Mean	13.513	-0.107	13.620
		SEM	3.313	3.494	3.831
		95% CI	( 7.0,20.0)	( -7.0, 6.7)	( 6.1,21.1)
		Pr >  t			0.0004
	Week 72	n	47	35	
		LS Mean	11.297	2.252	9.045
		SEM	3.315	3.674	3.997
		95% CI	( 4.8,17.8)	( -5.0, 9.5)	( 1.2,16.9)
		Pr >  t			0.0238
	Week 84	n	39	33	
		LS Mean	15.987	1.599	14.388
		SEM	3.500	3.736	4.195
		95% CI	( 9.1,22.9)	( -5.7, 8.9)	( 6.2,22.6)
		Pr >  t			0.0006
	Week 96	n	34	24	
		LS Mean	18.560	-3.523	22.083
		SEM	3.632	4.122	4.651
		95% CI	( 11.4,25.7)	( -11.6, 4.6)	( 13.0,31.2)
		Pr >  t			<.0001
	Week 108	n	26	21	
		LS Mean	10.068	-1.238	11.306

Subgroup	Time Window	Alpelisib	Placebo qd +	Treatment difference
		300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	SEM	3.956	4.310	5.060
	95% CI	( 2.3,17.8)	( -9.7, 7.2)	( 1.4,21.2)
	Pr >  t			0.0256
	n	28	16	
	LS Mean	10.570	0.638	9.931
Week 132	SEM	3.856	4.745	5.370
	95% CI	( 3.0,18.1)	( -8.7, 9.9)	( -0.6,20.5)
	Pr >  t			0.0646
	n	20	8	
	LS Mean	8.737	-0.044	8.781
Week 144	SEM	4.320	6.233	6.993
	95% CI	( 0.3,17.2)	(-12.3,12.2)	( -4.9,22.5)
	Pr >  t			0.2094
	n	15	5	
	LS Mean	11.624	-0.980	12.604
Week 156	SEM	4.785	7.651	8.541
	95% CI	( 2.2,21.0)	(-16.0,14.0)	( -4.1,29.4)
	Pr >  t			0.1402
	n	10	3	
	LS Mean	15.875	0.367	15.509
Week 168	SEM	5.632	9.654	10.78
	95% CI	( 4.8,26.9)	(-18.6,19.3)	( -5.6,36.7)
	Pr >  t			0.1506
	n	4	2	
	LS Mean	20.336	0.369	19.967
Week 180	SEM	8.411	11.69	14.10
	95% CI	( 3.8,36.8)	(-22.6,23.3)	( -7.7,47.6)
	Pr >  t			0.1569
	n	1	1	
	LS Mean	51.066	0.255	50.812
Week 192	SEM	16.30	16.31	22.87
	95% CI	( 19.1,83.0)	(-31.7,32.3)	( 5.9,95.7)
	Pr >  t			0.0265
	n	1	1	
	LS Mean	84.396	0.255	84.142
	SEM	16.30	16.31	22.87
	95% CI	( 52.4, 116)	(-31.7,32.3)	( 39.3, 129)
	Pr >  t			0.0002

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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#### 4.8.3.2 Krankheitssymptomatik: BPI-SF – 2. Datenschnitt

Tabelle 4H-31: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Stärkster Schmerz“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-29i**  
 Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item  
 in subgroups i  
 (Full Analysis Set, PIK3CA mutant cohort)

Subgroup	Time Window		Alpelisib	Placebo	Treatment difference	
			300mg qd + Fulv N=169	qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Presence of Liver Metastases (L)	No	Week 8	n	104	96	
			LS Mean	-0.184	-0.041	-0.143
			SEM	0.393	0.391	0.336
			95% CI	(-1.0, 0.6)	(-0.8, 0.7)	(-0.8, 0.5)
			Pr >  t			0.6704
			Week 16	n	92	75
			LS Mean	-0.259	0.383	-0.642
			SEM	0.399	0.415	0.362
			95% CI	(-1.0, 0.5)	(-0.4, 1.2)	(-1.4, 0.1)
			Pr >  t			0.0769
		Week 24	n	83	65	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 32	LS Mean	-0.060	0.718	-0.779	
	SEM	0.406	0.424	0.380	
	95% CI	(-0.9, 0.7)	(-0.1, 1.6)	(-1.5, -0.0)	
	Pr >  t			0.0407	
	n	72	59		
Week 40	LS Mean	0.700	0.369	0.331	
	SEM	0.416	0.433	0.397	
	95% CI	(-0.1, 1.5)	(-0.5, 1.2)	(-0.4, 1.1)	
	Pr >  t			0.4037	
	n	64	50		
Week 48	LS Mean	0.298	0.095	0.203	
	SEM	0.423	0.447	0.418	
	95% CI	(-0.5, 1.1)	(-0.8, 1.0)	(-0.6, 1.0)	
	Pr >  t			0.6264	
	n	58	44		
Week 56	LS Mean	0.491	0.561	-0.070	
	SEM	0.429	0.458	0.436	
	95% CI	(-0.4, 1.3)	(-0.3, 1.5)	(-0.9, 0.8)	
	Pr >  t			0.8724	
	n	49	38		
Week 64	LS Mean	0.310	-0.011	0.322	
	SEM	0.441	0.471	0.462	
	95% CI	(-0.6, 1.2)	(-0.9, 0.9)	(-0.6, 1.2)	
	Pr >  t			0.4862	
	n	39	37		
Week 72	LS Mean	0.353	0.193	0.159	
	SEM	0.460	0.474	0.483	
	95% CI	(-0.6, 1.3)	(-0.7, 1.1)	(-0.8, 1.1)	
	Pr >  t			0.7415	
	n	41	32		
Week 84	LS Mean	0.365	0.370	-0.005	
	SEM	0.456	0.489	0.493	
	95% CI	(-0.5, 1.3)	(-0.6, 1.3)	(-1.0, 1.0)	
	Pr >  t			0.9921	
	n	33	29		
Week 84	LS Mean	0.481	0.767	-0.286	
	SEM	0.479	0.500	0.523	
	95% CI	(-0.5, 1.4)	(-0.2, 1.7)	(-1.3, 0.7)	
	Pr >  t			0.5841	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 96	n	31	21		
	LS Mean	0.465	0.576	-0.111	
	SEM	0.484	0.542	0.569	
	95% CI	(-0.5, 1.4)	(-0.5, 1.6)	(-1.2, 1.0)	
	Pr >  t			0.8455	
Week 108	n	23	18		
	LS Mean	0.608	0.010	0.598	
	SEM	0.522	0.565	0.622	
	95% CI	(-0.4, 1.6)	(-1.1, 1.1)	(-0.6, 1.8)	
	Pr >  t			0.3363	
Week 120	n	25	15		
	LS Mean	0.183	0.051	0.133	
	SEM	0.510	0.597	0.642	
	95% CI	(-0.8, 1.2)	(-1.1, 1.2)	(-1.1, 1.4)	
	Pr >  t			0.8365	
Week 132	n	17	8		
	LS Mean	0.117	0.135	-0.018	
	SEM	0.568	0.738	0.814	
	95% CI	(-1.0, 1.2)	(-1.3, 1.6)	(-1.6, 1.6)	
	Pr >  t			0.9822	
Week 144	n	15	5		
	LS Mean	0.572	0.036	0.536	
	SEM	0.588	0.889	0.965	
	95% CI	(-0.6, 1.7)	(-1.7, 1.8)	(-1.4, 2.4)	
	Pr >  t			0.5787	
Week 156	n	9	3		
	LS Mean	0.254	1.565	-1.311	
	SEM	0.701	1.104	1.227	
	95% CI	(-1.1, 1.6)	(-0.6, 3.7)	(-3.7, 1.1)	
	Pr >  t			0.2857	
Week 168	n	4	2		
	LS Mean	0.059	-0.196	0.256	
	SEM	0.969	1.326	1.579	
	95% CI	(-1.8, 2.0)	(-2.8, 2.4)	(-2.8, 3.4)	
	Pr >  t			0.8713	
Week 180	n	1	1		
	LS Mean	2.095	0.405	1.690	
	SEM	1.833	1.834	2.553	
	95% CI	(-1.5, 5.7)	(-3.2, 4.0)	(-3.3, 6.7)	

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 192	Pr >  t			0.5080
		n	1	1	
		LS Mean	1.095	-0.595	1.690
		SEM	1.833	1.834	2.553
		95% CI	( -2.5, 4.7)	( -4.2, 3.0)	( -3.3, 6.7)
		Pr >  t			0.5080
Yes	Week 8	n	38	41	
		LS Mean	0.251	0.947	-0.697
		SEM	0.485	0.527	0.491
		95% CI	( -0.7, 1.2)	( -0.1, 2.0)	( -1.7, 0.3)
		Pr >  t			0.1580
	Week 16	n	32	30	
		LS Mean	0.479	1.141	-0.662
		SEM	0.519	0.555	0.543
		95% CI	( -0.5, 1.5)	( 0.0, 2.2)	( -1.7, 0.4)
		Pr >  t			0.2239
	Week 24	n	22	15	
		LS Mean	0.966	1.146	-0.180
		SEM	0.559	0.664	0.685
		95% CI	( -0.1, 2.1)	( -0.2, 2.5)	( -1.5, 1.2)
		Pr >  t			0.7929
	Week 32	n	14	13	
		LS Mean	0.450	0.468	-0.017
		SEM	0.645	0.691	0.771
		95% CI	( -0.8, 1.7)	( -0.9, 1.8)	( -1.5, 1.5)
		Pr >  t			0.9819
	Week 40	n	11	11	
		LS Mean	0.505	1.032	-0.527
		SEM	0.694	0.724	0.840
		95% CI	( -0.9, 1.9)	( -0.4, 2.5)	( -2.2, 1.1)
		Pr >  t			0.5309
	Week 48	n	11	6	
		LS Mean	0.414	2.423	-2.009
		SEM	0.694	0.876	0.973
		95% CI	( -1.0, 1.8)	( 0.7, 4.1)	( -3.9,-0.1)
		Pr >  t			0.0400
	Week 56	n	10	7	
		LS Mean	1.046	3.038	-1.992
		SEM	0.714	0.832	0.950

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	(-0.4, 2.5)	(-1.4, 4.7)	(-3.9,-0.1)
		Pr >  t			0.0368
	Week 64	n	8	5	
		LS Mean	0.162	0.394	-0.233
		SEM	0.766	0.930	1.073
		95% CI	(-1.3, 1.7)	(-1.4, 2.2)	(-2.3, 1.9)
		Pr >  t			0.8283
	Week 72	n	7	3	
		LS Mean	0.491	1.244	-0.753
		SEM	0.801	1.126	1.269
		95% CI	(-1.1, 2.1)	(-1.0, 3.5)	(-3.3, 1.7)
		Pr >  t			0.5536
	Week 84	n	7	4	
		LS Mean	2.634	0.384	2.250
		SEM	0.801	1.008	1.166
		95% CI	( 1.1, 4.2)	(-1.6, 2.4)	(-0.0, 4.5)
		Pr >  t			0.0548
	Week 96	n	4	3	
		LS Mean	0.952	1.577	-0.626
		SEM	0.982	1.126	1.391
		95% CI	(-1.0, 2.9)	(-0.6, 3.8)	(-3.4, 2.1)
		Pr >  t			0.6531
	Week 108	n	3	3	
		LS Mean	0.366	1.702	-1.336
		SEM	1.100	1.128	1.478
		95% CI	(-1.8, 2.5)	(-0.5, 3.9)	(-4.2, 1.6)
		Pr >  t			0.3669
	Week 120	n	3	1	
		LS Mean	2.232	-1.934	4.166
		SEM	1.101	1.803	2.041
		95% CI	( 0.1, 4.4)	(-5.5, 1.6)	( 0.1, 8.2)
		Pr >  t			0.0423
	Week 132	n	3		
		LS Mean	2.472		
		SEM	1.101		
		95% CI	( 0.3, 4.6)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	N=172	N=172	
Stratum 2 - Prior CDK4/6 inhibitor (L) No prior use	Week 8	n	134	131		
		LS Mean	-0.590	-0.407		-0.184
		SEM	0.201	0.203		0.285
		95% CI	(-1.0,-0.2)	(-0.8,-0.0)		(-0.7, 0.4)
	Week 16	Pr >  t				0.5201
		n	118	102		
		LS Mean	-0.582	-0.049		-0.534
		SEM	0.211	0.225		0.309
	Week 24	95% CI	(-1.0,-0.2)	(-0.5, 0.4)		(-1.1, 0.1)
		Pr >  t				0.0842
		n	100	78		
		LS Mean	-0.407	0.253		-0.661
	Week 32	SEM	0.225	0.250		0.337
		95% CI	(-0.8, 0.0)	(-0.2, 0.7)		(-1.3,-0.0)
		Pr >  t				0.0499
		n	84	71		
	Week 40	LS Mean	0.180	-0.151		0.331
		SEM	0.240	0.260		0.354
		95% CI	(-0.3, 0.7)	(-0.7, 0.4)		(-0.4, 1.0)
		Pr >  t				0.3503
	Week 48	n	73	61		
		LS Mean	-0.148	-0.285		0.137
		SEM	0.254	0.275		0.374
		95% CI	(-0.6, 0.3)	(-0.8, 0.3)		(-0.6, 0.9)
	Week 56	Pr >  t				0.7138
		n	67	50		
		LS Mean	-0.013	0.280		-0.293
		SEM	0.262	0.297		0.396
Week 56	95% CI	(-0.5, 0.5)	(-0.3, 0.9)		(-1.1, 0.5)	
	Pr >  t				0.4600	
Week 56	n	57	45			
	LS Mean	-0.047	-0.076		0.029	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.279	0.310	0.417
	95% CI	(-0.6, 0.5)	(-0.7, 0.5)	(-0.8, 0.8)
	Pr >  t			0.9449
	n	45	42	
Week 72	LS Mean	-0.235	-0.275	0.040
	SEM	0.305	0.319	0.441
	95% CI	(-0.8, 0.4)	(-0.9, 0.4)	(-0.8, 0.9)
	Pr >  t			0.9278
Week 84	n	46	35	
	LS Mean	-0.155	-0.028	-0.127
	SEM	0.303	0.343	0.457
	95% CI	(-0.7, 0.4)	(-0.7, 0.6)	(-1.0, 0.8)
Week 96	Pr >  t			0.7815
	n	40	33	
	LS Mean	0.357	0.229	0.128
	SEM	0.320	0.351	0.475
Week 108	95% CI	(-0.3, 1.0)	(-0.5, 0.9)	(-0.8, 1.1)
	Pr >  t			0.7879
	n	34	24	
	LS Mean	0.071	0.193	-0.122
Week 120	SEM	0.342	0.401	0.527
	95% CI	(-0.6, 0.7)	(-0.6, 1.0)	(-1.2, 0.9)
	Pr >  t			0.8171
	n	26	21	
Week 132	LS Mean	0.115	-0.281	0.396
	SEM	0.383	0.425	0.572
	95% CI	(-0.6, 0.9)	(-1.1, 0.6)	(-0.7, 1.5)
	Pr >  t			0.4889
Week 144	n	27	16	
	LS Mean	-0.036	-0.528	0.492
	SEM	0.378	0.479	0.610
	95% CI	(-0.8, 0.7)	(-1.5, 0.4)	(-0.7, 1.7)
Week 132	Pr >  t			0.4199
	n	20	8	
	LS Mean	-0.019	-0.264	0.245
	SEM	0.429	0.657	0.785
Week 144	95% CI	(-0.9, 0.8)	(-1.6, 1.0)	(-1.3, 1.8)
	Pr >  t			0.7550
Week 144	n	14	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Prior use	Week 156	LS Mean	0.250	-0.363	0.613
		SEM	0.504	0.822	0.964
		95% CI	(-0.7, 1.2)	(-2.0, 1.2)	(-1.3, 2.5)
		Pr >  t			0.5249
		n	9	3	
	Week 168	LS Mean	-0.131	1.166	-1.297
		SEM	0.618	1.051	1.220
		95% CI	(-1.3, 1.1)	(-0.9, 3.2)	(-3.7, 1.1)
		Pr >  t			0.2877
		n	4	2	
	Week 180	LS Mean	-0.334	-0.592	0.258
		SEM	0.911	1.282	1.573
		95% CI	(-2.1, 1.5)	(-3.1, 1.9)	(-2.8, 3.3)
		Pr >  t			0.8696
		n	1	1	
	Week 192	LS Mean	1.698	-0.004	1.702
		SEM	1.802	1.802	2.549
		95% CI	(-1.8, 5.2)	(-3.5, 3.5)	(-3.3, 6.7)
		Pr >  t			0.5043
		n	1	1	
	Week 8	LS Mean	0.698	-1.004	1.702
		SEM	1.802	1.802	2.549
		95% CI	(-2.8, 4.2)	(-4.5, 2.5)	(-3.3, 6.7)
		Pr >  t			0.5043
n		8	6		
Week 16	LS Mean	-0.169	2.086	-2.255	
	SEM	0.837	1.007	1.268	
	95% CI	(-2.0, 1.6)	(-0.1, 4.2)	(-5.0, 0.4)	
	Pr >  t			0.0953	
	n	6	3		
Week 24	LS Mean	-0.404	2.799	-3.204	
	SEM	0.941	1.371	1.619	
	95% CI	(-2.4, 1.6)	(-0.0, 5.6)	(-6.6, 0.2)	
	Pr >  t			0.0606	
	n	5	2		
Week 24	LS Mean	1.475	1.907	-0.432	
	SEM	0.996	1.575	1.830	
	95% CI	(-0.6, 3.5)	(-1.3, 5.1)	(-4.2, 3.3)	
	Pr >  t			0.8150	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172		Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	n	2	1		
	LS Mean	0.696	1.708		-1.013
	SEM	1.404	2.006		2.445
	95% CI	(-2.2, 3.6)	(-2.4, 5.8)		(-6.0, 4.0)
	Pr >  t				0.6819
Week 40	n	2			
	LS Mean	0.696			
	SEM	1.404			
	95% CI	(-2.2, 3.6)			
	Pr >  t				
Week 48	n	2			
	LS Mean	1.196			
	SEM	1.404			
	95% CI	(-1.7, 4.1)			
	Pr >  t				
Week 56	n	2			
	LS Mean	0.696			
	SEM	1.404			
	95% CI	(-2.2, 3.6)			
	Pr >  t				
Week 64	n	2			
	LS Mean	2.196			
	SEM	1.404			
	95% CI	(-0.7, 5.1)			
	Pr >  t				
Week 72	n	2			
	LS Mean	2.196			
	SEM	1.404			
	95% CI	(-0.7, 5.1)			
	Pr >  t				
Week 96	n	1			
	LS Mean	0.353			
	SEM	1.832			
	95% CI	(-3.4, 4.1)			
	Pr >  t				
Week 120	n	1			
	LS Mean	0.353			
	SEM	1.832			
	95% CI	(-3.4, 4.1)			
	Pr >  t				

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
	Week 144	Pr >  t  n	1		
		LS Mean	0.353		
		SEM	1.832		
		95% CI	( -3.4, 4.1)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	67			
			LS Mean	-0.060	0.627	-0.686		
			SEM	0.351	0.370	0.368		
			95% CI	(-0.8, 0.6)	(-0.1, 1.4)	(-1.4, 0.0)		
					Pr >  t			0.0624
		Week 16	n	70	50			
			LS Mean	-0.291	0.665	-0.955		
			SEM	0.362	0.409	0.406		
			95% CI	(-1.0, 0.4)	(-0.1, 1.5)	(-1.8,-0.2)		
					Pr >  t			0.0189
		Week 24	n	61	36			
			LS Mean	0.201	0.872	-0.671		
			SEM	0.374	0.449	0.451		
			95% CI	(-0.5, 0.9)	(-0.0, 1.8)	(-1.6, 0.2)		
					Pr >  t			0.1375
		Week 32	n	48	32			
			LS Mean	0.489	0.198	0.291		
			SEM	0.400	0.464	0.483		
			95% CI	(-0.3, 1.3)	(-0.7, 1.1)	(-0.7, 1.2)		
					Pr >  t			0.5475
Week 40	n	42	30					
	LS Mean	-0.036	0.438	-0.474				
	SEM	0.413	0.473	0.503				
	95% CI	(-0.8, 0.8)	(-0.5, 1.4)	(-1.5, 0.5)				
			Pr >  t			0.3457		
Week 48	n	40	24					
	LS Mean	0.664	0.839	-0.176				
	SEM	0.418	0.503	0.535				
	95% CI	(-0.2, 1.5)	(-0.1, 1.8)	(-1.2, 0.9)				
			Pr >  t			0.7429		
Week 56	n	35	20					
	LS Mean	0.124	1.102	-0.978				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.432	0.531	0.574	
	95% CI	(-0.7, 1.0)	(0.1, 2.1)	(-2.1, 0.1)	
	Pr >  t			0.0887	
	n	29	18		
	LS Mean	0.279	-0.211	0.489	
Week 72	SEM	0.454	0.550	0.608	
	95% CI	(-0.6, 1.2)	(-1.3, 0.9)	(-0.7, 1.7)	
	Pr >  t			0.4209	
	n	28	18		
	LS Mean	0.171	0.805	-0.634	
Week 84	SEM	0.459	0.550	0.611	
	95% CI	(-0.7, 1.1)	(-0.3, 1.9)	(-1.8, 0.6)	
	Pr >  t			0.3000	
	n	27	17		
	LS Mean	0.796	0.749	0.047	
Week 96	SEM	0.467	0.560	0.624	
	95% CI	(-0.1, 1.7)	(-0.4, 1.8)	(-1.2, 1.3)	
	Pr >  t			0.9403	
	n	23	14		
	LS Mean	0.424	1.059	-0.635	
Week 108	SEM	0.489	0.597	0.674	
	95% CI	(-0.5, 1.4)	(-0.1, 2.2)	(-2.0, 0.7)	
	Pr >  t			0.3462	
	n	19	12		
	LS Mean	0.590	0.703	-0.113	
Week 120	SEM	0.522	0.630	0.725	
	95% CI	(-0.4, 1.6)	(-0.5, 1.9)	(-1.5, 1.3)	
	Pr >  t			0.8768	
	n	18	8		
	LS Mean	0.292	0.012	0.280	
Week 132	SEM	0.529	0.734	0.823	
	95% CI	(-0.7, 1.3)	(-1.4, 1.5)	(-1.3, 1.9)	
	Pr >  t			0.7341	
	n	11	4		
	LS Mean	-0.119	0.490	-0.610	
Week 144	SEM	0.633	0.980	1.104	
	95% CI	(-1.4, 1.1)	(-1.4, 2.4)	(-2.8, 1.6)	
	Pr >  t			0.5809	
	n	11	4		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
>= 65 Years	Week 156	LS Mean	0.516	0.322	0.194
		SEM	0.631	0.981	1.105
		95% CI	(-0.7, 1.8)	(-1.6, 2.2)	(-2.0, 2.4)
		Pr >  t			0.8607
		n	4	2	
	Week 168	LS Mean	-1.043	2.638	-3.681
		SEM	0.967	1.342	1.610
		95% CI	(-2.9, 0.9)	( 0.0, 5.3)	(-6.8,-0.5)
		Pr >  t			0.0225
		n	1	2	
	Week 180	LS Mean	-2.323	0.138	-2.462
		SEM	1.853	1.342	2.256
		95% CI	(-6.0, 1.3)	(-2.5, 2.8)	(-6.9, 2.0)
		Pr >  t			0.2756
		n		1	
	Week 192	LS Mean		0.664	
		SEM		1.862	
		95% CI		(-3.0, 4.3)	
		Pr >  t			
		n		1	
	Week 8	LS Mean		-0.336	
		SEM		1.862	
		95% CI		(-4.0, 3.3)	
		Pr >  t			
n		63	70		
Week 16	LS Mean	-0.187	-0.261	0.073	
	SEM	0.590	0.588	0.425	
	95% CI	(-1.4, 1.0)	(-1.4, 0.9)	(-0.8, 0.9)	
	Pr >  t			0.8630	
	n	54	55		
Week 24	LS Mean	0.121	0.392	-0.271	
	SEM	0.606	0.599	0.458	
	95% CI	(-1.1, 1.3)	(-0.8, 1.6)	(-1.2, 0.6)	
	Pr >  t			0.5547	
	n	44	44		
	LS Mean	0.061	0.667	-0.606	
	SEM	0.618	0.611	0.493	
	95% CI	(-1.2, 1.3)	(-0.5, 1.9)	(-1.6, 0.4)	
	Pr >  t			0.2199	
	n				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 32	n	38	40		
	LS Mean	0.906	0.480		0.427
	SEM	0.633	0.622		0.514
	95% CI	(-0.3, 2.2)	(-0.7, 1.7)		(-0.6, 1.4)
	Pr >  t				0.4069
Week 40	n	33	31		
	LS Mean	0.832	0.036		0.796
	SEM	0.644	0.645		0.550
	95% CI	(-0.4, 2.1)	(-1.2, 1.3)		(-0.3, 1.9)
	Pr >  t				0.1485
Week 48	n	29	26		
	LS Mean	0.244	0.751		-0.508
	SEM	0.654	0.661		0.581
	95% CI	(-1.0, 1.5)	(-0.6, 2.1)		(-1.6, 0.6)
	Pr >  t				0.3825
Week 56	n	24	25		
	LS Mean	0.859	-0.108		0.967
	SEM	0.672	0.665		0.605
	95% CI	(-0.5, 2.2)	(-1.4, 1.2)		(-0.2, 2.2)
	Pr >  t				0.1104
Week 64	n	18	24		
	LS Mean	0.322	0.543		-0.221
	SEM	0.704	0.669		0.645
	95% CI	(-1.1, 1.7)	(-0.8, 1.9)		(-1.5, 1.0)
	Pr >  t				0.7325
Week 72	n	20	17		
	LS Mean	0.698	0.162		0.536
	SEM	0.692	0.709		0.674
	95% CI	(-0.7, 2.1)	(-1.2, 1.6)		(-0.8, 1.9)
	Pr >  t				0.4268
Week 84	n	13	16		
	LS Mean	0.891	0.753		0.137
	SEM	0.750	0.717		0.741
	95% CI	(-0.6, 2.4)	(-0.7, 2.2)		(-1.3, 1.6)
	Pr >  t				0.8530
Week 96	n	12	10		
	LS Mean	0.735	0.275		0.460
	SEM	0.763	0.795		0.829
	95% CI	(-0.8, 2.2)	(-1.3, 1.8)		(-1.2, 2.1)
	Pr >  t				

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108		Pr >  t			0.5791
		n	7	9	
		LS Mean	0.551	-0.337	0.889
		SEM	0.875	0.816	0.951
		95% CI	(-1.2, 2.3)	(-1.9, 1.3)	(-1.0, 2.8)
Week 120		Pr >  t			0.3502
		n	10	8	
		LS Mean	0.633	-0.068	0.701
		SEM	0.798	0.843	0.905
		95% CI	(-0.9, 2.2)	(-1.7, 1.6)	(-1.1, 2.5)
Week 132		Pr >  t			0.4387
		n	9	4	
		LS Mean	1.203	-0.029	1.231
		SEM	0.817	1.045	1.110
		95% CI	(-0.4, 2.8)	(-2.1, 2.0)	(-0.9, 3.4)
Week 144		Pr >  t			0.2676
		n	4	1	
		LS Mean	0.831	-0.056	0.888
		SEM	1.045	1.838	1.985
		95% CI	(-1.2, 2.9)	(-3.7, 3.6)	(-3.0, 4.8)
Week 156		Pr >  t			0.6549
		n	5	1	
		LS Mean	1.547	-0.056	1.603
		SEM	0.970	1.838	1.947
		95% CI	(-0.4, 3.5)	(-3.7, 3.6)	(-2.2, 5.4)
Week 168		Pr >  t			0.4106
		n	3		
		LS Mean	1.222		
		SEM	1.161		
		95% CI	(-1.1, 3.5)		
Week 180		Pr >  t			
		n	1		
		LS Mean	2.507		
		SEM	1.837		
		95% CI	(-1.1, 6.1)		
Week 192		Pr >  t			
		n	1		
		LS Mean	1.507		
		SEM	1.837		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI Pr >  t	(-2.1, 5.1)	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Pooled Race Group 1 (L)	Asian	Week 8	n	32	34	
			LS Mean	0.408	-0.088	0.496
			SEM	0.592	0.563	0.527
			95% CI	(-0.8, 1.6)	(-1.2, 1.0)	(-0.5, 1.5)
					Pr >  t	0.3479
		Week 16	n	30	29	
			LS Mean	0.576	0.392	0.185
			SEM	0.597	0.592	0.550
			95% CI	(-0.6, 1.8)	(-0.8, 1.6)	(-0.9, 1.3)
					Pr >  t	0.7376
		Week 24	n	21	25	
			LS Mean	0.696	0.331	0.365
			SEM	0.633	0.605	0.608
			95% CI	(-0.6, 1.9)	(-0.9, 1.5)	(-0.8, 1.6)
					Pr >  t	0.5490
		Week 32	n	19	23	
			LS Mean	0.625	0.139	0.486
			SEM	0.645	0.614	0.630
			95% CI	(-0.7, 1.9)	(-1.1, 1.4)	(-0.8, 1.7)
					Pr >  t	0.4414
		Week 40	n	16	18	
			LS Mean	0.363	0.598	-0.235
			SEM	0.667	0.653	0.683
			95% CI	(-1.0, 1.7)	(-0.7, 1.9)	(-1.6, 1.1)
					Pr >  t	0.7309
		Week 48	n	16	17	
			LS Mean	0.801	0.829	-0.028
			SEM	0.667	0.660	0.690
95% CI	(-0.5, 2.1)		(-0.5, 2.1)	(-1.4, 1.3)		
			Pr >  t	0.9679		
Week 56	n	12	14			
	LS Mean	0.821	1.244	-0.423		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.710	0.689	0.760	
	95% CI	(-0.6, 2.2)	(-0.1, 2.6)	(-1.9, 1.1)	
	Pr >  t			0.5787	
	n	12	11		
	LS Mean	0.821	0.670	0.151	
Week 72	SEM	0.710	0.730	0.797	
	95% CI	(-0.6, 2.2)	(-0.8, 2.1)	(-1.4, 1.7)	
	Pr >  t			0.8497	
	n	10	9		
	LS Mean	0.764	0.229	0.535	
Week 84	SEM	0.743	0.770	0.864	
	95% CI	(-0.7, 2.2)	(-1.3, 1.7)	(-1.2, 2.2)	
	Pr >  t			0.5356	
	n	8	8		
	LS Mean	1.020	1.545	-0.525	
Week 96	SEM	0.799	0.797	0.928	
	95% CI	(-0.6, 2.6)	(-0.0, 3.1)	(-2.4, 1.3)	
	Pr >  t			0.5723	
	n	6	6		
	LS Mean	1.572	0.184	1.387	
Week 108	SEM	0.872	0.870	1.052	
	95% CI	(-0.1, 3.3)	(-1.5, 1.9)	(-0.7, 3.5)	
	Pr >  t			0.1880	
	n	4	5		
	LS Mean	0.096	0.287	-0.190	
Week 120	SEM	1.000	0.925	1.202	
	95% CI	(-1.9, 2.1)	(-1.5, 2.1)	(-2.6, 2.2)	
	Pr >  t			0.8742	
	n	4	4		
	LS Mean	0.596	1.873	-1.277	
Week 132	SEM	1.000	1.001	1.262	
	95% CI	(-1.4, 2.6)	(-0.1, 3.8)	(-3.8, 1.2)	
	Pr >  t			0.3123	
	n	3	2		
	LS Mean	2.323	0.425	1.898	
Week 144	SEM	1.113	1.309	1.594	
	95% CI	( 0.1, 4.5)	(-2.1, 3.0)	(-1.2, 5.0)	
	Pr >  t			0.2344	
	n	3	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		N=169	Placebo qd + Fulv N=172			
Other	Week 156	LS Mean	1.323	0.349	0.974	
		SEM	1.113	1.772	1.992	
		95% CI	(-0.9, 3.5)	(-3.1, 3.8)	(-2.9, 4.9)	
		Pr >  t			0.6252	
		n	2	1		
	Week 168	LS Mean	1.693	0.349	1.343	
		SEM	1.309	1.772	2.107	
		95% CI	(-0.9, 4.3)	(-3.1, 3.8)	(-2.8, 5.5)	
		Pr >  t			0.5243	
		n	1			
	Other	Week 8	LS Mean	3.143		
			SEM	1.769		
			95% CI	(-0.3, 6.6)		
			Pr >  t			
			n	16	17	
		Week 16	LS Mean	-0.458	0.302	-0.760
			SEM	1.483	1.433	0.908
			95% CI	(-3.4, 2.5)	(-2.5, 3.2)	(-2.6, 1.0)
			Pr >  t			0.4053
			n	15	14	
Week 24		LS Mean	0.296	1.251	-0.954	
		SEM	1.492	1.351	0.978	
		95% CI	(-2.7, 3.3)	(-1.4, 3.9)	(-2.9, 1.0)	
		Pr >  t			0.3317	
		n	12	11		
Week 32		LS Mean	0.550	1.626	-1.076	
		SEM	1.518	1.476	1.057	
		95% CI	(-2.5, 3.6)	(-1.3, 4.6)	(-3.2, 1.0)	
		Pr >  t			0.3111	
		n	8	9		
Week 40	LS Mean	0.709	2.350	-1.641		
	SEM	1.581	1.509	1.183		
	95% CI	(-2.4, 3.9)	(-0.6, 5.3)	(-4.0, 0.7)		
	Pr >  t			0.1681		
	n	6	7			
Week 40	LS Mean	1.467	0.983	0.484		
	SEM	1.638	1.552	1.304		
	95% CI	(-1.8, 4.7)	(-2.1, 4.1)	(-2.1, 3.1)		
	Pr >  t			0.7112		
	n					

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48		n	4	6	
		LS Mean	-0.403	2.688	-3.092
		SEM	1.741	1.583	1.467
		95% CI	(-3.9, 3.0)	(-0.5, 5.8)	(-6.0,-0.2)
		Pr >  t			0.0369
Week 56		n	4	6	
		LS Mean	1.850	2.240	-0.391
		SEM	1.740	1.587	1.469
		95% CI	(-1.6, 5.3)	(-0.9, 5.4)	(-3.3, 2.5)
		Pr >  t			0.7906
Week 64		n	4	4	
		LS Mean	0.539	1.984	-1.445
		SEM	1.743	1.690	1.580
		95% CI	(-2.9, 4.0)	(-1.4, 5.3)	(-4.6, 1.7)
		Pr >  t			0.3619
Week 72		n	4	4	
		LS Mean	0.039	1.484	-1.445
		SEM	1.743	1.690	1.580
		95% CI	(-3.4, 3.5)	(-1.9, 4.8)	(-4.6, 1.7)
		Pr >  t			0.3619
Week 84		n	4	4	
		LS Mean	2.347	1.484	0.862
		SEM	1.741	1.690	1.581
		95% CI	(-1.1, 5.8)	(-1.9, 4.8)	(-2.3, 4.0)
		Pr >  t			0.5865
Week 96		n	3	2	
		LS Mean	0.738	2.335	-1.597
		SEM	1.837	1.964	1.959
		95% CI	(-2.9, 4.4)	(-1.5, 6.2)	(-5.5, 2.3)
		Pr >  t			0.4161
Week 108		n	3	3	
		LS Mean	1.404	1.402	0.002
		SEM	1.837	1.788	1.782
		95% CI	(-2.2, 5.0)	(-2.1, 4.9)	(-3.5, 3.5)
		Pr >  t			0.9992
Week 120		n	2	1	
		LS Mean	0.511	-0.468	0.979
		SEM	2.012	2.416	2.549
		95% CI	(-3.5, 4.5)	(-5.2, 4.3)	(-4.1, 6.0)

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 132	Pr >  t			0.7015
		n	2	1	
		LS Mean	2.354	-0.468	2.822
		SEM	2.008	2.416	2.547
		95% CI	(-1.6, 6.3)	(-5.2, 4.3)	(-2.2, 7.9)
	Week 156	Pr >  t			0.2699
		n	1		
		LS Mean	0.517		
		SEM	2.459		
		95% CI	(-4.3, 5.4)		
	Week 168	Pr >  t			
		n	1		
		LS Mean	0.517		
		SEM	2.459		
		95% CI	(-4.3, 5.4)		
White	Week 8	Pr >  t			
		n	93	84	
		LS Mean	-0.027	0.497	-0.524
		SEM	0.367	0.387	0.353
	Week 16	95% CI	(-0.7, 0.7)	(-0.3, 1.3)	(-1.2, 0.2)
		Pr >  t			0.1389
		n	79	60	
		LS Mean	-0.270	0.680	-0.950
	Week 24	SEM	0.381	0.422	0.394
		95% CI	(-1.0, 0.5)	(-0.1, 1.5)	(-1.7,-0.2)
		Pr >  t			0.0161
		n	71	43	
Week 32	LS Mean	0.075	1.141	-1.066	
	SEM	0.390	0.451	0.432	
	95% CI	(-0.7, 0.8)	( 0.3, 2.0)	(-1.9,-0.2)	
	Pr >  t			0.0138	
Week 40	n	59	39		
	LS Mean	0.836	0.362	0.474	
	SEM	0.409	0.464	0.454	
	95% CI	( 0.0, 1.6)	(-0.5, 1.3)	(-0.4, 1.4)	
Week 40	Pr >  t			0.2975	
	n	52	35		
	LS Mean	0.349	0.266	0.082	
		SEM	0.419	0.475	0.475



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	(-0.5, 1.2)	(-0.7, 1.2)	(-0.9, 1.0)
		Pr >  t			0.8626
	Week 48	n	48	26	
		LS Mean	0.511	0.714	-0.203
		SEM	0.425	0.511	0.515
		95% CI	(-0.3, 1.3)	(-0.3, 1.7)	(-1.2, 0.8)
		Pr >  t			0.6931
	Week 56	n	42	24	
		LS Mean	0.265	0.036	0.229
		SEM	0.437	0.521	0.536
		95% CI	(-0.6, 1.1)	(-1.0, 1.1)	(-0.8, 1.3)
		Pr >  t			0.6692
	Week 64	n	30	26	
		LS Mean	0.315	0.098	0.217
		SEM	0.471	0.511	0.555
		95% CI	(-0.6, 1.2)	(-0.9, 1.1)	(-0.9, 1.3)
		Pr >  t			0.6958
	Week 72	n	34	21	
		LS Mean	0.482	0.617	-0.135
		SEM	0.458	0.540	0.571
		95% CI	(-0.4, 1.4)	(-0.4, 1.7)	(-1.3, 1.0)
		Pr >  t			0.8137
	Week 84	n	28	20	
		LS Mean	0.754	0.563	0.191
		SEM	0.481	0.547	0.596
		95% CI	(-0.2, 1.7)	(-0.5, 1.6)	(-1.0, 1.4)
		Pr >  t			0.7489
	Week 96	n	26	15	
		LS Mean	0.414	0.961	-0.546
		SEM	0.489	0.596	0.648
		95% CI	(-0.5, 1.4)	(-0.2, 2.1)	(-1.8, 0.7)
		Pr >  t			0.3993
	Week 108	n	19	12	
		LS Mean	0.739	0.286	0.453
		SEM	0.536	0.641	0.722
		95% CI	(-0.3, 1.8)	(-1.0, 1.5)	(-1.0, 1.9)
		Pr >  t			0.5304
	Week 120	n	22	10	
		LS Mean	0.494	-0.372	0.866

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	0.513	0.682	0.744
		95% CI	(-0.5, 1.5)	(-1.7, 1.0)	(-0.6, 2.3)
		Pr >  t			0.2450
	Week 132	n	15	4	
		LS Mean	-0.017	0.381	-0.397
		SEM	0.577	0.978	1.055
		95% CI	(-1.1, 1.1)	(-1.5, 2.3)	(-2.5, 1.7)
		Pr >  t			0.7066
	Week 144	n	12	4	
		LS Mean	0.599	0.195	0.404
		SEM	0.620	0.978	1.081
		95% CI	(-0.6, 1.8)	(-1.7, 2.1)	(-1.7, 2.5)
		Pr >  t			0.7088
	Week 156	n	6	2	
		LS Mean	0.100	2.519	-2.419
		SEM	0.811	1.330	1.500
		95% CI	(-1.5, 1.7)	(-0.1, 5.1)	(-5.4, 0.5)
		Pr >  t			0.1072
	Week 168	n	2	2	
		LS Mean	-1.051	0.019	-1.069
		SEM	1.318	1.330	1.825
		95% CI	(-3.6, 1.5)	(-2.6, 2.6)	(-4.7, 2.5)
		Pr >  t			0.5580
	Week 180	n	1	1	
		LS Mean	2.071	0.590	1.481
		SEM	1.833	1.839	2.563
		95% CI	(-1.5, 5.7)	(-3.0, 4.2)	(-3.5, 6.5)
		Pr >  t			0.5635
	Week 192	n	1	1	
		LS Mean	1.071	-0.410	1.481
		SEM	1.833	1.839	2.563
		95% CI	(-2.5, 4.7)	(-4.0, 3.2)	(-3.5, 6.5)
		Pr >  t			0.5635

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Geographic Region 1 (L)	Asia	Week 8	n	30	33			
			LS Mean	0.474	-0.073	0.547		
			SEM	0.607	0.572	0.546		
			95% CI	(-0.7, 1.7)	(-1.2, 1.1)	(-0.5, 1.6)		
					Pr >  t			0.3180
		Week 16	n	28	28			
			LS Mean	0.512	0.462	0.050		
			SEM	0.612	0.602	0.570		
			95% CI	(-0.7, 1.7)	(-0.7, 1.7)	(-1.1, 1.2)		
					Pr >  t			0.9301
		Week 24	n	21	24			
			LS Mean	0.695	0.364	0.331		
			SEM	0.641	0.616	0.620		
			95% CI	(-0.6, 2.0)	(-0.9, 1.6)	(-0.9, 1.6)		
					Pr >  t			0.5938
		Week 32	n	19	22			
			LS Mean	0.626	0.164	0.462		
			SEM	0.653	0.626	0.643		
			95% CI	(-0.7, 1.9)	(-1.1, 1.4)	(-0.8, 1.7)		
					Pr >  t			0.4728
		Week 40	n	16	17			
			LS Mean	0.364	0.707	-0.343		
			SEM	0.674	0.667	0.698		
			95% CI	(-1.0, 1.7)	(-0.6, 2.0)	(-1.7, 1.0)		
					Pr >  t			0.6231
		Week 48	n	16	16			
			LS Mean	0.801	0.955	-0.154		
			SEM	0.674	0.675	0.706		
95% CI	(-0.5, 2.1)		(-0.4, 2.3)	(-1.5, 1.2)				
			Pr >  t			0.8278		
Week 56	n	12	14					
	LS Mean	0.824	1.299	-0.476				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.717	0.695	0.767	
	95% CI	(-0.6, 2.2)	(-0.1, 2.7)	(-2.0, 1.0)	
	Pr >  t			0.5355	
	n	12	11		
	LS Mean	0.824	0.727	0.097	
Week 72	SEM	0.717	0.736	0.803	
	95% CI	(-0.6, 2.2)	(-0.7, 2.2)	(-1.5, 1.7)	
	Pr >  t			0.9044	
	n	10	8		
	LS Mean	0.763	0.355	0.408	
Week 84	SEM	0.750	0.802	0.893	
	95% CI	(-0.7, 2.2)	(-1.2, 1.9)	(-1.3, 2.2)	
	Pr >  t			0.6484	
	n	8	8		
	LS Mean	1.017	1.605	-0.588	
Week 96	SEM	0.805	0.802	0.934	
	95% CI	(-0.6, 2.6)	( 0.0, 3.2)	(-2.4, 1.2)	
	Pr >  t			0.5292	
	n	6	6		
	LS Mean	1.569	0.246	1.322	
Week 108	SEM	0.877	0.875	1.057	
	95% CI	(-0.2, 3.3)	(-1.5, 2.0)	(-0.8, 3.4)	
	Pr >  t			0.2116	
	n	4	5		
	LS Mean	0.094	0.350	-0.256	
Week 120	SEM	1.005	0.930	1.207	
	95% CI	(-1.9, 2.1)	(-1.5, 2.2)	(-2.6, 2.1)	
	Pr >  t			0.8322	
	n	4	4		
	LS Mean	0.594	1.937	-1.344	
Week 132	SEM	1.005	1.006	1.266	
	95% CI	(-1.4, 2.6)	(-0.0, 3.9)	(-3.8, 1.1)	
	Pr >  t			0.2893	
	n	3	2		
	LS Mean	2.320	0.484	1.837	
Week 144	SEM	1.117	1.312	1.597	
	95% CI	( 0.1, 4.5)	(-2.1, 3.1)	(-1.3, 5.0)	
	Pr >  t			0.2509	
	n	3	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Europe	Week 156	LS Mean	1.320	0.412	0.908
		SEM	1.117	1.774	1.994
		95% CI	(-0.9, 3.5)	(-3.1, 3.9)	(-3.0, 4.8)
		Pr >  t			0.6491
		n	2	1	
	Week 168	LS Mean	1.688	0.412	1.276
		SEM	1.312	1.774	2.109
		95% CI	(-0.9, 4.3)	(-3.1, 3.9)	(-2.9, 5.4)
		Pr >  t			0.5456
		n	1		
	Week 8	LS Mean	3.146		
		SEM	1.771		
		95% CI	(-0.3, 6.6)		
		Pr >  t			
		n	66	67	
	Week 16	LS Mean	-0.073	0.096	-0.170
		SEM	0.712	0.711	0.406
		95% CI	(-1.5, 1.3)	(-1.3, 1.5)	(-1.0, 0.6)
		Pr >  t			0.6759
		n	58	47	
	Week 24	LS Mean	-0.237	0.516	-0.753
		SEM	0.717	0.726	0.452
		95% CI	(-1.7, 1.2)	(-0.9, 1.9)	(-1.6, 0.1)
		Pr >  t			0.0965
n		51	36		
Week 32	LS Mean	-0.379	0.878	-1.257	
	SEM	0.723	0.742	0.492	
	95% CI	(-1.8, 1.0)	(-0.6, 2.3)	(-2.2,-0.3)	
	Pr >  t			0.0109	
	n	43	30		
Week 40	LS Mean	0.447	0.421	0.026	
	SEM	0.741	0.766	0.528	
	95% CI	(-1.0, 1.9)	(-1.1, 1.9)	(-1.0, 1.1)	
	Pr >  t			0.9604	
	n	37	25		
	LS Mean	0.248	0.053	0.196	
	SEM	0.750	0.781	0.564	
	95% CI	(-1.2, 1.7)	(-1.5, 1.6)	(-0.9, 1.3)	
	Pr >  t			0.7288	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 48	n	33	21	
	LS Mean	0.390	0.652	-0.262
	SEM	0.758	0.799	0.598
	95% CI	(-1.1, 1.9)	(-0.9, 2.2)	(-1.4, 0.9)
	Pr >  t			0.6617
Week 56	n	29	20	
	LS Mean	0.185	-0.058	0.243
	SEM	0.768	0.805	0.618
	95% CI	(-1.3, 1.7)	(-1.6, 1.5)	(-1.0, 1.5)
	Pr >  t			0.6944
Week 64	n	23	20	
	LS Mean	0.226	-0.125	0.351
	SEM	0.788	0.805	0.643
	95% CI	(-1.3, 1.8)	(-1.7, 1.5)	(-0.9, 1.6)
	Pr >  t			0.5855
Week 72	n	25	19	
	LS Mean	-0.323	0.688	-1.010
	SEM	0.781	0.811	0.641
	95% CI	(-1.9, 1.2)	(-0.9, 2.3)	(-2.3, 0.2)
	Pr >  t			0.1154
Week 84	n	22	17	
	LS Mean	0.388	0.597	-0.209
	SEM	0.792	0.824	0.672
	95% CI	(-1.2, 1.9)	(-1.0, 2.2)	(-1.5, 1.1)
	Pr >  t			0.7558
Week 96	n	20	13	
	LS Mean	0.291	0.739	-0.448
	SEM	0.803	0.861	0.729
	95% CI	(-1.3, 1.9)	(-1.0, 2.4)	(-1.9, 1.0)
	Pr >  t			0.5389
Week 108	n	15	11	
	LS Mean	0.744	0.465	0.279
	SEM	0.838	0.889	0.799
	95% CI	(-0.9, 2.4)	(-1.3, 2.2)	(-1.3, 1.8)
	Pr >  t			0.7266
Week 120	n	16	8	
	LS Mean	0.012	-0.594	0.606
	SEM	0.830	0.953	0.862
	95% CI	(-1.6, 1.6)	(-2.5, 1.3)	(-1.1, 2.3)

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 132	Pr >  t			0.4821
		n	12	3	
		LS Mean	-0.049	0.289	-0.338
		SEM	0.872	1.276	1.238
		95% CI	(-1.8, 1.7)	(-2.2, 2.8)	(-2.8, 2.1)
	Week 144	Pr >  t			0.7847
		n	7	4	
		LS Mean	0.719	0.070	0.649
		SEM	0.982	1.158	1.204
		95% CI	(-1.2, 2.6)	(-2.2, 2.3)	(-1.7, 3.0)
	Week 156	Pr >  t			0.5902
		n	5	2	
		LS Mean	-0.652	2.383	-3.036
		SEM	1.077	1.483	1.582
		95% CI	(-2.8, 1.5)	(-0.5, 5.3)	(-6.1, 0.1)
	Week 168	Pr >  t			0.0554
		n	2	2	
		LS Mean	-1.396	-0.117	-1.279
		SEM	1.479	1.483	1.879
		95% CI	(-4.3, 1.5)	(-3.0, 2.8)	(-5.0, 2.4)
	Week 180	Pr >  t			0.4961
		n		1	
		LS Mean		0.436	
		SEM		1.976	
		95% CI		(-3.4, 4.3)	
	Week 192	Pr >  t			
		n		1	
		LS Mean		-0.564	
		SEM		1.976	
		95% CI		(-4.4, 3.3)	
	Week 8	Pr >  t			
Latin America		n	14	13	
		LS Mean	-1.314	-0.831	-0.483
		SEM	0.678	0.697	0.989
		95% CI	(-2.7, 0.0)	(-2.2, 0.6)	(-2.5, 1.5)
	Week 16	Pr >  t			0.6268
		n	13	12	
		LS Mean	-1.033	-0.492	-0.541
		SEM	0.697	0.722	1.019



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	(-2.4, 0.4)	(-1.9, 0.9)	(-2.6, 1.5)
		Pr >  t			0.5975
	Week 24	n	12	10	
		LS Mean	0.601	-0.111	0.713
		SEM	0.716	0.769	1.066
		95% CI	(-0.8, 2.0)	(-1.6, 1.4)	(-1.4, 2.8)
		Pr >  t			0.5057
	Week 32	n	9	10	
		LS Mean	0.449	-0.411	0.860
		SEM	0.799	0.769	1.128
		95% CI	(-1.1, 2.0)	(-1.9, 1.1)	(-1.4, 3.1)
		Pr >  t			0.4481
	Week 40	n	7	10	
		LS Mean	0.431	-0.711	1.142
		SEM	0.873	0.769	1.181
		95% CI	(-1.3, 2.2)	(-2.2, 0.8)	(-1.2, 3.5)
		Pr >  t			0.3361
	Week 48	n	7	7	
		LS Mean	-0.141	-0.403	0.262
		SEM	0.873	0.872	1.249
		95% CI	(-1.9, 1.6)	(-2.1, 1.3)	(-2.2, 2.7)
		Pr >  t			0.8341
	Week 56	n	6	7	
		LS Mean	0.285	-0.317	0.602
		SEM	0.926	0.875	1.291
		95% CI	(-1.5, 2.1)	(-2.1, 1.4)	(-2.0, 3.2)
		Pr >  t			0.6419
	Week 64	n	4	7	
		LS Mean	-0.394	-0.384	-0.010
		SEM	1.080	0.869	1.397
		95% CI	(-2.5, 1.7)	(-2.1, 1.3)	(-2.8, 2.8)
		Pr >  t			0.9944
	Week 72	n	4	4	
		LS Mean	0.106	-1.233	1.339
		SEM	1.080	1.076	1.535
		95% CI	(-2.0, 2.2)	(-3.4, 0.9)	(-1.7, 4.4)
		Pr >  t			0.3846
	Week 84	n	4	5	
		LS Mean	2.228	-0.864	3.092

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
North America	Week 96	SEM	1.081	0.985	1.476
		95% CI	( 0.1, 4.4)	( -2.8, 1.1)	( 0.2, 6.0)
		Pr >  t			0.0381
		n	3	2	
		LS Mean	-0.270	1.979	-2.249
	Week 108	SEM	1.215	1.443	1.897
		95% CI	( -2.7, 2.1)	( -0.9, 4.8)	( -6.0, 1.5)
		Pr >  t			0.2378
		n	2	3	
		LS Mean	0.992	-1.585	2.577
	Week 120	SEM	1.444	1.218	1.900
		95% CI	( -1.9, 3.8)	( -4.0, 0.8)	( -1.2, 6.3)
		Pr >  t			0.1769
		n	2	2	
		LS Mean	2.220	-1.620	3.841
	Week 132	SEM	1.446	1.442	2.051
		95% CI	( -0.6, 5.1)	( -4.5, 1.2)	( -0.2, 7.9)
		Pr >  t			0.0630
		n	1	2	
		LS Mean	-0.300	-1.620	1.321
	Week 8	SEM	1.980	1.442	2.456
		95% CI	( -4.2, 3.6)	( -4.5, 1.2)	( -3.5, 6.2)
		Pr >  t			0.5915
		n	16	19	
LS Mean		-1.196	0.872	-2.068	
Week 16	SEM	0.671	0.651	0.802	
	95% CI	( -2.5, 0.1)	( -0.4, 2.2)	( -3.7,-0.5)	
	Pr >  t			0.0122	
	n	12	14		
	LS Mean	-1.164	0.774	-1.938	
Week 24	SEM	0.729	0.712	0.888	
	95% CI	( -2.6, 0.3)	( -0.6, 2.2)	( -3.7,-0.2)	
	Pr >  t			0.0320	
	n	12	8		
	LS Mean	-1.142	1.892	-3.034	
Week 32	SEM	0.729	0.851	0.999	
	95% CI	( -2.6, 0.3)	( 0.2, 3.6)	( -5.0,-1.1)	
	Pr >  t			0.0031	
	n	9	7		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	LS Mean	0.147	0.987	-0.840	
	SEM	0.797	0.888	1.072	
	95% CI	(-1.4, 1.7)	(-0.8, 2.7)	(-3.0, 1.3)	
	Pr >  t			0.4348	
	n	9	7		
Week 48	LS Mean	-0.134	0.702	-0.836	
	SEM	0.799	0.888	1.075	
	95% CI	(-1.7, 1.5)	(-1.1, 2.5)	(-3.0, 1.3)	
	Pr >  t			0.4385	
	n	8	5		
Week 56	LS Mean	-0.238	2.101	-2.339	
	SEM	0.826	0.984	1.176	
	95% CI	(-1.9, 1.4)	( 0.2, 4.0)	(-4.7,-0.0)	
	Pr >  t			0.0489	
	n	7	3		
Week 64	LS Mean	0.152	0.200	-0.048	
	SEM	0.857	1.175	1.362	
	95% CI	(-1.5, 1.9)	(-2.1, 2.5)	(-2.7, 2.6)	
	Pr >  t			0.9719	
	n	5	3		
Week 72	LS Mean	-0.316	0.867	-1.183	
	SEM	0.952	1.175	1.426	
	95% CI	(-2.2, 1.6)	(-1.5, 3.2)	(-4.0, 1.6)	
	Pr >  t			0.4082	
	n	5	3		
Week 84	LS Mean	2.067	1.246	0.820	
	SEM	0.949	1.174	1.421	
	95% CI	( 0.2, 3.9)	(-1.1, 3.6)	(-2.0, 3.6)	
	Pr >  t			0.5647	
	n	2	2		
Week 96	LS Mean	3.442	1.110	2.332	
	SEM	1.345	1.372	1.853	
	95% CI	( 0.8, 6.1)	(-1.6, 3.8)	(-1.3, 6.0)	
	Pr >  t			0.2103	
	n	3	2		
Week 96	LS Mean	-0.319	0.610	-0.929	
	SEM	1.138	1.372	1.712	
	95% CI	(-2.6, 1.9)	(-2.1, 3.3)	(-4.3, 2.5)	
	Pr >  t			0.5883	
	n				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 108	n	1	2	
	LS Mean	-0.053	0.610	-0.663
	SEM	1.808	1.372	2.212
	95% CI	(-3.6, 3.5)	(-2.1, 3.3)	(-5.0, 3.7)
	Pr >  t			0.7649
Week 120	n	3	2	
	LS Mean	0.348	-0.390	0.738
	SEM	1.138	1.372	1.712
	95% CI	(-1.9, 2.6)	(-3.1, 2.3)	(-2.6, 4.1)
	Pr >  t			0.6671
Week 132	n	1	1	
	LS Mean	-1.224	2.066	-3.290
	SEM	1.810	1.829	2.523
	95% CI	(-4.8, 2.4)	(-1.6, 5.7)	(-8.3, 1.7)
	Pr >  t			0.1946
Week 144	n	2		
	LS Mean	-0.452		
	SEM	1.337		
	95% CI	(-3.1, 2.2)		
	Pr >  t			
Week 156	n	1		
	LS Mean	2.776		
	SEM	1.810		
	95% CI	(-0.8, 6.4)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-0.224		
	SEM	1.810		
	95% CI	(-3.8, 3.4)		
	Pr >  t			
Week 180	n	1		
	LS Mean	1.776		
	SEM	1.810		
	95% CI	(-1.8, 5.4)		
	Pr >  t			
Week 192	n	1		
	LS Mean	0.776		
	SEM	1.810		
	95% CI	(-2.8, 4.4)		
	Pr >  t			

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Other	Week 8	Pr >  t				
		n	16	5		
		LS Mean	0.949	1.564	-0.616	
			SEM	0.836	1.303	1.414
			95% CI	(-0.8, 2.7)	(-1.1, 4.2)	(-3.5, 2.3)
			Pr >  t			0.6667
	Week 16	n	13	4		
		LS Mean	1.299	2.591	-1.292	
		SEM	0.882	1.444	1.536	
		95% CI	(-0.5, 3.1)	(-0.3, 5.5)	(-4.4, 1.8)	
			Pr >  t			0.4061
	Week 24	n	9	2		
		LS Mean	2.691	2.342	0.349	
		SEM	0.961	1.743	1.855	
		95% CI	( 0.7, 4.6)	(-1.2, 5.8)	(-3.4, 4.1)	
			Pr >  t			0.8516
	Week 32	n	6	3		
		LS Mean	3.158	2.044	1.114	
		SEM	1.074	1.552	1.739	
		95% CI	( 1.0, 5.3)	(-1.1, 5.2)	(-2.4, 4.6)	
			Pr >  t			0.5249
	Week 40	n	6	2		
		LS Mean	1.409	0.632	0.777	
		SEM	1.087	1.739	1.911	
95% CI		(-0.8, 3.6)	(-2.9, 4.1)	(-3.1, 4.6)		
		Pr >  t			0.6858	
Week 48	n	5	1			
	LS Mean	2.115	1.446	0.669		
	SEM	1.141	2.202	2.373		
	95% CI	(-0.2, 4.4)	(-2.9, 5.8)	(-4.1, 5.4)		
		Pr >  t			0.7787	
Week 56	n	5	1			
	LS Mean	1.515	1.446	0.069		
	SEM	1.141	2.202	2.373		
	95% CI	(-0.8, 3.8)	(-2.9, 5.8)	(-4.7, 4.8)		
		Pr >  t			0.9768	
Week 64	n	3	1			
	LS Mean	1.053	1.446	-0.394		
	SEM	1.322	2.202	2.466		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 72	95% CI	(-1.6, 3.7)	(-2.9, 5.8)	(-5.3, 4.5)	
	Pr >  t			0.8736	
	n	4	1		
	LS Mean	2.239	1.446	0.793	
	SEM	1.215	2.202	2.410	
Week 84	95% CI	(-0.2, 4.7)	(-2.9, 5.8)	(-4.0, 5.6)	
	Pr >  t			0.7430	
	n	4	1		
	LS Mean	0.989	1.446	-0.457	
	SEM	1.215	2.202	2.410	
Week 96	95% CI	(-1.4, 3.4)	(-2.9, 5.8)	(-5.3, 4.3)	
	Pr >  t			0.8502	
	n	3	1		
	LS Mean	1.719	1.446	0.273	
	SEM	1.322	2.202	2.466	
Week 108	95% CI	(-0.9, 4.4)	(-2.9, 5.8)	(-4.6, 5.2)	
	Pr >  t			0.9121	
	n	4			
	LS Mean	1.239			
	SEM	1.215			
Week 120	95% CI	(-1.2, 3.7)			
	Pr >  t				
	n	3			
	LS Mean	1.386			
	SEM	1.322			
Week 132	95% CI	(-1.3, 4.0)			
	Pr >  t				
	n	3			
	LS Mean	2.053			
	SEM	1.322			
Week 144	95% CI	(-0.6, 4.7)			
	Pr >  t				
	n	3			
	LS Mean	1.583			
	SEM	1.323			
Week 156	95% CI	(-1.1, 4.2)			
	Pr >  t				
	n	1			
	LS Mean	0.733			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	1.966		
	95% CI	(-3.2, 4.6)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Baseline ECOG performance status	0 Week 8	n	98	88		
		LS Mean	-0.309	0.177	-0.485	
		SEM	0.424	0.415	0.341	
		95% CI	(-1.1, 0.5)	(-0.6, 1.0)	(-1.2, 0.2)	
			Pr >  t			0.1550
	Week 16	n	88	70		
		LS Mean	0.052	0.475	-0.422	
		SEM	0.432	0.444	0.366	
		95% CI	(-0.8, 0.9)	(-0.4, 1.3)	(-1.1, 0.3)	
			Pr >  t			0.2485
	Week 24	n	75	54		
		LS Mean	0.122	0.861	-0.738	
		SEM	0.440	0.461	0.397	
		95% CI	(-0.7, 1.0)	(-0.0, 1.8)	(-1.5, 0.0)	
			Pr >  t			0.0634
	Week 32	n	62	52		
		LS Mean	0.907	0.230	0.677	
		SEM	0.453	0.464	0.413	
		95% CI	(0.0, 1.8)	(-0.7, 1.1)	(-0.1, 1.5)	
			Pr >  t			0.1022
	Week 40	n	51	46		
		LS Mean	0.472	0.028	0.444	
		SEM	0.466	0.476	0.438	
		95% CI	(-0.4, 1.4)	(-0.9, 1.0)	(-0.4, 1.3)	
			Pr >  t			0.3114
	Week 48	n	50	37		
		LS Mean	0.584	0.583	0.002	
		SEM	0.468	0.495	0.460	
95% CI		(-0.3, 1.5)	(-0.4, 1.6)	(-0.9, 0.9)		
		Pr >  t			0.9971	
Week 56	n	43	33			
	LS Mean	0.653	0.220	0.433		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.479	0.506	0.483	
	95% CI	(-0.3, 1.6)	(-0.8, 1.2)	(-0.5, 1.4)	
	Pr >  t			0.3700	
	n	35	33		
	LS Mean	0.463	-0.211	0.673	
Week 72	SEM	0.496	0.506	0.501	
	95% CI	(-0.5, 1.4)	(-1.2, 0.8)	(-0.3, 1.7)	
	Pr >  t			0.1793	
	n	35	31		
	LS Mean	0.400	0.440	-0.040	
Week 84	SEM	0.496	0.512	0.507	
	95% CI	(-0.6, 1.4)	(-0.6, 1.4)	(-1.0, 1.0)	
	Pr >  t			0.9379	
	n	31	29		
	LS Mean	0.971	0.596	0.374	
Week 96	SEM	0.510	0.519	0.526	
	95% CI	(-0.0, 2.0)	(-0.4, 1.6)	(-0.7, 1.4)	
	Pr >  t			0.4765	
	n	27	22		
	LS Mean	0.667	0.421	0.246	
Week 108	SEM	0.523	0.552	0.572	
	95% CI	(-0.4, 1.7)	(-0.7, 1.5)	(-0.9, 1.4)	
	Pr >  t			0.6678	
	n	19	20		
	LS Mean	0.670	0.230	0.440	
Week 120	SEM	0.570	0.565	0.626	
	95% CI	(-0.4, 1.8)	(-0.9, 1.3)	(-0.8, 1.7)	
	Pr >  t			0.4826	
	n	20	15		
	LS Mean	0.466	-0.005	0.471	
Week 132	SEM	0.561	0.611	0.661	
	95% CI	(-0.6, 1.6)	(-1.2, 1.2)	(-0.8, 1.8)	
	Pr >  t			0.4764	
	n	15	7		
	LS Mean	0.885	0.411	0.474	
Week 144	SEM	0.608	0.784	0.856	
	95% CI	(-0.3, 2.1)	(-1.1, 1.9)	(-1.2, 2.2)	
	Pr >  t			0.5795	
	n	10	5		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
1	Week 156	LS Mean	1.135	0.075	1.059
		SEM	0.686	0.893	1.010
		95% CI	(-0.2, 2.5)	(-1.7, 1.8)	(-0.9, 3.0)
		Pr >  t			0.2944
	Week 168	n	5	3	
		LS Mean	0.842	1.607	-0.764
		SEM	0.890	1.103	1.325
		95% CI	(-0.9, 2.6)	(-0.6, 3.8)	(-3.4, 1.8)
	Week 180	Pr >  t			0.5643
		n	3	2	
		LS Mean	-0.508	-0.154	-0.354
		SEM	1.102	1.320	1.645
Week 192	95% CI	(-2.7, 1.7)	(-2.7, 2.4)	(-3.6, 2.9)	
	Pr >  t			0.8295	
	n	1	1		
	LS Mean	2.316	0.452	1.864	
Week 192	SEM	1.821	1.820	2.525	
	95% CI	(-1.3, 5.9)	(-3.1, 4.0)	(-3.1, 6.8)	
	Pr >  t			0.4606	
	n	1	1		
Week 8	LS Mean	1.316	-0.548	1.864	
	SEM	1.821	1.820	2.525	
	95% CI	(-2.3, 4.9)	(-4.1, 3.0)	(-3.1, 6.8)	
	Pr >  t			0.4606	
Week 16	n	43	49		
	LS Mean	0.096	-0.048	0.144	
	SEM	0.467	0.486	0.486	
	95% CI	(-0.8, 1.0)	(-1.0, 0.9)	(-0.8, 1.1)	
Week 24	Pr >  t			0.7674	
	n	35	34		
	LS Mean	-0.776	0.435	-1.211	
	SEM	0.493	0.511	0.545	
Week 24	95% CI	(-1.7, 0.2)	(-0.6, 1.4)	(-2.3,-0.1)	
	Pr >  t			0.0271	
	n	29	25		
	LS Mean	-0.048	0.408	-0.456	
Week 24	SEM	0.518	0.557	0.600	
	95% CI	(-1.1, 1.0)	(-0.7, 1.5)	(-1.6, 0.7)	
	Pr >  t			0.4474	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 32	n	23	20		
	LS Mean	-0.141	0.600	-0.740	
	SEM	0.555	0.595	0.653	
	95% CI	(-1.2, 1.0)	(-0.6, 1.8)	(-2.0, 0.5)	
	Pr >  t			0.2576	
Week 40	n	23	15		
	LS Mean	-0.156	0.759	-0.915	
	SEM	0.556	0.642	0.697	
	95% CI	(-1.3, 0.9)	(-0.5, 2.0)	(-2.3, 0.5)	
	Pr >  t			0.1896	
Week 48	n	18	13		
	LS Mean	0.077	1.348	-1.271	
	SEM	0.590	0.669	0.750	
	95% CI	(-1.1, 1.2)	( 0.0, 2.7)	(-2.7, 0.2)	
	Pr >  t			0.0910	
Week 56	n	15	12		
	LS Mean	-0.392	0.986	-1.378	
	SEM	0.621	0.685	0.790	
	95% CI	(-1.6, 0.8)	(-0.4, 2.3)	(-2.9, 0.2)	
	Pr >  t			0.0819	
Week 64	n	11	9		
	LS Mean	-0.260	1.796	-2.056	
	SEM	0.680	0.750	0.892	
	95% CI	(-1.6, 1.1)	( 0.3, 3.3)	(-3.8,-0.3)	
	Pr >  t			0.0217	
Week 72	n	12	4		
	LS Mean	0.257	0.381	-0.123	
	SEM	0.663	1.010	1.110	
	95% CI	(-1.0, 1.6)	(-1.6, 2.4)	(-2.3, 2.1)	
	Pr >  t			0.9116	
Week 84	n	8	4		
	LS Mean	-0.693	1.381	-2.073	
	SEM	0.762	1.010	1.170	
	95% CI	(-2.2, 0.8)	(-0.6, 3.4)	(-4.4, 0.2)	
	Pr >  t			0.0771	
Week 96	n	8	2		
	LS Mean	-0.068	3.032	-3.100	
	SEM	0.762	1.353	1.475	
	95% CI	(-1.6, 1.4)	( 0.4, 5.7)	(-6.0,-0.2)	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.0363
	Week 108	n	6	1	
		LS Mean	0.396	-1.357	1.753
		SEM	0.845	1.855	1.980
		95% CI	(-1.3, 2.1)	(-5.0, 2.3)	(-2.1, 5.6)
		Pr >  t			0.3764
	Week 120	n	8	1	
		LS Mean	0.083	-1.357	1.440
		SEM	0.764	1.855	1.946
		95% CI	(-1.4, 1.6)	(-5.0, 2.3)	(-2.4, 5.3)
		Pr >  t			0.4597
	Week 132	n	5	1	
		LS Mean	-0.990	-1.357	0.367
		SEM	0.906	1.855	2.006
		95% CI	(-2.8, 0.8)	(-5.0, 2.3)	(-3.6, 4.3)
		Pr >  t			0.8550
	Week 144	n	5		
		LS Mean	-0.590		
		SEM	0.906		
		95% CI	(-2.4, 1.2)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	-0.693		
		SEM	0.989		
		95% CI	(-2.6, 1.3)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	1.990		
		SEM	1.828		
		95% CI	(-1.6, 5.6)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	71		
			LS Mean	-0.768	-0.816	0.048	
			SEM	0.975	1.005	0.393	
			95% CI	(-2.7, 1.2)	(-2.8, 1.2)	(-0.7, 0.8)	
					Pr >  t	0.9037	
		Week 16	n	69	54		
			LS Mean	-0.729	-0.589	-0.139	
			SEM	0.976	1.015	0.423	
			95% CI	(-2.7, 1.2)	(-2.6, 1.4)	(-1.0, 0.7)	
					Pr >  t	0.7416	
		Week 24	n	54	46		
			LS Mean	-0.849	-0.050	-0.799	
			SEM	0.981	1.021	0.456	
			95% CI	(-2.8, 1.1)	(-2.1, 2.0)	(-1.7, 0.1)	
					Pr >  t	0.0802	
		Week 32	n	49	41		
			LS Mean	0.074	-0.451	0.525	
			SEM	0.994	1.026	0.474	
			95% CI	(-1.9, 2.0)	(-2.5, 1.6)	(-0.4, 1.5)	
					Pr >  t	0.2685	
		Week 40	n	40	33		
			LS Mean	-0.848	-0.981	0.133	
			SEM	1.003	1.035	0.512	
			95% CI	(-2.8, 1.1)	(-3.0, 1.1)	(-0.9, 1.1)	
					Pr >  t	0.7955	
		Week 48	n	38	28		
			LS Mean	-0.355	-0.491	0.137	
			SEM	1.005	1.045	0.535	
95% CI	(-2.3, 1.6)		(-2.6, 1.6)	(-0.9, 1.2)			
			Pr >  t	0.7983			
Week 56	n	32	28				
	LS Mean	-0.668	-0.719	0.051			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	1.014	1.045	0.550	
	95% CI	(-2.7, 1.3)	(-2.8, 1.3)	(-1.0, 1.1)	
	Pr >  t			0.9262	
	n	23	26		
	LS Mean	-0.297	-0.918	0.621	
Week 72	SEM	1.034	1.049	0.594	
	95% CI	(-2.3, 1.7)	(-3.0, 1.2)	(-0.5, 1.8)	
	Pr >  t			0.2961	
	n	27	25		
	LS Mean	-0.734	-0.446	-0.288	
Week 84	SEM	1.023	1.051	0.580	
	95% CI	(-2.8, 1.3)	(-2.5, 1.6)	(-1.4, 0.9)	
	Pr >  t			0.6200	
	n	23	22		
	LS Mean	0.019	0.087	-0.068	
Week 96	SEM	1.034	1.060	0.614	
	95% CI	(-2.0, 2.1)	(-2.0, 2.2)	(-1.3, 1.1)	
	Pr >  t			0.9118	
	n	20	16		
	LS Mean	-0.358	-0.033	-0.325	
Week 108	SEM	1.044	1.086	0.674	
	95% CI	(-2.4, 1.7)	(-2.2, 2.1)	(-1.6, 1.0)	
	Pr >  t			0.6299	
	n	20	14		
	LS Mean	-0.528	-0.532	0.005	
Week 120	SEM	1.044	1.100	0.696	
	95% CI	(-2.6, 1.5)	(-2.7, 1.6)	(-1.4, 1.4)	
	Pr >  t			0.9944	
	n	17	11		
	LS Mean	-0.695	-0.692	-0.003	
Week 132	SEM	1.058	1.128	0.759	
	95% CI	(-2.8, 1.4)	(-2.9, 1.5)	(-1.5, 1.5)	
	Pr >  t			0.9970	
	n	13	6		
	LS Mean	-0.400	-0.675	0.275	
Week 144	SEM	1.086	1.232	0.938	
	95% CI	(-2.5, 1.7)	(-3.1, 1.7)	(-1.6, 2.1)	
	Pr >  t			0.7697	
	n	10	5		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Second Line	Week 156	LS Mean	0.286	-0.776	1.062
		SEM	1.119	1.275	1.031
		95% CI	(-1.9, 2.5)	(-3.3, 1.7)	(-1.0, 3.1)
		Pr >  t			0.3035
		n	6	3	
	Week 168	LS Mean	-0.906	0.755	-1.661
		SEM	1.212	1.434	1.307
		95% CI	(-3.3, 1.5)	(-2.1, 3.6)	(-4.2, 0.9)
		Pr >  t			0.2041
		n	3	2	
	Week 180	LS Mean	-0.739	-1.006	0.267
		SEM	1.416	1.611	1.668
		95% CI	(-3.5, 2.0)	(-4.2, 2.2)	(-3.0, 3.5)
		Pr >  t			0.8729
		n		1	
	Week 192	LS Mean		-0.393	
		SEM		2.049	
		95% CI		(-4.4, 3.6)	
		Pr >  t			
		n		1	
	Week 8	LS Mean		-1.393	
		SEM		2.049	
		95% CI		(-5.4, 2.6)	
		Pr >  t			
n		66	66		
Week 16	LS Mean	-0.233	0.499	-0.731	
	SEM	0.360	0.362	0.399	
	95% CI	(-0.9, 0.5)	(-0.2, 1.2)	(-1.5, 0.1)	
	Pr >  t			0.0673	
	n	54	51		
Week 24	LS Mean	-0.386	1.017	-1.403	
	SEM	0.381	0.395	0.439	
	95% CI	(-1.1, 0.4)	( 0.2, 1.8)	(-2.3,-0.5)	
	Pr >  t			0.0015	
	n	49	34		
	LS Mean	0.427	0.973	-0.546	
	SEM	0.393	0.441	0.488	
	95% CI	(-0.3, 1.2)	( 0.1, 1.8)	(-1.5, 0.4)	
	Pr >  t			0.2631	



Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32		n	36	31	
		LS Mean	0.460	0.568	-0.109
		SEM	0.428	0.454	0.524
		95% CI	(-0.4, 1.3)	(-0.3, 1.5)	(-1.1, 0.9)
		Pr >  t			0.8356
Week 40		n	33	28	
		LS Mean	0.849	0.937	-0.088
		SEM	0.438	0.470	0.544
		95% CI	(-0.0, 1.7)	( 0.0, 1.9)	(-1.2, 1.0)
		Pr >  t			0.8710
Week 48		n	29	22	
		LS Mean	0.437	1.629	-1.192
		SEM	0.453	0.504	0.585
		95% CI	(-0.5, 1.3)	( 0.6, 2.6)	(-2.3,-0.0)
		Pr >  t			0.0421
Week 56		n	25	17	
		LS Mean	0.782	1.174	-0.392
		SEM	0.472	0.545	0.636
		95% CI	(-0.1, 1.7)	( 0.1, 2.2)	(-1.6, 0.9)
		Pr >  t			0.5380
Week 64		n	22	16	
		LS Mean	0.261	0.980	-0.719
		SEM	0.490	0.557	0.660
		95% CI	(-0.7, 1.2)	(-0.1, 2.1)	(-2.0, 0.6)
		Pr >  t			0.2762
Week 72		n	20	10	
		LS Mean	0.917	0.813	0.104
		SEM	0.505	0.657	0.756
		95% CI	(-0.1, 1.9)	(-0.5, 2.1)	(-1.4, 1.6)
		Pr >  t			0.8902
Week 84		n	16	11	
		LS Mean	1.026	0.536	0.490
		SEM	0.545	0.634	0.763
		95% CI	(-0.0, 2.1)	(-0.7, 1.8)	(-1.0, 2.0)
		Pr >  t			0.5207
Week 96		n	15	8	
		LS Mean	0.734	0.689	0.046
		SEM	0.556	0.715	0.839
		95% CI	(-0.4, 1.8)	(-0.7, 2.1)	(-1.6, 1.7)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 108	Pr >  t			0.9566	
	n	6	7		
	LS Mean	1.652	0.256	1.396	
	SEM	0.791	0.753	1.037	
	95% CI	( 0.1, 3.2)	( -1.2, 1.7)	( -0.6, 3.4)	
Week 120	Pr >  t			0.1786	
	n	11	5		
	LS Mean	0.985	-0.202	1.187	
	SEM	0.622	0.865	1.010	
	95% CI	( -0.2, 2.2)	( -1.9, 1.5)	( -0.8, 3.2)	
Week 132	Pr >  t			0.2405	
	n	7	2		
	LS Mean	0.643	0.595	0.048	
	SEM	0.742	1.299	1.457	
	95% CI	( -0.8, 2.1)	( -2.0, 3.1)	( -2.8, 2.9)	
Week 144	Pr >  t			0.9736	
	n	5			
	LS Mean	-0.138			
	SEM	0.852			
	95% CI	( -1.8, 1.5)			
Week 156	Pr >  t				
	n	3			
	LS Mean	1.295			
	SEM	1.071			
	95% CI	( -0.8, 3.4)			
Week 168	Pr >  t				
	n	1			
	LS Mean	0.335			
	SEM	1.796			
	95% CI	( -3.2, 3.9)			
Week 180	Pr >  t				
	n	1			
	LS Mean	2.335			
	SEM	1.796			
	95% CI	( -1.2, 5.9)			
Week 192	Pr >  t				
	n	1			
	LS Mean	1.335			
	SEM	1.796			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-2.2, 4.9)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	55	
		LS Mean	-0.507	-0.475	-0.031
		SEM	0.954	0.999	0.455
		95% CI	(-2.4, 1.4)	(-2.5, 1.5)	(-0.9, 0.9)
		Pr >  t			0.9452
	Week 16	n	51	40	
		LS Mean	-0.411	-0.049	-0.362
		SEM	0.958	1.017	0.500
		95% CI	(-2.3, 1.5)	(-2.1, 2.0)	(-1.3, 0.6)
		Pr >  t			0.4697
	Week 24	n	38	33	
		LS Mean	-0.723	0.680	-1.403
		SEM	0.966	1.029	0.552
		95% CI	(-2.6, 1.2)	(-1.4, 2.7)	(-2.5,-0.3)
		Pr >  t			0.0114
	Week 32	n	34	28	
		LS Mean	0.232	0.088	0.144
		SEM	0.987	1.038	0.581
		95% CI	(-1.7, 2.2)	(-2.0, 2.1)	(-1.0, 1.3)
		Pr >  t			0.8037
	Week 40	n	26	23	
		LS Mean	-0.581	-0.897	0.315
		SEM	1.005	1.052	0.632
		95% CI	(-2.6, 1.4)	(-3.0, 1.2)	(-0.9, 1.6)
		Pr >  t			0.6183
	Week 48	n	24	17	
		LS Mean	-0.116	-0.005	-0.111
		SEM	1.011	1.079	0.686
95% CI		(-2.1, 1.9)	(-2.1, 2.1)	(-1.5, 1.2)	
	Pr >  t			0.8714	
Week 56	n	21	17		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	-0.224	-0.321	0.097
		SEM	1.022	1.080	0.702
		95% CI	(-2.2, 1.8)	(-2.5, 1.8)	(-1.3, 1.5)
		Pr >  t			0.8904
	Week 64	n	15	15	
		LS Mean	-0.028	-0.498	0.470
		SEM	1.055	1.092	0.767
		95% CI	(-2.1, 2.1)	(-2.7, 1.7)	(-1.0, 2.0)
		Pr >  t			0.5401
	Week 72	n	16	15	
		LS Mean	-0.716	-0.633	-0.083
		SEM	1.048	1.092	0.757
		95% CI	(-2.8, 1.4)	(-2.8, 1.5)	(-1.6, 1.4)
		Pr >  t			0.9133
	Week 84	n	14	13	
		LS Mean	-0.561	0.442	-1.003
		SEM	1.063	1.108	0.802
		95% CI	(-2.7, 1.5)	(-1.7, 2.6)	(-2.6, 0.6)
		Pr >  t			0.2119
	Week 96	n	12	9	
		LS Mean	-0.538	0.739	-1.277
		SEM	1.083	1.162	0.899
		95% CI	(-2.7, 1.6)	(-1.6, 3.0)	(-3.0, 0.5)
		Pr >  t			0.1558
	Week 108	n	13	8	
		LS Mean	-0.043	-0.726	0.682
		SEM	1.072	1.182	0.913
		95% CI	(-2.2, 2.1)	(-3.1, 1.6)	(-1.1, 2.5)
		Pr >  t			0.4553
	Week 120	n	11	6	
		LS Mean	-0.616	-1.022	0.407
		SEM	1.095	1.243	1.016
		95% CI	(-2.8, 1.5)	(-3.5, 1.4)	(-1.6, 2.4)
		Pr >  t			0.6890
	Week 132	n	8	3	
		LS Mean	-0.241	-0.265	0.024
		SEM	1.148	1.460	1.318
		95% CI	(-2.5, 2.0)	(-3.1, 2.6)	(-2.6, 2.6)
		Pr >  t			0.9857

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
First Line Endocrine Sensitive	Week 144	n	5	1	
		LS Mean	0.977	0.185	0.793
		SEM	1.257	2.112	2.080
		95% CI	(-1.5, 3.4)	(-4.0, 4.3)	(-3.3, 4.9)
		Pr >  t			0.7033
	Week 156	n	2	1	
		LS Mean	-1.893	4.185	-6.078
		SEM	1.620	2.112	2.317
		95% CI	(-5.1, 1.3)	( 0.0, 8.3)	(-10.6,-1.5)
		Pr >  t			0.0090
	Week 168	n	2	1	
		LS Mean	-1.893	0.185	-2.078
		SEM	1.620	2.112	2.317
		95% CI	(-5.1, 1.3)	(-4.0, 4.3)	(-6.6, 2.5)
		Pr >  t			0.3702
	Week 180	n		1	
		LS Mean		0.185	
		SEM		2.112	
		95% CI		(-4.0, 4.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.815	
		SEM		2.112	
		95% CI		(-5.0, 3.3)	
Pr >  t					
Week 8	n	17	16		
	LS Mean	-0.592	-0.366	-0.226	
	SEM	0.545	0.557	0.771	
	95% CI	(-1.7, 0.5)	(-1.5, 0.7)	(-1.8, 1.3)	
	Pr >  t			0.7700	
Week 16	n	18	14		
	LS Mean	-0.659	-0.727	0.068	
	SEM	0.535	0.588	0.794	
	95% CI	(-1.7, 0.4)	(-1.9, 0.4)	(-1.5, 1.6)	
	Pr >  t			0.9317	
Week 24	n	16	13		
	LS Mean	-0.320	-0.653	0.333	
	SEM	0.559	0.602	0.821	
	95% CI	(-1.4, 0.8)	(-1.8, 0.5)	(-1.3, 2.0)	

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172		
		Pr >  t			0.6853
	Week 32	n	15	13	
		LS Mean	0.515	-0.573	1.088
		SEM	0.568	0.604	0.828
		95% CI	(-0.6, 1.6)	(-1.8, 0.6)	(-0.6, 2.7)
		Pr >  t			0.1918
	Week 40	n	14	10	
		LS Mean	-0.616	-0.107	-0.509
		SEM	0.584	0.658	0.879
		95% CI	(-1.8, 0.5)	(-1.4, 1.2)	(-2.2, 1.2)
		Pr >  t			0.5634
	Week 48	n	14	11	
		LS Mean	-0.045	-0.435	0.391
		SEM	0.584	0.639	0.865
		95% CI	(-1.2, 1.1)	(-1.7, 0.8)	(-1.3, 2.1)
		Pr >  t			0.6525
	Week 56	n	11	11	
		LS Mean	-0.800	-0.526	-0.274
		SEM	0.630	0.639	0.898
		95% CI	(-2.0, 0.4)	(-1.8, 0.7)	(-2.0, 1.5)
		Pr >  t			0.7604
	Week 64	n	8	11	
		LS Mean	-0.147	-0.799	0.652
		SEM	0.700	0.639	0.949
		95% CI	(-1.5, 1.2)	(-2.1, 0.5)	(-1.2, 2.5)
		Pr >  t			0.4929
	Week 72	n	11	10	
		LS Mean	-0.164	0.576	-0.740
		SEM	0.630	0.660	0.912
		95% CI	(-1.4, 1.1)	(-0.7, 1.9)	(-2.5, 1.1)
		Pr >  t			0.4189
	Week 84	n	9	9	
		LS Mean	1.525	0.324	1.201
		SEM	0.672	0.682	0.959
		95% CI	( 0.2, 2.9)	(-1.0, 1.7)	(-0.7, 3.1)
		Pr >  t			0.2122
	Week 96	n	8	7	
		LS Mean	0.491	-0.383	0.874
		SEM	0.701	0.743	1.022

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.9, 1.9)	(-1.8, 1.1)	(-1.1, 2.9)
		Pr >  t			0.3938
	Week 108	n	7	6	
		LS Mean	-0.796	0.409	-1.205
		SEM	0.735	0.786	1.078
		95% CI	(-2.2, 0.7)	(-1.1, 2.0)	(-3.3, 0.9)
		Pr >  t			0.2648
	Week 120	n	6	5	
		LS Mean	-0.228	0.411	-0.638
		SEM	0.779	0.843	1.148
		95% CI	(-1.8, 1.3)	(-1.3, 2.1)	(-2.9, 1.6)
		Pr >  t			0.5788
	Week 132	n	5	3	
		LS Mean	-0.091	-0.460	0.369
		SEM	0.835	1.033	1.330
		95% CI	(-1.7, 1.6)	(-2.5, 1.6)	(-2.2, 3.0)
		Pr >  t			0.7817
	Week 144	n	5	4	
		LS Mean	0.109	-0.614	0.723
		SEM	0.835	0.919	1.243
		95% CI	(-1.5, 1.8)	(-2.4, 1.2)	(-1.7, 3.2)
		Pr >  t			0.5615
	Week 156	n	4	2	
		LS Mean	-0.027	-0.522	0.495
		SEM	0.911	1.230	1.532
		95% CI	(-1.8, 1.8)	(-2.9, 1.9)	(-2.5, 3.5)
		Pr >  t			0.7467
	Week 168	n	1	1	
		LS Mean	2.165	-1.578	3.742
		SEM	1.681	1.688	2.383
		95% CI	(-1.1, 5.5)	(-4.9, 1.7)	(-0.9, 8.4)
		Pr >  t			0.1175
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	0.009	0.204	-0.195
		SEM	0.686	0.625	0.765
		95% CI	(-1.4, 1.4)	(-1.0, 1.5)	(-1.7, 1.3)
		Pr >  t			0.7991
	Week 16	n	15	17	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	-0.017	1.063	-1.080
		SEM	0.718	0.655	0.794
		95% CI	(-1.5, 1.4)	(-0.2, 2.4)	(-2.7, 0.5)
		Pr >  t			0.1776
	Week 24	n	14	11	
		LS Mean	-0.004	0.154	-0.158
		SEM	0.727	0.711	0.859
		95% CI	(-1.5, 1.4)	(-1.3, 1.6)	(-1.9, 1.5)
		Pr >  t			0.8545
	Week 32	n	12	9	
		LS Mean	-0.121	-0.328	0.207
		SEM	0.755	0.752	0.908
		95% CI	(-1.6, 1.4)	(-1.8, 1.2)	(-1.6, 2.0)
		Pr >  t			0.8203
	Week 40	n	11	7	
		LS Mean	1.378	0.907	0.471
		SEM	0.771	0.815	0.964
		95% CI	(-0.2, 2.9)	(-0.7, 2.5)	(-1.4, 2.4)
		Pr >  t			0.6264
	Week 48	n	8	6	
		LS Mean	0.303	0.932	-0.630
		SEM	0.823	0.851	1.037
		95% CI	(-1.3, 1.9)	(-0.8, 2.6)	(-2.7, 1.4)
		Pr >  t			0.5446
	Week 56	n	7	5	
		LS Mean	1.854	0.473	1.381
		SEM	0.848	0.894	1.096
		95% CI	( 0.2, 3.5)	(-1.3, 2.2)	(-0.8, 3.5)
		Pr >  t			0.2095
	Week 64	n	5	3	
		LS Mean	0.060	2.818	-2.759
		SEM	0.923	1.056	1.282
		95% CI	(-1.8, 1.9)	( 0.7, 4.9)	(-5.3,-0.2)
		Pr >  t			0.0329
	Week 72	n	5	2	
		LS Mean	1.524	0.597	0.927
		SEM	0.928	1.228	1.430
		95% CI	(-0.3, 3.4)	(-1.8, 3.0)	(-1.9, 3.7)
		Pr >  t			0.5176

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172	
Week 84	n	4	2	
	LS Mean	0.438	1.097	-0.659
	SEM	0.983	1.228	1.467
	95% CI	(-1.5, 2.4)	(-1.3, 3.5)	(-3.6, 2.2)
	Pr >  t			0.6539
Week 96	n	4	2	
	LS Mean	0.445	0.597	-0.152
	SEM	0.984	1.228	1.468
	95% CI	(-1.5, 2.4)	(-1.8, 3.0)	(-3.0, 2.7)
	Pr >  t			0.9174
Week 108	n	1	2	
	LS Mean	0.932	-0.755	1.686
	SEM	1.627	1.222	1.956
	95% CI	(-2.3, 4.1)	(-3.2, 1.7)	(-2.2, 5.5)
	Pr >  t			0.3899
Week 120	n	5	1	
	LS Mean	2.324	1.459	0.866
	SEM	0.928	1.620	1.778
	95% CI	( 0.5, 4.2)	(-1.7, 4.7)	(-2.6, 4.4)
	Pr >  t			0.6271
Week 132	n	3	1	
	LS Mean	0.190	0.459	-0.269
	SEM	1.076	1.620	1.861
	95% CI	(-1.9, 2.3)	(-2.7, 3.7)	(-3.9, 3.4)
	Pr >  t			0.8852
Week 144	n	3		
	LS Mean	0.190		
	SEM	1.076		
	95% CI	(-1.9, 2.3)		
	Pr >  t			
Week 156	n	3		
	LS Mean	1.523		
	SEM	1.076		
	95% CI	(-0.6, 3.6)		
	Pr >  t			
Week 168	n	1		
	LS Mean	0.580		
	SEM	1.626		
	95% CI	(-2.6, 3.8)		
	Pr >  t			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		N=169	N=172		
Second Line (progression following metastatic treatment only)	Week 180	Pr >  t			
		n	1		
		LS Mean	2.580		
		SEM	1.626		
	Week 192	Pr >  t			
		n	1		
		LS Mean	1.580		
		SEM	1.626		
	Week 8	Pr >  t			
		n	37	38	
		LS Mean	-0.275	0.481	-0.755
		SEM	0.493	0.499	0.554
Week 16	Pr >  t				
	n	30	28		
	LS Mean	-0.374	0.974	-1.348	
	SEM	0.515	0.555	0.619	
Week 24	Pr >  t				
	n	26	19		
	LS Mean	0.739	1.515	-0.776	
	SEM	0.540	0.631	0.698	
Week 32	Pr >  t				
	n	18	19		
	LS Mean	0.519	0.883	-0.364	
	SEM	0.602	0.631	0.746	
Week 40	Pr >  t				
	n	18	18		
	LS Mean	0.401	1.178	-0.777	
	SEM	0.602	0.640	0.753	
Week 48	Pr >  t				
	n	16	13		
	LS Mean	0.404	2.015	-1.611	
	SEM	0.623	0.700	0.822	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	( -0.8, 1.6)	( 0.6, 3.4)	( -3.2, 0.0)
		Pr >  t			0.0509
	Week 56	n	14	10	
		LS Mean	0.495	1.455	-0.960
		SEM	0.648	0.759	0.893
		95% CI	( -0.8, 1.8)	( -0.0, 2.9)	( -2.7, 0.8)
		Pr >  t			0.2831
	Week 64	n	13	11	
		LS Mean	0.287	0.646	-0.359
		SEM	0.664	0.737	0.887
		95% CI	( -1.0, 1.6)	( -0.8, 2.1)	( -2.1, 1.4)
		Pr >  t			0.6859
	Week 72	n	10	6	
		LS Mean	0.970	1.019	-0.049
		SEM	0.722	0.908	1.073
		95% CI	( -0.5, 2.4)	( -0.8, 2.8)	( -2.2, 2.1)
		Pr >  t			0.9636
	Week 84	n	8	7	
		LS Mean	1.992	0.276	1.716
		SEM	0.791	0.858	1.075
		95% CI	( 0.4, 3.5)	( -1.4, 2.0)	( -0.4, 3.8)
		Pr >  t			0.1112
	Week 96	n	6	5	
		LS Mean	1.372	0.902	0.470
		SEM	0.878	0.972	1.232
		95% CI	( -0.4, 3.1)	( -1.0, 2.8)	( -2.0, 2.9)
		Pr >  t			0.7028
	Week 108	n	2	4	
		LS Mean	2.824	0.162	2.662
		SEM	1.408	1.063	1.706
		95% CI	( 0.1, 5.6)	( -1.9, 2.3)	( -0.7, 6.0)
		Pr >  t			0.1195
	Week 120	n	4	4	
		LS Mean	-0.095	-0.588	0.494
		SEM	1.034	1.063	1.417
		95% CI	( -2.1, 1.9)	( -2.7, 1.5)	( -2.3, 3.3)
		Pr >  t			0.7276
	Week 132	n	3	1	
		LS Mean	0.568	0.602	-0.034

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	1.175	1.958	2.237
		95% CI	( -1.7, 2.9)	( -3.2, 4.5)	( -4.4, 4.4)
		Pr >  t			0.9878
	Week 144	n	2		
		LS Mean	-0.310		
		SEM	1.399		
		95% CI	( -3.1, 2.4)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Progesterone Receptor Status (L) Negative	Week 8	n	42	35	
		LS Mean	0.495	-0.132	0.627
		SEM	0.546	0.601	0.590
		95% CI	(-0.6, 1.6)	(-1.3, 1.1)	(-0.5, 1.8)
			Pr >  t		0.2895
	Week 16	n	35	22	
		LS Mean	0.481	-0.090	0.570
		SEM	0.573	0.697	0.681
		95% CI	(-0.7, 1.6)	(-1.5, 1.3)	(-0.8, 1.9)
			Pr >  t		0.4036
	Week 24	n	28	16	
		LS Mean	0.735	0.962	-0.228
		SEM	0.600	0.751	0.764
		95% CI	(-0.5, 1.9)	(-0.5, 2.4)	(-1.7, 1.3)
			Pr >  t		0.7660
	Week 32	n	22	16	
		LS Mean	0.880	1.151	-0.271
		SEM	0.646	0.754	0.792
		95% CI	(-0.4, 2.2)	(-0.3, 2.6)	(-1.8, 1.3)
			Pr >  t		0.7326
	Week 40	n	19	12	
		LS Mean	0.673	0.544	0.129
		SEM	0.670	0.812	0.869
		95% CI	(-0.6, 2.0)	(-1.1, 2.1)	(-1.6, 1.8)
		Pr >  t		0.8821	
Week 48	n	16	10		
	LS Mean	1.431	1.601	-0.170	
	SEM	0.701	0.857	0.933	
	95% CI	( 0.1, 2.8)	(-0.1, 3.3)	(-2.0, 1.7)	
		Pr >  t		0.8556	
Week 56	n	14	7		
	LS Mean	0.888	0.724	0.164	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.727	0.957	1.047	
	95% CI	(-0.5, 2.3)	(-1.2, 2.6)	(-1.9, 2.2)	
	Pr >  t			0.8756	
	n	8	7		
Week 72	LS Mean	0.898	0.373	0.525	
	SEM	0.862	0.958	1.147	
	95% CI	(-0.8, 2.6)	(-1.5, 2.3)	(-1.7, 2.8)	
	Pr >  t			0.6476	
Week 84	n	12	6		
	LS Mean	0.937	-0.170	1.108	
	SEM	0.760	1.009	1.117	
	95% CI	(-0.6, 2.4)	(-2.2, 1.8)	(-1.1, 3.3)	
Week 96	Pr >  t			0.3222	
	n	8	5		
	LS Mean	2.444	-0.128	2.571	
	SEM	0.870	1.075	1.248	
Week 108	95% CI	( 0.7, 4.2)	(-2.2, 2.0)	( 0.1, 5.0)	
	Pr >  t			0.0401	
	n	5	5		
	LS Mean	0.650	0.472	0.178	
Week 120	SEM	1.030	1.075	1.365	
	95% CI	(-1.4, 2.7)	(-1.6, 2.6)	(-2.5, 2.9)	
	Pr >  t			0.8963	
	n	7	5		
Week 132	LS Mean	1.501	0.272	1.229	
	SEM	0.911	1.075	1.278	
	95% CI	(-0.3, 3.3)	(-1.8, 2.4)	(-1.3, 3.7)	
	Pr >  t			0.3368	
Week 144	n	5	3		
	LS Mean	0.842	1.873	-1.031	
	SEM	1.031	1.305	1.553	
	95% CI	(-1.2, 2.9)	(-0.7, 4.4)	(-4.1, 2.0)	
Week 132	Pr >  t			0.5074	
	n	2	2		
	LS Mean	1.653	-0.414	2.067	
	SEM	1.508	1.535	2.068	
Week 144	95% CI	(-1.3, 4.6)	(-3.4, 2.6)	(-2.0, 6.1)	
	Pr >  t			0.3183	
Week 144	n	2			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169			Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	SEM	95% CI	Pr >  t	
Positive	Week 156	LS Mean	5.105			
		SEM	1.509			
		95% CI	( 2.1, 8.1)			
		Pr >  t				
	Week 168	n	1			
		LS Mean	0.470			
		SEM	2.075			
		95% CI	( -3.6, 4.6)			
	Week 8	n	98	101		
		LS Mean	-0.284	0.262		-0.546
		SEM	0.380	0.377		0.319
		95% CI	( -1.0, 0.5)	( -0.5, 1.0)		( -1.2, 0.1)
	Week 16	n	87	82		
		LS Mean	-0.276	0.677		-0.954
		SEM	0.389	0.390		0.341
		95% CI	( -1.0, 0.5)	( -0.1, 1.4)		( -1.6,-0.3)
	Week 24	n	76	64		
		LS Mean	-0.031	0.748		-0.780
		SEM	0.398	0.408		0.368
		95% CI	( -0.8, 0.8)	( -0.1, 1.6)		( -1.5,-0.1)
Week 32	n	62	56			
	LS Mean	0.678	0.169		0.509	
	SEM	0.413	0.419		0.391	
	95% CI	( -0.1, 1.5)	( -0.7, 1.0)		( -0.3, 1.3)	
Week 40	n	54	49			
	LS Mean	0.234	0.199		0.035	
	SEM	0.422	0.431		0.412	
	95% CI	( -0.6, 1.1)	( -0.6, 1.0)		( -0.8, 0.8)	
		Pr >  t			0.9332	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 48	n	52	40		
	LS Mean	0.175	0.641	-0.465	
	SEM	0.425	0.448	0.432	
	95% CI	(-0.7, 1.0)	(-0.2, 1.5)	(-1.3, 0.4)	
	Pr >  t			0.2815	
Week 56	n	44	38		
	LS Mean	0.293	0.427	-0.134	
	SEM	0.437	0.453	0.449	
	95% CI	(-0.6, 1.2)	(-0.5, 1.3)	(-1.0, 0.7)	
	Pr >  t			0.7664	
Week 64	n	39	35		
	LS Mean	0.158	0.263	-0.105	
	SEM	0.447	0.460	0.467	
	95% CI	(-0.7, 1.0)	(-0.6, 1.2)	(-1.0, 0.8)	
	Pr >  t			0.8221	
Week 72	n	36	29		
	LS Mean	0.255	0.677	-0.422	
	SEM	0.455	0.480	0.493	
	95% CI	(-0.6, 1.1)	(-0.3, 1.6)	(-1.4, 0.5)	
	Pr >  t			0.3928	
Week 84	n	32	28		
	LS Mean	0.463	0.952	-0.489	
	SEM	0.467	0.484	0.507	
	95% CI	(-0.5, 1.4)	( 0.0, 1.9)	(-1.5, 0.5)	
	Pr >  t			0.3352	
Week 96	n	30	19		
	LS Mean	0.471	0.824	-0.353	
	SEM	0.473	0.535	0.562	
	95% CI	(-0.5, 1.4)	(-0.2, 1.9)	(-1.5, 0.7)	
	Pr >  t			0.5298	
Week 108	n	18	16		
	LS Mean	0.436	0.271	0.165	
	SEM	0.540	0.562	0.643	
	95% CI	(-0.6, 1.5)	(-0.8, 1.4)	(-1.1, 1.4)	
	Pr >  t			0.7978	
Week 120	n	23	13		
	LS Mean	0.319	-0.383	0.703	
	SEM	0.504	0.600	0.649	
	95% CI	(-0.7, 1.3)	(-1.6, 0.8)	(-0.6, 2.0)	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.2789
	Week 132	n	18	6	
		LS Mean	0.249	0.550	-0.301
		SEM	0.540	0.793	0.852
		95% CI	(-0.8, 1.3)	(-1.0, 2.1)	(-2.0, 1.4)
		Pr >  t			0.7239
	Week 144	n	13	5	
		LS Mean	-0.050	0.192	-0.242
		SEM	0.594	0.854	0.944
		95% CI	(-1.2, 1.1)	(-1.5, 1.9)	(-2.1, 1.6)
		Pr >  t			0.7974
	Week 156	n	8	3	
		LS Mean	0.225	1.727	-1.502
		SEM	0.707	1.062	1.197
		95% CI	(-1.2, 1.6)	(-0.4, 3.8)	(-3.9, 0.8)
		Pr >  t			0.2098
	Week 168	n	3	2	
		LS Mean	0.044	-0.035	0.079
		SEM	1.058	1.275	1.597
		95% CI	(-2.0, 2.1)	(-2.5, 2.5)	(-3.1, 3.2)
		Pr >  t			0.9605
	Week 180	n	1	1	
		LS Mean	2.035	0.522	1.513
		SEM	1.764	1.764	2.455
		95% CI	(-1.4, 5.5)	(-2.9, 4.0)	(-3.3, 6.3)
		Pr >  t			0.5378
	Week 192	n	1	1	
		LS Mean	1.035	-0.478	1.513
		SEM	1.764	1.764	2.455
		95% CI	(-2.4, 4.5)	(-3.9, 3.0)	(-3.3, 6.3)
		Pr >  t			0.5378

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	101			
			LS Mean	-0.267	0.253	-0.520		
			SEM	0.382	0.378	0.321		
			95% CI	(-1.0, 0.5)	(-0.5, 1.0)	(-1.2, 0.1)		
					Pr >  t			0.1059
		Week 16	n	85	82			
			LS Mean	-0.258	0.668	-0.926		
			SEM	0.391	0.391	0.343		
			95% CI	(-1.0, 0.5)	(-0.1, 1.4)	(-1.6,-0.3)		
					Pr >  t			0.0071
		Week 24	n	75	64			
			LS Mean	-0.015	0.740	-0.755		
			SEM	0.400	0.409	0.369		
			95% CI	(-0.8, 0.8)	(-0.1, 1.5)	(-1.5,-0.0)		
					Pr >  t			0.0411
		Week 32	n	61	56			
			LS Mean	0.575	0.160	0.415		
			SEM	0.415	0.420	0.393		
			95% CI	(-0.2, 1.4)	(-0.7, 1.0)	(-0.4, 1.2)		
					Pr >  t			0.2917
		Week 40	n	53	49			
			LS Mean	0.236	0.191	0.045		
			SEM	0.424	0.431	0.413		
			95% CI	(-0.6, 1.1)	(-0.7, 1.0)	(-0.8, 0.9)		
					Pr >  t			0.9128
		Week 48	n	51	40			
			LS Mean	0.157	0.632	-0.475		
			SEM	0.427	0.448	0.434		
95% CI	(-0.7, 1.0)		(-0.2, 1.5)	(-1.3, 0.4)				
			Pr >  t			0.2732		
Week 56	n	43	38					
	LS Mean	0.324	0.418	-0.095				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.440	0.453	0.451	
	95% CI	(-0.5, 1.2)	(-0.5, 1.3)	(-1.0, 0.8)	
	Pr >  t			0.8340	
	n	39	35		
	LS Mean	0.164	0.255	-0.091	
Week 72	SEM	0.448	0.461	0.467	
	95% CI	(-0.7, 1.0)	(-0.6, 1.2)	(-1.0, 0.8)	
	Pr >  t			0.8460	
	n	35	29		
	LS Mean	0.301	0.669	-0.368	
Week 84	SEM	0.458	0.480	0.495	
	95% CI	(-0.6, 1.2)	(-0.3, 1.6)	(-1.3, 0.6)	
	Pr >  t			0.4578	
	n	31	28		
	LS Mean	0.489	0.944	-0.455	
Week 96	SEM	0.471	0.484	0.510	
	95% CI	(-0.4, 1.4)	(-0.0, 1.9)	(-1.5, 0.5)	
	Pr >  t			0.3729	
	n	29	19		
	LS Mean	0.534	0.816	-0.282	
Week 108	SEM	0.477	0.534	0.564	
	95% CI	(-0.4, 1.5)	(-0.2, 1.9)	(-1.4, 0.8)	
	Pr >  t			0.6175	
	n	18	16		
	LS Mean	0.444	0.263	0.181	
Week 120	SEM	0.540	0.562	0.641	
	95% CI	(-0.6, 1.5)	(-0.8, 1.4)	(-1.1, 1.4)	
	Pr >  t			0.7784	
	n	23	13		
	LS Mean	0.326	-0.391	0.717	
Week 132	SEM	0.504	0.599	0.647	
	95% CI	(-0.7, 1.3)	(-1.6, 0.8)	(-0.6, 2.0)	
	Pr >  t			0.2681	
	n	18	6		
	LS Mean	0.257	0.542	-0.285	
Week 144	SEM	0.540	0.792	0.850	
	95% CI	(-0.8, 1.3)	(-1.0, 2.1)	(-2.0, 1.4)	
	Pr >  t			0.7371	
	n	13	5		

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	LS Mean	-0.042	0.185	-0.227
		SEM	0.594	0.852	0.941
		95% CI	(-1.2, 1.1)	(-1.5, 1.9)	(-2.1, 1.6)
		Pr >  t			0.8099
		n	8	3	
		LS Mean	0.233	1.719	-1.486
	Week 168	SEM	0.706	1.059	1.193
		95% CI	(-1.2, 1.6)	(-0.4, 3.8)	(-3.8, 0.9)
		Pr >  t			0.2131
		n	3	2	
		LS Mean	0.051	-0.043	0.094
		SEM	1.055	1.271	1.592
	Week 180	95% CI	(-2.0, 2.1)	(-2.5, 2.5)	(-3.0, 3.2)
		Pr >  t			0.9531
		n	1	1	
		LS Mean	2.043	0.517	1.526
		SEM	1.758	1.758	2.446
		95% CI	(-1.4, 5.5)	(-2.9, 4.0)	(-3.3, 6.3)
	Week 192	Pr >  t			0.5328
		n	1	1	
		LS Mean	1.043	-0.483	1.526
		SEM	1.758	1.758	2.446
		95% CI	(-2.4, 4.5)	(-3.9, 3.0)	(-3.3, 6.3)
		Pr >  t			0.5328
Week 8	n	42	35		
	LS Mean	0.495	-0.132	0.627	
	SEM	0.546	0.601	0.590	
	95% CI	(-0.6, 1.6)	(-1.3, 1.1)	(-0.5, 1.8)	
	Pr >  t			0.2895	
	n	35	22		
Week 16	LS Mean	0.481	-0.090	0.570	
	SEM	0.573	0.697	0.681	
	95% CI	(-0.7, 1.6)	(-1.5, 1.3)	(-0.8, 1.9)	
	Pr >  t			0.4036	
	n	28	16		
	LS Mean	0.735	0.962	-0.228	
Week 24	SEM	0.600	0.751	0.764	
	95% CI	(-0.5, 1.9)	(-0.5, 2.4)	(-1.7, 1.3)	
	Pr >  t			0.7660	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	22	16	
	LS Mean	0.880	1.151	-0.271
	SEM	0.646	0.754	0.792
	95% CI	(-0.4, 2.2)	(-0.3, 2.6)	(-1.8, 1.3)
	Pr >  t			0.7326
Week 40	n	19	12	
	LS Mean	0.673	0.544	0.129
	SEM	0.670	0.812	0.869
	95% CI	(-0.6, 2.0)	(-1.1, 2.1)	(-1.6, 1.8)
	Pr >  t			0.8821
Week 48	n	16	10	
	LS Mean	1.431	1.601	-0.170
	SEM	0.701	0.857	0.933
	95% CI	( 0.1, 2.8)	(-0.1, 3.3)	(-2.0, 1.7)
	Pr >  t			0.8556
Week 56	n	14	7	
	LS Mean	0.888	0.724	0.164
	SEM	0.727	0.957	1.047
	95% CI	(-0.5, 2.3)	(-1.2, 2.6)	(-1.9, 2.2)
	Pr >  t			0.8756
Week 64	n	8	7	
	LS Mean	0.898	0.373	0.525
	SEM	0.862	0.958	1.147
	95% CI	(-0.8, 2.6)	(-1.5, 2.3)	(-1.7, 2.8)
	Pr >  t			0.6476
Week 72	n	12	6	
	LS Mean	0.937	-0.170	1.108
	SEM	0.760	1.009	1.117
	95% CI	(-0.6, 2.4)	(-2.2, 1.8)	(-1.1, 3.3)
	Pr >  t			0.3222
Week 84	n	8	5	
	LS Mean	2.444	-0.128	2.571
	SEM	0.870	1.075	1.248
	95% CI	( 0.7, 4.2)	(-2.2, 2.0)	( 0.1, 5.0)
	Pr >  t			0.0401
Week 96	n	5	5	
	LS Mean	0.650	0.472	0.178
	SEM	1.030	1.075	1.365
	95% CI	(-1.4, 2.7)	(-1.6, 2.6)	(-2.5, 2.9)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.8963
	Week 108	n	7	5	
		LS Mean	1.501	0.272	1.229
		SEM	0.911	1.075	1.278
		95% CI	(-0.3, 3.3)	(-1.8, 2.4)	(-1.3, 3.7)
		Pr >  t			0.3368
	Week 120	n	5	3	
		LS Mean	0.842	1.873	-1.031
		SEM	1.031	1.305	1.553
		95% CI	(-1.2, 2.9)	(-0.7, 4.4)	(-4.1, 2.0)
		Pr >  t			0.5074
	Week 132	n	2	2	
		LS Mean	1.653	-0.414	2.067
		SEM	1.508	1.535	2.068
		95% CI	(-1.3, 4.6)	(-3.4, 2.6)	(-2.0, 6.1)
		Pr >  t			0.3183
	Week 144	n	2		
		LS Mean	5.105		
		SEM	1.509		
		95% CI	( 2.1, 8.1)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	0.470		
		SEM	2.075		
		95% CI	(-3.6, 4.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	0.470		
		SEM	2.075		
		95% CI	(-3.6, 4.6)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation	E542K	Week 8	n	16	24			
			LS Mean	-0.491	-0.584	0.093		
			SEM	0.853	0.932	0.837		
			95% CI	(-2.2, 1.2)	(-2.5, 1.3)	(-1.6, 1.8)		
					Pr >  t			0.9122
		Week 16	n	14	17			
			LS Mean	-1.317	0.184	-1.502		
			SEM	0.868	0.973	0.906		
			95% CI	(-3.0, 0.4)	(-1.8, 2.1)	(-3.3, 0.3)		
					Pr >  t			0.1003
		Week 24	n	14	11			
			LS Mean	-0.746	0.185	-0.931		
			SEM	0.868	1.041	0.977		
			95% CI	(-2.5, 1.0)	(-1.9, 2.3)	(-2.9, 1.0)		
					Pr >  t			0.3427
		Week 32	n	10	10			
			LS Mean	0.290	0.212	0.079		
			SEM	0.971	1.060	1.047		
			95% CI	(-1.6, 2.2)	(-1.9, 2.3)	(-2.0, 2.1)		
					Pr >  t			0.9401
		Week 40	n	8	10			
			LS Mean	-0.393	0.242	-0.635		
			SEM	1.018	1.059	1.088		
			95% CI	(-2.4, 1.6)	(-1.9, 2.3)	(-2.8, 1.5)		
					Pr >  t			0.5601
		Week 48	n	7	11			
			LS Mean	-1.005	0.602	-1.607		
			SEM	1.049	1.044	1.105		
95% CI	(-3.1, 1.1)		(-1.5, 2.7)	(-3.8, 0.6)				
			Pr >  t			0.1479		
Week 56	n	6	9					
	LS Mean	-1.085	-0.085	-1.000				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	1.088	1.081	1.180	
	95% CI	(-3.2, 1.1)	(-2.2, 2.1)	(-3.3, 1.3)	
	Pr >  t			0.3976	
	n	5	8		
	LS Mean	-1.082	-0.025	-1.057	
Week 72	SEM	1.140	1.104	1.248	
	95% CI	(-3.3, 1.2)	(-2.2, 2.2)	(-3.5, 1.4)	
	Pr >  t			0.3980	
	n	7	7		
	LS Mean	-1.337	1.750	-3.087	
Week 84	SEM	1.048	1.133	1.192	
	95% CI	(-3.4, 0.7)	(-0.5, 4.0)	(-5.4,-0.7)	
	Pr >  t			0.0104	
	n	7	7		
	LS Mean	0.520	1.321	-0.802	
Week 96	SEM	1.048	1.133	1.192	
	95% CI	(-1.6, 2.6)	(-0.9, 3.6)	(-3.2, 1.6)	
	Pr >  t			0.5023	
	n	5	6		
	LS Mean	-0.946	0.007	-0.953	
Week 108	SEM	1.140	1.170	1.306	
	95% CI	(-3.2, 1.3)	(-2.3, 2.3)	(-3.5, 1.6)	
	Pr >  t			0.4664	
	n	4	6		
	LS Mean	-0.425	0.840	-1.265	
Week 120	SEM	1.215	1.170	1.372	
	95% CI	(-2.8, 2.0)	(-1.5, 3.2)	(-4.0, 1.4)	
	Pr >  t			0.3575	
	n	4	4		
	LS Mean	0.462	0.102	0.359	
Week 132	SEM	1.215	1.291	1.478	
	95% CI	(-1.9, 2.9)	(-2.5, 2.7)	(-2.6, 3.3)	
	Pr >  t			0.8081	
	n	3	1		
	LS Mean	-0.018	1.537	-1.556	
Week 144	SEM	1.329	2.065	2.251	
	95% CI	(-2.6, 2.6)	(-2.5, 5.6)	(-6.0, 2.9)	
	Pr >  t			0.4902	
	n	1	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
E545X	Week 8	LS Mean	6.526	-1.673	8.200
		SEM	2.016	2.068	2.716
		95% CI	( 2.6,10.5)	( -5.7, 2.4)	( 2.8,13.6)
		Pr >  t			0.0029
	Week 16	n	35	36	
		LS Mean	0.875	1.019	-0.145
		SEM	1.193	1.249	0.548
		95% CI	( -1.5, 3.2)	( -1.4, 3.5)	( -1.2, 0.9)
	Week 24	Pr >  t			0.7918
		n	34	30	
		LS Mean	1.204	1.999	-0.795
		SEM	1.230	1.258	0.569
	Week 32	95% CI	( -1.2, 3.6)	( -0.5, 4.5)	( -1.9, 0.3)
		Pr >  t			0.1641
		n	32	23	
		LS Mean	1.039	2.641	-1.603
	Week 40	SEM	1.233	1.273	0.609
		95% CI	( -1.4, 3.5)	( 0.1, 5.2)	( -2.8,-0.4)
		Pr >  t			0.0091
		n	21	22	
	Week 48	LS Mean	1.852	1.703	0.149
		SEM	1.254	1.276	0.662
		95% CI	( -0.6, 4.3)	( -0.8, 4.2)	( -1.2, 1.5)
		Pr >  t			0.8221
Week 56	n	20	20		
	LS Mean	1.620	1.700	-0.080	
	SEM	1.259	1.282	0.681	
	95% CI	( -0.9, 4.1)	( -0.8, 4.2)	( -1.4, 1.3)	
Week 8	Pr >  t			0.9062	
	n	19	12		
	LS Mean	1.760	2.440	-0.680	
	SEM	1.262	1.325	0.764	
Week 16	95% CI	( -0.7, 4.2)	( -0.2, 5.1)	( -2.2, 0.8)	
	Pr >  t			0.3742	
	n	16	8		
	LS Mean	2.275	1.219	1.056	
Week 24	SEM	1.275	1.378	0.869	
	95% CI	( -0.2, 4.8)	( -1.5, 3.9)	( -0.7, 2.8)	
	Pr >  t			0.2251	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172		Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n	12	11		
	LS Mean	1.450	1.734		-0.284
	SEM	1.301	1.336		0.843
	95% CI	(-1.1, 4.0)	(-0.9, 4.4)		(-1.9, 1.4)
	Pr >  t				0.7363
Week 72	n	13	7		
	LS Mean	2.016	1.433		0.583
	SEM	1.295	1.399		0.929
	95% CI	(-0.5, 4.6)	(-1.3, 4.2)		(-1.2, 2.4)
	Pr >  t				0.5305
Week 84	n	12	6		
	LS Mean	2.735	1.708		1.027
	SEM	1.301	1.428		0.979
	95% CI	(0.2, 5.3)	(-1.1, 4.5)		(-0.9, 3.0)
	Pr >  t				0.2946
Week 96	n	7	6		
	LS Mean	1.209	2.531		-1.323
	SEM	1.372	1.427		1.072
	95% CI	(-1.5, 3.9)	(-0.3, 5.3)		(-3.4, 0.8)
	Pr >  t				0.2181
Week 108	n	5	3		
	LS Mean	2.305	1.003		1.302
	SEM	1.437	1.603		1.366
	95% CI	(-0.5, 5.1)	(-2.2, 4.2)		(-1.4, 4.0)
	Pr >  t				0.3412
Week 120	n	8	3		
	LS Mean	1.888	2.003		-0.114
	SEM	1.355	1.603		1.278
	95% CI	(-0.8, 4.6)	(-1.2, 5.2)		(-2.6, 2.4)
	Pr >  t				0.9288
Week 132	n	2	1		
	LS Mean	3.181	1.629		1.552
	SEM	1.735	2.163		2.216
	95% CI	(-0.2, 6.6)	(-2.6, 5.9)		(-2.8, 5.9)
	Pr >  t				0.4843
Week 144	n	2			
	LS Mean	1.918			
	SEM	1.738			
	95% CI	(-1.5, 5.3)			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 156	Pr >  t			
		n	1		
		LS Mean	2.076		
		SEM	2.141		
		95% CI	(-2.1, 6.3)		
		Pr >  t			
H1047X	Week 8	n	81	63	
		LS Mean	-0.056	0.562	-0.618
		SEM	0.394	0.411	0.394
		95% CI	(-0.8, 0.7)	(-0.2, 1.4)	(-1.4, 0.2)
		Pr >  t			0.1179
	Week 16	n	70	51	
		LS Mean	-0.001	0.325	-0.326
		SEM	0.406	0.437	0.425
		95% CI	(-0.8, 0.8)	(-0.5, 1.2)	(-1.2, 0.5)
		Pr >  t			0.4428
	Week 24	n	54	39	
		LS Mean	0.374	0.435	-0.060
		SEM	0.426	0.466	0.470
		95% CI	(-0.5, 1.2)	(-0.5, 1.4)	(-1.0, 0.9)
		Pr >  t			0.8982
	Week 32	n	50	35	
		LS Mean	0.668	0.402	0.266
		SEM	0.435	0.478	0.487
		95% CI	(-0.2, 1.5)	(-0.5, 1.3)	(-0.7, 1.2)
		Pr >  t			0.5857
	Week 40	n	42	27	
		LS Mean	0.441	-0.029	0.471
		SEM	0.449	0.510	0.530
		95% CI	(-0.4, 1.3)	(-1.0, 1.0)	(-0.6, 1.5)
		Pr >  t			0.3751
	Week 48	n	38	23	
		LS Mean	0.637	0.715	-0.078
		SEM	0.458	0.532	0.558
		95% CI	(-0.3, 1.5)	(-0.3, 1.8)	(-1.2, 1.0)
		Pr >  t			0.8890
	Week 56	n	33	24	
		LS Mean	0.259	0.767	-0.508
		SEM	0.472	0.526	0.565

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.7, 1.2)	(-0.3, 1.8)	(-1.6, 0.6)
		Pr >  t			0.3690
	Week 64	n	27	19	
		LS Mean	0.322	0.171	0.151
		SEM	0.495	0.561	0.615
		95% CI	(-0.6, 1.3)	(-0.9, 1.3)	(-1.1, 1.4)
		Pr >  t			0.8058
	Week 72	n	26	17	
		LS Mean	0.583	0.167	0.416
		SEM	0.499	0.579	0.635
		95% CI	(-0.4, 1.6)	(-1.0, 1.3)	(-0.8, 1.7)
		Pr >  t			0.5125
	Week 84	n	18	16	
		LS Mean	0.533	0.492	0.040
		SEM	0.555	0.589	0.687
		95% CI	(-0.6, 1.6)	(-0.7, 1.6)	(-1.3, 1.4)
		Pr >  t			0.9532
	Week 96	n	20	10	
		LS Mean	0.875	0.431	0.445
		SEM	0.537	0.685	0.759
		95% CI	(-0.2, 1.9)	(-0.9, 1.8)	(-1.0, 1.9)
		Pr >  t			0.5583
	Week 108	n	14	10	
		LS Mean	0.372	-0.168	0.541
		SEM	0.600	0.685	0.804
		95% CI	(-0.8, 1.6)	(-1.5, 1.2)	(-1.0, 2.1)
		Pr >  t			0.5015
	Week 120	n	14	7	
		LS Mean	0.281	-0.536	0.816
		SEM	0.598	0.780	0.886
		95% CI	(-0.9, 1.5)	(-2.1, 1.0)	(-0.9, 2.6)
		Pr >  t			0.3570
	Week 132	n	12	5	
		LS Mean	0.279	-0.113	0.392
		SEM	0.631	0.890	1.004
		95% CI	(-1.0, 1.5)	(-1.9, 1.6)	(-1.6, 2.4)
		Pr >  t			0.6962
	Week 144	n	11	4	
		LS Mean	0.224	0.475	-0.250

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.647	0.976	1.092
		95% CI	(-1.0, 1.5)	(-1.4, 2.4)	(-2.4, 1.9)
		Pr >  t			0.8188
	Week 156	n	8	3	
		LS Mean	0.323	1.594	-1.271
		SEM	0.729	1.104	1.252
		95% CI	(-1.1, 1.8)	(-0.6, 3.8)	(-3.7, 1.2)
		Pr >  t			0.3102
	Week 168	n	4	2	
		LS Mean	0.175	-0.162	0.337
		SEM	0.965	1.323	1.581
		95% CI	(-1.7, 2.1)	(-2.8, 2.4)	(-2.8, 3.4)
		Pr >  t			0.8312
	Week 180	n	1	1	
		LS Mean	2.228	0.439	1.789
		SEM	1.823	1.828	2.546
		95% CI	(-1.4, 5.8)	(-3.1, 4.0)	(-3.2, 6.8)
		Pr >  t			0.4826
	Week 192	n	1	1	
		LS Mean	1.228	-0.561	1.789
		SEM	1.823	1.828	2.546
		95% CI	(-2.4, 4.8)	(-4.1, 3.0)	(-3.2, 6.8)
		Pr >  t			0.4826

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	63			
			LS Mean	-0.056	0.562	-0.618		
			SEM	0.394	0.411	0.394		
			95% CI	(-0.8, 0.7)	(-0.2, 1.4)	(-1.4, 0.2)		
					Pr >  t			0.1179
		Week 16	n	70	51			
			LS Mean	-0.001	0.325	-0.326		
			SEM	0.406	0.437	0.425		
			95% CI	(-0.8, 0.8)	(-0.5, 1.2)	(-1.2, 0.5)		
					Pr >  t			0.4428
		Week 24	n	54	39			
			LS Mean	0.374	0.435	-0.060		
			SEM	0.426	0.466	0.470		
			95% CI	(-0.5, 1.2)	(-0.5, 1.4)	(-1.0, 0.9)		
					Pr >  t			0.8982
		Week 32	n	50	35			
			LS Mean	0.668	0.402	0.266		
			SEM	0.435	0.478	0.487		
			95% CI	(-0.2, 1.5)	(-0.5, 1.3)	(-0.7, 1.2)		
					Pr >  t			0.5857
		Week 40	n	42	27			
			LS Mean	0.441	-0.029	0.471		
			SEM	0.449	0.510	0.530		
			95% CI	(-0.4, 1.3)	(-1.0, 1.0)	(-0.6, 1.5)		
					Pr >  t			0.3751
		Week 48	n	38	23			
			LS Mean	0.637	0.715	-0.078		
			SEM	0.458	0.532	0.558		
95% CI	(-0.3, 1.5)		(-0.3, 1.8)	(-1.2, 1.0)				
			Pr >  t			0.8890		
Week 56	n	33	24					
	LS Mean	0.259	0.767	-0.508				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.472	0.526	0.565	
	95% CI	(-0.7, 1.2)	(-0.3, 1.8)	(-1.6, 0.6)	
	Pr >  t			0.3690	
	n	27	19		
	LS Mean	0.322	0.171	0.151	
Week 72	SEM	0.495	0.561	0.615	
	95% CI	(-0.6, 1.3)	(-0.9, 1.3)	(-1.1, 1.4)	
	Pr >  t			0.8058	
	n	26	17		
	LS Mean	0.583	0.167	0.416	
Week 84	SEM	0.499	0.579	0.635	
	95% CI	(-0.4, 1.6)	(-1.0, 1.3)	(-0.8, 1.7)	
	Pr >  t			0.5125	
	n	18	16		
	LS Mean	0.533	0.492	0.040	
Week 96	SEM	0.555	0.589	0.687	
	95% CI	(-0.6, 1.6)	(-0.7, 1.6)	(-1.3, 1.4)	
	Pr >  t			0.9532	
	n	20	10		
	LS Mean	0.875	0.431	0.445	
Week 108	SEM	0.537	0.685	0.759	
	95% CI	(-0.2, 1.9)	(-0.9, 1.8)	(-1.0, 1.9)	
	Pr >  t			0.5583	
	n	14	10		
	LS Mean	0.372	-0.168	0.541	
Week 120	SEM	0.600	0.685	0.804	
	95% CI	(-0.8, 1.6)	(-1.5, 1.2)	(-1.0, 2.1)	
	Pr >  t			0.5015	
	n	14	7		
	LS Mean	0.281	-0.536	0.816	
Week 132	SEM	0.598	0.780	0.886	
	95% CI	(-0.9, 1.5)	(-2.1, 1.0)	(-0.9, 2.6)	
	Pr >  t			0.3570	
	n	12	5		
	LS Mean	0.279	-0.113	0.392	
Week 144	SEM	0.631	0.890	1.004	
	95% CI	(-1.0, 1.5)	(-1.9, 1.6)	(-1.6, 2.4)	
	Pr >  t			0.6962	
	n	11	4		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Exon 9	Week 156	LS Mean	0.224	0.475	-0.250
		SEM	0.647	0.976	1.092
		95% CI	(-1.0, 1.5)	(-1.4, 2.4)	(-2.4, 1.9)
		Pr >  t			0.8188
	Week 168	n	8	3	
		LS Mean	0.323	1.594	-1.271
		SEM	0.729	1.104	1.252
		95% CI	(-1.1, 1.8)	(-0.6, 3.8)	(-3.7, 1.2)
	Week 180	Pr >  t			0.3102
		n	4	2	
		LS Mean	0.175	-0.162	0.337
		SEM	0.965	1.323	1.581
	Week 192	95% CI	(-1.7, 2.1)	(-2.8, 2.4)	(-2.8, 3.4)
		Pr >  t			0.8312
		n	1	1	
		LS Mean	2.228	0.439	1.789
	Week 192	SEM	1.823	1.828	2.546
		95% CI	(-1.4, 5.8)	(-3.1, 4.0)	(-3.2, 6.8)
		Pr >  t			0.4826
		n	1	1	
	Week 8	LS Mean	1.228	-0.561	1.789
		SEM	1.823	1.828	2.546
		95% CI	(-2.4, 4.8)	(-4.1, 3.0)	(-3.2, 6.8)
		Pr >  t			0.4826
Week 16	n	53	63		
	LS Mean	-0.431	-0.405	-0.026	
	SEM	0.617	0.662	0.438	
	95% CI	(-1.6, 0.8)	(-1.7, 0.9)	(-0.9, 0.8)	
Week 24	Pr >  t			0.9520	
	n	48	48		
	LS Mean	-0.454	0.500	-0.955	
	SEM	0.633	0.678	0.470	
Week 24	95% CI	(-1.7, 0.8)	(-0.8, 1.8)	(-1.9,-0.0)	
	Pr >  t			0.0429	
	n	46	36		
	LS Mean	-0.408	1.036	-1.444	
Week 24	SEM	0.635	0.698	0.503	
	95% CI	(-1.7, 0.8)	(-0.3, 2.4)	(-2.4,-0.5)	
	Pr >  t			0.0043	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	n	31	33	
	LS Mean	0.492	0.300	0.191
	SEM	0.678	0.705	0.549
	95% CI	(-0.8, 1.8)	(-1.1, 1.7)	(-0.9, 1.3)
	Pr >  t			0.7280
Week 40	n	28	30	
	LS Mean	0.096	0.349	-0.253
	SEM	0.687	0.712	0.570
	95% CI	(-1.3, 1.4)	(-1.1, 1.8)	(-1.4, 0.9)
	Pr >  t			0.6574
Week 48	n	26	23	
	LS Mean	0.050	0.930	-0.880
	SEM	0.694	0.738	0.609
	95% CI	(-1.3, 1.4)	(-0.5, 2.4)	(-2.1, 0.3)
	Pr >  t			0.1490
Week 56	n	22	17	
	LS Mean	0.399	-0.021	0.420
	SEM	0.711	0.774	0.670
	95% CI	(-1.0, 1.8)	(-1.5, 1.5)	(-0.9, 1.7)
	Pr >  t			0.5311
Week 64	n	17	19	
	LS Mean	-0.222	0.275	-0.498
	SEM	0.742	0.760	0.688
	95% CI	(-1.7, 1.2)	(-1.2, 1.8)	(-1.8, 0.9)
	Pr >  t			0.4697
Week 72	n	20	14	
	LS Mean	0.045	0.996	-0.951
	SEM	0.722	0.802	0.713
	95% CI	(-1.4, 1.5)	(-0.6, 2.6)	(-2.4, 0.4)
	Pr >  t			0.1829
Week 84	n	19	13	
	LS Mean	1.160	0.957	0.203
	SEM	0.728	0.813	0.732
	95% CI	(-0.3, 2.6)	(-0.6, 2.6)	(-1.2, 1.6)
	Pr >  t			0.7815
Week 96	n	12	12	
	LS Mean	-0.363	0.675	-1.037
	SEM	0.795	0.826	0.813
	95% CI	(-1.9, 1.2)	(-1.0, 2.3)	(-2.6, 0.6)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.2024
	Week 108	n	9	9	
		LS Mean	0.498	0.542	-0.044
		SEM	0.851	0.881	0.920
		95% CI	(-1.2, 2.2)	(-1.2, 2.3)	(-1.9, 1.8)
		Pr >  t			0.9616
	Week 120	n	12	7	
		LS Mean	0.575	0.431	0.144
		SEM	0.797	0.940	0.928
		95% CI	(-1.0, 2.1)	(-1.4, 2.3)	(-1.7, 2.0)
		Pr >  t			0.8771
	Week 132	n	5	2	
		LS Mean	0.987	1.024	-0.037
		SEM	1.008	1.435	1.556
		95% CI	(-1.0, 3.0)	(-1.8, 3.8)	(-3.1, 3.0)
		Pr >  t			0.9811
	Week 144	n	3	1	
		LS Mean	2.626	-1.530	4.156
		SEM	1.209	1.929	2.128
		95% CI	( 0.3, 5.0)	(-5.3, 2.3)	(-0.0, 8.3)
		Pr >  t			0.0513
	Week 156	n	1		
		LS Mean	0.614		
		SEM	1.909		
		95% CI	(-3.1, 4.4)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle Fehler! Kein Text mit angegebener Formatvorlage im Dokument.H-32: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Schweregrad-Index“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	71	
		LS Mean	-0.253	0.156	-0.409	
		SEM	0.311	0.315	0.282	
		95% CI	(-0.9, 0.4)	(-0.5, 0.8)	(-1.0, 0.1)	
			Pr >  t			0.1484
	Week 16	n	67	54		
		LS Mean	-0.394	0.191	-0.585	
		SEM	0.316	0.334	0.306	
		95% CI	(-1.0, 0.2)	(-0.5, 0.8)	(-1.2, 0.0)	
			Pr >  t			0.0567
	Week 24	n	61	45		
		LS Mean	-0.064	0.432	-0.497	
		SEM	0.322	0.343	0.322	
		95% CI	(-0.7, 0.6)	(-0.2, 1.1)	(-1.1, 0.1)	
			Pr >  t			0.1235
	Week 32	n	52	40		
		LS Mean	0.362	0.228	0.134	
		SEM	0.333	0.352	0.337	
		95% CI	(-0.3, 1.0)	(-0.5, 0.9)	(-0.5, 0.8)	
			Pr >  t			0.6920
Week 40	n	45	35			
	LS Mean	0.053	-0.059	0.112		
	SEM	0.340	0.362	0.353		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	(-0.6, 0.7)	(-0.8, 0.7)	(-0.6, 0.8)
		Pr >  t			0.7514
	Week 48	n	42	29	
		LS Mean	0.415	0.338	0.078
		SEM	0.344	0.375	0.370
		95% CI	(-0.3, 1.1)	(-0.4, 1.1)	(-0.6, 0.8)
		Pr >  t			0.8336
	Week 56	n	35	24	
		LS Mean	0.469	-0.203	0.672
		SEM	0.355	0.391	0.395
		95% CI	(-0.2, 1.2)	(-1.0, 0.6)	(-0.1, 1.4)
		Pr >  t			0.0897
	Week 64	n	25	25	
		LS Mean	0.374	-0.250	0.625
		SEM	0.378	0.387	0.414
		95% CI	(-0.4, 1.1)	(-1.0, 0.5)	(-0.2, 1.4)
		Pr >  t			0.1320
	Week 72	n	27	20	
		LS Mean	0.371	0.358	0.013
		SEM	0.372	0.407	0.428
		95% CI	(-0.4, 1.1)	(-0.4, 1.2)	(-0.8, 0.9)
		Pr >  t			0.9753
	Week 84	n	23	19	
		LS Mean	0.021	0.588	-0.567
		SEM	0.387	0.412	0.444
		95% CI	(-0.7, 0.8)	(-0.2, 1.4)	(-1.4, 0.3)
		Pr >  t			0.2016
	Week 96	n	20	13	
		LS Mean	0.146	0.305	-0.159
		SEM	0.400	0.455	0.494
		95% CI	(-0.6, 0.9)	(-0.6, 1.2)	(-1.1, 0.8)
		Pr >  t			0.7471
	Week 108	n	17	13	
		LS Mean	0.615	-0.306	0.922
		SEM	0.416	0.455	0.508
		95% CI	(-0.2, 1.4)	(-1.2, 0.6)	(-0.1, 1.9)
		Pr >  t			0.0701
	Week 120	n	17	12	
		LS Mean	0.422	-0.402	0.824

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Present	Week 132	SEM	0.416	0.466	0.518
		95% CI	(-0.4, 1.2)	(-1.3, 0.5)	(-0.2, 1.8)
		Pr >  t			0.1119
	Week 144	n	13	6	
		LS Mean	0.009	0.080	-0.071
		SEM	0.448	0.586	0.649
	Week 156	95% CI	(-0.9, 0.9)	(-1.1, 1.2)	(-1.3, 1.2)
		Pr >  t			0.9131
		n	11	4	
	Week 168	LS Mean	0.157	-0.363	0.520
		SEM	0.471	0.686	0.755
		95% CI	(-0.8, 1.1)	(-1.7, 1.0)	(-1.0, 2.0)
Week 180	Pr >  t			0.4912	
	n	6	2		
	LS Mean	-0.186	1.027	-1.214	
Week 192	SEM	0.580	0.920	1.030	
	95% CI	(-1.3, 1.0)	(-0.8, 2.8)	(-3.2, 0.8)	
	Pr >  t			0.2388	
Week 8	n	3	1		
	LS Mean	-0.274	0.147	-0.421	
	SEM	0.766	1.265	1.436	
Week 16	95% CI	(-1.8, 1.2)	(-2.3, 2.6)	(-3.2, 2.4)	
	Pr >  t			0.7695	
	n	1	1		
Week 8	LS Mean	1.393	0.397	0.996	
	SEM	1.261	1.265	1.751	
	95% CI	(-1.1, 3.9)	(-2.1, 2.9)	(-2.4, 4.4)	
Week 16	Pr >  t			0.5697	
	n	1	1		
	LS Mean	0.393	-0.353	0.746	
Week 8	SEM	1.261	1.265	1.751	
	95% CI	(-2.1, 2.9)	(-2.8, 2.1)	(-2.7, 4.2)	
	Pr >  t			0.6703	
Week 16	n	65	66		
	LS Mean	0.434	0.374	0.060	
	SEM	0.390	0.402	0.339	
Week 8	95% CI	(-0.3, 1.2)	(-0.4, 1.2)	(-0.6, 0.7)	
	Pr >  t			0.8596	
	n	57	51		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.617	0.939	-0.322
		SEM	0.405	0.420	0.366
		95% CI	(-0.2, 1.4)	( 0.1, 1.8)	(-1.0, 0.4)
		Pr >  t			0.3792
	Week 24	n	44	35	
		LS Mean	0.692	1.056	-0.364
		SEM	0.419	0.451	0.412
		95% CI	(-0.1, 1.5)	( 0.2, 1.9)	(-1.2, 0.4)
		Pr >  t			0.3771
	Week 32	n	34	32	
		LS Mean	0.673	0.806	-0.133
		SEM	0.439	0.459	0.439
		95% CI	(-0.2, 1.5)	(-0.1, 1.7)	(-1.0, 0.7)
		Pr >  t			0.7620
	Week 40	n	30	26	
		LS Mean	0.668	1.071	-0.402
		SEM	0.450	0.476	0.467
		95% CI	(-0.2, 1.6)	( 0.1, 2.0)	(-1.3, 0.5)
		Pr >  t			0.3893
	Week 48	n	27	21	
		LS Mean	0.896	1.150	-0.254
		SEM	0.458	0.498	0.496
		95% CI	(-0.0, 1.8)	( 0.2, 2.1)	(-1.2, 0.7)
		Pr >  t			0.6093
	Week 56	n	24	21	
		LS Mean	0.564	1.451	-0.887
		SEM	0.468	0.498	0.506
		95% CI	(-0.4, 1.5)	( 0.5, 2.4)	(-1.9, 0.1)
		Pr >  t			0.0805
	Week 64	n	22	17	
		LS Mean	0.373	1.248	-0.874
		SEM	0.477	0.521	0.537
		95% CI	(-0.6, 1.3)	( 0.2, 2.3)	(-1.9, 0.2)
		Pr >  t			0.1042
	Week 72	n	21	15	
		LS Mean	0.727	0.714	0.013
		SEM	0.482	0.537	0.557
		95% CI	(-0.2, 1.7)	(-0.3, 1.8)	(-1.1, 1.1)
		Pr >  t			0.9810

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 84	n	17	14	
	LS Mean	1.700	1.206	0.495
	SEM	0.507	0.546	0.586
	95% CI	( 0.7, 2.7)	( 0.1, 2.3)	( -0.7, 1.6)
	Pr >  t			0.3989
Week 96	n	15	11	
	LS Mean	1.405	1.205	0.201
	SEM	0.521	0.582	0.633
	95% CI	( 0.4, 2.4)	( 0.1, 2.3)	( -1.0, 1.4)
	Pr >  t			0.7513
Week 108	n	9	8	
	LS Mean	0.605	1.254	-0.648
	SEM	0.604	0.641	0.751
	95% CI	( -0.6, 1.8)	( -0.0, 2.5)	( -2.1, 0.8)
	Pr >  t			0.3881
Week 120	n	11	4	
	LS Mean	0.627	1.927	-1.299
	SEM	0.567	0.818	0.885
	95% CI	( -0.5, 1.7)	( 0.3, 3.5)	( -3.0, 0.4)
	Pr >  t			0.1424
Week 132	n	7	2	
	LS Mean	1.124	1.099	0.025
	SEM	0.655	1.085	1.181
	95% CI	( -0.2, 2.4)	( -1.0, 3.2)	( -2.3, 2.3)
	Pr >  t			0.9833
Week 144	n	4	1	
	LS Mean	0.457	1.239	-0.782
	SEM	0.800	1.484	1.624
	95% CI	( -1.1, 2.0)	( -1.7, 4.2)	( -4.0, 2.4)
	Pr >  t			0.6302
Week 156	n	3	1	
	LS Mean	1.098	0.989	0.109
	SEM	0.905	1.484	1.676
	95% CI	( -0.7, 2.9)	( -1.9, 3.9)	( -3.2, 3.4)
	Pr >  t			0.9480
Week 168	n	1	1	
	LS Mean	0.438	-0.011	0.449
	SEM	1.479	1.484	2.044
	95% CI	( -2.5, 3.3)	( -2.9, 2.9)	( -3.6, 4.5)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
				Pr >  t  0.8263

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Bone Lesions Only (L)	No	Week 8	n	104	109		
			LS Mean	0.075	0.175	-0.100	
				SEM	0.286	0.285	0.253
				95% CI	(-0.5, 0.6)	(-0.4, 0.7)	(-0.6, 0.4)
				Pr >  t			0.6932
		Week 16	n	92	83		
	LS Mean		0.095	0.434	-0.339		
				SEM	0.294	0.302	0.273
				95% CI	(-0.5, 0.7)	(-0.2, 1.0)	(-0.9, 0.2)
				Pr >  t			0.2145
		Week 24	n	77	59		
	LS Mean		0.214	0.626	-0.412		
				SEM	0.301	0.322	0.302
				95% CI	(-0.4, 0.8)	(-0.0, 1.3)	(-1.0, 0.2)
				Pr >  t			0.1727
		Week 32	n	57	53		
	LS Mean		0.454	0.457	-0.003		
				SEM	0.320	0.328	0.324
				95% CI	(-0.2, 1.1)	(-0.2, 1.1)	(-0.6, 0.6)
				Pr >  t			0.9938
		Week 40	n	50	44		
	LS Mean		0.227	0.507	-0.279		
				SEM	0.328	0.342	0.344
				95% CI	(-0.4, 0.9)	(-0.2, 1.2)	(-1.0, 0.4)
			Pr >  t			0.4178	
	Week 48	n	47	37			
LS Mean		0.508	0.802	-0.294			
			SEM	0.332	0.354	0.361	
			95% CI	(-0.1, 1.2)	( 0.1, 1.5)	(-1.0, 0.4)	
			Pr >  t			0.4148	
	Week 56	n	40	32			
LS Mean		0.413	0.714	-0.301			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.343	0.366	0.382
	95% CI	(-0.3, 1.1)	(-0.0, 1.4)	(-1.1, 0.4)
	Pr >  t			0.4314
	n	32	27	
	LS Mean	0.178	0.605	-0.426
Week 72	SEM	0.360	0.382	0.412
	95% CI	(-0.5, 0.9)	(-0.1, 1.4)	(-1.2, 0.4)
	Pr >  t			0.3013
	n	31	23	
	LS Mean	0.575	0.448	0.128
Week 84	SEM	0.363	0.398	0.430
	95% CI	(-0.1, 1.3)	(-0.3, 1.2)	(-0.7, 1.0)
	Pr >  t			0.7662
	n	27	21	
	LS Mean	0.872	1.153	-0.281
Week 96	SEM	0.376	0.408	0.449
	95% CI	( 0.1, 1.6)	( 0.4, 2.0)	(-1.2, 0.6)
	Pr >  t			0.5313
	n	23	16	
	LS Mean	0.683	0.684	-0.002
Week 108	SEM	0.391	0.442	0.493
	95% CI	(-0.1, 1.5)	(-0.2, 1.6)	(-1.0, 1.0)
	Pr >  t			0.9972
	n	15	14	
	LS Mean	0.528	0.678	-0.150
Week 120	SEM	0.444	0.460	0.551
	95% CI	(-0.3, 1.4)	(-0.2, 1.6)	(-1.2, 0.9)
	Pr >  t			0.7855
	n	18	8	
	LS Mean	0.536	1.002	-0.466
Week 132	SEM	0.420	0.560	0.621
	95% CI	(-0.3, 1.4)	(-0.1, 2.1)	(-1.7, 0.8)
	Pr >  t			0.4531
	n	12	4	
	LS Mean	0.138	0.788	-0.649
Week 144	SEM	0.478	0.740	0.819
	95% CI	(-0.8, 1.1)	(-0.7, 2.2)	(-2.3, 1.0)
	Pr >  t			0.4283
	n	8	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
	Week 156	LS Mean	0.012	0.118	-0.106
		SEM	0.552	0.841	0.953
		95% CI	(-1.1, 1.1)	(-1.5, 1.8)	(-2.0, 1.8)
		Pr >  t			0.9118
	Week 168	n	5	1	
		LS Mean	0.991	0.518	0.473
		SEM	0.669	1.398	1.516
		95% CI	(-0.3, 2.3)	(-2.2, 3.3)	(-2.5, 3.4)
	Week 180	n	2	1	
		LS Mean	-0.155	-0.482	0.327
		SEM	1.006	1.398	1.692
		95% CI	(-2.1, 1.8)	(-3.2, 2.3)	(-3.0, 3.6)
Week 192	n	1			
	LS Mean	1.620			
	SEM	1.394			
	95% CI	(-1.1, 4.4)			
Yes	Week 8	Pr >  t			0.8470
		n	1		
		LS Mean	0.620		
		SEM	1.394		
	Week 16	n	38	28	
		LS Mean	-0.110	0.422	-0.532
		SEM	0.488	0.526	0.437
		95% CI	(-1.1, 0.9)	(-0.6, 1.5)	(-1.4, 0.3)
	Week 24	Pr >  t			0.2256
		n	32	22	
		LS Mean	-0.147	0.793	-0.940
		SEM	0.495	0.542	0.471
	95% CI	(-1.1, 0.8)	(-0.3, 1.9)	(-1.9, -0.0)	
	Pr >  t			0.0476	
	n	28	21		
	LS Mean	0.325	0.900	-0.575	
	SEM	0.508	0.545	0.484	
	95% CI	(-0.7, 1.3)	(-0.2, 2.0)	(-1.5, 0.4)	
	Pr >  t			0.2365	

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172	
Week 32	n	29	19	
	LS Mean	0.549	0.502	0.047
	SEM	0.506	0.559	0.491
	95% CI	(-0.5, 1.6)	(-0.6, 1.6)	(-0.9, 1.0)
	Pr >  t			0.9233
Week 40	n	25	17	
	LS Mean	0.441	0.204	0.237
	SEM	0.515	0.568	0.510
	95% CI	(-0.6, 1.5)	(-0.9, 1.3)	(-0.8, 1.2)
	Pr >  t			0.6435
Week 48	n	22	13	
	LS Mean	0.816	0.364	0.452
	SEM	0.523	0.592	0.545
	95% CI	(-0.2, 1.9)	(-0.8, 1.5)	(-0.6, 1.5)
	Pr >  t			0.4078
Week 56	n	19	13	
	LS Mean	0.686	0.122	0.564
	SEM	0.533	0.592	0.556
	95% CI	(-0.4, 1.7)	(-1.0, 1.3)	(-0.5, 1.7)
	Pr >  t			0.3116
Week 64	n	15	15	
	LS Mean	0.644	-0.038	0.683
	SEM	0.551	0.579	0.561
	95% CI	(-0.4, 1.7)	(-1.2, 1.1)	(-0.4, 1.8)
	Pr >  t			0.2246
Week 72	n	17	12	
	LS Mean	0.375	0.643	-0.268
	SEM	0.541	0.600	0.573
	95% CI	(-0.7, 1.4)	(-0.5, 1.8)	(-1.4, 0.9)
	Pr >  t			0.6406
Week 84	n	13	12	
	LS Mean	0.392	0.333	0.059
	SEM	0.569	0.600	0.596
	95% CI	(-0.7, 1.5)	(-0.9, 1.5)	(-1.1, 1.2)
	Pr >  t			0.9213
Week 96	n	12	8	
	LS Mean	0.625	0.721	-0.096
	SEM	0.577	0.650	0.654
	95% CI	(-0.5, 1.8)	(-0.6, 2.0)	(-1.4, 1.2)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 108		Pr >  t			0.8830
	n	11	7		
	LS Mean	0.803	-0.347		1.150
	SEM	0.587	0.670		0.682
	95% CI	(-0.4, 2.0)	(-1.7, 1.0)		(-0.2, 2.5)
Week 120		Pr >  t			0.0928
	n	10	8		
	LS Mean	0.460	-0.371		0.831
	SEM	0.598	0.650		0.673
	95% CI	(-0.7, 1.6)	(-1.7, 0.9)		(-0.5, 2.2)
Week 132		Pr >  t			0.2174
	n	8	4		
	LS Mean	0.864	0.147		0.716
	SEM	0.628	0.779		0.820
	95% CI	(-0.4, 2.1)	(-1.4, 1.7)		(-0.9, 2.3)
Week 144		Pr >  t			0.3829
	n	7	2		
	LS Mean	0.686	0.267		0.419
	SEM	0.648	0.987		1.032
	95% CI	(-0.6, 2.0)	(-1.7, 2.2)		(-1.6, 2.4)
Week 156		Pr >  t			0.6849
	n	4	2		
	LS Mean	-0.583	1.267		-1.849
	SEM	0.759	0.987		1.105
	95% CI	(-2.1, 0.9)	(-0.7, 3.2)		(-4.0, 0.3)
Week 168		Pr >  t			0.0949
	n	2	1		
	LS Mean	0.163	0.382		-0.219
	SEM	0.969	1.305		1.521
	95% CI	(-1.7, 2.1)	(-2.2, 2.9)		(-3.2, 2.8)
Week 180		Pr >  t			0.8855
	n		1		
	LS Mean		0.632		
	SEM		1.305		
	95% CI		(-1.9, 3.2)		
Week 192		Pr >  t			
	n		1		
	LS Mean		-0.118		
		SEM		1.305	



<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
		95% CI		(-2.7, 2.4)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		N=169	N=172	N=172	N=172		
Stratum 2 - Prior CDK4/6 inhibitor (L) No prior use	Week 8	n	134	131			
		LS Mean	-0.402	-0.281		-0.121	
		SEM	0.156	0.157		0.222	
		95% CI	(-0.7,-0.1)	(-0.6, 0.0)		(-0.6, 0.3)	
	Week 16	Pr >  t					0.5855
		n	118	102			
		LS Mean	-0.378	-0.011		-0.368	
		SEM	0.163	0.174		0.238	
	Week 24	95% CI	(-0.7,-0.1)	(-0.4, 0.3)		(-0.8, 0.1)	
		Pr >  t					0.1236
		n	100	78			
		LS Mean	-0.210	0.212		-0.423	
	Week 32	SEM	0.173	0.192		0.258	
		95% CI	(-0.6, 0.1)	(-0.2, 0.6)		(-0.9, 0.1)	
		Pr >  t					0.1023
		n	84	71			
	Week 40	LS Mean	0.068	-0.027		0.095	
		SEM	0.184	0.199		0.271	
		95% CI	(-0.3, 0.4)	(-0.4, 0.4)		(-0.4, 0.6)	
		Pr >  t					0.7259
Week 48	n	73	61				
	LS Mean	-0.119	-0.085		-0.034		
	SEM	0.194	0.210		0.285		
	95% CI	(-0.5, 0.3)	(-0.5, 0.3)		(-0.6, 0.5)		
Week 56	Pr >  t					0.9052	
	n	67	50				
	LS Mean	0.190	0.175		0.015		
	SEM	0.200	0.225		0.301		
Week 56	95% CI	(-0.2, 0.6)	(-0.3, 0.6)		(-0.6, 0.6)		
	Pr >  t					0.9605	
Week 56	n	57	45				
	LS Mean	0.082	0.031		0.051		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.212	0.234	0.316
	95% CI	(-0.3, 0.5)	(-0.4, 0.5)	(-0.6, 0.7)
	Pr >  t			0.8723
	n	45	42	
	LS Mean	-0.129	-0.131	0.002
Week 72	SEM	0.231	0.241	0.333
	95% CI	(-0.6, 0.3)	(-0.6, 0.3)	(-0.7, 0.7)
	Pr >  t			0.9960
	n	46	35	
	LS Mean	0.040	0.005	0.035
Week 84	SEM	0.229	0.258	0.345
	95% CI	(-0.4, 0.5)	(-0.5, 0.5)	(-0.6, 0.7)
	Pr >  t			0.9184
	n	40	33	
	LS Mean	0.286	0.347	-0.060
Week 96	SEM	0.241	0.264	0.358
	95% CI	(-0.2, 0.8)	(-0.2, 0.9)	(-0.8, 0.6)
	Pr >  t			0.8664
	n	34	24	
	LS Mean	0.252	0.181	0.071
Week 108	SEM	0.257	0.300	0.395
	95% CI	(-0.3, 0.8)	(-0.4, 0.8)	(-0.7, 0.8)
	Pr >  t			0.8566
	n	26	21	
	LS Mean	0.215	-0.183	0.398
Week 120	SEM	0.287	0.317	0.428
	95% CI	(-0.3, 0.8)	(-0.8, 0.4)	(-0.4, 1.2)
	Pr >  t			0.3522
	n	27	16	
	LS Mean	0.100	-0.179	0.280
Week 132	SEM	0.283	0.357	0.455
	95% CI	(-0.5, 0.7)	(-0.9, 0.5)	(-0.6, 1.2)
	Pr >  t			0.5388
	n	20	8	
	LS Mean	0.001	-0.009	0.010
Week 144	SEM	0.320	0.487	0.582
	95% CI	(-0.6, 0.6)	(-1.0, 0.9)	(-1.1, 1.2)
	Pr >  t			0.9861
	n	14	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Prior use	Week 156	LS Mean	-0.085	-0.326	0.241
		SEM	0.374	0.607	0.713
		95% CI	(-0.8, 0.6)	(-1.5, 0.9)	(-1.2, 1.6)
		Pr >  t			0.7356
		n	9	3	
	Week 168	LS Mean	-0.138	0.600	-0.738
		SEM	0.458	0.775	0.900
		95% CI	(-1.0, 0.8)	(-0.9, 2.1)	(-2.5, 1.0)
		Pr >  t			0.4126
		n	4	2	
	Week 180	LS Mean	-0.423	-0.493	0.070
		SEM	0.672	0.945	1.159
		95% CI	(-1.7, 0.9)	(-2.3, 1.4)	(-2.2, 2.3)
		Pr >  t			0.9515
		n	1	1	
	Week 192	LS Mean	1.205	0.258	0.946
		SEM	1.326	1.327	1.876
		95% CI	(-1.4, 3.8)	(-2.3, 2.9)	(-2.7, 4.6)
		Pr >  t			0.6140
		n	1	1	
Week 8	LS Mean	0.220	1.261	-1.041	
	SEM	0.691	0.838	1.069	
	95% CI	(-1.3, 1.7)	(-0.5, 3.0)	(-3.3, 1.2)	
	Pr >  t			0.3448	
	n	8	6		
Week 16	LS Mean	-0.187	2.174	-2.361	
	SEM	0.790	1.155	1.378	
	95% CI	(-1.8, 1.5)	(-0.2, 4.6)	(-5.2, 0.5)	
	Pr >  t			0.1007	
	n	6	3		
Week 24	LS Mean	0.968	0.911	0.057	
	SEM	0.844	1.357	1.583	
	95% CI	(-0.8, 2.7)	(-1.9, 3.7)	(-3.2, 3.3)	
	Pr >  t			0.9714	
	n	5	2		

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32		n	2	1	
		LS Mean	0.364	1.066	-0.702
		SEM	1.222	1.745	2.132
		95% CI	(-2.1, 2.9)	(-2.5, 4.6)	(-5.1, 3.7)
		Pr >  t			0.7446
Week 40		n	2		
		LS Mean	0.364		
		SEM	1.222		
		95% CI	(-2.1, 2.9)		
		Pr >  t			
Week 48		n	2		
		LS Mean	0.614		
		SEM	1.222		
		95% CI	(-1.9, 3.1)		
		Pr >  t			
Week 56		n	2		
		LS Mean	0.614		
		SEM	1.222		
		95% CI	(-1.9, 3.1)		
		Pr >  t			
Week 64		n	2		
		LS Mean	1.364		
		SEM	1.222		
		95% CI	(-1.1, 3.9)		
		Pr >  t			
Week 72		n	2		
		LS Mean	1.614		
		SEM	1.222		
		95% CI	(-0.9, 4.1)		
		Pr >  t			
Week 96		n	1		
		LS Mean	0.364		
		SEM	1.607		
		95% CI	(-3.0, 3.7)		
		Pr >  t			
Week 120		n	1		
		LS Mean	0.364		
		SEM	1.607		
		95% CI	(-3.0, 3.7)		
		Pr >  t			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 144	Pr >  t  n	1		
		LS Mean	0.364		
		SEM	1.607		
		95% CI	(-3.0, 3.7)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	67			
			LS Mean	0.070	0.521	-0.451		
			SEM	0.280	0.295	0.287		
			95% CI	(-0.5, 0.6)	(-0.1, 1.1)	(-1.0, 0.1)		
					Pr >  t			0.1170
		Week 16	n	70	50			
			LS Mean	-0.106	0.569	-0.675		
			SEM	0.288	0.322	0.314		
			95% CI	(-0.7, 0.5)	(-0.1, 1.2)	(-1.3,-0.1)		
					Pr >  t			0.0321
		Week 24	n	61	36			
			LS Mean	0.348	0.735	-0.386		
			SEM	0.296	0.350	0.346		
			95% CI	(-0.2, 0.9)	( 0.0, 1.4)	(-1.1, 0.3)		
					Pr >  t			0.2646
		Week 32	n	48	32			
			LS Mean	0.366	0.228	0.137		
			SEM	0.313	0.360	0.368		
			95% CI	(-0.3, 1.0)	(-0.5, 0.9)	(-0.6, 0.9)		
					Pr >  t			0.7093
		Week 40	n	42	30			
			LS Mean	0.015	0.362	-0.347		
			SEM	0.322	0.366	0.382		
			95% CI	(-0.6, 0.6)	(-0.4, 1.1)	(-1.1, 0.4)		
					Pr >  t			0.3635
		Week 48	n	40	24			
			LS Mean	0.782	0.667	0.115		
			SEM	0.326	0.386	0.404		
95% CI	( 0.1, 1.4)		(-0.1, 1.4)	(-0.7, 0.9)				
			Pr >  t			0.7767		
Week 56	n	35	20					
	LS Mean	0.247	0.741	-0.494				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 64	SEM	0.335	0.406	0.431
	95% CI	(-0.4, 0.9)	(-0.1, 1.5)	(-1.3, 0.4)
	Pr >  t			0.2517
	n	29	18	
	LS Mean	0.244	0.048	0.195
Week 72	SEM	0.350	0.418	0.455
	95% CI	(-0.4, 0.9)	(-0.8, 0.9)	(-0.7, 1.1)
	Pr >  t			0.6678
	n	28	18	
	LS Mean	0.242	0.699	-0.457
Week 84	SEM	0.353	0.418	0.457
	95% CI	(-0.5, 0.9)	(-0.1, 1.5)	(-1.4, 0.4)
	Pr >  t			0.3170
	n	27	17	
	LS Mean	0.592	0.891	-0.299
Week 96	SEM	0.359	0.425	0.466
	95% CI	(-0.1, 1.3)	(0.1, 1.7)	(-1.2, 0.6)
	Pr >  t			0.5214
	n	23	14	
	LS Mean	0.576	0.996	-0.419
Week 108	SEM	0.373	0.451	0.501
	95% CI	(-0.2, 1.3)	(0.1, 1.9)	(-1.4, 0.6)
	Pr >  t			0.4027
	n	19	12	
	LS Mean	0.552	0.623	-0.071
Week 120	SEM	0.396	0.474	0.537
	95% CI	(-0.2, 1.3)	(-0.3, 1.6)	(-1.1, 1.0)
	Pr >  t			0.8954
	n	18	8	
	LS Mean	0.525	0.115	0.410
Week 132	SEM	0.401	0.546	0.606
	95% CI	(-0.3, 1.3)	(-1.0, 1.2)	(-0.8, 1.6)
	Pr >  t			0.4988
	n	11	4	
	LS Mean	-0.075	0.720	-0.795
Week 144	SEM	0.473	0.719	0.805
	95% CI	(-1.0, 0.9)	(-0.7, 2.1)	(-2.4, 0.8)
	Pr >  t			0.3238
	n	11	4	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
>= 65 Years	Week 156	LS Mean	0.300	0.208	0.092
		SEM	0.471	0.720	0.806
		95% CI	(-0.6, 1.2)	(-1.2, 1.6)	(-1.5, 1.7)
		Pr >  t			0.9089
		n	4	2	
	Week 168	LS Mean	-0.954	1.598	-2.552
		SEM	0.708	0.977	1.167
		95% CI	(-2.3, 0.4)	(-0.3, 3.5)	(-4.8,-0.3)
		Pr >  t			0.0291
		n	1	2	
	Week 180	LS Mean	-1.528	0.098	-1.627
		SEM	1.341	0.977	1.631
		95% CI	(-4.2, 1.1)	(-1.8, 2.0)	(-4.8, 1.6)
		Pr >  t			0.3189
		n		1	
	Week 192	LS Mean		0.816	
		SEM		1.349	
		95% CI		(-1.8, 3.5)	
		Pr >  t			
		n		1	
	Week 8	LS Mean		0.066	
		SEM		1.349	
		95% CI		(-2.6, 2.7)	
		Pr >  t			
n		63	70		
Week 16	LS Mean	-0.003	-0.066	0.062	
	SEM	0.465	0.464	0.331	
	95% CI	(-0.9, 0.9)	(-1.0, 0.8)	(-0.6, 0.7)	
	Pr >  t			0.8507	
	n	54	55		
Week 24	LS Mean	0.242	0.434	-0.193	
	SEM	0.477	0.472	0.355	
	95% CI	(-0.7, 1.2)	(-0.5, 1.4)	(-0.9, 0.5)	
	Pr >  t			0.5879	
	n	44	44		
	LS Mean	0.139	0.606	-0.467	
	SEM	0.486	0.481	0.382	
	95% CI	(-0.8, 1.1)	(-0.3, 1.6)	(-1.2, 0.3)	
	Pr >  t			0.2216	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 32	n	38	40		
	LS Mean	0.686	0.594		0.092
	SEM	0.497	0.489		0.397
	95% CI	(-0.3, 1.7)	(-0.4, 1.6)		(-0.7, 0.9)
	Pr >  t				0.8166
Week 40	n	33	31		
	LS Mean	0.707	0.404		0.303
	SEM	0.505	0.505		0.424
	95% CI	(-0.3, 1.7)	(-0.6, 1.4)		(-0.5, 1.1)
	Pr >  t				0.4757
Week 48	n	29	26		
	LS Mean	0.399	0.613		-0.214
	SEM	0.512	0.517		0.447
	95% CI	(-0.6, 1.4)	(-0.4, 1.6)		(-1.1, 0.7)
	Pr >  t				0.6321
Week 56	n	24	25		
	LS Mean	0.892	0.294		0.598
	SEM	0.525	0.520		0.464
	95% CI	(-0.1, 1.9)	(-0.7, 1.3)		(-0.3, 1.5)
	Pr >  t				0.1984
Week 64	n	18	24		
	LS Mean	0.477	0.537		-0.060
	SEM	0.549	0.523		0.494
	95% CI	(-0.6, 1.6)	(-0.5, 1.6)		(-1.0, 0.9)
	Pr >  t				0.9038
Week 72	n	20	17		
	LS Mean	0.901	0.226		0.675
	SEM	0.540	0.552		0.516
	95% CI	(-0.2, 2.0)	(-0.9, 1.3)		(-0.3, 1.7)
	Pr >  t				0.1910
Week 84	n	13	16		
	LS Mean	0.936	0.728		0.208
	SEM	0.582	0.558		0.566
	95% CI	(-0.2, 2.1)	(-0.4, 1.8)		(-0.9, 1.3)
	Pr >  t				0.7133
Week 96	n	12	10		
	LS Mean	0.834	0.172		0.662
	SEM	0.592	0.615		0.632
	95% CI	(-0.3, 2.0)	(-1.0, 1.4)		(-0.6, 1.9)
	Pr >  t				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 108	Pr >  t				0.2949
	n	7	9		
	LS Mean	0.816	-0.166		0.983
	SEM	0.674	0.631		0.723
	95% CI	(-0.5, 2.1)	(-1.4, 1.1)		(-0.4, 2.4)
Week 120	Pr >  t				0.1745
	n	10	8		
	LS Mean	0.478	0.421		0.057
	SEM	0.618	0.650		0.689
	95% CI	(-0.7, 1.7)	(-0.9, 1.7)		(-1.3, 1.4)
Week 132	Pr >  t				0.9341
	n	9	4		
	LS Mean	1.089	0.156		0.932
	SEM	0.632	0.800		0.842
	95% CI	(-0.2, 2.3)	(-1.4, 1.7)		(-0.7, 2.6)
Week 144	Pr >  t				0.2686
	n	4	1		
	LS Mean	0.232	0.104		0.128
	SEM	0.801	1.394		1.501
	95% CI	(-1.3, 1.8)	(-2.6, 2.8)		(-2.8, 3.1)
Week 156	Pr >  t				0.9320
	n	5	1		
	LS Mean	1.369	0.104		1.265
	SEM	0.745	1.394		1.472
	95% CI	(-0.1, 2.8)	(-2.6, 2.8)		(-1.6, 4.2)
Week 168	Pr >  t				0.3905
	n	3			
	LS Mean	0.715			
	SEM	0.887			
	95% CI	(-1.0, 2.5)			
Week 180	Pr >  t				
	n	1			
	LS Mean	1.888			
	SEM	1.394			
	95% CI	(-0.8, 4.6)			
Week 192	Pr >  t				
	n	1			
	LS Mean	0.888			
	SEM	1.394			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-1.8, 3.6)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Pooled Race Group 1 (L)	Asian	Week 8	n	32	34	
			LS Mean	0.595	0.073	0.522
			SEM	0.514	0.490	0.434
			95% CI	(-0.4, 1.6)	(-0.9, 1.0)	(-0.3, 1.4)
					Pr >  t	0.2310
		Week 16	n	30	29	
			LS Mean	0.744	0.425	0.319
			SEM	0.517	0.510	0.451
			95% CI	(-0.3, 1.8)	(-0.6, 1.4)	(-0.6, 1.2)
					Pr >  t	0.4814
		Week 24	n	21	25	
			LS Mean	0.789	0.294	0.496
			SEM	0.541	0.519	0.491
			95% CI	(-0.3, 1.9)	(-0.7, 1.3)	(-0.5, 1.5)
					Pr >  t	0.3143
		Week 32	n	19	23	
			LS Mean	0.793	0.439	0.354
			SEM	0.549	0.525	0.507
			95% CI	(-0.3, 1.9)	(-0.6, 1.5)	(-0.6, 1.4)
					Pr >  t	0.4857
		Week 40	n	16	18	
			LS Mean	0.173	0.612	-0.439
			SEM	0.563	0.549	0.544
			95% CI	(-0.9, 1.3)	(-0.5, 1.7)	(-1.5, 0.6)
					Pr >  t	0.4199
		Week 48	n	16	17	
			LS Mean	0.767	0.719	0.047
			SEM	0.563	0.554	0.549
95% CI	(-0.3, 1.9)		(-0.4, 1.8)	(-1.0, 1.1)		
			Pr >  t	0.9315		
Week 56	n	12	14			
	LS Mean	0.876	0.887	-0.011		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.591	0.573	0.597	
	95% CI	(-0.3, 2.0)	(-0.2, 2.0)	(-1.2, 1.2)	
	Pr >  t			0.9859	
	n	12	11		
	LS Mean	0.793	0.752	0.041	
Week 72	SEM	0.591	0.600	0.623	
	95% CI	(-0.4, 2.0)	(-0.4, 1.9)	(-1.2, 1.3)	
	Pr >  t			0.9472	
	n	10	9		
	LS Mean	1.018	0.303	0.715	
Week 84	SEM	0.613	0.627	0.669	
	95% CI	(-0.2, 2.2)	(-0.9, 1.5)	(-0.6, 2.0)	
	Pr >  t			0.2862	
	n	8	8		
	LS Mean	1.066	1.381	-0.315	
Week 96	SEM	0.649	0.645	0.715	
	95% CI	(-0.2, 2.3)	( 0.1, 2.7)	(-1.7, 1.1)	
	Pr >  t			0.6594	
	n	6	6		
	LS Mean	1.785	0.162	1.623	
Week 108	SEM	0.698	0.695	0.802	
	95% CI	( 0.4, 3.2)	(-1.2, 1.5)	( 0.0, 3.2)	
	Pr >  t			0.0439	
	n	4	5		
	LS Mean	0.872	0.435	0.438	
Week 120	SEM	0.786	0.732	0.910	
	95% CI	(-0.7, 2.4)	(-1.0, 1.9)	(-1.4, 2.2)	
	Pr >  t			0.6308	
	n	4	4		
	LS Mean	0.560	1.730	-1.170	
Week 132	SEM	0.786	0.784	0.953	
	95% CI	(-1.0, 2.1)	( 0.2, 3.3)	(-3.0, 0.7)	
	Pr >  t			0.2201	
	n	3	2		
	LS Mean	2.277	0.563	1.714	
Week 144	SEM	0.865	1.000	1.192	
	95% CI	( 0.6, 4.0)	(-1.4, 2.5)	(-0.6, 4.1)	
	Pr >  t			0.1512	
	n	3	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Other	Week 156	LS Mean	0.694	0.404	0.289
		SEM	0.865	1.332	1.481
		95% CI	(-1.0, 2.4)	(-2.2, 3.0)	(-2.6, 3.2)
		Pr >  t			0.8452
		n	2	1	
	Week 168	LS Mean	1.667	0.404	1.263
		SEM	1.002	1.332	1.565
		95% CI	(-0.3, 3.6)	(-2.2, 3.0)	(-1.8, 4.3)
		Pr >  t			0.4203
		n	1		
	Week 8	LS Mean	2.251		
		SEM	1.331		
		95% CI	(-0.4, 4.9)		
		Pr >  t			
		n	16	17	
	Week 16	LS Mean	-0.853	0.283	-1.136
		SEM	1.154	1.107	0.704
		95% CI	(-3.2, 1.4)	(-1.9, 2.5)	(-2.5, 0.3)
		Pr >  t			0.1114
		n	15	14	
	Week 24	LS Mean	-0.328	0.600	-0.928
		SEM	1.161	1.047	0.757
		95% CI	(-2.6, 2.0)	(-1.5, 2.7)	(-2.4, 0.6)
		Pr >  t			0.2239
n		12	11		
Week 32	LS Mean	-0.238	1.237	-1.474	
	SEM	1.180	1.136	0.813	
	95% CI	(-2.6, 2.1)	(-1.0, 3.5)	(-3.1, 0.1)	
	Pr >  t			0.0731	
	n	8	9		
Week 40	LS Mean	-0.179	1.674	-1.853	
	SEM	1.224	1.160	0.903	
	95% CI	(-2.6, 2.3)	(-0.6, 4.0)	(-3.6,-0.1)	
	Pr >  t			0.0425	
	n	6	7		
	LS Mean	0.523	0.927	-0.404	
	SEM	1.264	1.190	0.990	
	95% CI	(-2.0, 3.0)	(-1.4, 3.3)	(-2.4, 1.6)	
	Pr >  t			0.6838	

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48		n	4	6	
		LS Mean	-0.587	1.656	-2.243
		SEM	1.338	1.212	1.108
		95% CI	(-3.2, 2.1)	(-0.8, 4.1)	(-4.4,-0.1)
		Pr >  t			0.0449
Week 56		n	4	6	
		LS Mean	0.928	1.772	-0.844
		SEM	1.336	1.214	1.109
		95% CI	(-1.7, 3.6)	(-0.6, 4.2)	(-3.0, 1.3)
		Pr >  t			0.4481
Week 64		n	4	4	
		LS Mean	0.049	1.128	-1.079
		SEM	1.338	1.288	1.189
		95% CI	(-2.6, 2.7)	(-1.4, 3.7)	(-3.4, 1.3)
		Pr >  t			0.3655
Week 72		n	4	4	
		LS Mean	-0.326	1.003	-1.329
		SEM	1.338	1.288	1.189
		95% CI	(-3.0, 2.3)	(-1.5, 3.6)	(-3.7, 1.0)
		Pr >  t			0.2654
Week 84		n	4	4	
		LS Mean	0.913	0.878	0.034
		SEM	1.338	1.288	1.190
		95% CI	(-1.7, 3.6)	(-1.7, 3.4)	(-2.3, 2.4)
		Pr >  t			0.9769
Week 96		n	3	2	
		LS Mean	-0.022	1.525	-1.547
		SEM	1.404	1.485	1.463
		95% CI	(-2.8, 2.8)	(-1.4, 4.5)	(-4.4, 1.3)
		Pr >  t			0.2922
Week 108		n	3	3	
		LS Mean	0.645	0.695	-0.051
		SEM	1.404	1.358	1.336
		95% CI	(-2.1, 3.4)	(-2.0, 3.4)	(-2.7, 2.6)
		Pr >  t			0.9698
Week 120		n	2	1	
		LS Mean	-0.090	-0.523	0.433
		SEM	1.529	1.811	1.893
		95% CI	(-3.1, 2.9)	(-4.1, 3.1)	(-3.3, 4.2)



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
White	Week 132	Pr >  t			0.8195
		n	2	1	
		LS Mean	1.902	-0.523	2.425
		SEM	1.526	1.811	1.892
	Week 156	95% CI	(-1.1, 4.9)	(-4.1, 3.1)	(-1.3, 6.2)
		Pr >  t			0.2021
		n	1		
		LS Mean	-0.060		
	Week 168	SEM	1.849		
		95% CI	(-3.7, 3.6)		
		Pr >  t			
		n	1		
	Week 8	LS Mean	-0.060		
		SEM	1.849		
		95% CI	(-3.7, 3.6)		
		Pr >  t			
Week 16	n	93	84		
	LS Mean	0.075	0.376	-0.301	
	SEM	0.280	0.295	0.267	
	95% CI	(-0.5, 0.6)	(-0.2, 1.0)	(-0.8, 0.2)	
Week 24	Pr >  t			0.2606	
	n	79	60		
	LS Mean	-0.106	0.672	-0.778	
	SEM	0.290	0.320	0.297	
Week 32	95% CI	(-0.7, 0.5)	(0.0, 1.3)	(-1.4, -0.2)	
	Pr >  t			0.0091	
	n	71	43		
	LS Mean	0.213	0.919	-0.705	
Week 40	SEM	0.296	0.341	0.325	
	95% CI	(-0.4, 0.8)	(0.2, 1.6)	(-1.3, -0.1)	
	Pr >  t			0.0301	
	n	59	39		
Week 40	LS Mean	0.552	0.324	0.227	
	SEM	0.310	0.350	0.341	
	95% CI	(-0.1, 1.2)	(-0.4, 1.0)	(-0.4, 0.9)	
	Pr >  t			0.5051	
Week 40	n	52	35		
	LS Mean	0.365	0.336	0.029	
	SEM	0.317	0.359	0.356	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.3, 1.0)	(-0.4, 1.0)	(-0.7, 0.7)
		Pr >  t			0.9357
	Week 48	n	48	26	
		LS Mean	0.656	0.562	0.094
		SEM	0.321	0.384	0.385
		95% CI	( 0.0, 1.3)	(-0.2, 1.3)	(-0.7, 0.8)
		Pr >  t			0.8070
	Week 56	n	42	24	
		LS Mean	0.384	0.241	0.143
		SEM	0.330	0.391	0.400
		95% CI	(-0.3, 1.0)	(-0.5, 1.0)	(-0.6, 0.9)
		Pr >  t			0.7213
	Week 64	n	30	26	
		LS Mean	0.342	0.219	0.123
		SEM	0.354	0.384	0.414
		95% CI	(-0.4, 1.0)	(-0.5, 1.0)	(-0.7, 0.9)
		Pr >  t			0.7662
	Week 72	n	34	21	
		LS Mean	0.517	0.545	-0.028
		SEM	0.345	0.405	0.425
		95% CI	(-0.2, 1.2)	(-0.3, 1.3)	(-0.9, 0.8)
		Pr >  t			0.9482
	Week 84	n	28	20	
		LS Mean	0.633	0.750	-0.116
		SEM	0.361	0.410	0.443
		95% CI	(-0.1, 1.3)	(-0.1, 1.6)	(-1.0, 0.8)
		Pr >  t			0.7928
	Week 96	n	26	15	
		LS Mean	0.524	0.918	-0.394
		SEM	0.367	0.445	0.481
		95% CI	(-0.2, 1.2)	( 0.0, 1.8)	(-1.3, 0.5)
		Pr >  t			0.4124
	Week 108	n	19	12	
		LS Mean	0.620	0.422	0.198
		SEM	0.401	0.477	0.535
		95% CI	(-0.2, 1.4)	(-0.5, 1.4)	(-0.9, 1.2)
		Pr >  t			0.7111
	Week 120	n	22	10	
		LS Mean	0.583	-0.023	0.605

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 132	SEM	0.384	0.507	0.551	
	95% CI	(-0.2, 1.3)	(-1.0, 1.0)	(-0.5, 1.7)	
	Pr >  t			0.2718	
	n	15	4		
	LS Mean	-0.115	0.660	-0.775	
Week 144	SEM	0.430	0.722	0.777	
	95% CI	(-1.0, 0.7)	(-0.8, 2.1)	(-2.3, 0.8)	
	Pr >  t			0.3193	
	n	12	4		
	LS Mean	0.307	0.145	0.162	
Week 156	SEM	0.462	0.723	0.796	
	95% CI	(-0.6, 1.2)	(-1.3, 1.6)	(-1.4, 1.7)	
	Pr >  t			0.8384	
	n	6	2		
	LS Mean	-0.024	1.534	-1.558	
Week 168	SEM	0.600	0.979	1.103	
	95% CI	(-1.2, 1.2)	(-0.4, 3.5)	(-3.7, 0.6)	
	Pr >  t			0.1581	
	n	2	2		
	LS Mean	-0.947	0.034	-0.981	
Week 180	SEM	0.970	0.979	1.340	
	95% CI	(-2.9, 1.0)	(-1.9, 2.0)	(-3.6, 1.7)	
	Pr >  t			0.4647	
	n	1	1		
	LS Mean	1.512	0.762	0.750	
Week 192	SEM	1.347	1.352	1.881	
	95% CI	(-1.1, 4.2)	(-1.9, 3.4)	(-2.9, 4.4)	
	Pr >  t			0.6900	
	n	1	1		
	LS Mean	0.512	0.012	0.500	
Week 192	SEM	1.347	1.352	1.881	
	95% CI	(-2.1, 3.2)	(-2.6, 2.7)	(-3.2, 4.2)	
	Pr >  t			0.7903	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Geographic Region 1 (L)	Asia	Week 8	n	30	33			
			LS Mean	0.593	0.088	0.505		
			SEM	0.526	0.498	0.449		
			95% CI	(-0.5, 1.6)	(-0.9, 1.1)	(-0.4, 1.4)		
					Pr >  t			0.2624
		Week 16	n	28	28			
			LS Mean	0.711	0.482	0.229		
			SEM	0.530	0.518	0.466		
			95% CI	(-0.3, 1.8)	(-0.5, 1.5)	(-0.7, 1.2)		
					Pr >  t			0.6248
		Week 24	n	21	24			
			LS Mean	0.778	0.308	0.471		
			SEM	0.548	0.528	0.500		
			95% CI	(-0.3, 1.9)	(-0.7, 1.4)	(-0.5, 1.5)		
					Pr >  t			0.3484
		Week 32	n	19	22			
			LS Mean	0.784	0.458	0.327		
			SEM	0.556	0.534	0.516		
			95% CI	(-0.3, 1.9)	(-0.6, 1.5)	(-0.7, 1.3)		
					Pr >  t			0.5277
		Week 40	n	16	17			
			LS Mean	0.164	0.699	-0.535		
			SEM	0.570	0.560	0.553		
			95% CI	(-1.0, 1.3)	(-0.4, 1.8)	(-1.6, 0.6)		
					Pr >  t			0.3343
		Week 48	n	16	16			
			LS Mean	0.758	0.816	-0.058		
			SEM	0.570	0.565	0.558		
95% CI	(-0.4, 1.9)		(-0.3, 1.9)	(-1.2, 1.0)				
			Pr >  t			0.9167		
Week 56	n	12	14					
	LS Mean	0.869	0.934	-0.066				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.597	0.578	0.600	
	95% CI	(-0.3, 2.0)	(-0.2, 2.1)	(-1.2, 1.1)	
	Pr >  t			0.9129	
	n	12	11		
	LS Mean	0.785	0.803	-0.017	
Week 72	SEM	0.597	0.604	0.625	
	95% CI	(-0.4, 2.0)	(-0.4, 2.0)	(-1.2, 1.2)	
	Pr >  t			0.9779	
	n	10	8		
	LS Mean	1.008	0.405	0.603	
Week 84	SEM	0.617	0.647	0.686	
	95% CI	(-0.2, 2.2)	(-0.9, 1.7)	(-0.7, 2.0)	
	Pr >  t			0.3805	
	n	8	8		
	LS Mean	1.054	1.436	-0.382	
Week 96	SEM	0.653	0.647	0.714	
	95% CI	(-0.2, 2.3)	( 0.2, 2.7)	(-1.8, 1.0)	
	Pr >  t			0.5932	
	n	6	6		
	LS Mean	1.773	0.218	1.555	
Week 108	SEM	0.700	0.695	0.799	
	95% CI	( 0.4, 3.2)	(-1.2, 1.6)	(-0.0, 3.1)	
	Pr >  t			0.0526	
	n	4	5		
	LS Mean	0.861	0.491	0.370	
Week 120	SEM	0.785	0.732	0.904	
	95% CI	(-0.7, 2.4)	(-1.0, 1.9)	(-1.4, 2.1)	
	Pr >  t			0.6823	
	n	4	4		
	LS Mean	0.549	1.786	-1.238	
Week 132	SEM	0.785	0.783	0.946	
	95% CI	(-1.0, 2.1)	( 0.2, 3.3)	(-3.1, 0.6)	
	Pr >  t			0.1915	
	n	3	2		
	LS Mean	2.263	0.611	1.653	
Week 144	SEM	0.861	0.992	1.180	
	95% CI	( 0.6, 4.0)	(-1.3, 2.6)	(-0.7, 4.0)	
	Pr >  t			0.1622	
	n	3	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Europe	Week 156	LS Mean	0.680	0.457	0.223
		SEM	0.861	1.317	1.463
		95% CI	(-1.0, 2.4)	(-2.1, 3.0)	(-2.7, 3.1)
		Pr >  t			0.8789
		n	2	1	
	Week 168	LS Mean	1.649	0.457	1.193
		SEM	0.995	1.317	1.546
		95% CI	(-0.3, 3.6)	(-2.1, 3.0)	(-1.8, 4.2)
		Pr >  t			0.4410
		n	1		
	Week 8	LS Mean	2.238		
		SEM	1.317		
		95% CI	(-0.4, 4.8)		
		Pr >  t			
		n	66	67	
	Week 16	LS Mean	-0.191	-0.013	-0.177
		SEM	0.553	0.552	0.309
		95% CI	(-1.3, 0.9)	(-1.1, 1.1)	(-0.8, 0.4)
		Pr >  t			0.5670
		n	58	47	
	Week 24	LS Mean	-0.299	0.368	-0.667
		SEM	0.557	0.563	0.344
		95% CI	(-1.4, 0.8)	(-0.7, 1.5)	(-1.3, 0.0)
		Pr >  t			0.0527
n		51	36		
Week 32	LS Mean	-0.213	0.606	-0.819	
	SEM	0.561	0.574	0.373	
	95% CI	(-1.3, 0.9)	(-0.5, 1.7)	(-1.6,-0.1)	
	Pr >  t			0.0284	
	n	43	30		
Week 40	LS Mean	0.142	0.267	-0.125	
	SEM	0.574	0.591	0.399	
	95% CI	(-1.0, 1.3)	(-0.9, 1.4)	(-0.9, 0.7)	
	Pr >  t			0.7540	
	n	37	25		
		LS Mean	0.156	0.004	0.152
		SEM	0.581	0.602	0.425
		95% CI	(-1.0, 1.3)	(-1.2, 1.2)	(-0.7, 1.0)
		Pr >  t			0.7209

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 48	n	33	21	
	LS Mean	0.551	0.409	0.141
	SEM	0.586	0.615	0.450
	95% CI	(-0.6, 1.7)	(-0.8, 1.6)	(-0.7, 1.0)
	Pr >  t			0.7535
Week 56	n	29	20	
	LS Mean	0.177	0.012	0.165
	SEM	0.593	0.619	0.465
	95% CI	(-1.0, 1.3)	(-1.2, 1.2)	(-0.7, 1.1)
	Pr >  t			0.7228
Week 64	n	23	20	
	LS Mean	0.204	-0.086	0.290
	SEM	0.608	0.619	0.483
	95% CI	(-1.0, 1.4)	(-1.3, 1.1)	(-0.7, 1.2)
	Pr >  t			0.5484
Week 72	n	25	19	
	LS Mean	-0.017	0.460	-0.477
	SEM	0.602	0.623	0.482
	95% CI	(-1.2, 1.2)	(-0.8, 1.7)	(-1.4, 0.5)
	Pr >  t			0.3220
Week 84	n	22	17	
	LS Mean	0.211	0.618	-0.407
	SEM	0.610	0.633	0.504
	95% CI	(-1.0, 1.4)	(-0.6, 1.9)	(-1.4, 0.6)
	Pr >  t			0.4199
Week 96	n	20	13	
	LS Mean	0.322	0.585	-0.263
	SEM	0.618	0.659	0.546
	95% CI	(-0.9, 1.5)	(-0.7, 1.9)	(-1.3, 0.8)
	Pr >  t			0.6296
Week 108	n	15	11	
	LS Mean	0.469	0.483	-0.014
	SEM	0.644	0.679	0.598
	95% CI	(-0.8, 1.7)	(-0.9, 1.8)	(-1.2, 1.2)
	Pr >  t			0.9814
Week 120	n	16	8	
	LS Mean	0.096	-0.294	0.390
	SEM	0.638	0.726	0.644
	95% CI	(-1.2, 1.4)	(-1.7, 1.1)	(-0.9, 1.7)



Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 132	Pr >  t			0.5447
		n	12	3	
		LS Mean	-0.156	0.586	-0.742
		SEM	0.668	0.960	0.921
		95% CI	(-1.5, 1.2)	(-1.3, 2.5)	(-2.6, 1.1)
	Week 144	Pr >  t			0.4210
		n	7	4	
		LS Mean	0.230	-0.072	0.302
		SEM	0.747	0.874	0.897
		95% CI	(-1.2, 1.7)	(-1.8, 1.6)	(-1.5, 2.1)
	Week 156	Pr >  t			0.7365
		n	5	2	
		LS Mean	-0.858	1.313	-2.171
		SEM	0.816	1.112	1.176
		95% CI	(-2.5, 0.7)	(-0.9, 3.5)	(-4.5, 0.1)
	Week 168	Pr >  t			0.0653
		n	2	2	
		LS Mean	-1.041	-0.187	-0.854
		SEM	1.110	1.112	1.396
		95% CI	(-3.2, 1.1)	(-2.4, 2.0)	(-3.6, 1.9)
	Week 180	Pr >  t			0.5407
		n		1	
		LS Mean		0.530	
		SEM		1.474	
		95% CI		(-2.4, 3.4)	
	Week 192	Pr >  t			
		n		1	
		LS Mean		-0.220	
		SEM		1.474	
		95% CI		(-3.1, 2.7)	
	Latin America	Pr >  t			
	Week 8	n	14	13	
		LS Mean	-0.873	-0.361	-0.513
		SEM	0.474	0.489	0.690
		95% CI	(-1.8, 0.1)	(-1.3, 0.6)	(-1.9, 0.9)
	Week 16	Pr >  t			0.4604
		n	13	12	
		LS Mean	-0.749	-0.425	-0.324
		SEM	0.487	0.506	0.711

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 24	95% CI	(-1.7, 0.2)	(-1.4, 0.6)	(-1.7, 1.1)	
	Pr >  t			0.6497	
	n	12	10		
	LS Mean	0.052	-0.197	0.248	
	SEM	0.500	0.537	0.741	
Week 32	95% CI	(-0.9, 1.1)	(-1.3, 0.9)	(-1.2, 1.7)	
	Pr >  t			0.7386	
	n	9	10		
	LS Mean	0.013	-0.197	0.210	
	SEM	0.555	0.537	0.782	
Week 40	95% CI	(-1.1, 1.1)	(-1.3, 0.9)	(-1.3, 1.8)	
	Pr >  t			0.7894	
	n	7	10		
	LS Mean	0.235	-0.272	0.507	
	SEM	0.607	0.537	0.819	
Week 48	95% CI	(-1.0, 1.4)	(-1.3, 0.8)	(-1.1, 2.1)	
	Pr >  t			0.5379	
	n	7	7		
	LS Mean	-0.122	-0.344	0.222	
	SEM	0.607	0.607	0.865	
Week 56	95% CI	(-1.3, 1.1)	(-1.5, 0.9)	(-1.5, 1.9)	
	Pr >  t			0.7982	
	n	6	7		
	LS Mean	0.440	0.056	0.384	
	SEM	0.643	0.609	0.894	
Week 64	95% CI	(-0.8, 1.7)	(-1.2, 1.3)	(-1.4, 2.2)	
	Pr >  t			0.6687	
	n	4	7		
	LS Mean	-0.483	-0.358	-0.125	
	SEM	0.749	0.604	0.968	
Week 72	95% CI	(-2.0, 1.0)	(-1.6, 0.8)	(-2.0, 1.8)	
	Pr >  t			0.8978	
	n	4	4		
	LS Mean	-0.170	-0.896	0.726	
	SEM	0.749	0.746	1.062	
Week 84	95% CI	(-1.7, 1.3)	(-2.4, 0.6)	(-1.4, 2.8)	
	Pr >  t			0.4957	
	n	4	5		
	LS Mean	0.652	-0.514	1.166	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
North America	Week 96	SEM	0.749	0.684	1.020
		95% CI	(-0.8, 2.1)	(-1.9, 0.8)	(-0.9, 3.2)
		Pr >  t			0.2554
		n	3	2	
		LS Mean	0.010	1.658	-1.648
	Week 108	SEM	0.842	0.998	1.311
		95% CI	(-1.7, 1.7)	(-0.3, 3.6)	(-4.2, 0.9)
		Pr >  t			0.2106
		n	2	3	
		LS Mean	0.464	-1.637	2.101
	Week 120	SEM	1.000	0.845	1.315
		95% CI	(-1.5, 2.4)	(-3.3, 0.0)	(-0.5, 4.7)
		Pr >  t			0.1122
		n	2	2	
		LS Mean	1.320	-1.263	2.583
	Week 132	SEM	1.000	0.998	1.416
		95% CI	(-0.7, 3.3)	(-3.2, 0.7)	(-0.2, 5.4)
		Pr >  t			0.0701
		n	1	2	
		LS Mean	-0.286	-1.263	0.977
	Week 8	SEM	1.368	0.998	1.696
		95% CI	(-3.0, 2.4)	(-3.2, 0.7)	(-2.4, 4.3)
		Pr >  t			0.5656
		n	16	19	
LS Mean		-0.900	0.664	-1.565	
Week 16	SEM	0.550	0.529	0.653	
	95% CI	(-2.0, 0.2)	(-0.4, 1.7)	(-2.9,-0.3)	
	Pr >  t			0.0198	
	n	12	14		
	LS Mean	-0.790	0.671	-1.461	
Week 24	SEM	0.594	0.577	0.719	
	95% CI	(-2.0, 0.4)	(-0.5, 1.8)	(-2.9,-0.0)	
	Pr >  t			0.0456	
	n	12	8		
	LS Mean	-0.997	1.969	-2.965	
Week 32	SEM	0.594	0.685	0.804	
	95% CI	(-2.2, 0.2)	( 0.6, 3.3)	(-4.6,-1.4)	
	Pr >  t			0.0004	
	n	9	7		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	LS Mean	0.279	0.830	-0.550	
	SEM	0.645	0.713	0.859	
	95% CI	(-1.0, 1.6)	(-0.6, 2.2)	(-2.3, 1.2)	
	Pr >  t			0.5230	
	n	9	7		
Week 48	LS Mean	-0.229	1.044	-1.273	
	SEM	0.645	0.713	0.861	
	95% CI	(-1.5, 1.1)	(-0.4, 2.5)	(-3.0, 0.4)	
	Pr >  t			0.1423	
	n	8	5		
Week 56	LS Mean	-0.014	1.406	-1.420	
	SEM	0.665	0.786	0.938	
	95% CI	(-1.3, 1.3)	(-0.1, 3.0)	(-3.3, 0.4)	
	Pr >  t			0.1327	
	n	7	3		
Week 64	LS Mean	0.126	0.682	-0.555	
	SEM	0.689	0.931	1.080	
	95% CI	(-1.2, 1.5)	(-1.2, 2.5)	(-2.7, 1.6)	
	Pr >  t			0.6079	
	n	5	3		
Week 72	LS Mean	-0.641	0.848	-1.489	
	SEM	0.761	0.931	1.129	
	95% CI	(-2.1, 0.9)	(-1.0, 2.7)	(-3.7, 0.7)	
	Pr >  t			0.1896	
	n	5	3		
Week 84	LS Mean	1.022	1.068	-0.045	
	SEM	0.758	0.931	1.126	
	95% CI	(-0.5, 2.5)	(-0.8, 2.9)	(-2.3, 2.2)	
	Pr >  t			0.9679	
	n	2	2		
Week 96	LS Mean	3.732	0.845	2.888	
	SEM	1.061	1.083	1.458	
	95% CI	( 1.6, 5.8)	(-1.3, 3.0)	( 0.0, 5.8)	
	Pr >  t			0.0497	
	n	3	2		
Week 96	LS Mean	-0.415	0.345	-0.760	
	SEM	0.903	1.083	1.349	
	95% CI	(-2.2, 1.4)	(-1.8, 2.5)	(-3.4, 1.9)	
	Pr >  t			0.5741	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 108	n	1	2	
	LS Mean	0.483	0.095	0.389
	SEM	1.419	1.083	1.735
	95% CI	(-2.3, 3.3)	(-2.0, 2.2)	(-3.0, 3.8)
	Pr >  t			0.8231
Week 120	n	3	2	
	LS Mean	0.668	0.220	0.448
	SEM	0.903	1.083	1.349
	95% CI	(-1.1, 2.5)	(-1.9, 2.4)	(-2.2, 3.1)
	Pr >  t			0.7401
Week 132	n	1	1	
	LS Mean	-1.072	1.537	-2.610
	SEM	1.421	1.435	1.976
	95% CI	(-3.9, 1.7)	(-1.3, 4.4)	(-6.5, 1.3)
	Pr >  t			0.1890
Week 144	n	2		
	LS Mean	-0.365		
	SEM	1.056		
	95% CI	(-2.5, 1.7)		
	Pr >  t			
Week 156	n	1		
	LS Mean	2.678		
	SEM	1.421		
	95% CI	(-0.1, 5.5)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-0.822		
	SEM	1.421		
	95% CI	(-3.6, 2.0)		
	Pr >  t			
Week 180	n	1		
	LS Mean	1.178		
	SEM	1.421		
	95% CI	(-1.6, 4.0)		
	Pr >  t			
Week 192	n	1		
	LS Mean	0.178		
	SEM	1.421		
	95% CI	(-2.6, 3.0)		
	Pr >  t			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	N=172	N=172	
Other	Week 8	Pr >  t				
		n	16	5		
		LS Mean	1.025	0.924	0.101	
		SEM	0.611	0.945	1.031	
	Week 16	95% CI	(-0.2, 2.3)	(-1.0, 2.9)	(-2.0, 2.2)	
		Pr >  t			0.9230	
		n	13	4		
		LS Mean	1.137	1.954	-0.817	
	Week 24	SEM	0.643	1.040	1.111	
		95% CI	(-0.2, 2.5)	(-0.2, 4.1)	(-3.1, 1.4)	
		Pr >  t			0.4675	
		n	9	2		
	Week 32	LS Mean	2.433	1.561	0.872	
		SEM	0.698	1.253	1.335	
		95% CI	( 1.0, 3.8)	(-1.0, 4.1)	(-1.8, 3.6)	
		Pr >  t			0.5167	
	Week 40	n	6	3		
		LS Mean	1.717	1.125	0.592	
		SEM	0.777	1.120	1.255	
		95% CI	( 0.2, 3.3)	(-1.1, 3.4)	(-1.9, 3.1)	
	Week 48	Pr >  t			0.6392	
		n	6	2		
		LS Mean	1.308	0.417	0.892	
		SEM	0.787	1.252	1.377	
Week 56	95% CI	(-0.3, 2.9)	(-2.1, 2.9)	(-1.9, 3.7)		
	Pr >  t			0.5201		
	n	5	1			
	LS Mean	1.358	1.002	0.356		
Week 64	SEM	0.824	1.583	1.706		
	95% CI	(-0.3, 3.0)	(-2.2, 4.2)	(-3.0, 3.8)		
	Pr >  t			0.8354		
	n	5	1			
Week 64	LS Mean	1.058	1.002	0.056		
	SEM	0.824	1.583	1.706		
	95% CI	(-0.6, 2.7)	(-2.2, 4.2)	(-3.3, 3.5)		
	Pr >  t			0.9740		
Week 64	n	3	1			
	LS Mean	1.029	1.002	0.027		
	SEM	0.953	1.583	1.772		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 72	95% CI	(-0.9, 2.9)	(-2.2, 4.2)	(-3.5, 3.6)	
	Pr >  t			0.9881	
	n	4	1		
	LS Mean	1.547	1.002	0.545	
	SEM	0.876	1.583	1.732	
Week 84	95% CI	(-0.2, 3.3)	(-2.2, 4.2)	(-2.9, 4.0)	
	Pr >  t			0.7539	
	n	4	1		
	LS Mean	0.860	1.002	-0.142	
	SEM	0.876	1.583	1.732	
Week 96	95% CI	(-0.9, 2.6)	(-2.2, 4.2)	(-3.6, 3.3)	
	Pr >  t			0.9347	
	n	3	1		
	LS Mean	1.195	1.002	0.193	
	SEM	0.953	1.583	1.772	
Week 108	95% CI	(-0.7, 3.1)	(-2.2, 4.2)	(-3.3, 3.7)	
	Pr >  t			0.9135	
	n	4			
	LS Mean	1.047			
	SEM	0.876			
Week 120	95% CI	(-0.7, 2.8)			
	Pr >  t				
	n	3			
	LS Mean	1.029			
	SEM	0.953			
Week 132	95% CI	(-0.9, 2.9)			
	Pr >  t				
	n	3			
	LS Mean	1.362			
	SEM	0.953			
Week 144	95% CI	(-0.5, 3.3)			
	Pr >  t				
	n	3			
	LS Mean	0.915			
	SEM	0.953			
Week 156	95% CI	(-1.0, 2.8)			
	Pr >  t				
	n	1			
	LS Mean	0.480			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	1.408		
	95% CI	(-2.3, 3.3)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Baseline ECOG performance status	0 Week 8	n	98	88		
		LS Mean	-0.158	0.160	-0.318	
		SEM	0.331	0.324	0.262	
		95% CI	(-0.8, 0.5)	(-0.5, 0.8)	(-0.8, 0.2)	
					Pr >  t	0.2261
	Week 16	n	88	70		
		LS Mean	0.066	0.363	-0.297	
		SEM	0.337	0.345	0.280	
		95% CI	(-0.6, 0.7)	(-0.3, 1.0)	(-0.8, 0.3)	
					Pr >  t	0.2891
	Week 24	n	75	54		
		LS Mean	0.144	0.575	-0.430	
		SEM	0.343	0.357	0.303	
		95% CI	(-0.5, 0.8)	(-0.1, 1.3)	(-1.0, 0.2)	
					Pr >  t	0.1554
	Week 32	n	62	52		
		LS Mean	0.601	0.224	0.377	
		SEM	0.352	0.359	0.314	
		95% CI	(-0.1, 1.3)	(-0.5, 0.9)	(-0.2, 1.0)	
					Pr >  t	0.2311
	Week 40	n	51	46		
		LS Mean	0.275	0.144	0.131	
		SEM	0.361	0.367	0.332	
		95% CI	(-0.4, 1.0)	(-0.6, 0.9)	(-0.5, 0.8)	
					Pr >  t	0.6933
	Week 48	n	50	37		
		LS Mean	0.619	0.415	0.205	
		SEM	0.362	0.380	0.347	
95% CI		(-0.1, 1.3)	(-0.3, 1.2)	(-0.5, 0.9)		
				Pr >  t	0.5552	
Week 56	n	43	33			
	LS Mean	0.568	0.232	0.336		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.369	0.388	0.363	
	95% CI	(-0.2, 1.3)	(-0.5, 1.0)	(-0.4, 1.0)	
	Pr >  t			0.3556	
	n	35	33		
	LS Mean	0.318	-0.055	0.373	
Week 72	SEM	0.382	0.388	0.376	
	95% CI	(-0.4, 1.1)	(-0.8, 0.7)	(-0.4, 1.1)	
	Pr >  t			0.3214	
	n	35	31		
	LS Mean	0.379	0.321	0.058	
Week 84	SEM	0.382	0.392	0.381	
	95% CI	(-0.4, 1.1)	(-0.4, 1.1)	(-0.7, 0.8)	
	Pr >  t			0.8793	
	n	31	29		
	LS Mean	0.779	0.616	0.164	
Week 96	SEM	0.391	0.397	0.394	
	95% CI	(0.0, 1.5)	(-0.2, 1.4)	(-0.6, 0.9)	
	Pr >  t			0.6780	
	n	27	22		
	LS Mean	0.782	0.316	0.466	
Week 108	SEM	0.400	0.420	0.427	
	95% CI	(-0.0, 1.6)	(-0.5, 1.1)	(-0.4, 1.3)	
	Pr >  t			0.2751	
	n	19	20		
	LS Mean	0.640	0.179	0.460	
Week 120	SEM	0.433	0.429	0.466	
	95% CI	(-0.2, 1.5)	(-0.7, 1.0)	(-0.5, 1.4)	
	Pr >  t			0.3229	
	n	20	15		
	LS Mean	0.540	0.203	0.337	
Week 132	SEM	0.426	0.461	0.491	
	95% CI	(-0.3, 1.4)	(-0.7, 1.1)	(-0.6, 1.3)	
	Pr >  t			0.4923	
	n	15	7		
	LS Mean	0.681	0.497	0.184	
Week 144	SEM	0.460	0.584	0.631	
	95% CI	(-0.2, 1.6)	(-0.6, 1.6)	(-1.1, 1.4)	
	Pr >  t			0.7705	
	n	10	5		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.641	-0.018	0.658
		SEM	0.515	0.662	0.742
		95% CI	(-0.4, 1.7)	(-1.3, 1.3)	(-0.8, 2.1)
		Pr >  t			0.3752
	Week 156	n	5	3	
		LS Mean	0.827	0.910	-0.083
		SEM	0.660	0.814	0.971
		95% CI	(-0.5, 2.1)	(-0.7, 2.5)	(-2.0, 1.8)
		Pr >  t			0.9320
	Week 168	n	3	2	
		LS Mean	-0.489	-0.184	-0.305
		SEM	0.813	0.971	1.203
		95% CI	(-2.1, 1.1)	(-2.1, 1.7)	(-2.7, 2.1)
		Pr >  t			0.8003
	Week 180	n	1	1	
		LS Mean	1.678	0.584	1.094
		SEM	1.334	1.333	1.844
		95% CI	(-0.9, 4.3)	(-2.0, 3.2)	(-2.5, 4.7)
		Pr >  t			0.5532
	Week 192	n	1	1	
		LS Mean	0.678	-0.166	0.844
		SEM	1.334	1.333	1.844
		95% CI	(-1.9, 3.3)	(-2.8, 2.4)	(-2.8, 4.5)
		Pr >  t			0.6473
1	Week 8	n	43	49	
		LS Mean	0.180	0.040	0.140
		SEM	0.371	0.388	0.386
		95% CI	(-0.6, 0.9)	(-0.7, 0.8)	(-0.6, 0.9)
		Pr >  t			0.7167
	Week 16	n	35	34	
		LS Mean	-0.358	0.494	-0.852
		SEM	0.391	0.407	0.432
		95% CI	(-1.1, 0.4)	(-0.3, 1.3)	(-1.7, -0.0)
		Pr >  t			0.0495
	Week 24	n	29	25	
		LS Mean	0.203	0.526	-0.323
		SEM	0.410	0.442	0.474
		95% CI	(-0.6, 1.0)	(-0.3, 1.4)	(-1.3, 0.6)
		Pr >  t			0.4962

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 32	n	23	20		
	LS Mean	-0.072	0.679	-0.750	
	SEM	0.439	0.472	0.515	
	95% CI	(-0.9, 0.8)	(-0.3, 1.6)	(-1.8, 0.3)	
	Pr >  t			0.1463	
Week 40	n	23	15		
	LS Mean	0.096	0.760	-0.664	
	SEM	0.440	0.508	0.549	
	95% CI	(-0.8, 1.0)	(-0.2, 1.8)	(-1.7, 0.4)	
	Pr >  t			0.2275	
Week 48	n	18	13		
	LS Mean	0.327	0.992	-0.665	
	SEM	0.466	0.529	0.591	
	95% CI	(-0.6, 1.2)	(-0.0, 2.0)	(-1.8, 0.5)	
	Pr >  t			0.2614	
Week 56	n	15	12		
	LS Mean	-0.007	0.941	-0.948	
	SEM	0.490	0.541	0.622	
	95% CI	(-1.0, 1.0)	(-0.1, 2.0)	(-2.2, 0.3)	
	Pr >  t			0.1281	
Week 64	n	11	9		
	LS Mean	0.093	1.346	-1.253	
	SEM	0.536	0.591	0.701	
	95% CI	(-1.0, 1.1)	( 0.2, 2.5)	(-2.6, 0.1)	
	Pr >  t			0.0745	
Week 72	n	12	4		
	LS Mean	0.635	0.513	0.122	
	SEM	0.523	0.793	0.870	
	95% CI	(-0.4, 1.7)	(-1.0, 2.1)	(-1.6, 1.8)	
	Pr >  t			0.8886	
Week 84	n	8	4		
	LS Mean	-0.123	1.200	-1.324	
	SEM	0.599	0.793	0.916	
	95% CI	(-1.3, 1.1)	(-0.4, 2.8)	(-3.1, 0.5)	
	Pr >  t			0.1495	
Week 96	n	8	2		
	LS Mean	-0.061	2.559	-2.620	
	SEM	0.599	1.059	1.155	
	95% CI	(-1.2, 1.1)	( 0.5, 4.6)	(-4.9,-0.4)	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.0238
	Week 108	n	6	1	
		LS Mean	0.420	-0.894	1.314
		SEM	0.664	1.451	1.548
		95% CI	(-0.9, 1.7)	(-3.7, 2.0)	(-1.7, 4.4)
		Pr >  t			0.3963
	Week 120	n	8	1	
		LS Mean	0.129	-0.894	1.023
		SEM	0.601	1.451	1.521
		95% CI	(-1.1, 1.3)	(-3.7, 2.0)	(-2.0, 4.0)
		Pr >  t			0.5016
	Week 132	n	5	1	
		LS Mean	-0.661	-0.894	0.233
		SEM	0.711	1.451	1.568
		95% CI	(-2.1, 0.7)	(-3.7, 2.0)	(-2.9, 3.3)
		Pr >  t			0.8819
	Week 144	n	5		
		LS Mean	-0.661		
		SEM	0.711		
		95% CI	(-2.1, 0.7)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	-0.756		
		SEM	0.776		
		95% CI	(-2.3, 0.8)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	1.246		
		SEM	1.429		
		95% CI	(-1.6, 4.1)		
		Pr >  t			

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Final



**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Endocrine Status (L) Primary resistant	Week 8	n	21	15	
		LS Mean	-0.612	0.042	-0.654
		SEM	0.464	0.548	0.560
		95% CI	(-1.5, 0.3)	(-1.1, 1.1)	(-1.8, 0.5)
		Pr >  t			0.2477
	Week 16	n	17	9	
		LS Mean	0.041	0.416	-0.375
		SEM	0.496	0.635	0.656
		95% CI	(-1.0, 1.0)	(-0.9, 1.7)	(-1.7, 0.9)
		Pr >  t			0.5695
	Week 24	n	9	5	
		LS Mean	-0.006	0.780	-0.786
		SEM	0.567	0.741	0.824
		95% CI	(-1.1, 1.1)	(-0.7, 2.3)	(-2.4, 0.8)
		Pr >  t			0.3425
	Week 32	n	8	4	
		LS Mean	-0.714	0.321	-1.035
		SEM	0.588	0.794	0.886
		95% CI	(-1.9, 0.5)	(-1.3, 1.9)	(-2.8, 0.7)
		Pr >  t			0.2453
	Week 40	n	5	4	
		LS Mean	-0.606	-0.429	-0.177
		SEM	0.668	0.794	0.949
		95% CI	(-1.9, 0.7)	(-2.0, 1.1)	(-2.1, 1.7)
	Pr >  t			0.8523	
Week 48	n	5	3		
	LS Mean	0.094	0.315	-0.220	
	SEM	0.668	0.867	1.010	
	95% CI	(-1.2, 1.4)	(-1.4, 2.0)	(-2.2, 1.8)	
	Pr >  t			0.8277	
Week 56	n	4	3		
	LS Mean	0.026	-0.269	0.294	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.716	0.867	1.045
	95% CI	(-1.4, 1.4)	(-2.0, 1.5)	(-1.8, 2.4)
	Pr >  t			0.7787
	n	4	3	
	LS Mean	0.213	-0.269	0.482
Week 72	SEM	0.716	0.867	1.045
	95% CI	(-1.2, 1.6)	(-2.0, 1.5)	(-1.6, 2.6)
	Pr >  t			0.6457
	n	4	3	
	LS Mean	0.776	0.231	0.544
Week 84	SEM	0.716	0.867	1.045
	95% CI	(-0.6, 2.2)	(-1.5, 2.0)	(-1.5, 2.6)
	Pr >  t			0.6035
	n	2	3	
	LS Mean	1.418	0.981	0.437
Week 96	SEM	0.934	0.867	1.195
	95% CI	(-0.4, 3.3)	(-0.7, 2.7)	(-1.9, 2.8)
	Pr >  t			0.7157
	n	1	3	
	LS Mean	-0.359	0.648	-1.007
Week 108	SEM	1.235	0.867	1.459
	95% CI	(-2.8, 2.1)	(-1.1, 2.4)	(-3.9, 1.9)
	Pr >  t			0.4916
	n		2	
	LS Mean		0.124	
Week 120	SEM		0.988	
	95% CI		(-1.8, 2.1)	
	Pr >  t			
	n	1	1	
	LS Mean	-0.359	-0.560	0.200
Week 132	SEM	1.235	1.282	1.740
	95% CI	(-2.8, 2.1)	(-3.1, 2.0)	(-3.3, 3.7)
	Pr >  t			0.9087
	n		1	
	LS Mean		0.940	
Week 144	SEM		1.282	
	95% CI		(-1.6, 3.5)	
	Pr >  t			
	n	1		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169			Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	SEM	95% CI	Pr >  t	
Secondary resistant	Week 8	LS Mean	-0.359			
		SEM	1.235			
		95% CI	(-2.8, 2.1)			
		Pr >  t				
	Week 16	n	98	104		
		LS Mean	0.255	0.438		-0.182
		SEM	0.302	0.302		0.257
		95% CI	(-0.3, 0.8)	(-0.2, 1.0)		(-0.7, 0.3)
	Week 24	Pr >  t				0.4786
		n	83	80		
		LS Mean	0.121	0.765		-0.644
		SEM	0.311	0.317		0.280
	Week 32	95% CI	(-0.5, 0.7)	(0.1, 1.4)		(-1.2,-0.1)
		Pr >  t				0.0216
		n	75	61		
		LS Mean	0.403	1.020		-0.617
	Week 40	SEM	0.317	0.333		0.300
		95% CI	(-0.2, 1.0)	(0.4, 1.7)		(-1.2,-0.0)
		Pr >  t				0.0402
		n	59	55		
	Week 48	LS Mean	0.683	0.718		-0.035
		SEM	0.333	0.339		0.319
		95% CI	(0.0, 1.3)	(0.1, 1.4)		(-0.7, 0.6)
		Pr >  t				0.9124
Week 56	n	52	47			
	LS Mean	0.689	0.691		-0.002	
	SEM	0.340	0.349		0.336	
	95% CI	(0.0, 1.4)	(0.0, 1.4)		(-0.7, 0.7)	
Week 8	Pr >  t				0.9948	
	n	47	36			
	LS Mean	0.905	0.955		-0.050	
	SEM	0.346	0.368		0.361	
Week 16	95% CI	(0.2, 1.6)	(0.2, 1.7)		(-0.8, 0.7)	
	Pr >  t				0.8890	
	n	41	31			
	LS Mean	0.943	0.880		0.064	
Week 24	SEM	0.355	0.379		0.381	
	95% CI	(0.2, 1.6)	(0.1, 1.6)		(-0.7, 0.8)	
	Pr >  t				0.8676	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	n	32	28		
	LS Mean	0.584	0.741	-0.156	
	SEM	0.373	0.388	0.407	
	95% CI	(-0.1, 1.3)	(-0.0, 1.5)	(-1.0, 0.6)	
	Pr >  t			0.7010	
Week 72	n	29	22		
	LS Mean	0.600	0.588	0.012	
	SEM	0.382	0.412	0.437	
	95% CI	(-0.1, 1.3)	(-0.2, 1.4)	(-0.8, 0.9)	
	Pr >  t			0.9774	
Week 84	n	26	21		
	LS Mean	0.749	0.845	-0.096	
	SEM	0.391	0.417	0.450	
	95% CI	(-0.0, 1.5)	( 0.0, 1.7)	(-1.0, 0.8)	
	Pr >  t			0.8316	
Week 96	n	23	14		
	LS Mean	0.787	0.998	-0.210	
	SEM	0.403	0.468	0.507	
	95% CI	(-0.0, 1.6)	( 0.1, 1.9)	(-1.2, 0.8)	
	Pr >  t			0.6783	
Week 108	n	18	13		
	LS Mean	1.103	0.082	1.021	
	SEM	0.431	0.479	0.539	
	95% CI	( 0.3, 1.9)	(-0.9, 1.0)	(-0.0, 2.1)	
	Pr >  t			0.0586	
Week 120	n	19	10		
	LS Mean	0.893	0.226	0.666	
	SEM	0.425	0.523	0.574	
	95% CI	( 0.1, 1.7)	(-0.8, 1.3)	(-0.5, 1.8)	
	Pr >  t			0.2456	
Week 132	n	13	4		
	LS Mean	0.725	0.594	0.130	
	SEM	0.475	0.744	0.809	
	95% CI	(-0.2, 1.7)	(-0.9, 2.1)	(-1.5, 1.7)	
	Pr >  t			0.8724	
Week 144	n	8	1		
	LS Mean	0.922	0.834	0.088	
	SEM	0.562	1.399	1.466	
	95% CI	(-0.2, 2.0)	(-1.9, 3.6)	(-2.8, 3.0)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Sensitive	Week 156	Pr >  t			0.9521
		n	4	1	
		LS Mean	0.752	2.834	-2.082
		SEM	0.741	1.399	1.543
	Week 168	95% CI	(-0.7, 2.2)	(0.1, 5.6)	(-5.1, 0.9)
		Pr >  t			0.1777
		n	3	1	
		LS Mean	-0.298	0.834	-1.131
	Week 180	SEM	0.839	1.399	1.593
		95% CI	(-1.9, 1.3)	(-1.9, 3.6)	(-4.3, 2.0)
		Pr >  t			0.4777
		n	1	1	
	Week 192	LS Mean	1.867	1.084	0.783
		SEM	1.393	1.399	1.943
		95% CI	(-0.9, 4.6)	(-1.7, 3.8)	(-3.0, 4.6)
		Pr >  t			0.6869
	Week 8	n	1	1	
		LS Mean	0.867	0.334	0.533
		SEM	1.393	1.399	1.943
		95% CI	(-1.9, 3.6)	(-2.4, 3.1)	(-3.3, 4.3)
Week 16	Pr >  t			0.7837	
	n	17	16		
	LS Mean	-0.470	-0.413	-0.057	
	SEM	0.463	0.475	0.653	
Week 24	95% CI	(-1.4, 0.5)	(-1.4, 0.5)	(-1.4, 1.2)	
	Pr >  t			0.9303	
	n	18	14		
	LS Mean	-0.245	-0.701	0.455	
Week 32	SEM	0.455	0.497	0.668	
	95% CI	(-1.2, 0.7)	(-1.7, 0.3)	(-0.9, 1.8)	
	Pr >  t			0.4972	
	n	16	13		
Week 8	LS Mean	0.019	-0.634	0.653	
	SEM	0.473	0.507	0.687	
	95% CI	(-0.9, 1.0)	(-1.6, 0.4)	(-0.7, 2.0)	
	Pr >  t			0.3446	
Week 16	n	15	13		
	LS Mean	0.589	-0.503	1.092	
	SEM	0.480	0.508	0.694	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-0.4, 1.5)	(-1.5, 0.5)	(-0.3, 2.5)	
	Pr >  t			0.1189	
	n	14	10		
	LS Mean	-0.422	-0.409	-0.012	
	SEM	0.491	0.547	0.730	
Week 48	95% CI	(-1.4, 0.6)	(-1.5, 0.7)	(-1.5, 1.4)	
	Pr >  t			0.9865	
	n	14	11		
	LS Mean	0.275	-0.301	0.576	
	SEM	0.491	0.533	0.719	
Week 56	95% CI	(-0.7, 1.2)	(-1.4, 0.8)	(-0.9, 2.0)	
	Pr >  t			0.4251	
	n	11	11		
	LS Mean	-0.446	-0.506	0.060	
	SEM	0.524	0.533	0.743	
Week 64	95% CI	(-1.5, 0.6)	(-1.6, 0.6)	(-1.4, 1.5)	
	Pr >  t			0.9356	
	n	8	11		
	LS Mean	-0.236	-0.756	0.520	
	SEM	0.575	0.533	0.780	
Week 72	95% CI	(-1.4, 0.9)	(-1.8, 0.3)	(-1.0, 2.1)	
	Pr >  t			0.5063	
	n	11	10		
	LS Mean	0.259	-0.043	0.302	
	SEM	0.524	0.548	0.753	
Week 84	95% CI	(-0.8, 1.3)	(-1.1, 1.0)	(-1.2, 1.8)	
	Pr >  t			0.6893	
	n	9	9		
	LS Mean	0.885	0.391	0.494	
	SEM	0.554	0.565	0.787	
Week 96	95% CI	(-0.2, 2.0)	(-0.7, 1.5)	(-1.1, 2.1)	
	Pr >  t			0.5315	
	n	8	7		
	LS Mean	0.926	-0.478	1.404	
	SEM	0.575	0.609	0.834	
Week 108	95% CI	(-0.2, 2.1)	(-1.7, 0.7)	(-0.2, 3.1)	
	Pr >  t			0.0942	
	LS Mean	-0.249	0.417	-0.666	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 120	SEM	0.600	0.640	0.874	
	95% CI	(-1.4, 0.9)	(-0.8, 1.7)	(-2.4, 1.1)	
	Pr >  t			0.4474	
	n	6	5		
	LS Mean	-0.133	0.260	-0.394	
Week 132	SEM	0.632	0.682	0.927	
	95% CI	(-1.4, 1.1)	(-1.1, 1.6)	(-2.2, 1.4)	
	Pr >  t			0.6713	
	n	5	3		
	LS Mean	0.132	-0.443	0.575	
Week 144	SEM	0.674	0.824	1.062	
	95% CI	(-1.2, 1.5)	(-2.1, 1.2)	(-1.5, 2.7)	
	Pr >  t			0.5887	
	n	5	4		
	LS Mean	-0.418	-0.723	0.305	
Week 156	SEM	0.674	0.739	0.997	
	95% CI	(-1.7, 0.9)	(-2.2, 0.7)	(-1.7, 2.3)	
	Pr >  t			0.7600	
	n	4	2		
	LS Mean	-0.178	-0.490	0.312	
Week 168	SEM	0.730	0.972	1.214	
	95% CI	(-1.6, 1.3)	(-2.4, 1.4)	(-2.1, 2.7)	
	Pr >  t			0.7973	
	n	1	1		
	LS Mean	1.323	-1.466	2.789	
	SEM	1.315	1.321	1.863	
	95% CI	(-1.3, 3.9)	(-4.1, 1.1)	(-0.9, 6.5)	
	Pr >  t			0.1356	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	71	
			LS Mean	-0.598	-0.702	0.105
		SEM	0.783	0.806	0.306	
		95% CI	(-2.1, 0.9)	(-2.3, 0.9)	(-0.5, 0.7)	
		Pr >  t			0.7322	
		Week 16	n	69	54	
			LS Mean	-0.533	-0.494	-0.039
			SEM	0.784	0.813	0.327
			95% CI	(-2.1, 1.0)	(-2.1, 1.1)	(-0.7, 0.6)
		Week 24	n	54	46	
			LS Mean	-0.637	-0.070	-0.567
			SEM	0.787	0.817	0.350
			95% CI	(-2.2, 0.9)	(-1.7, 1.5)	(-1.3, 0.1)
		Week 32	n	49	41	
			LS Mean	-0.062	-0.296	0.234
			SEM	0.796	0.820	0.363
			95% CI	(-1.6, 1.5)	(-1.9, 1.3)	(-0.5, 0.9)
		Week 40	n	40	33	
			LS Mean	-0.690	-0.750	0.060
			SEM	0.802	0.827	0.390
			95% CI	(-2.3, 0.9)	(-2.4, 0.9)	(-0.7, 0.8)
		Week 48	n	38	28	
			LS Mean	-0.098	-0.420	0.322
			SEM	0.803	0.833	0.406
			95% CI	(-1.7, 1.5)	(-2.1, 1.2)	(-0.5, 1.1)
		Week 56	n	32	28	
			LS Mean	-0.485	-0.603	0.117

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.809	0.833	0.417
	95% CI	(-2.1, 1.1)	(-2.2, 1.0)	(-0.7, 0.9)
	Pr >  t			0.7782
	n	23	26	
	LS Mean	-0.375	-0.656	0.281
Week 72	SEM	0.823	0.836	0.448
	95% CI	(-2.0, 1.2)	(-2.3, 1.0)	(-0.6, 1.2)
	Pr >  t			0.5305
	n	27	25	
	LS Mean	-0.458	-0.426	-0.033
Week 84	SEM	0.816	0.838	0.438
	95% CI	(-2.1, 1.1)	(-2.1, 1.2)	(-0.9, 0.8)
	Pr >  t			0.9407
	n	23	22	
	LS Mean	-0.258	0.213	-0.470
Week 96	SEM	0.822	0.843	0.462
	95% CI	(-1.9, 1.4)	(-1.5, 1.9)	(-1.4, 0.4)
	Pr >  t			0.3086
	n	20	16	
	LS Mean	-0.052	-0.072	0.020
Week 108	SEM	0.829	0.861	0.505
	95% CI	(-1.7, 1.6)	(-1.8, 1.6)	(-1.0, 1.0)
	Pr >  t			0.9687
	n	20	14	
	LS Mean	-0.407	-0.373	-0.034
Week 120	SEM	0.830	0.870	0.520
	95% CI	(-2.0, 1.2)	(-2.1, 1.3)	(-1.1, 1.0)
	Pr >  t			0.9473
	n	17	11	
	LS Mean	-0.509	-0.441	-0.069
Week 132	SEM	0.839	0.889	0.566
	95% CI	(-2.2, 1.1)	(-2.2, 1.3)	(-1.2, 1.0)
	Pr >  t			0.9033
	n	13	6	
	LS Mean	-0.418	-0.374	-0.044
Week 144	SEM	0.857	0.960	0.694
	95% CI	(-2.1, 1.3)	(-2.3, 1.5)	(-1.4, 1.3)
	Pr >  t			0.9499
	n	10	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Second Line	Week 156	LS Mean	-0.298	-0.712	0.414
		SEM	0.880	0.990	0.762
		95% CI	(-2.0, 1.4)	(-2.7, 1.2)	(-1.1, 1.9)
		Pr >  t			0.5869
		n	6	3	
	Week 168	LS Mean	-0.878	0.214	-1.093
		SEM	0.943	1.100	0.961
		95% CI	(-2.7, 1.0)	(-1.9, 2.4)	(-3.0, 0.8)
		Pr >  t			0.2559
		n	3	2	
	Week 180	LS Mean	-0.686	-0.880	0.195
		SEM	1.085	1.224	1.224
		95% CI	(-2.8, 1.4)	(-3.3, 1.5)	(-2.2, 2.6)
		Pr >  t			0.8737
		n		1	
	Week 192	LS Mean		-0.110	
		SEM		1.534	
		95% CI		(-3.1, 2.9)	
		Pr >  t			
		n		1	
	Week 8	LS Mean		-0.860	
		SEM		1.534	
		95% CI		(-3.9, 2.2)	
		Pr >  t			
n		66	66		
Week 16	LS Mean	-0.081	0.460	-0.542	
	SEM	0.282	0.284	0.310	
	95% CI	(-0.6, 0.5)	(-0.1, 1.0)	(-1.2, 0.1)	
	Pr >  t			0.0820	
	n	54	51		
Week 24	LS Mean	-0.223	0.840	-1.063	
	SEM	0.298	0.308	0.340	
	95% CI	(-0.8, 0.4)	( 0.2, 1.4)	(-1.7,-0.4)	
	Pr >  t			0.0019	
	n	49	34		
	LS Mean	0.415	0.735	-0.321	
	SEM	0.306	0.341	0.375	
	95% CI	(-0.2, 1.0)	( 0.1, 1.4)	(-1.1, 0.4)	
	Pr >  t			0.3935	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	36	31	
	LS Mean	0.224	0.500	-0.275
	SEM	0.331	0.351	0.402
	95% CI	(-0.4, 0.9)	(-0.2, 1.2)	(-1.1, 0.5)
	Pr >  t			0.4940
Week 40	n	33	28	
	LS Mean	0.546	0.941	-0.394
	SEM	0.338	0.362	0.416
	95% CI	(-0.1, 1.2)	(0.2, 1.7)	(-1.2, 0.4)
	Pr >  t			0.3439
Week 48	n	29	22	
	LS Mean	0.390	1.143	-0.753
	SEM	0.350	0.386	0.446
	95% CI	(-0.3, 1.1)	(0.4, 1.9)	(-1.6, 0.1)
	Pr >  t			0.0922
Week 56	n	25	17	
	LS Mean	0.731	1.124	-0.393
	SEM	0.363	0.416	0.483
	95% CI	(0.0, 1.4)	(0.3, 1.9)	(-1.3, 0.6)
	Pr >  t			0.4170
Week 64	n	22	16	
	LS Mean	0.356	0.788	-0.432
	SEM	0.376	0.425	0.500
	95% CI	(-0.4, 1.1)	(-0.0, 1.6)	(-1.4, 0.6)
	Pr >  t			0.3880
Week 72	n	20	10	
	LS Mean	0.764	0.763	0.001
	SEM	0.387	0.497	0.571
	95% CI	(0.0, 1.5)	(-0.2, 1.7)	(-1.1, 1.1)
	Pr >  t			0.9984
Week 84	n	16	11	
	LS Mean	1.037	0.508	0.529
	SEM	0.415	0.481	0.575
	95% CI	(0.2, 1.9)	(-0.4, 1.5)	(-0.6, 1.7)
	Pr >  t			0.3581
Week 96	n	15	8	
	LS Mean	0.615	0.600	0.015
	SEM	0.423	0.539	0.631
	95% CI	(-0.2, 1.4)	(-0.5, 1.7)	(-1.2, 1.3)

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108		Pr >  t			0.9806
		n	6	7	
		LS Mean	1.534	0.098	1.436
		SEM	0.595	0.567	0.777
		95% CI	( 0.4, 2.7)	( -1.0, 1.2)	( -0.1, 3.0)
Week 120		Pr >  t			0.0650
		n	11	5	
		LS Mean	0.913	0.232	0.681
		SEM	0.472	0.649	0.757
		95% CI	( -0.0, 1.8)	( -1.0, 1.5)	( -0.8, 2.2)
Week 132		Pr >  t			0.3690
		n	7	2	
		LS Mean	0.584	0.601	-0.017
		SEM	0.559	0.970	1.086
		95% CI	( -0.5, 1.7)	( -1.3, 2.5)	( -2.2, 2.1)
Week 144		Pr >  t			0.9877
		n	5		
		LS Mean	0.020		
		SEM	0.640		
		95% CI	( -1.2, 1.3)		
Week 156		Pr >  t			
		n	3		
		LS Mean	1.077		
		SEM	0.801		
		95% CI	( -0.5, 2.6)		
Week 168		Pr >  t			
		n	1		
		LS Mean	-0.319		
		SEM	1.337		
		95% CI	( -2.9, 2.3)		
Week 180		Pr >  t			
		n	1		
		LS Mean	1.681		
		SEM	1.337		
		95% CI	( -0.9, 4.3)		
Week 192		Pr >  t			
		n	1		
		LS Mean	0.681		
		SEM	1.337		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-1.9, 3.3)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	65		
			LS Mean	0.083	0.370	-0.287	
			SEM	0.441	0.432	0.325	
			95% CI	(-0.8, 1.0)	(-0.5, 1.2)	(-0.9, 0.4)	
					Pr >  t	0.3781	
		Week 16	n	60	51		
			LS Mean	-0.085	0.428	-0.513	
			SEM	0.448	0.449	0.342	
			95% CI	(-1.0, 0.8)	(-0.5, 1.3)	(-1.2, 0.2)	
					Pr >  t	0.1350	
		Week 24	n	51	42		
			LS Mean	0.273	0.639	-0.366	
			SEM	0.453	0.457	0.361	
			95% CI	(-0.6, 1.2)	(-0.3, 1.5)	(-1.1, 0.3)	
					Pr >  t	0.3102	
		Week 32	n	46	36		
			LS Mean	0.484	0.439	0.046	
			SEM	0.459	0.467	0.375	
			95% CI	(-0.4, 1.4)	(-0.5, 1.4)	(-0.7, 0.8)	
					Pr >  t	0.9031	
		Week 40	n	40	33		
			LS Mean	0.400	0.606	-0.206	
			SEM	0.465	0.471	0.387	
			95% CI	(-0.5, 1.3)	(-0.3, 1.5)	(-1.0, 0.6)	
			Pr >  t	0.5941			
Week 48	n	37	28				
	LS Mean	0.462	0.970	-0.508			
	SEM	0.468	0.480	0.401			
	95% CI	(-0.5, 1.4)	( 0.0, 1.9)	(-1.3, 0.3)			
			Pr >  t	0.2061			
Week 56	n	33	23				
	LS Mean	0.563	0.612	-0.049			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		SEM	0.474	0.492	0.422
		95% CI	(-0.4, 1.5)	(-0.4, 1.6)	(-0.9, 0.8)
		Pr >  t			0.9073
	Week 64	n	26	20	
		LS Mean	0.208	0.220	-0.013
		SEM	0.486	0.502	0.446
		95% CI	(-0.7, 1.2)	(-0.8, 1.2)	(-0.9, 0.9)
		Pr >  t			0.9772
	Week 72	n	28	17	
		LS Mean	0.329	0.596	-0.266
		SEM	0.482	0.514	0.456
		95% CI	(-0.6, 1.3)	(-0.4, 1.6)	(-1.2, 0.6)
		Pr >  t			0.5596
	Week 84	n	23	17	
		LS Mean	0.405	0.755	-0.350
		SEM	0.493	0.514	0.468
		95% CI	(-0.6, 1.4)	(-0.3, 1.8)	(-1.3, 0.6)
		Pr >  t			0.4557
	Week 96	n	23	11	
		LS Mean	0.574	0.945	-0.371
		SEM	0.493	0.557	0.515
		95% CI	(-0.4, 1.5)	(-0.2, 2.0)	(-1.4, 0.6)
		Pr >  t			0.4713
	Week 108	n	15	13	
		LS Mean	0.628	0.713	-0.085
		SEM	0.526	0.539	0.528
		95% CI	(-0.4, 1.7)	(-0.3, 1.8)	(-1.1, 1.0)
		Pr >  t			0.8720
	Week 120	n	16	9	
		LS Mean	0.499	0.749	-0.250
		SEM	0.521	0.583	0.567
		95% CI	(-0.5, 1.5)	(-0.4, 1.9)	(-1.4, 0.9)
		Pr >  t			0.6595
	Week 132	n	14	5	
		LS Mean	0.563	0.935	-0.371
		SEM	0.532	0.682	0.678
		95% CI	(-0.5, 1.6)	(-0.4, 2.3)	(-1.7, 1.0)
		Pr >  t			0.5839
	Week 144	n	8	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Neoadjuvant	Week 156	LS Mean	0.011	0.729	-0.718
		SEM	0.599	0.808	0.850
		95% CI	(-1.2, 1.2)	(-0.9, 2.3)	(-2.4, 1.0)
		Pr >  t			0.3985
		n	7	2	
	Week 168	LS Mean	0.315	1.694	-1.379
		SEM	0.619	0.941	0.990
		95% CI	(-0.9, 1.5)	(-0.2, 3.5)	(-3.3, 0.6)
		Pr >  t			0.1641
		n	4	2	
	Week 180	LS Mean	-0.003	0.194	-0.197
		SEM	0.730	0.941	1.064
		95% CI	(-1.4, 1.4)	(-1.7, 2.0)	(-2.3, 1.9)
		Pr >  t			0.8534
		n	1	1	
	Week 192	LS Mean	1.622	0.987	0.634
		SEM	1.258	1.258	1.696
		95% CI	(-0.8, 4.1)	(-1.5, 3.5)	(-2.7, 4.0)
		Pr >  t			0.7085
		n	1	1	
	Week 8	LS Mean	0.622	0.237	0.384
		SEM	1.258	1.258	1.696
		95% CI	(-1.8, 3.1)	(-2.2, 2.7)	(-2.9, 3.7)
		Pr >  t			0.8208
n		18	17		
Week 16	LS Mean	-0.004	0.122	-0.126	
	SEM	0.448	0.469	0.649	
	95% CI	(-0.9, 0.9)	(-0.8, 1.1)	(-1.4, 1.2)	
	Pr >  t			0.8468	
	n	17	11		
Week 24	LS Mean	0.608	0.288	0.320	
	SEM	0.458	0.560	0.723	
	95% CI	(-0.3, 1.5)	(-0.8, 1.4)	(-1.1, 1.8)	
	Pr >  t			0.6591	
	n	15	5		
	LS Mean	0.239	0.744	-0.505	
	SEM	0.480	0.774	0.910	
	95% CI	(-0.7, 1.2)	(-0.8, 2.3)	(-2.3, 1.3)	
	Pr >  t			0.5797	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 32	n	13	5		
	LS Mean	0.830	-0.356		1.186
	SEM	0.506	0.774		0.925
	95% CI	(-0.2, 1.8)	(-1.9, 1.2)		(-0.6, 3.0)
	Pr >  t				0.2018
Week 40	n	11	5		
	LS Mean	-0.041	-0.456		0.414
	SEM	0.537	0.774		0.942
	95% CI	(-1.1, 1.0)	(-2.0, 1.1)		(-1.4, 2.3)
	Pr >  t				0.6608
Week 48	n	11	2		
	LS Mean	1.985	0.235		1.750
	SEM	0.537	1.121		1.243
	95% CI	( 0.9, 3.0)	(-2.0, 2.4)		(-0.7, 4.2)
	Pr >  t				0.1611
Week 56	n	8	2		
	LS Mean	0.843	0.110		0.733
	SEM	0.602	1.121		1.273
	95% CI	(-0.3, 2.0)	(-2.1, 2.3)		(-1.8, 3.2)
	Pr >  t				0.5656
Week 64	n	7	3		
	LS Mean	-0.009	-0.632		0.623
	SEM	0.632	0.949		1.140
	95% CI	(-1.3, 1.2)	(-2.5, 1.2)		(-1.6, 2.9)
	Pr >  t				0.5857
Week 72	n	7	3		
	LS Mean	0.455	0.201		0.254
	SEM	0.634	0.949		1.141
	95% CI	(-0.8, 1.7)	(-1.7, 2.1)		(-2.0, 2.5)
	Pr >  t				0.8243
Week 84	n	7	2		
	LS Mean	0.955	-0.640		1.595
	SEM	0.634	1.121		1.288
	95% CI	(-0.3, 2.2)	(-2.9, 1.6)		(-0.9, 4.1)
	Pr >  t				0.2172
Week 96	n	6	3		
	LS Mean	0.837	0.035		0.803
	SEM	0.672	0.949		1.163
	95% CI	(-0.5, 2.2)	(-1.8, 1.9)		(-1.5, 3.1)

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 108	Pr >  t			0.4910
		n	7	2	
		LS Mean	0.491	-0.151	0.642
		SEM	0.634	1.119	1.286
		95% CI	(-0.8, 1.7)	(-2.4, 2.1)	(-1.9, 3.2)
		Pr >  t			0.6183
	Week 120	n	6	1	
		LS Mean	0.170	-1.116	1.286
		SEM	0.672	1.525	1.666
		95% CI	(-1.2, 1.5)	(-4.1, 1.9)	(-2.0, 4.6)
		Pr >  t			0.4411
	Week 132	n	4		
		LS Mean	0.884		
		SEM	0.790		
		95% CI	(-0.7, 2.4)		
		Pr >  t			
	Week 144	n	5		
		LS Mean	1.090		
		SEM	0.722		
		95% CI	(-0.3, 2.5)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	0.305		
		SEM	1.067		
		95% CI	(-1.8, 2.4)		
		Pr >  t			
No Prior Use	Week 8	n	59	55	
		LS Mean	-0.180	0.029	-0.209
		SEM	0.304	0.324	0.339
		95% CI	(-0.8, 0.4)	(-0.6, 0.7)	(-0.9, 0.5)
		Pr >  t			0.5368
	Week 16	n	47	42	
		LS Mean	-0.211	0.593	-0.804
		SEM	0.323	0.349	0.378
		95% CI	(-0.8, 0.4)	(-0.1, 1.3)	(-1.5,-0.1)
		Pr >  t			0.0342
	Week 24	n	39	33	
		LS Mean	0.027	0.723	-0.696
		SEM	0.341	0.376	0.415



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169			Placebo qd + Fulv N=172			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv							
		95% CI	Pr >  t	n	LS Mean	SEM	95% CI		Pr >  t	n	LS Mean	SEM	95% CI	Pr >  t	
		(-0.6, 0.7)												(-1.5, 0.1)	0.0946
	Week 32			27	0.147	0.383	(-0.6, 0.9)		31	0.587	0.383	(-0.2, 1.3)		-0.440	0.453
	Week 40			24	0.069	0.396	(-0.7, 0.8)		23	0.296	0.418	(-0.5, 1.1)		-0.226	0.493
	Week 48			21	-0.048	0.413	(-0.9, 0.8)		20	0.326	0.436	(-0.5, 1.2)		-0.374	0.522
	Week 56			18	0.065	0.434	(-0.8, 0.9)		20	0.460	0.436	(-0.4, 1.3)		-0.395	0.539
	Week 64			14	0.550	0.472	(-0.4, 1.5)		19	0.626	0.443	(-0.2, 1.5)		-0.076	0.577
	Week 72			13	0.742	0.485	(-0.2, 1.7)		15	0.398	0.478	(-0.5, 1.3)		0.344	0.614
	Week 84			10	1.118	0.539	( 0.1, 2.2)		14	1.147	0.489	( 0.2, 2.1)		-0.028	0.662
	Week 96			6	0.682				10	0.454				0.229	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		SEM	0.659	0.550	0.807
		95% CI	(-0.6, 2.0)	(-0.6, 1.5)	(-1.4, 1.8)
		Pr >  t			0.7771
	Week 108	n	4	6	
		LS Mean	0.997	-0.405	1.402
		SEM	0.789	0.671	0.991
		95% CI	(-0.6, 2.5)	(-1.7, 0.9)	(-0.5, 3.3)
		Pr >  t			0.1578
	Week 120	n	6	6	
		LS Mean	0.820	-0.095	0.915
		SEM	0.659	0.671	0.894
		95% CI	(-0.5, 2.1)	(-1.4, 1.2)	(-0.8, 2.7)
		Pr >  t			0.3067
	Week 132	n	2	3	
		LS Mean	-1.468	-0.159	-1.308
		SEM	1.080	0.901	1.374
		95% CI	(-3.6, 0.7)	(-1.9, 1.6)	(-4.0, 1.4)
		Pr >  t			0.3415
	Week 144	n	2	2	
		LS Mean	-0.243	-0.579	0.336
		SEM	1.076	1.086	1.503
		95% CI	(-2.4, 1.9)	(-2.7, 1.6)	(-2.6, 3.3)
		Pr >  t			0.8234
	Week 156	n		1	
		LS Mean		0.036	
		SEM		1.502	
		95% CI		(-2.9, 3.0)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>n</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	55	
		LS Mean	-0.335	-0.392	0.057
		SEM	0.740	0.773	0.341
		95% CI	(-1.8, 1.1)	(-1.9, 1.1)	(-0.6, 0.7)
		Pr >  t			0.8666
	Week 16	n	51	40	
		LS Mean	-0.303	-0.020	-0.282
		SEM	0.742	0.785	0.372
		95% CI	(-1.8, 1.2)	(-1.6, 1.5)	(-1.0, 0.4)
		Pr >  t			0.4485
	Week 24	n	38	33	
		LS Mean	-0.573	0.554	-1.127
		SEM	0.748	0.792	0.407
		95% CI	(-2.1, 0.9)	(-1.0, 2.1)	(-1.9,-0.3)
		Pr >  t			0.0059
	Week 32	n	34	28	
		LS Mean	-0.003	0.190	-0.193
		SEM	0.762	0.798	0.427
		95% CI	(-1.5, 1.5)	(-1.4, 1.8)	(-1.0, 0.6)
		Pr >  t			0.6518
	Week 40	n	26	23	
		LS Mean	-0.444	-0.515	0.072
		SEM	0.774	0.807	0.464
		95% CI	(-2.0, 1.1)	(-2.1, 1.1)	(-0.8, 1.0)
	Pr >  t			0.8769	
Week 48	n	24	17		
	LS Mean	0.101	-0.100	0.201	
	SEM	0.778	0.825	0.501	
	95% CI	(-1.4, 1.6)	(-1.7, 1.5)	(-0.8, 1.2)	
	Pr >  t			0.6885	
Week 56	n	21	17		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	-0.134	-0.267	0.133
		SEM	0.786	0.826	0.512
		95% CI	(-1.7, 1.4)	(-1.9, 1.4)	(-0.9, 1.1)
		Pr >  t			0.7950
	Week 64	n	15	15	
		LS Mean	-0.097	-0.201	0.104
		SEM	0.808	0.834	0.558
		95% CI	(-1.7, 1.5)	(-1.8, 1.4)	(-1.0, 1.2)
		Pr >  t			0.8524
	Week 72	n	16	15	
		LS Mean	-0.533	-0.299	-0.235
		SEM	0.803	0.834	0.551
		95% CI	(-2.1, 1.1)	(-1.9, 1.3)	(-1.3, 0.8)
		Pr >  t			0.6705
	Week 84	n	14	13	
		LS Mean	-0.593	0.483	-1.076
		SEM	0.813	0.845	0.583
		95% CI	(-2.2, 1.0)	(-1.2, 2.2)	(-2.2, 0.1)
		Pr >  t			0.0653
	Week 96	n	12	9	
		LS Mean	-0.305	0.617	-0.922
		SEM	0.826	0.881	0.651
		95% CI	(-1.9, 1.3)	(-1.1, 2.4)	(-2.2, 0.4)
		Pr >  t			0.1567
	Week 108	n	13	8	
		LS Mean	-0.144	-0.580	0.436
		SEM	0.819	0.895	0.661
		95% CI	(-1.8, 1.5)	(-2.3, 1.2)	(-0.9, 1.7)
		Pr >  t			0.5097
	Week 120	n	11	6	
		LS Mean	-0.371	-0.600	0.228
		SEM	0.834	0.936	0.733
		95% CI	(-2.0, 1.3)	(-2.4, 1.2)	(-1.2, 1.7)
		Pr >  t			0.7556
	Week 132	n	8	3	
		LS Mean	-0.392	0.118	-0.510
		SEM	0.870	1.084	0.947
		95% CI	(-2.1, 1.3)	(-2.0, 2.2)	(-2.4, 1.3)
		Pr >  t			0.5903

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172		
First Line Endocrine Sensitive	Week 144	n	5	1	
		LS Mean	0.379	0.105	0.274
		SEM	0.943	1.538	1.490
		95% CI	(-1.5, 2.2)	(-2.9, 3.1)	(-2.7, 3.2)
		Pr >  t			0.8539
	Week 156	n	2	1	
		LS Mean	-1.386	2.105	-3.491
		SEM	1.194	1.538	1.659
		95% CI	(-3.7, 1.0)	(-0.9, 5.1)	(-6.8,-0.2)
		Pr >  t			0.0359
	Week 168	n	2	1	
		LS Mean	-1.386	0.105	-1.491
		SEM	1.194	1.538	1.659
		95% CI	(-3.7, 1.0)	(-2.9, 3.1)	(-4.8, 1.8)
		Pr >  t			0.3693
	Week 180	n		1	
		LS Mean		0.355	
		SEM		1.538	
		95% CI		(-2.7, 3.4)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.395	
		SEM		1.538	
		95% CI		(-3.4, 2.6)	
Pr >  t					
Week 8	n	17	16		
	LS Mean	-0.470	-0.413	-0.057	
	SEM	0.463	0.475	0.653	
	95% CI	(-1.4, 0.5)	(-1.4, 0.5)	(-1.4, 1.2)	
	Pr >  t			0.9303	
Week 16	n	18	14		
	LS Mean	-0.245	-0.701	0.455	
	SEM	0.455	0.497	0.668	
	95% CI	(-1.2, 0.7)	(-1.7, 0.3)	(-0.9, 1.8)	
	Pr >  t			0.4972	
Week 24	n	16	13		
	LS Mean	0.019	-0.634	0.653	
	SEM	0.473	0.507	0.687	
	95% CI	(-0.9, 1.0)	(-1.6, 0.4)	(-0.7, 2.0)	

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172		
		Pr >  t			0.3446
	Week 32	n	15	13	
		LS Mean	0.589	-0.503	1.092
		SEM	0.480	0.508	0.694
		95% CI	(-0.4, 1.5)	(-1.5, 0.5)	(-0.3, 2.5)
		Pr >  t			0.1189
	Week 40	n	14	10	
		LS Mean	-0.422	-0.409	-0.012
		SEM	0.491	0.547	0.730
		95% CI	(-1.4, 0.6)	(-1.5, 0.7)	(-1.5, 1.4)
		Pr >  t			0.9865
	Week 48	n	14	11	
		LS Mean	0.275	-0.301	0.576
		SEM	0.491	0.533	0.719
		95% CI	(-0.7, 1.2)	(-1.4, 0.8)	(-0.9, 2.0)
		Pr >  t			0.4251
	Week 56	n	11	11	
		LS Mean	-0.446	-0.506	0.060
		SEM	0.524	0.533	0.743
		95% CI	(-1.5, 0.6)	(-1.6, 0.6)	(-1.4, 1.5)
		Pr >  t			0.9356
	Week 64	n	8	11	
		LS Mean	-0.236	-0.756	0.520
		SEM	0.575	0.533	0.780
		95% CI	(-1.4, 0.9)	(-1.8, 0.3)	(-1.0, 2.1)
		Pr >  t			0.5063
	Week 72	n	11	10	
		LS Mean	0.259	-0.043	0.302
		SEM	0.524	0.548	0.753
		95% CI	(-0.8, 1.3)	(-1.1, 1.0)	(-1.2, 1.8)
		Pr >  t			0.6893
	Week 84	n	9	9	
		LS Mean	0.885	0.391	0.494
		SEM	0.554	0.565	0.787
		95% CI	(-0.2, 2.0)	(-0.7, 1.5)	(-1.1, 2.1)
		Pr >  t			0.5315
	Week 96	n	8	7	
		LS Mean	0.926	-0.478	1.404
		SEM	0.575	0.609	0.834

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.2, 2.1)	(-1.7, 0.7)	(-0.2, 3.1)
		Pr >  t			0.0942
	Week 108	n	7	6	
		LS Mean	-0.249	0.417	-0.666
		SEM	0.600	0.640	0.874
		95% CI	(-1.4, 0.9)	(-0.8, 1.7)	(-2.4, 1.1)
		Pr >  t			0.4474
	Week 120	n	6	5	
		LS Mean	-0.133	0.260	-0.394
		SEM	0.632	0.682	0.927
		95% CI	(-1.4, 1.1)	(-1.1, 1.6)	(-2.2, 1.4)
		Pr >  t			0.6713
	Week 132	n	5	3	
		LS Mean	0.132	-0.443	0.575
		SEM	0.674	0.824	1.062
		95% CI	(-1.2, 1.5)	(-2.1, 1.2)	(-1.5, 2.7)
		Pr >  t			0.5887
	Week 144	n	5	4	
		LS Mean	-0.418	-0.723	0.305
		SEM	0.674	0.739	0.997
		95% CI	(-1.7, 0.9)	(-2.2, 0.7)	(-1.7, 2.3)
		Pr >  t			0.7600
	Week 156	n	4	2	
		LS Mean	-0.178	-0.490	0.312
		SEM	0.730	0.972	1.214
		95% CI	(-1.6, 1.3)	(-2.4, 1.4)	(-2.1, 2.7)
		Pr >  t			0.7973
	Week 168	n	1	1	
		LS Mean	1.323	-1.466	2.789
		SEM	1.315	1.321	1.863
		95% CI	(-1.3, 3.9)	(-4.1, 1.1)	(-0.9, 6.5)
		Pr >  t			0.1356
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-0.069	0.211	-0.279
		SEM	0.533	0.488	0.598
		95% CI	(-1.1, 1.0)	(-0.8, 1.2)	(-1.5, 0.9)
		Pr >  t			0.6419
	Week 16	n	15	17	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	-0.160	0.848	-1.008
		SEM	0.560	0.512	0.623
		95% CI	(-1.3, 1.0)	(-0.2, 1.9)	(-2.2, 0.2)
		Pr >  t			0.1098
	Week 24	n	14	11	
		LS Mean	-0.174	-0.002	-0.172
		SEM	0.568	0.560	0.677
		95% CI	(-1.3, 1.0)	(-1.1, 1.1)	(-1.5, 1.2)
		Pr >  t			0.7998
	Week 32	n	12	9	
		LS Mean	-0.252	-0.217	-0.035
		SEM	0.591	0.594	0.718
		95% CI	(-1.4, 0.9)	(-1.4, 1.0)	(-1.5, 1.4)
		Pr >  t			0.9610
	Week 40	n	11	7	
		LS Mean	0.718	0.647	0.071
		SEM	0.605	0.646	0.764
		95% CI	(-0.5, 1.9)	(-0.6, 1.9)	(-1.4, 1.6)
		Pr >  t			0.9259
	Week 48	n	8	6	
		LS Mean	0.283	0.844	-0.561
		SEM	0.648	0.676	0.825
		95% CI	(-1.0, 1.6)	(-0.5, 2.2)	(-2.2, 1.1)
		Pr >  t			0.4973
	Week 56	n	7	5	
		LS Mean	1.216	0.697	0.519
		SEM	0.669	0.712	0.873
		95% CI	(-0.1, 2.5)	(-0.7, 2.1)	(-1.2, 2.2)
		Pr >  t			0.5534
	Week 64	n	5	3	
		LS Mean	0.011	2.124	-2.112
		SEM	0.732	0.845	1.027
		95% CI	(-1.4, 1.5)	( 0.5, 3.8)	(-4.1,-0.1)
		Pr >  t			0.0412
	Week 72	n	5	2	
		LS Mean	1.245	0.652	0.593
		SEM	0.735	0.986	1.148
		95% CI	(-0.2, 2.7)	(-1.3, 2.6)	(-1.7, 2.9)
		Pr >  t			0.6062



Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172	
Week 84	n	4	2	
	LS Mean	0.211	1.152	-0.941
	SEM	0.781	0.986	1.178
	95% CI	(-1.3, 1.8)	(-0.8, 3.1)	(-3.3, 1.4)
	Pr >  t			0.4256
Week 96	n	4	2	
	LS Mean	0.205	0.277	-0.072
	SEM	0.782	0.986	1.179
	95% CI	(-1.3, 1.8)	(-1.7, 2.2)	(-2.4, 2.3)
	Pr >  t			0.9515
Week 108	n	1	2	
	LS Mean	0.440	-0.938	1.378
	SEM	1.310	0.982	1.578
	95% CI	(-2.1, 3.0)	(-2.9, 1.0)	(-1.7, 4.5)
	Pr >  t			0.3840
Week 120	n	5	1	
	LS Mean	1.545	1.664	-0.119
	SEM	0.735	1.306	1.433
	95% CI	( 0.1, 3.0)	(-0.9, 4.2)	(-2.9, 2.7)
	Pr >  t			0.9339
Week 132	n	3	1	
	LS Mean	-0.090	0.664	-0.754
	SEM	0.858	1.306	1.500
	95% CI	(-1.8, 1.6)	(-1.9, 3.2)	(-3.7, 2.2)
	Pr >  t			0.6160
Week 144	n	3		
	LS Mean	-0.090		
	SEM	0.858		
	95% CI	(-1.8, 1.6)		
	Pr >  t			
Week 156	n	3		
	LS Mean	0.993		
	SEM	0.858		
	95% CI	(-0.7, 2.7)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-0.362		
	SEM	1.309		
	95% CI	(-2.9, 2.2)		
	Pr >  t			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		N=169	N=172		
Second Line (progression following metastatic treatment only)	Week 180	Pr >  t			
		n	1		
		LS Mean	1.638		
		SEM	1.309		
	Week 192	Pr >  t			
		n	1		
		LS Mean	0.638		
		SEM	1.309		
	Week 8	Pr >  t			
		n	37	38	
		LS Mean	-0.150	0.370	-0.520
		SEM	0.388	0.394	0.436
Week 16	Pr >  t				
	n	30	28		
	LS Mean	-0.296	0.805	-1.101	
	SEM	0.404	0.435	0.485	
Week 24	Pr >  t				
	n	26	19		
	LS Mean	0.624	1.064	-0.440	
	SEM	0.423	0.491	0.544	
Week 32	Pr >  t				
	n	18	19		
	LS Mean	0.271	0.735	-0.464	
	SEM	0.468	0.491	0.578	
Week 40	Pr >  t				
	n	18	18		
	LS Mean	0.283	1.206	-0.923	
	SEM	0.468	0.497	0.584	
Week 48	Pr >  t				
	n	16	13		
	LS Mean	0.227	1.303	-1.076	
	SEM	0.483	0.542	0.635	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	( -0.7, 1.2)	( 0.2, 2.4)	( -2.3, 0.2)
		Pr >  t			0.0910
	Week 56	n	14	10	
		LS Mean	0.472	1.261	-0.789
		SEM	0.502	0.585	0.686
		95% CI	( -0.5, 1.5)	( 0.1, 2.4)	( -2.1, 0.6)
		Pr >  t			0.2513
	Week 64	n	13	11	
		LS Mean	0.437	0.505	-0.068
		SEM	0.513	0.569	0.682
		95% CI	( -0.6, 1.4)	( -0.6, 1.6)	( -1.4, 1.3)
		Pr >  t			0.9211
	Week 72	n	10	6	
		LS Mean	0.621	0.771	-0.150
		SEM	0.556	0.694	0.819
		95% CI	( -0.5, 1.7)	( -0.6, 2.1)	( -1.8, 1.5)
		Pr >  t			0.8546
	Week 84	n	8	7	
		LS Mean	1.832	0.227	1.604
		SEM	0.606	0.658	0.820
		95% CI	( 0.6, 3.0)	( -1.1, 1.5)	( -0.0, 3.2)
		Pr >  t			0.0513
	Week 96	n	6	5	
		LS Mean	0.817	0.797	0.020
		SEM	0.670	0.742	0.937
		95% CI	( -0.5, 2.1)	( -0.7, 2.3)	( -1.8, 1.9)
		Pr >  t			0.9831
	Week 108	n	2	4	
		LS Mean	2.966	0.106	2.860
		SEM	1.065	0.809	1.290
		95% CI	( 0.9, 5.1)	( -1.5, 1.7)	( 0.3, 5.4)
		Pr >  t			0.0272
	Week 120	n	4	4	
		LS Mean	0.220	-0.144	0.365
		SEM	0.786	0.809	1.075
		95% CI	( -1.3, 1.8)	( -1.7, 1.4)	( -1.7, 2.5)
		Pr >  t			0.7346
	Week 132	n	3	1	
		LS Mean	0.788	0.391	0.398

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
		SEM	0.891	1.688
		95% CI	( -1.0, 2.5)	( -2.9, 3.7)
		Pr >  t		0.8139
	Week 144	n	2	
		LS Mean	0.049	
		SEM	1.058	
		95% CI	( -2.0, 2.1)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation	E542K	Week 8	n	16	24			
			LS Mean	-0.461	-0.669	0.208		
			SEM	0.686	0.755	0.660		
			95% CI	(-1.8, 0.9)	(-2.2, 0.8)	(-1.1, 1.5)		
					Pr >  t			0.7534
		Week 16	n	14	17			
			LS Mean	-0.996	0.188	-1.184		
			SEM	0.695	0.783	0.706		
			95% CI	(-2.4, 0.4)	(-1.4, 1.8)	(-2.6, 0.2)		
					Pr >  t			0.0973
		Week 24	n	14	11			
			LS Mean	-0.728	0.074	-0.802		
			SEM	0.695	0.826	0.752		
			95% CI	(-2.1, 0.7)	(-1.6, 1.7)	(-2.3, 0.7)		
					Pr >  t			0.2891
		Week 32	n	10	10			
			LS Mean	-0.377	0.145	-0.522		
			SEM	0.758	0.838	0.797		
			95% CI	(-1.9, 1.1)	(-1.5, 1.8)	(-2.1, 1.1)		
					Pr >  t			0.5135
		Week 40	n	8	10			
			LS Mean	-0.474	0.462	-0.936		
			SEM	0.788	0.837	0.822		
			95% CI	(-2.0, 1.1)	(-1.2, 2.1)	(-2.6, 0.7)		
					Pr >  t			0.2569
		Week 48	n	7	11			
			LS Mean	-0.709	0.556	-1.265		
			SEM	0.807	0.828	0.834		
95% CI	(-2.3, 0.9)		(-1.1, 2.2)	(-2.9, 0.4)				
			Pr >  t			0.1317		
Week 56	n	6	9					
	LS Mean	-0.795	0.163	-0.958				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.832	0.851	0.882
	95% CI	(-2.4, 0.9)	(-1.5, 1.9)	(-2.7, 0.8)
	Pr >  t			0.2793
	n	5	8	
	LS Mean	-0.815	-0.371	-0.444
Week 72	SEM	0.865	0.865	0.927
	95% CI	(-2.5, 0.9)	(-2.1, 1.4)	(-2.3, 1.4)
	Pr >  t			0.6328
	n	7	7	
	LS Mean	-1.114	0.443	-1.557
Week 84	SEM	0.806	0.883	0.891
	95% CI	(-2.7, 0.5)	(-1.3, 2.2)	(-3.3, 0.2)
	Pr >  t			0.0825
	n	7	7	
	LS Mean	-0.542	1.264	-1.807
Week 96	SEM	0.806	0.883	0.891
	95% CI	(-2.1, 1.1)	(-0.5, 3.0)	(-3.6, -0.0)
	Pr >  t			0.0443
	n	5	6	
	LS Mean	-0.613	-0.358	-0.255
Week 108	SEM	0.865	0.906	0.965
	95% CI	(-2.3, 1.1)	(-2.2, 1.4)	(-2.2, 1.6)
	Pr >  t			0.7920
	n	4	6	
	LS Mean	-0.633	0.392	-1.025
Week 120	SEM	0.912	0.906	1.008
	95% CI	(-2.4, 1.2)	(-1.4, 2.2)	(-3.0, 1.0)
	Pr >  t			0.3102
	n	4	4	
	LS Mean	0.359	0.522	-0.162
Week 132	SEM	0.913	0.983	1.077
	95% CI	(-1.4, 2.2)	(-1.4, 2.5)	(-2.3, 2.0)
	Pr >  t			0.8803
	n	3	1	
	LS Mean	-0.289	0.923	-1.212
Week 144	SEM	0.986	1.488	1.596
	95% CI	(-2.2, 1.7)	(-2.0, 3.9)	(-4.4, 1.9)
	Pr >  t			0.4488
	n	1	1	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
E545X	Week 8	LS Mean	3.072	-1.417	4.488
		SEM	1.442	1.491	1.914
		95% CI	( 0.2, 5.9)	( -4.4, 1.5)	( 0.7, 8.3)
		Pr >  t			0.0200
	Week 16	n	35	36	
		LS Mean	1.459	1.547	-0.088
		SEM	0.911	0.955	0.421
		95% CI	( -0.3, 3.3)	( -0.3, 3.4)	( -0.9, 0.7)
	Week 24	Pr >  t			0.8344
		n	34	30	
		LS Mean	1.767	2.000	-0.233
		SEM	0.938	0.962	0.437
	Week 32	95% CI	( -0.1, 3.6)	( 0.1, 3.9)	( -1.1, 0.6)
		Pr >  t			0.5946
		n	32	23	
		LS Mean	1.694	2.468	-0.775
	Week 40	SEM	0.940	0.974	0.466
		95% CI	( -0.2, 3.5)	( 0.5, 4.4)	( -1.7, 0.1)
		Pr >  t			0.0981
		n	21	22	
	Week 48	LS Mean	1.928	1.916	0.011
		SEM	0.957	0.976	0.505
		95% CI	( 0.0, 3.8)	( -0.0, 3.8)	( -1.0, 1.0)
		Pr >  t			0.9821
	Week 56	n	20	20	
		LS Mean	2.145	2.121	0.025
		SEM	0.960	0.980	0.519
		95% CI	( 0.3, 4.0)	( 0.2, 4.1)	( -1.0, 1.0)
Week 8	Pr >  t			0.9624	
	n	19	12		
	LS Mean	2.174	2.484	-0.310	
	SEM	0.962	1.012	0.581	
Week 16	95% CI	( 0.3, 4.1)	( 0.5, 4.5)	( -1.5, 0.8)	
	Pr >  t			0.5944	
	n	16	8		
	LS Mean	2.524	1.881	0.643	
Week 24	SEM	0.972	1.050	0.658	
	95% CI	( 0.6, 4.4)	( -0.2, 4.0)	( -0.7, 1.9)	
	Pr >  t			0.3289	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	n	12	11		
	LS Mean	1.797	2.112	-0.315	
	SEM	0.991	1.020	0.639	
	95% CI	(-0.2, 3.8)	(0.1, 4.1)	(-1.6, 0.9)	
	Pr >  t			0.6226	
Week 72	n	13	7		
	LS Mean	2.161	2.329	-0.168	
	SEM	0.986	1.066	0.702	
	95% CI	(0.2, 4.1)	(0.2, 4.4)	(-1.5, 1.2)	
	Pr >  t			0.8107	
Week 84	n	12	6		
	LS Mean	2.993	2.543	0.449	
	SEM	0.991	1.086	0.739	
	95% CI	(1.0, 4.9)	(0.4, 4.7)	(-1.0, 1.9)	
	Pr >  t			0.5437	
Week 96	n	7	6		
	LS Mean	1.699	2.884	-1.185	
	SEM	1.043	1.086	0.808	
	95% CI	(-0.4, 3.8)	(0.7, 5.0)	(-2.8, 0.4)	
	Pr >  t			0.1436	
Week 108	n	5	3		
	LS Mean	2.778	2.020	0.758	
	SEM	1.091	1.216	1.027	
	95% CI	(0.6, 4.9)	(-0.4, 4.4)	(-1.3, 2.8)	
	Pr >  t			0.4607	
Week 120	n	8	3		
	LS Mean	2.178	2.603	-0.424	
	SEM	1.030	1.216	0.961	
	95% CI	(0.1, 4.2)	(0.2, 5.0)	(-2.3, 1.5)	
	Pr >  t			0.6590	
Week 132	n	2	1		
	LS Mean	2.903	2.356	0.547	
	SEM	1.311	1.629	1.660	
	95% CI	(0.3, 5.5)	(-0.8, 5.6)	(-2.7, 3.8)	
	Pr >  t			0.7422	
Week 144	n	2			
	LS Mean	1.839			
	SEM	1.313			
	95% CI	(-0.7, 4.4)			



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 156	Pr >  t			
		n	1		
		LS Mean	1.794		
		SEM	1.611		
		95% CI	(-1.4, 5.0)		
		Pr >  t			
H1047X	Week 8	n	81	63	
		LS Mean	0.114	0.532	-0.418
		SEM	0.315	0.329	0.310
		95% CI	(-0.5, 0.7)	(-0.1, 1.2)	(-1.0, 0.2)
		Pr >  t			0.1789
	Week 16	n	70	51	
		LS Mean	0.102	0.433	-0.331
		SEM	0.323	0.347	0.332
		95% CI	(-0.5, 0.7)	(-0.2, 1.1)	(-1.0, 0.3)
		Pr >  t			0.3199
	Week 24	n	54	39	
		LS Mean	0.418	0.499	-0.081
		SEM	0.337	0.368	0.365
		95% CI	(-0.2, 1.1)	(-0.2, 1.2)	(-0.8, 0.6)
		Pr >  t			0.8251
	Week 32	n	50	35	
		LS Mean	0.654	0.548	0.107
		SEM	0.343	0.376	0.377
		95% CI	(-0.0, 1.3)	(-0.2, 1.3)	(-0.6, 0.8)
		Pr >  t			0.7769
	Week 40	n	42	27	
		LS Mean	0.316	0.082	0.233
		SEM	0.354	0.399	0.407
		95% CI	(-0.4, 1.0)	(-0.7, 0.9)	(-0.6, 1.0)
		Pr >  t			0.5672
	Week 48	n	38	23	
		LS Mean	0.795	0.472	0.323
		SEM	0.360	0.414	0.428
		95% CI	( 0.1, 1.5)	(-0.3, 1.3)	(-0.5, 1.2)
		Pr >  t			0.4497
	Week 56	n	33	24	
		LS Mean	0.375	0.590	-0.215
		SEM	0.370	0.410	0.433

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.4, 1.1)	(-0.2, 1.4)	(-1.1, 0.6)
		Pr >  t			0.6196
	Week 64	n	27	19	
		LS Mean	0.304	0.367	-0.063
		SEM	0.385	0.434	0.469
		95% CI	(-0.5, 1.1)	(-0.5, 1.2)	(-1.0, 0.9)
		Pr >  t			0.8938
	Week 72	n	26	17	
		LS Mean	0.810	0.348	0.463
		SEM	0.389	0.447	0.483
		95% CI	( 0.0, 1.6)	(-0.5, 1.2)	(-0.5, 1.4)
		Pr >  t			0.3381
	Week 84	n	18	16	
		LS Mean	0.665	0.409	0.256
		SEM	0.428	0.454	0.520
		95% CI	(-0.2, 1.5)	(-0.5, 1.3)	(-0.8, 1.3)
		Pr >  t			0.6230
	Week 96	n	20	10	
		LS Mean	1.094	0.471	0.623
		SEM	0.415	0.522	0.572
		95% CI	( 0.3, 1.9)	(-0.6, 1.5)	(-0.5, 1.7)
		Pr >  t			0.2766
	Week 108	n	14	10	
		LS Mean	0.372	-0.072	0.444
		SEM	0.460	0.522	0.604
		95% CI	(-0.5, 1.3)	(-1.1, 1.0)	(-0.7, 1.6)
		Pr >  t			0.4624
	Week 120	n	14	7	
		LS Mean	0.383	-0.287	0.670
		SEM	0.458	0.590	0.664
		95% CI	(-0.5, 1.3)	(-1.4, 0.9)	(-0.6, 2.0)
		Pr >  t			0.3132
	Week 132	n	12	5	
		LS Mean	0.266	0.238	0.028
		SEM	0.482	0.670	0.749
		95% CI	(-0.7, 1.2)	(-1.1, 1.6)	(-1.4, 1.5)
		Pr >  t			0.9705
	Week 144	n	11	4	
		LS Mean	0.110	0.357	-0.247

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 156	SEM	0.494	0.732	0.814	
	95% CI	(-0.9, 1.1)	(-1.1, 1.8)	(-1.8, 1.3)	
	Pr >  t			0.7614	
	n	8	3		
	LS Mean	0.347	0.976	-0.629	
Week 168	SEM	0.552	0.825	0.931	
	95% CI	(-0.7, 1.4)	(-0.6, 2.6)	(-2.5, 1.2)	
	Pr >  t			0.4995	
	n	4	2		
	LS Mean	0.058	-0.115	0.173	
Week 180	SEM	0.722	0.985	1.172	
	95% CI	(-1.4, 1.5)	(-2.0, 1.8)	(-2.1, 2.5)	
	Pr >  t			0.8825	
	n	1	1		
	LS Mean	1.704	0.633	1.071	
Week 192	SEM	1.350	1.354	1.881	
	95% CI	(-0.9, 4.4)	(-2.0, 3.3)	(-2.6, 4.8)	
	Pr >  t			0.5691	
	n	1	1		
	LS Mean	0.704	-0.117	0.821	
	SEM	1.350	1.354	1.881	
	95% CI	(-1.9, 3.4)	(-2.8, 2.5)	(-2.9, 4.5)	
	Pr >  t			0.6625	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	63	
		LS Mean	0.114	0.532	-0.418	
		SEM	0.315	0.329	0.310	
		95% CI	(-0.5, 0.7)	(-0.1, 1.2)	(-1.0, 0.2)	
			Pr >  t			0.1789
		Week 16	n	70	51	
			LS Mean	0.102	0.433	-0.331
			SEM	0.323	0.347	0.332
			95% CI	(-0.5, 0.7)	(-0.2, 1.1)	(-1.0, 0.3)
			Pr >  t			0.3199
		Week 24	n	54	39	
			LS Mean	0.418	0.499	-0.081
			SEM	0.337	0.368	0.365
			95% CI	(-0.2, 1.1)	(-0.2, 1.2)	(-0.8, 0.6)
			Pr >  t			0.8251
		Week 32	n	50	35	
			LS Mean	0.654	0.548	0.107
			SEM	0.343	0.376	0.377
			95% CI	(-0.0, 1.3)	(-0.2, 1.3)	(-0.6, 0.8)
			Pr >  t			0.7769
		Week 40	n	42	27	
			LS Mean	0.316	0.082	0.233
			SEM	0.354	0.399	0.407
			95% CI	(-0.4, 1.0)	(-0.7, 0.9)	(-0.6, 1.0)
			Pr >  t			0.5672
		Week 48	n	38	23	
			LS Mean	0.795	0.472	0.323
			SEM	0.360	0.414	0.428
		95% CI	( 0.1, 1.5)	(-0.3, 1.3)	(-0.5, 1.2)	
		Pr >  t			0.4497	
	Week 56	n	33	24		
		LS Mean	0.375	0.590	-0.215	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.370	0.410	0.433	
	95% CI	(-0.4, 1.1)	(-0.2, 1.4)	(-1.1, 0.6)	
	Pr >  t			0.6196	
	n	27	19		
	LS Mean	0.304	0.367	-0.063	
Week 72	SEM	0.385	0.434	0.469	
	95% CI	(-0.5, 1.1)	(-0.5, 1.2)	(-1.0, 0.9)	
	Pr >  t			0.8938	
	n	26	17		
	LS Mean	0.810	0.348	0.463	
Week 84	SEM	0.389	0.447	0.483	
	95% CI	( 0.0, 1.6)	(-0.5, 1.2)	(-0.5, 1.4)	
	Pr >  t			0.3381	
	n	18	16		
	LS Mean	0.665	0.409	0.256	
Week 96	SEM	0.428	0.454	0.520	
	95% CI	(-0.2, 1.5)	(-0.5, 1.3)	(-0.8, 1.3)	
	Pr >  t			0.6230	
	n	20	10		
	LS Mean	1.094	0.471	0.623	
Week 108	SEM	0.415	0.522	0.572	
	95% CI	( 0.3, 1.9)	(-0.6, 1.5)	(-0.5, 1.7)	
	Pr >  t			0.2766	
	n	14	10		
	LS Mean	0.372	-0.072	0.444	
Week 120	SEM	0.460	0.522	0.604	
	95% CI	(-0.5, 1.3)	(-1.1, 1.0)	(-0.7, 1.6)	
	Pr >  t			0.4624	
	n	14	7		
	LS Mean	0.383	-0.287	0.670	
Week 132	SEM	0.458	0.590	0.664	
	95% CI	(-0.5, 1.3)	(-1.4, 0.9)	(-0.6, 2.0)	
	Pr >  t			0.3132	
	n	12	5		
	LS Mean	0.266	0.238	0.028	
Week 144	SEM	0.482	0.670	0.749	
	95% CI	(-0.7, 1.2)	(-1.1, 1.6)	(-1.4, 1.5)	
	Pr >  t			0.9705	
	n	11	4		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Exon 9	Week 156	LS Mean	0.110	0.357	-0.247
		SEM	0.494	0.732	0.814
		95% CI	(-0.9, 1.1)	(-1.1, 1.8)	(-1.8, 1.3)
		Pr >  t			0.7614
	Week 168	n	8	3	
		LS Mean	0.347	0.976	-0.629
		SEM	0.552	0.825	0.931
		95% CI	(-0.7, 1.4)	(-0.6, 2.6)	(-2.5, 1.2)
	Week 180	Pr >  t			0.4995
		n	4	2	
		LS Mean	0.058	-0.115	0.173
		SEM	0.722	0.985	1.172
	Week 192	95% CI	(-1.4, 1.5)	(-2.0, 1.8)	(-2.1, 2.5)
		Pr >  t			0.8825
		n	1	1	
		LS Mean	1.704	0.633	1.071
	Week 8	SEM	1.350	1.354	1.881
		95% CI	(-0.9, 4.4)	(-2.0, 3.3)	(-2.6, 4.8)
		Pr >  t			0.5691
		n	1	1	
	Week 16	LS Mean	0.704	-0.117	0.821
		SEM	1.350	1.354	1.881
		95% CI	(-1.9, 3.4)	(-2.8, 2.5)	(-2.9, 4.5)
		Pr >  t			0.6625
Week 24	n	53	63		
	LS Mean	-0.135	-0.179	0.043	
	SEM	0.489	0.525	0.340	
	95% CI	(-1.1, 0.8)	(-1.2, 0.9)	(-0.6, 0.7)	
Week 8	Pr >  t			0.8988	
	n	48	48		
	LS Mean	-0.099	0.446	-0.545	
	SEM	0.500	0.536	0.363	
Week 16	95% CI	(-1.1, 0.9)	(-0.6, 1.5)	(-1.3, 0.2)	
	Pr >  t			0.1343	
	n	46	36		
	LS Mean	-0.077	0.807	-0.883	
Week 24	SEM	0.501	0.550	0.386	
	95% CI	(-1.1, 0.9)	(-0.3, 1.9)	(-1.6,-0.1)	
	Pr >  t			0.0227	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	31	33	
	LS Mean	0.208	0.353	-0.145
	SEM	0.531	0.555	0.419
	95% CI	(-0.8, 1.3)	(-0.7, 1.4)	(-1.0, 0.7)
	Pr >  t			0.7285
Week 40	n	28	30	
	LS Mean	0.317	0.617	-0.300
	SEM	0.537	0.560	0.434
	95% CI	(-0.7, 1.4)	(-0.5, 1.7)	(-1.2, 0.6)
	Pr >  t			0.4894
Week 48	n	26	23	
	LS Mean	0.286	0.896	-0.610
	SEM	0.542	0.577	0.461
	95% CI	(-0.8, 1.4)	(-0.2, 2.0)	(-1.5, 0.3)
	Pr >  t			0.1866
Week 56	n	22	17	
	LS Mean	0.517	0.414	0.104
	SEM	0.553	0.602	0.504
	95% CI	(-0.6, 1.6)	(-0.8, 1.6)	(-0.9, 1.1)
	Pr >  t			0.8373
Week 64	n	17	19	
	LS Mean	-0.022	0.296	-0.318
	SEM	0.575	0.593	0.517
	95% CI	(-1.2, 1.1)	(-0.9, 1.5)	(-1.3, 0.7)
	Pr >  t			0.5381
Week 72	n	20	14	
	LS Mean	0.112	0.764	-0.653
	SEM	0.561	0.621	0.535
	95% CI	(-1.0, 1.2)	(-0.5, 2.0)	(-1.7, 0.4)
	Pr >  t			0.2231
Week 84	n	19	13	
	LS Mean	0.833	1.315	-0.483
	SEM	0.565	0.629	0.548
	95% CI	(-0.3, 1.9)	( 0.1, 2.6)	(-1.6, 0.6)
	Pr >  t			0.3792
Week 96	n	12	12	
	LS Mean	-0.005	0.636	-0.642
	SEM	0.611	0.638	0.606
	95% CI	(-1.2, 1.2)	(-0.6, 1.9)	(-1.8, 0.5)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.2900
	Week 108	n	9	9	
		LS Mean	0.606	0.641	-0.036
		SEM	0.650	0.676	0.683
		95% CI	(-0.7, 1.9)	(-0.7, 2.0)	(-1.4, 1.3)
		Pr >  t			0.9583
	Week 120	n	12	7	
		LS Mean	0.624	0.932	-0.308
		SEM	0.613	0.717	0.689
		95% CI	(-0.6, 1.8)	(-0.5, 2.3)	(-1.7, 1.0)
		Pr >  t			0.6552
	Week 132	n	5	2	
		LS Mean	0.727	1.034	-0.307
		SEM	0.761	1.067	1.142
		95% CI	(-0.8, 2.2)	(-1.1, 3.1)	(-2.5, 1.9)
		Pr >  t			0.7879
	Week 144	n	3	1	
		LS Mean	1.305	-1.029	2.333
		SEM	0.903	1.423	1.558
		95% CI	(-0.5, 3.1)	(-3.8, 1.8)	(-0.7, 5.4)
		Pr >  t			0.1347
	Week 156	n	1		
		LS Mean	0.051		
		SEM	1.406		
		95% CI	(-2.7, 2.8)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-33: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Interferenz-Index“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Presence of Lung Metastases (L)	No	Week 8	n	98	82		
			LS Mean	-0.161	0.152	-0.312	
				SEM	0.276	0.294	0.279
				95% CI	(-0.7, 0.4)	(-0.4, 0.7)	(-0.9, 0.2)
				Pr >  t			0.2630
		Week 16	n	86	66		
	LS Mean		-0.195	0.299	-0.495		
			SEM	0.283	0.308	0.300	
			95% CI	(-0.8, 0.4)	(-0.3, 0.9)	(-1.1, 0.1)	
			Pr >  t			0.1000	
		Week 24	n	73	46		
	LS Mean		0.090	0.445	-0.355		
			SEM	0.292	0.335	0.335	
			95% CI	(-0.5, 0.7)	(-0.2, 1.1)	(-1.0, 0.3)	
			Pr >  t			0.2898	
		Week 32	n	60	42		
	LS Mean		0.255	0.176	0.078		
			SEM	0.307	0.344	0.352	
			95% CI	(-0.3, 0.9)	(-0.5, 0.9)	(-0.6, 0.8)	
			Pr >  t			0.8237	
	Week 40	n	50	37			
LS Mean		0.298	0.131	0.167			
		SEM	0.319	0.356	0.372		
		95% CI	(-0.3, 0.9)	(-0.6, 0.8)	(-0.6, 0.9)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		Pr >  t			0.6543
	Week 48	n	48	30	
		LS Mean	0.638	0.330	0.308
		SEM	0.322	0.375	0.393
		95% CI	( 0.0, 1.3)	( -0.4, 1.1)	( -0.5, 1.1)
		Pr >  t			0.4338
	Week 56	n	41	25	
		LS Mean	-0.057	-0.071	0.014
		SEM	0.333	0.394	0.421
		95% CI	( -0.7, 0.6)	( -0.8, 0.7)	( -0.8, 0.8)
		Pr >  t			0.9729
	Week 64	n	30	24	
		LS Mean	0.171	0.254	-0.083
		SEM	0.360	0.398	0.446
		95% CI	( -0.5, 0.9)	( -0.5, 1.0)	( -1.0, 0.8)
		Pr >  t			0.8523
	Week 72	n	32	19	
		LS Mean	0.219	0.101	0.118
		SEM	0.354	0.426	0.467
		95% CI	( -0.5, 0.9)	( -0.7, 0.9)	( -0.8, 1.0)
		Pr >  t			0.8003
	Week 84	n	26	19	
		LS Mean	0.127	0.756	-0.629
		SEM	0.376	0.426	0.483
		95% CI	( -0.6, 0.9)	( -0.1, 1.6)	( -1.6, 0.3)
		Pr >  t			0.1928
	Week 96	n	23	14	
		LS Mean	0.195	0.045	0.150
		SEM	0.389	0.470	0.531
		95% CI	( -0.6, 1.0)	( -0.9, 1.0)	( -0.9, 1.2)
		Pr >  t			0.7773
	Week 108	n	19	13	
		LS Mean	0.569	-0.505	1.074
		SEM	0.413	0.482	0.559
		95% CI	( -0.2, 1.4)	( -1.5, 0.4)	( -0.0, 2.2)
		Pr >  t			0.0550
	Week 120	n	19	11	
		LS Mean	0.523	-0.448	0.971
		SEM	0.412	0.511	0.584

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.3, 1.3)	(-1.5, 0.6)	(-0.2, 2.1)
		Pr >  t			0.0968
	Week 132	n	15	5	
		LS Mean	0.255	0.658	-0.403
		SEM	0.446	0.695	0.769
		95% CI	(-0.6, 1.1)	(-0.7, 2.0)	(-1.9, 1.1)
		Pr >  t			0.6003
	Week 144	n	12	3	
		LS Mean	0.316	-0.475	0.791
		SEM	0.481	0.869	0.948
		95% CI	(-0.6, 1.3)	(-2.2, 1.2)	(-1.1, 2.7)
		Pr >  t			0.4041
	Week 156	n	6	2	
		LS Mean	-0.306	0.984	-1.290
		SEM	0.634	1.045	1.185
		95% CI	(-1.5, 0.9)	(-1.1, 3.0)	(-3.6, 1.0)
		Pr >  t			0.2764
	Week 168	n	3	1	
		LS Mean	-0.771	-0.319	-0.453
		SEM	0.859	1.450	1.659
		95% CI	(-2.5, 0.9)	(-3.2, 2.5)	(-3.7, 2.8)
		Pr >  t			0.7850
	Week 180	n	1	1	
		LS Mean	2.379	0.251	2.127
		SEM	1.445	1.450	2.025
		95% CI	(-0.5, 5.2)	(-2.6, 3.1)	(-1.8, 6.1)
		Pr >  t			0.2938
	Week 192	n	1	1	
		LS Mean	0.229	-0.459	0.687
		SEM	1.445	1.450	2.025
		95% CI	(-2.6, 3.1)	(-3.3, 2.4)	(-3.3, 4.7)
		Pr >  t			0.7344
Yes	Week 8	n	44	55	
		LS Mean	0.923	0.548	0.375
		SEM	0.587	0.560	0.370
		95% CI	(-0.2, 2.1)	(-0.6, 1.7)	(-0.4, 1.1)
		Pr >  t			0.3126
	Week 16	n	38	39	
		LS Mean	1.072	0.674	0.398

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 24	SEM	0.604	0.593	0.403	
	95% CI	(-0.1, 2.3)	(-0.5, 1.8)	(-0.4, 1.2)	
	Pr >  t			0.3250	
	n	32	33		
	LS Mean	0.723	0.777	-0.054	
Week 32	SEM	0.613	0.601	0.428	
	95% CI	(-0.5, 1.9)	(-0.4, 2.0)	(-0.9, 0.8)	
	Pr >  t			0.9001	
	n	26	30		
	LS Mean	0.762	1.037	-0.275	
Week 40	SEM	0.624	0.606	0.452	
	95% CI	(-0.5, 2.0)	(-0.2, 2.2)	(-1.2, 0.6)	
	Pr >  t			0.5430	
	n	25	24		
	LS Mean	1.058	1.172	-0.114	
Week 48	SEM	0.627	0.619	0.472	
	95% CI	(-0.2, 2.3)	(-0.0, 2.4)	(-1.0, 0.8)	
	Pr >  t			0.8098	
	n	21	20		
	LS Mean	1.433	1.192	0.241	
Week 56	SEM	0.638	0.632	0.502	
	95% CI	(0.2, 2.7)	(-0.1, 2.4)	(-0.7, 1.2)	
	Pr >  t			0.6318	
	n	18	20		
	LS Mean	0.974	1.154	-0.180	
Week 64	SEM	0.649	0.632	0.516	
	95% CI	(-0.3, 2.3)	(-0.1, 2.4)	(-1.2, 0.8)	
	Pr >  t			0.7278	
	n	17	18		
	LS Mean	0.863	1.235	-0.372	
Week 72	SEM	0.653	0.640	0.531	
	95% CI	(-0.4, 2.1)	(-0.0, 2.5)	(-1.4, 0.7)	
	Pr >  t			0.4845	
	n	16	16		
	LS Mean	0.710	0.806	-0.096	
Week 84	SEM	0.658	0.650	0.549	
	95% CI	(-0.6, 2.0)	(-0.5, 2.1)	(-1.2, 1.0)	
	Pr >  t			0.8610	
	n	14	14		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference
		N=169	Placebo qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	LS Mean	1.761	1.023	0.737
	SEM	0.670	0.661	0.576
	95% CI	( 0.4, 3.1)	( -0.3, 2.3)	( -0.4, 1.9)
	Pr >  t			0.2014
	n	12	10	
Week 108	LS Mean	0.995	1.233	-0.238
	SEM	0.685	0.698	0.635
	95% CI	( -0.4, 2.3)	( -0.1, 2.6)	( -1.5, 1.0)
	Pr >  t			0.7080
	n	7	8	
Week 120	LS Mean	1.081	1.518	-0.437
	SEM	0.756	0.728	0.741
	95% CI	( -0.4, 2.6)	( 0.1, 2.9)	( -1.9, 1.0)
	Pr >  t			0.5553
	n	9	5	
Week 132	LS Mean	1.132	1.123	0.009
	SEM	0.721	0.812	0.791
	95% CI	( -0.3, 2.5)	( -0.5, 2.7)	( -1.5, 1.6)
	Pr >  t			0.9910
	n	5	3	
Week 144	LS Mean	0.544	1.036	-0.492
	SEM	0.818	0.941	1.000
	95% CI	( -1.1, 2.2)	( -0.8, 2.9)	( -2.5, 1.5)
	Pr >  t			0.6226
	n	3	2	
Week 156	LS Mean	1.751	0.801	0.950
	SEM	0.945	1.081	1.228
	95% CI	( -0.1, 3.6)	( -1.3, 2.9)	( -1.5, 3.4)
	Pr >  t			0.4395
	n	3	1	
Week 168	LS Mean	1.259	0.495	0.764
	SEM	0.946	1.420	1.535
	95% CI	( -0.6, 3.1)	( -2.3, 3.3)	( -2.3, 3.8)
	Pr >  t			0.6188
	n	1	1	
Week 168	LS Mean	0.361	0.635	-0.274
	SEM	1.426	1.420	1.870
	95% CI	( -2.4, 3.2)	( -2.2, 3.4)	( -3.9, 3.4)
	Pr >  t			0.8837
	n			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Presence of Liver Metastases (L)	No	Week 8	n	104	96		
			LS Mean	0.035	-0.061	0.096	
				SEM	0.317	0.315	0.269
				95% CI	(-0.6, 0.7)	(-0.7, 0.6)	(-0.4, 0.6)
				Pr >  t			0.7222
		Week 16	n	92	75		
	LS Mean		0.045	0.224	-0.179		
			SEM	0.321	0.334	0.289	
			95% CI	(-0.6, 0.7)	(-0.4, 0.9)	(-0.7, 0.4)	
			Pr >  t			0.5354	
		Week 24	n	83	64		
	LS Mean		0.014	0.411	-0.397		
			SEM	0.327	0.341	0.303	
			95% CI	(-0.6, 0.7)	(-0.3, 1.1)	(-1.0, 0.2)	
			Pr >  t			0.1902	
		Week 32	n	72	59		
	LS Mean		0.392	0.325	0.066		
			SEM	0.334	0.347	0.315	
			95% CI	(-0.3, 1.0)	(-0.4, 1.0)	(-0.6, 0.7)	
			Pr >  t			0.8337	
		Week 40	n	64	50		
	LS Mean		0.480	0.360	0.120		
			SEM	0.339	0.358	0.331	
			95% CI	(-0.2, 1.1)	(-0.3, 1.1)	(-0.5, 0.8)	
		Pr >  t			0.7164		
	Week 48	n	58	44			
LS Mean		0.722	0.262	0.460			
		SEM	0.344	0.366	0.345		
		95% CI	( 0.0, 1.4)	(-0.5, 1.0)	(-0.2, 1.1)		
		Pr >  t			0.1821		
	Week 56	n	49	38			
LS Mean		0.132	-0.005	0.137			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		SEM	0.353	0.376	0.365
		95% CI	(-0.6, 0.8)	(-0.7, 0.7)	(-0.6, 0.9)
		Pr >  t			0.7067
	Week 64	n	39	37	
		LS Mean	0.292	0.439	-0.147
		SEM	0.367	0.378	0.381
		95% CI	(-0.4, 1.0)	(-0.3, 1.2)	(-0.9, 0.6)
		Pr >  t			0.6995
	Week 72	n	41	32	
		LS Mean	0.283	0.153	0.130
		SEM	0.364	0.389	0.389
		95% CI	(-0.4, 1.0)	(-0.6, 0.9)	(-0.6, 0.9)
		Pr >  t			0.7376
	Week 84	n	33	29	
		LS Mean	0.631	0.668	-0.037
		SEM	0.382	0.397	0.412
		95% CI	(-0.1, 1.4)	(-0.1, 1.4)	(-0.8, 0.8)
		Pr >  t			0.9289
	Week 96	n	31	21	
		LS Mean	0.351	0.312	0.040
		SEM	0.386	0.429	0.447
		95% CI	(-0.4, 1.1)	(-0.5, 1.2)	(-0.8, 0.9)
		Pr >  t			0.9294
	Week 108	n	23	18	
		LS Mean	0.685	0.185	0.500
		SEM	0.414	0.447	0.487
		95% CI	(-0.1, 1.5)	(-0.7, 1.1)	(-0.5, 1.5)
		Pr >  t			0.3048
	Week 120	n	25	15	
		LS Mean	0.518	-0.092	0.610
		SEM	0.405	0.471	0.503
		95% CI	(-0.3, 1.3)	(-1.0, 0.8)	(-0.4, 1.6)
		Pr >  t			0.2254
	Week 132	n	17	8	
		LS Mean	0.101	0.583	-0.482
		SEM	0.449	0.579	0.635
		95% CI	(-0.8, 1.0)	(-0.6, 1.7)	(-1.7, 0.8)
		Pr >  t			0.4482
	Week 144	n	15	5	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Yes	Week 156	LS Mean	0.584	-0.191	0.775
		SEM	0.464	0.695	0.752
		95% CI	(-0.3, 1.5)	(-1.6, 1.2)	(-0.7, 2.3)
		Pr >  t			0.3031
		n	9	3	
	Week 168	LS Mean	0.090	0.652	-0.562
		SEM	0.551	0.861	0.955
		95% CI	(-1.0, 1.2)	(-1.0, 2.3)	(-2.4, 1.3)
		Pr >  t			0.5565
		n	4	2	
	Week 180	LS Mean	-0.550	-0.146	-0.404
		SEM	0.757	1.033	1.227
		95% CI	(-2.0, 0.9)	(-2.2, 1.9)	(-2.8, 2.0)
		Pr >  t			0.7419
		n	1	1	
	Week 192	LS Mean	2.513	0.351	2.161
		SEM	1.425	1.426	1.982
		95% CI	(-0.3, 5.3)	(-2.4, 3.1)	(-1.7, 6.1)
		Pr >  t			0.2758
		n	1	1	
Week 8	LS Mean	0.363	-0.359	0.721	
	SEM	1.425	1.426	1.982	
	95% CI	(-2.4, 3.2)	(-3.2, 2.4)	(-3.2, 4.6)	
	Pr >  t			0.7160	
	n	38	41		
Week 16	LS Mean	0.081	0.607	-0.526	
	SEM	0.388	0.421	0.395	
	95% CI	(-0.7, 0.9)	(-0.2, 1.4)	(-1.3, 0.3)	
	Pr >  t			0.1853	
	n	32	30		
Week 24	LS Mean	0.157	0.351	-0.194	
	SEM	0.413	0.442	0.432	
	95% CI	(-0.7, 1.0)	(-0.5, 1.2)	(-1.0, 0.7)	
	Pr >  t			0.6540	
	n	22	15		
Week 24	LS Mean	0.769	0.137	0.632	
	SEM	0.442	0.523	0.537	
	95% CI	(-0.1, 1.6)	(-0.9, 1.2)	(-0.4, 1.7)	
	Pr >  t			0.2404	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 32	n	14	13		
	LS Mean	-0.247	0.171	-0.419	
	SEM	0.503	0.542	0.598	
	95% CI	(-1.2, 0.7)	(-0.9, 1.2)	(-1.6, 0.8)	
	Pr >  t			0.4842	
Week 40	n	11	11		
	LS Mean	-0.016	0.146	-0.162	
	SEM	0.537	0.565	0.646	
	95% CI	(-1.1, 1.0)	(-1.0, 1.3)	(-1.4, 1.1)	
	Pr >  t			0.8020	
Week 48	n	11	6		
	LS Mean	0.932	1.729	-0.797	
	SEM	0.537	0.674	0.744	
	95% CI	(-0.1, 2.0)	( 0.4, 3.1)	(-2.3, 0.7)	
	Pr >  t			0.2848	
Week 56	n	10	7		
	LS Mean	0.156	1.423	-1.267	
	SEM	0.552	0.643	0.726	
	95% CI	(-0.9, 1.2)	( 0.2, 2.7)	(-2.7, 0.2)	
	Pr >  t			0.0822	
Week 64	n	8	5		
	LS Mean	0.059	0.256	-0.197	
	SEM	0.589	0.713	0.816	
	95% CI	(-1.1, 1.2)	(-1.1, 1.7)	(-1.8, 1.4)	
	Pr >  t			0.8092	
Week 72	n	7	3		
	LS Mean	0.002	0.010	-0.007	
	SEM	0.614	0.853	0.957	
	95% CI	(-1.2, 1.2)	(-1.7, 1.7)	(-1.9, 1.9)	
	Pr >  t			0.9940	
Week 84	n	7	4		
	LS Mean	0.104	0.211	-0.107	
	SEM	0.614	0.768	0.882	
	95% CI	(-1.1, 1.3)	(-1.3, 1.7)	(-1.8, 1.6)	
	Pr >  t			0.9032	
Week 96	n	4	3		
	LS Mean	0.088	0.200	-0.112	
	SEM	0.744	0.853	1.045	
	95% CI	(-1.4, 1.6)	(-1.5, 1.9)	(-2.2, 1.9)	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.9149
	Week 108	n	3	3	
		LS Mean	0.133	-0.695	0.828
		SEM	0.830	0.854	1.109
		95% CI	(-1.5, 1.8)	(-2.4, 1.0)	(-1.4, 3.0)
		Pr >  t			0.4558
	Week 120	n	3	1	
		LS Mean	1.259	-0.551	1.810
		SEM	0.830	1.347	1.521
		95% CI	(-0.4, 2.9)	(-3.2, 2.1)	(-1.2, 4.8)
		Pr >  t			0.2353
	Week 132	n	3		
		LS Mean	1.180		
		SEM	0.830		
		95% CI	(-0.5, 2.8)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Bone Lesions Only (L)	No	Week 8	n	104	109		
			LS Mean	-0.038	0.068	-0.106	
			SEM	0.283	0.282	0.251	
			95% CI	(-0.6, 0.5)	(-0.5, 0.6)	(-0.6, 0.4)	
					Pr >  t		0.6735
		Week 16	n	92	83		
			LS Mean	-0.005	0.029	-0.034	
			SEM	0.291	0.299	0.271	
			95% CI	(-0.6, 0.6)	(-0.6, 0.6)	(-0.6, 0.5)	
					Pr >  t		0.9014
		Week 24	n	77	58		
			LS Mean	0.126	0.242	-0.115	
			SEM	0.298	0.320	0.301	
			95% CI	(-0.5, 0.7)	(-0.4, 0.9)	(-0.7, 0.5)	
					Pr >  t		0.7018
		Week 32	n	57	53		
			LS Mean	0.109	0.174	-0.065	
			SEM	0.317	0.325	0.322	
			95% CI	(-0.5, 0.7)	(-0.5, 0.8)	(-0.7, 0.6)	
					Pr >  t		0.8413
		Week 40	n	50	44		
			LS Mean	0.288	0.280	0.008	
			SEM	0.325	0.339	0.342	
			95% CI	(-0.4, 0.9)	(-0.4, 0.9)	(-0.7, 0.7)	
					Pr >  t		0.9806
		Week 48	n	47	37		
			LS Mean	0.665	0.363	0.302	
			SEM	0.329	0.351	0.358	
95% CI	( 0.0, 1.3)		(-0.3, 1.1)	(-0.4, 1.0)			
			Pr >  t		0.3989		
Week 56	n	40	32				
	LS Mean	0.074	0.144	-0.070			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.340	0.363	0.380
	95% CI	(-0.6, 0.7)	(-0.6, 0.9)	(-0.8, 0.7)
	Pr >  t			0.8528
	n	32	27	
	LS Mean	-0.010	0.273	-0.283
Week 72	SEM	0.357	0.378	0.409
	95% CI	(-0.7, 0.7)	(-0.5, 1.0)	(-1.1, 0.5)
	Pr >  t			0.4897
	n	31	23	
	LS Mean	0.103	0.031	0.072
Week 84	SEM	0.360	0.395	0.427
	95% CI	(-0.6, 0.8)	(-0.7, 0.8)	(-0.8, 0.9)
	Pr >  t			0.8666
	n	27	21	
	LS Mean	0.416	0.382	0.034
Week 96	SEM	0.373	0.404	0.446
	95% CI	(-0.3, 1.1)	(-0.4, 1.2)	(-0.8, 0.9)
	Pr >  t			0.9389
	n	23	16	
	LS Mean	0.218	0.254	-0.036
Week 108	SEM	0.388	0.438	0.489
	95% CI	(-0.5, 1.0)	(-0.6, 1.1)	(-1.0, 0.9)
	Pr >  t			0.9416
	n	15	14	
	LS Mean	0.150	0.023	0.127
Week 120	SEM	0.441	0.457	0.547
	95% CI	(-0.7, 1.0)	(-0.9, 0.9)	(-0.9, 1.2)
	Pr >  t			0.8166
	n	18	8	
	LS Mean	0.350	-0.065	0.415
Week 132	SEM	0.416	0.556	0.616
	95% CI	(-0.5, 1.2)	(-1.2, 1.0)	(-0.8, 1.6)
	Pr >  t			0.5012
	n	12	4	
	LS Mean	-0.259	0.466	-0.725
Week 144	SEM	0.475	0.735	0.813
	95% CI	(-1.2, 0.7)	(-1.0, 1.9)	(-2.3, 0.9)
	Pr >  t			0.3729
	n	8	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.321	-0.907	1.229
		SEM	0.548	0.834	0.946
		95% CI	(-0.8, 1.4)	(-2.5, 0.7)	(-0.6, 3.1)
		Pr >  t			0.1943
	Week 156	n	5	1	
		LS Mean	0.709	-0.403	1.112
		SEM	0.664	1.388	1.504
		95% CI	(-0.6, 2.0)	(-3.1, 2.3)	(-1.8, 4.1)
		Pr >  t			0.4600
	Week 168	n	2	1	
		LS Mean	-0.659	-0.263	-0.396
		SEM	0.999	1.388	1.679
		95% CI	(-2.6, 1.3)	(-3.0, 2.5)	(-3.7, 2.9)
		Pr >  t			0.8137
	Week 180	n	1		
		LS Mean	2.428		
		SEM	1.384		
		95% CI	(-0.3, 5.1)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	0.278		
		SEM	1.384		
		95% CI	(-2.4, 3.0)		
		Pr >  t			
Yes	Week 8	n	38	28	
		LS Mean	0.242	0.313	-0.071
		SEM	0.535	0.578	0.488
		95% CI	(-0.8, 1.3)	(-0.8, 1.5)	(-1.0, 0.9)
		Pr >  t			0.8842
	Week 16	n	32	22	
		LS Mean	0.249	1.032	-0.783
		SEM	0.541	0.598	0.530
		95% CI	(-0.8, 1.3)	(-0.2, 2.2)	(-1.8, 0.3)
		Pr >  t			0.1410
	Week 24	n	28	21	
		LS Mean	0.278	0.807	-0.529
		SEM	0.558	0.602	0.546
		95% CI	(-0.8, 1.4)	(-0.4, 2.0)	(-1.6, 0.5)
		Pr >  t			0.3338

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172	
Week 32	n	29	19	
	LS Mean	0.723	0.791	-0.069
	SEM	0.556	0.620	0.555
	95% CI	(-0.4, 1.8)	(-0.4, 2.0)	(-1.2, 1.0)
	Pr >  t			0.9018
Week 40	n	25	17	
	LS Mean	0.727	0.596	0.130
	SEM	0.567	0.631	0.579
	95% CI	(-0.4, 1.9)	(-0.7, 1.8)	(-1.0, 1.3)
	Pr >  t			0.8218
Week 48	n	22	13	
	LS Mean	1.029	0.824	0.205
	SEM	0.577	0.662	0.623
	95% CI	(-0.1, 2.2)	(-0.5, 2.1)	(-1.0, 1.4)
	Pr >  t			0.7421
Week 56	n	19	13	
	LS Mean	0.344	0.561	-0.216
	SEM	0.590	0.663	0.636
	95% CI	(-0.8, 1.5)	(-0.7, 1.9)	(-1.5, 1.0)
	Pr >  t			0.7343
Week 64	n	15	15	
	LS Mean	0.867	0.949	-0.082
	SEM	0.614	0.645	0.642
	95% CI	(-0.3, 2.1)	(-0.3, 2.2)	(-1.3, 1.2)
	Pr >  t			0.8988
Week 72	n	17	12	
	LS Mean	0.588	0.606	-0.018
	SEM	0.601	0.673	0.657
	95% CI	(-0.6, 1.8)	(-0.7, 1.9)	(-1.3, 1.3)
	Pr >  t			0.9778
Week 84	n	13	12	
	LS Mean	0.858	1.292	-0.434
	SEM	0.637	0.673	0.686
	95% CI	(-0.4, 2.1)	(-0.0, 2.6)	(-1.8, 0.9)
	Pr >  t			0.5272
Week 96	n	12	8	
	LS Mean	0.583	0.607	-0.023
	SEM	0.648	0.737	0.758
	95% CI	(-0.7, 1.9)	(-0.8, 2.1)	(-1.5, 1.5)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		Pr >  t			0.9755
	Week 108	n	11	7	
		LS Mean	1.405	0.334	1.071
		SEM	0.660	0.762	0.793
		95% CI	( 0.1, 2.7)	( -1.2, 1.8)	( -0.5, 2.6)
		Pr >  t			0.1777
	Week 120	n	10	8	
		LS Mean	1.113	0.176	0.937
		SEM	0.674	0.736	0.781
		95% CI	( -0.2, 2.4)	( -1.3, 1.6)	( -0.6, 2.5)
		Pr >  t			0.2312
	Week 132	n	8	4	
		LS Mean	1.169	1.067	0.102
		SEM	0.712	0.898	0.963
		95% CI	( -0.2, 2.6)	( -0.7, 2.8)	( -1.8, 2.0)
		Pr >  t			0.9153
	Week 144	n	7	2	
		LS Mean	1.066	1.179	-0.113
		SEM	0.738	1.155	1.222
		95% CI	( -0.4, 2.5)	( -1.1, 3.4)	( -2.5, 2.3)
		Pr >  t			0.9265
	Week 156	n	4	2	
		LS Mean	-0.505	1.604	-2.110
		SEM	0.877	1.155	1.310
		95% CI	( -2.2, 1.2)	( -0.7, 3.9)	( -4.7, 0.5)
		Pr >  t			0.1081
	Week 168	n	2	1	
		LS Mean	-0.217	0.302	-0.519
		SEM	1.136	1.544	1.813
		95% CI	( -2.5, 2.0)	( -2.7, 3.3)	( -4.1, 3.0)
		Pr >  t			0.7747
	Week 180	n		1	
		LS Mean		0.872	
		SEM		1.544	
		95% CI		( -2.2, 3.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		0.162	
		SEM		1.544	



<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
		95% CI		(-2.9, 3.2)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
PTEN Loss of Expression (L)	No	Week 8	n	137	128	
			LS Mean	0.087	0.122	-0.035
			SEM	0.253	0.259	0.231
			95% CI	( -0.4, 0.6)	( -0.4, 0.6)	( -0.5, 0.4)
			Pr >  t			0.8799
		Week 16	n	119	96	
	LS Mean		0.135	0.317	-0.182	
			SEM	0.260	0.275	0.251
			95% CI	( -0.4, 0.6)	( -0.2, 0.9)	( -0.7, 0.3)
			Pr >  t			0.4685
		Week 24	n	100	73	
	LS Mean		0.197	0.482	-0.285	
			SEM	0.267	0.289	0.273
			95% CI	( -0.3, 0.7)	( -0.1, 1.1)	( -0.8, 0.3)
			Pr >  t			0.2969
		Week 32	n	82	68	
	LS Mean		0.326	0.339	-0.013	
			SEM	0.278	0.294	0.286
			95% CI	( -0.2, 0.9)	( -0.2, 0.9)	( -0.6, 0.5)
			Pr >  t			0.9636
		Week 40	n	73	57	
	LS Mean		0.507	0.361	0.146	
			SEM	0.284	0.305	0.301
			95% CI	( -0.1, 1.1)	( -0.2, 1.0)	( -0.4, 0.7)
		Pr >  t			0.6275	
	Week 48	n	66	47		
LS Mean		0.800	0.505	0.294		
		SEM	0.289	0.317	0.318	
		95% CI	( 0.2, 1.4)	( -0.1, 1.1)	( -0.3, 0.9)	
		Pr >  t			0.3548	
	Week 56	n	56	43		
LS Mean		0.241	0.160	0.081		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.298	0.323	0.333
		95% CI	( -0.3, 0.8)	( -0.5, 0.8)	( -0.6, 0.7)
		Pr >  t			0.8067
	Week 64	n	45	41	
		LS Mean	0.353	0.485	-0.132
		SEM	0.311	0.327	0.348
		95% CI	( -0.3, 1.0)	( -0.2, 1.1)	( -0.8, 0.6)
		Pr >  t			0.7040
	Week 72	n	46	34	
		LS Mean	0.338	0.203	0.134
		SEM	0.310	0.341	0.361
		95% CI	( -0.3, 0.9)	( -0.5, 0.9)	( -0.6, 0.8)
		Pr >  t			0.7097
	Week 84	n	37	32	
		LS Mean	0.737	0.689	0.048
		SEM	0.327	0.347	0.379
		95% CI	( 0.1, 1.4)	( 0.0, 1.4)	( -0.7, 0.8)
		Pr >  t			0.9003
	Week 96	n	33	23	
		LS Mean	0.341	0.355	-0.014
		SEM	0.336	0.379	0.417
		95% CI	( -0.3, 1.0)	( -0.4, 1.1)	( -0.8, 0.8)
		Pr >  t			0.9733
	Week 108	n	24	20	
		LS Mean	0.703	0.099	0.604
		SEM	0.367	0.395	0.456
		95% CI	( -0.0, 1.4)	( -0.7, 0.9)	( -0.3, 1.5)
		Pr >  t			0.1851
	Week 120	n	25	16	
		LS Mean	0.524	-0.058	0.582
		SEM	0.362	0.424	0.478
		95% CI	( -0.2, 1.2)	( -0.9, 0.8)	( -0.4, 1.5)
		Pr >  t			0.2234
	Week 132	n	19	8	
		LS Mean	0.496	0.653	-0.157
		SEM	0.394	0.545	0.607
		95% CI	( -0.3, 1.3)	( -0.4, 1.7)	( -1.3, 1.0)
		Pr >  t			0.7963
	Week 144	n	14	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
	Week 156	LS Mean	0.720	-0.122	0.842
		SEM	0.435	0.662	0.739
		95% CI	(-0.1, 1.6)	(-1.4, 1.2)	(-0.6, 2.3)
		Pr >  t			0.2545
	Week 168	n	9	3	
		LS Mean	0.171	0.723	-0.553
		SEM	0.514	0.828	0.932
		95% CI	(-0.8, 1.2)	(-0.9, 2.3)	(-2.4, 1.3)
	Week 180	Pr >  t			0.5532
		n	4	2	
		LS Mean	-0.469	-0.076	-0.393
		SEM	0.724	0.999	1.199
Week 192	95% CI	(-1.9, 1.0)	(-2.0, 1.9)	(-2.7, 2.0)	
	Pr >  t			0.7432	
	n	1	1		
	LS Mean	2.604	0.426	2.178	
Week 8	SEM	1.386	1.387	1.940	
	95% CI	(-0.1, 5.3)	(-2.3, 3.1)	(-1.6, 6.0)	
	Pr >  t			0.2618	
	n	1	1		
Week 16	LS Mean	0.454	-0.284	0.738	
	SEM	1.386	1.387	1.940	
	95% CI	(-2.3, 3.2)	(-3.0, 2.4)	(-3.1, 4.5)	
	Pr >  t			0.7037	
Week 24	n	5	8		
	LS Mean	-1.002	0.198	-1.200	
	SEM	0.716	0.565	0.922	
	95% CI	(-2.4, 0.4)	(-0.9, 1.3)	(-3.1, 0.7)	
Week 8	Pr >  t			0.1996	
	n	5	8		
	LS Mean	-1.458	-0.560	-0.899	
	SEM	0.716	0.559	0.918	
Week 16	95% CI	(-2.9,-0.0)	(-1.7, 0.6)	(-2.7, 1.0)	
	Pr >  t			0.3329	
	n	5	5		
	LS Mean	-0.490	-1.176	0.686	
Week 24	SEM	0.716	0.707	1.013	
	95% CI	(-1.9, 1.0)	(-2.6, 0.2)	(-1.4, 2.7)	
	Pr >  t			0.5019	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 32	n	4	3		
	LS Mean	-0.170	0.146	-0.316	
	SEM	0.797	0.924	1.230	
	95% CI	(-1.8, 1.4)	(-1.7, 2.0)	(-2.8, 2.2)	
	Pr >  t			0.7985	
Week 40	n	2	3		
	LS Mean	-2.020	0.052	-2.072	
	SEM	1.122	0.924	1.449	
	95% CI	(-4.3, 0.2)	(-1.8, 1.9)	(-5.0, 0.8)	
	Pr >  t			0.1589	
Week 48	n	3	2		
	LS Mean	0.321	-0.624	0.945	
	SEM	0.917	1.153	1.456	
	95% CI	(-1.5, 2.2)	(-2.9, 1.7)	(-2.0, 3.9)	
	Pr >  t			0.5195	
Week 56	n	3	1		
	LS Mean	-1.486	4.833	-6.318	
	SEM	0.917	1.611	1.865	
	95% CI	(-3.3, 0.4)	( 1.6, 8.1)	(-10.1,-2.6)	
	Pr >  t			0.0014	
Week 64	n	2			
	LS Mean	-1.665			
	SEM	1.122			
	95% CI	(-3.9, 0.6)			
	Pr >  t				
Week 72	n	2			
	LS Mean	-1.127			
	SEM	1.120			
	95% CI	(-3.4, 1.1)			
	Pr >  t				
Week 84	n	3			
	LS Mean	-2.012			
	SEM	0.917			
	95% CI	(-3.9,-0.2)			
	Pr >  t				
Week 96	n	2			
	LS Mean	-0.235			
	SEM	1.122			
	95% CI	(-2.5, 2.0)			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			
	Week 108	n	2		
		LS Mean	-0.384		
		SEM	1.131		
		95% CI	(-2.7, 1.9)		
		Pr >  t			
	Week 120	n	3		
		LS Mean	0.704		
		SEM	0.917		
		95% CI	(-1.1, 2.5)		
		Pr >  t			
	Week 132	n	1		
		LS Mean	-4.063		
		SEM	1.596		
		95% CI	(-7.3,-0.9)		
		Pr >  t			
	Week 144	n	1		
		LS Mean	-1.633		
		SEM	1.596		
		95% CI	(-4.8, 1.6)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	67	
			LS Mean	0.035	0.422	-0.387
			SEM	0.283	0.298	0.294
			95% CI	(-0.5, 0.6)	(-0.2, 1.0)	(-1.0, 0.2)
			Pr >  t			0.1892
		Week 16	n	70	50	
			LS Mean	-0.021	0.324	-0.345
			SEM	0.291	0.328	0.324
			95% CI	(-0.6, 0.6)	(-0.3, 1.0)	(-1.0, 0.3)
			Pr >  t			0.2866
		Week 24	n	61	36	
			LS Mean	0.365	0.464	-0.099
			SEM	0.301	0.359	0.359
			95% CI	(-0.2, 1.0)	(-0.2, 1.2)	(-0.8, 0.6)
			Pr >  t			0.7832
		Week 32	n	48	32	
			LS Mean	0.255	0.247	0.008
			SEM	0.321	0.370	0.384
			95% CI	(-0.4, 0.9)	(-0.5, 1.0)	(-0.7, 0.8)
			Pr >  t			0.9828
Week 40	n	42	30			
	LS Mean	0.358	0.269	0.089		
	SEM	0.331	0.377	0.399		
	95% CI	(-0.3, 1.0)	(-0.5, 1.0)	(-0.7, 0.9)		
	Pr >  t			0.8233		
Week 48	n	40	24			
	LS Mean	1.008	0.328	0.680		
	SEM	0.335	0.400	0.425		
	95% CI	( 0.4, 1.7)	(-0.5, 1.1)	(-0.2, 1.5)		
	Pr >  t			0.1096		
Week 56	n	35	20			
	LS Mean	0.097	0.027	0.070		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.346	0.423	0.455	
	95% CI	(-0.6, 0.8)	(-0.8, 0.9)	(-0.8, 1.0)	
	Pr >  t			0.8779	
	n	29	18		
	LS Mean	0.237	-0.057	0.294	
Week 72	SEM	0.363	0.437	0.481	
	95% CI	(-0.5, 0.9)	(-0.9, 0.8)	(-0.6, 1.2)	
	Pr >  t			0.5415	
	n	28	18		
	LS Mean	0.169	0.029	0.141	
Week 84	SEM	0.366	0.436	0.483	
	95% CI	(-0.6, 0.9)	(-0.8, 0.9)	(-0.8, 1.1)	
	Pr >  t			0.7713	
	n	27	17		
	LS Mean	0.569	0.363	0.205	
Week 96	SEM	0.372	0.444	0.493	
	95% CI	(-0.2, 1.3)	(-0.5, 1.2)	(-0.8, 1.2)	
	Pr >  t			0.6772	
	n	23	14		
	LS Mean	0.370	0.490	-0.120	
Week 108	SEM	0.389	0.473	0.532	
	95% CI	(-0.4, 1.1)	(-0.4, 1.4)	(-1.2, 0.9)	
	Pr >  t			0.8218	
	n	19	12		
	LS Mean	0.540	-0.090	0.629	
Week 120	SEM	0.414	0.499	0.573	
	95% CI	(-0.3, 1.4)	(-1.1, 0.9)	(-0.5, 1.8)	
	Pr >  t			0.2719	
	n	18	8		
	LS Mean	0.729	-0.190	0.918	
Week 132	SEM	0.420	0.580	0.649	
	95% CI	(-0.1, 1.6)	(-1.3, 0.9)	(-0.4, 2.2)	
	Pr >  t			0.1571	
	n	11	4		
	LS Mean	-0.055	0.640	-0.695	
Week 144	SEM	0.501	0.771	0.868	
	95% CI	(-1.0, 0.9)	(-0.9, 2.2)	(-2.4, 1.0)	
	Pr >  t			0.4233	
	n	11	4		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
>= 65 Years	Week 156	LS Mean	0.462	-0.521	0.983
		SEM	0.499	0.772	0.868
		95% CI	(-0.5, 1.4)	(-2.0, 1.0)	(-0.7, 2.7)
		Pr >  t			0.2580
		n	4	2	
	Week 168	LS Mean	-0.791	0.974	-1.765
		SEM	0.761	1.054	1.264
		95% CI	(-2.3, 0.7)	(-1.1, 3.0)	(-4.2, 0.7)
		Pr >  t			0.1629
		n	1	2	
	Week 180	LS Mean	-1.277	-0.171	-1.106
		SEM	1.454	1.054	1.770
		95% CI	(-4.1, 1.6)	(-2.2, 1.9)	(-4.6, 2.4)
		Pr >  t			0.5320
		n		1	
	Week 192	LS Mean		0.330	
		SEM		1.461	
		95% CI		(-2.5, 3.2)	
		Pr >  t			
		n		1	
	Week 8	LS Mean		-0.380	
		SEM		1.461	
		95% CI		(-3.2, 2.5)	
		Pr >  t			
n		63	70		
Week 16	LS Mean	0.013	-0.217	0.230	
	SEM	0.476	0.475	0.337	
	95% CI	(-0.9, 1.0)	(-1.2, 0.7)	(-0.4, 0.9)	
	Pr >  t			0.4951	
	n	54	55		
Week 24	LS Mean	0.150	0.111	0.039	
	SEM	0.487	0.483	0.361	
	95% CI	(-0.8, 1.1)	(-0.8, 1.1)	(-0.7, 0.7)	
	Pr >  t			0.9139	
	n	44	43		
	LS Mean	-0.138	0.198	-0.335	
	SEM	0.497	0.493	0.389	
	95% CI	(-1.1, 0.8)	(-0.8, 1.2)	(-1.1, 0.4)	
	Pr >  t			0.3892	

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32		n	38	40	
		LS Mean	0.299	0.272	0.027
		SEM	0.507	0.500	0.403
		95% CI	(-0.7, 1.3)	(-0.7, 1.3)	(-0.8, 0.8)
		Pr >  t			0.9465
Week 40		n	33	31	
		LS Mean	0.429	0.301	0.128
		SEM	0.515	0.516	0.430
		95% CI	(-0.6, 1.4)	(-0.7, 1.3)	(-0.7, 1.0)
		Pr >  t			0.7660
Week 48		n	29	26	
		LS Mean	0.371	0.492	-0.121
		SEM	0.523	0.528	0.452
		95% CI	(-0.7, 1.4)	(-0.5, 1.5)	(-1.0, 0.8)
		Pr >  t			0.7887
Week 56		n	24	25	
		LS Mean	0.139	0.289	-0.150
		SEM	0.535	0.531	0.470
		95% CI	(-0.9, 1.2)	(-0.8, 1.3)	(-1.1, 0.8)
		Pr >  t			0.7504
Week 64		n	18	24	
		LS Mean	0.230	0.714	-0.484
		SEM	0.559	0.534	0.500
		95% CI	(-0.9, 1.3)	(-0.3, 1.8)	(-1.5, 0.5)
		Pr >  t			0.3333
Week 72		n	20	17	
		LS Mean	0.295	0.206	0.089
		SEM	0.550	0.563	0.521
		95% CI	(-0.8, 1.4)	(-0.9, 1.3)	(-0.9, 1.1)
		Pr >  t			0.8652
Week 84		n	13	16	
		LS Mean	0.430	0.813	-0.383
		SEM	0.592	0.568	0.571
		95% CI	(-0.7, 1.6)	(-0.3, 1.9)	(-1.5, 0.7)
		Pr >  t			0.5030
Week 96		n	12	10	
		LS Mean	0.184	-0.075	0.259
		SEM	0.602	0.625	0.637
		95% CI	(-1.0, 1.4)	(-1.3, 1.2)	(-1.0, 1.5)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 108	Pr >  t			0.6840
		n	7	9	
		LS Mean	0.832	0.152	0.681
		SEM	0.684	0.641	0.729
		95% CI	(-0.5, 2.2)	(-1.1, 1.4)	(-0.7, 2.1)
		Pr >  t			0.3504
	Week 120	n	10	8	
		LS Mean	0.300	-0.123	0.423
		SEM	0.628	0.660	0.694
		95% CI	(-0.9, 1.5)	(-1.4, 1.2)	(-0.9, 1.8)
		Pr >  t			0.5426
	Week 132	n	9	4	
		LS Mean	0.606	0.460	0.147
		SEM	0.642	0.810	0.848
		95% CI	(-0.7, 1.9)	(-1.1, 2.0)	(-1.5, 1.8)
		Pr >  t			0.8625
	Week 144	n	4	1	
		LS Mean	0.827	0.841	-0.014
		SEM	0.810	1.404	1.509
		95% CI	(-0.8, 2.4)	(-1.9, 3.6)	(-3.0, 2.9)
		Pr >  t			0.9925
	Week 156	n	5	1	
		LS Mean	0.785	-0.019	0.805
		SEM	0.754	1.404	1.480
		95% CI	(-0.7, 2.3)	(-2.8, 2.7)	(-2.1, 3.7)
		Pr >  t			0.5869
	Week 168	n	3		
		LS Mean	-0.269		
		SEM	0.896		
		95% CI	(-2.0, 1.5)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	2.556		
		SEM	1.403		
		95% CI	(-0.2, 5.3)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	0.406		
		SEM	1.403		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-2.3, 3.2)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Geographic Region 1 (L)	Asia	Week 8	n	30	33	
			LS Mean	0.328	-0.429	0.757
			SEM	0.468	0.438	0.393
			95% CI	(-0.6, 1.3)	(-1.3, 0.4)	(-0.0, 1.5)
			Pr >  t			0.0563
		Week 16	n	28	28	
			LS Mean	0.343	-0.046	0.388
			SEM	0.469	0.456	0.409
			95% CI	(-0.6, 1.3)	(-1.0, 0.9)	(-0.4, 1.2)
			Pr >  t			0.3443
		Week 24	n	21	24	
			LS Mean	0.376	-0.097	0.473
			SEM	0.487	0.464	0.441
			95% CI	(-0.6, 1.3)	(-1.0, 0.8)	(-0.4, 1.3)
			Pr >  t			0.2844
		Week 32	n	19	22	
			LS Mean	0.327	-0.161	0.488
			SEM	0.493	0.469	0.455
			95% CI	(-0.7, 1.3)	(-1.1, 0.8)	(-0.4, 1.4)
			Pr >  t			0.2844
		Week 40	n	16	17	
			LS Mean	0.123	0.374	-0.251
			SEM	0.505	0.492	0.488
			95% CI	(-0.9, 1.1)	(-0.6, 1.3)	(-1.2, 0.7)
			Pr >  t			0.6075
		Week 48	n	16	16	
			LS Mean	0.696	0.548	0.148
			SEM	0.505	0.497	0.493
95% CI	(-0.3, 1.7)		(-0.4, 1.5)	(-0.8, 1.1)		
	Pr >  t			0.7636		
Week 56	n	12	14			
	LS Mean	0.227	0.098	0.129		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.528	0.508	0.529
		95% CI	(-0.8, 1.3)	(-0.9, 1.1)	(-0.9, 1.2)
		Pr >  t			0.8073
	Week 64	n	12	11	
		LS Mean	0.727	0.514	0.213
		SEM	0.528	0.531	0.552
		95% CI	(-0.3, 1.8)	(-0.5, 1.6)	(-0.9, 1.3)
		Pr >  t			0.7000
	Week 72	n	10	8	
		LS Mean	0.495	0.262	0.233
		SEM	0.547	0.570	0.605
		95% CI	(-0.6, 1.6)	(-0.9, 1.4)	(-1.0, 1.4)
		Pr >  t			0.7008
	Week 84	n	8	8	
		LS Mean	0.402	0.566	-0.164
		SEM	0.578	0.570	0.630
		95% CI	(-0.7, 1.5)	(-0.6, 1.7)	(-1.4, 1.1)
		Pr >  t			0.7946
	Week 96	n	6	6	
		LS Mean	0.244	0.365	-0.120
		SEM	0.619	0.612	0.705
		95% CI	(-1.0, 1.5)	(-0.8, 1.6)	(-1.5, 1.3)
		Pr >  t			0.8645
	Week 108	n	4	5	
		LS Mean	0.787	0.544	0.244
		SEM	0.694	0.644	0.798
		95% CI	(-0.6, 2.2)	(-0.7, 1.8)	(-1.3, 1.8)
		Pr >  t			0.7601
	Week 120	n	4	4	
		LS Mean	0.430	0.588	-0.158
		SEM	0.694	0.689	0.835
		95% CI	(-0.9, 1.8)	(-0.8, 1.9)	(-1.8, 1.5)
		Pr >  t			0.8497
	Week 132	n	3	2	
		LS Mean	0.545	0.125	0.420
		SEM	0.762	0.875	1.042
		95% CI	(-1.0, 2.0)	(-1.6, 1.8)	(-1.6, 2.5)
		Pr >  t			0.6871
	Week 144	n	3	1	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Europe	Week 156	LS Mean	1.118	0.834	0.285
		SEM	0.762	1.163	1.293
		95% CI	(-0.4, 2.6)	(-1.5, 3.1)	(-2.3, 2.8)
		Pr >  t			0.8259
		n	2	1	
	Week 168	LS Mean	0.552	-0.026	0.579
		SEM	0.880	1.163	1.365
		95% CI	(-1.2, 2.3)	(-2.3, 2.3)	(-2.1, 3.3)
		Pr >  t			0.6718
		n	1		
	Week 8	LS Mean	0.289		
		SEM	1.164		
		95% CI	(-2.0, 2.6)		
		Pr >  t			
		n	66	67	
	Week 16	LS Mean	-0.020	0.261	-0.280
		SEM	0.602	0.604	0.337
		95% CI	(-1.2, 1.2)	(-0.9, 1.5)	(-0.9, 0.4)
		Pr >  t			0.4063
		n	58	47	
Week 24	LS Mean	-0.139	0.181	-0.320	
	SEM	0.605	0.616	0.374	
	95% CI	(-1.3, 1.1)	(-1.0, 1.4)	(-1.1, 0.4)	
	Pr >  t			0.3927	
	n	51	35		
Week 32	LS Mean	-0.030	0.403	-0.433	
	SEM	0.610	0.630	0.408	
	95% CI	(-1.2, 1.2)	(-0.8, 1.6)	(-1.2, 0.4)	
	Pr >  t			0.2900	
	n	43	30		
Week 40	LS Mean	0.275	0.206	0.070	
	SEM	0.624	0.647	0.435	
	95% CI	(-1.0, 1.5)	(-1.1, 1.5)	(-0.8, 0.9)	
	Pr >  t			0.8726	
	n	37	25		
	LS Mean	0.339	0.176	0.163	
	SEM	0.632	0.659	0.464	
	95% CI	(-0.9, 1.6)	(-1.1, 1.5)	(-0.7, 1.1)	
	Pr >  t			0.7246	
	n				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Week 48	n	33	21		
	LS Mean	0.908	0.108	0.800	
	SEM	0.637	0.673	0.491	
	95% CI	(-0.3, 2.2)	(-1.2, 1.4)	(-0.2, 1.8)	
	Pr >  t			0.1041	
Week 56	n	29	20		
	LS Mean	-0.201	-0.112	-0.088	
	SEM	0.645	0.678	0.507	
	95% CI	(-1.5, 1.1)	(-1.4, 1.2)	(-1.1, 0.9)	
	Pr >  t			0.8617	
Week 64	n	23	20		
	LS Mean	0.121	-0.061	0.182	
	SEM	0.661	0.678	0.528	
	95% CI	(-1.2, 1.4)	(-1.4, 1.3)	(-0.9, 1.2)	
	Pr >  t			0.7298	
Week 72	n	25	19		
	LS Mean	-0.132	0.034	-0.165	
	SEM	0.655	0.682	0.526	
	95% CI	(-1.4, 1.2)	(-1.3, 1.4)	(-1.2, 0.9)	
	Pr >  t			0.7533	
Week 84	n	22	17		
	LS Mean	0.321	0.872	-0.551	
	SEM	0.664	0.693	0.551	
	95% CI	(-1.0, 1.6)	(-0.5, 2.2)	(-1.6, 0.5)	
	Pr >  t			0.3176	
Week 96	n	20	13		
	LS Mean	0.355	0.134	0.221	
	SEM	0.673	0.722	0.596	
	95% CI	(-1.0, 1.7)	(-1.3, 1.6)	(-0.9, 1.4)	
	Pr >  t			0.7111	
Week 108	n	15	11		
	LS Mean	0.437	0.091	0.346	
	SEM	0.701	0.744	0.653	
	95% CI	(-0.9, 1.8)	(-1.4, 1.6)	(-0.9, 1.6)	
	Pr >  t			0.5968	
Week 120	n	16	8		
	LS Mean	0.308	-0.420	0.727	
	SEM	0.695	0.795	0.704	
	95% CI	(-1.1, 1.7)	(-2.0, 1.1)	(-0.7, 2.1)	



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.3017
	Week 132	n	12	3	
		LS Mean	-0.058	0.837	-0.895
		SEM	0.727	1.051	1.008
		95% CI	(-1.5, 1.4)	(-1.2, 2.9)	(-2.9, 1.1)
		Pr >  t			0.3750
	Week 144	n	7	4	
		LS Mean	0.605	-0.544	1.148
		SEM	0.815	0.958	0.981
		95% CI	(-1.0, 2.2)	(-2.4, 1.3)	(-0.8, 3.1)
		Pr >  t			0.2421
	Week 156	n	5	2	
		LS Mean	-0.667	0.927	-1.594
		SEM	0.891	1.217	1.287
		95% CI	(-2.4, 1.1)	(-1.5, 3.3)	(-4.1, 0.9)
		Pr >  t			0.2161
	Week 168	n	2	2	
		LS Mean	-0.992	-0.218	-0.774
		SEM	1.213	1.217	1.528
		95% CI	(-3.4, 1.4)	(-2.6, 2.2)	(-3.8, 2.2)
		Pr >  t			0.6127
	Week 180	n		1	
		LS Mean		0.283	
		SEM		1.614	
		95% CI		(-2.9, 3.5)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.427	
		SEM		1.614	
		95% CI		(-3.6, 2.7)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	-0.797	-0.274	-0.522
		SEM	0.465	0.478	0.676
		95% CI	(-1.7, 0.1)	(-1.2, 0.7)	(-1.9, 0.8)
		Pr >  t			0.4415
	Week 16	n	13	12	
		LS Mean	-0.499	-0.321	-0.177
		SEM	0.479	0.498	0.698

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference
		N=169	Placebo qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.4, 0.5)	(-1.3, 0.7)	(-1.6, 1.2)
		Pr >  t			0.8000
	Week 24	n	12	10	
		LS Mean	-0.480	-0.286	-0.194
		SEM	0.494	0.534	0.732
		95% CI	(-1.5, 0.5)	(-1.3, 0.8)	(-1.6, 1.3)
		Pr >  t			0.7915
	Week 32	n	9	10	
		LS Mean	-0.553	-0.285	-0.268
		SEM	0.560	0.534	0.779
		95% CI	(-1.7, 0.6)	(-1.3, 0.8)	(-1.8, 1.3)
		Pr >  t			0.7312
	Week 40	n	7	10	
		LS Mean	0.869	-0.214	1.083
		SEM	0.622	0.534	0.825
		95% CI	(-0.4, 2.1)	(-1.3, 0.8)	(-0.6, 2.7)
		Pr >  t			0.1921
	Week 48	n	7	7	
		LS Mean	0.970	-0.221	1.191
		SEM	0.622	0.620	0.882
		95% CI	(-0.3, 2.2)	(-1.4, 1.0)	(-0.6, 2.9)
		Pr >  t			0.1791
	Week 56	n	6	7	
		LS Mean	0.462	0.391	0.071
		SEM	0.666	0.621	0.916
		95% CI	(-0.9, 1.8)	(-0.8, 1.6)	(-1.7, 1.9)
		Pr >  t			0.9387
	Week 64	n	4	7	
		LS Mean	-0.195	0.954	-1.149
		SEM	0.793	0.617	1.007
		95% CI	(-1.8, 1.4)	(-0.3, 2.2)	(-3.1, 0.8)
		Pr >  t			0.2557
	Week 72	n	4	4	
		LS Mean	0.625	-0.788	1.413
		SEM	0.793	0.788	1.121
		95% CI	(-0.9, 2.2)	(-2.3, 0.8)	(-0.8, 3.6)
		Pr >  t			0.2093
	Week 84	n	4	5	
		LS Mean	0.185	-0.756	0.940

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
North America	Week 96	SEM	0.792	0.714	1.069
		95% CI	(-1.4, 1.7)	(-2.2, 0.7)	(-1.2, 3.1)
		Pr >  t			0.3806
	Week 108	n	3	2	
		LS Mean	-0.572	-0.207	-0.365
		SEM	0.902	1.082	1.412
	Week 120	95% CI	(-2.4, 1.2)	(-2.3, 1.9)	(-3.2, 2.4)
		Pr >  t			0.7964
		n	2	3	
	Week 132	LS Mean	1.885	-2.088	3.973
		SEM	1.086	0.905	1.419
		95% CI	(-0.3, 4.0)	(-3.9,-0.3)	( 1.2, 6.8)
	Week 8	Pr >  t			0.0058
		n	2	2	
		LS Mean	1.650	-0.920	2.570
	Week 16	SEM	1.087	1.083	1.536
		95% CI	(-0.5, 3.8)	(-3.1, 1.2)	(-0.5, 5.6)
		Pr >  t			0.0964
	Week 24	n	1	2	
		LS Mean	-0.039	-0.565	0.526
		SEM	1.509	1.083	1.859
	Week 32	95% CI	(-3.0, 2.9)	(-2.7, 1.6)	(-3.1, 4.2)
		Pr >  t			0.7775
		n	16	19	
Week 8	LS Mean	-0.418	0.849	-1.267	
	SEM	0.527	0.511	0.637	
	95% CI	(-1.5, 0.6)	(-0.2, 1.9)	(-2.5, 0.0)	
Week 16	Pr >  t			0.0508	
	n	12	14		
	LS Mean	0.073	1.262	-1.189	
Week 24	SEM	0.576	0.559	0.705	
	95% CI	(-1.1, 1.2)	( 0.1, 2.4)	(-2.6, 0.2)	
	Pr >  t			0.0955	
Week 32	n	12	8		
	LS Mean	-0.424	1.333	-1.757	
	SEM	0.576	0.673	0.793	
Week 8	95% CI	(-1.6, 0.7)	(-0.0, 2.7)	(-3.3,-0.2)	
	Pr >  t			0.0290	
	n	9	7		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	LS Mean	0.485	2.485	-2.000	
	SEM	0.628	0.702	0.851	
	95% CI	(-0.8, 1.7)	( 1.1, 3.9)	(-3.7,-0.3)	
	Pr >  t			0.0204	
	n	9	7		
Week 48	LS Mean	0.527	1.382	-0.855	
	SEM	0.631	0.702	0.853	
	95% CI	(-0.7, 1.8)	(-0.0, 2.8)	(-2.5, 0.8)	
	Pr >  t			0.3185	
	n	8	5		
Week 56	LS Mean	0.032	1.976	-1.944	
	SEM	0.652	0.779	0.933	
	95% CI	(-1.3, 1.3)	( 0.4, 3.5)	(-3.8,-0.1)	
	Pr >  t			0.0393	
	n	7	3		
Week 64	LS Mean	0.639	1.051	-0.413	
	SEM	0.678	0.931	1.081	
	95% CI	(-0.7, 2.0)	(-0.8, 2.9)	(-2.5, 1.7)	
	Pr >  t			0.7033	
	n	5	3		
Week 72	LS Mean	-0.179	0.951	-1.131	
	SEM	0.754	0.931	1.131	
	95% CI	(-1.7, 1.3)	(-0.9, 2.8)	(-3.4, 1.1)	
	Pr >  t			0.3194	
	n	5	3		
Week 84	LS Mean	0.644	1.164	-0.520	
	SEM	0.752	0.930	1.127	
	95% CI	(-0.8, 2.1)	(-0.7, 3.0)	(-2.7, 1.7)	
	Pr >  t			0.6456	
	n	2	2		
Week 96	LS Mean	4.052	0.771	3.281	
	SEM	1.067	1.088	1.470	
	95% CI	( 1.9, 6.2)	(-1.4, 2.9)	( 0.4, 6.2)	
	Pr >  t			0.0272	
	n	3	2		
	LS Mean	0.546	1.271	-0.724	
	SEM	0.901	1.088	1.358	
	95% CI	(-1.2, 2.3)	(-0.9, 3.4)	(-3.4, 2.0)	
	Pr >  t			0.5946	
	n				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 108	n	1	2	
	LS Mean	1.084	1.271	-0.186
	SEM	1.434	1.088	1.755
	95% CI	(-1.8, 3.9)	(-0.9, 3.4)	(-3.7, 3.3)
	Pr >  t			0.9156
Week 120	n	3	2	
	LS Mean	1.500	0.341	1.159
	SEM	0.901	1.088	1.358
	95% CI	(-0.3, 3.3)	(-1.8, 2.5)	(-1.5, 3.8)
	Pr >  t			0.3949
Week 132	n	1	1	
	LS Mean	-0.672	2.387	-3.060
	SEM	1.435	1.451	2.002
	95% CI	(-3.5, 2.2)	(-0.5, 5.3)	(-7.0, 0.9)
	Pr >  t			0.1288
Week 144	n	2		
	LS Mean	0.347		
	SEM	1.059		
	95% CI	(-1.7, 2.4)		
	Pr >  t			
Week 156	n	1		
	LS Mean	2.468		
	SEM	1.435		
	95% CI	(-0.4, 5.3)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-0.672		
	SEM	1.435		
	95% CI	(-3.5, 2.2)		
	Pr >  t			
Week 180	n	1		
	LS Mean	2.618		
	SEM	1.435		
	95% CI	(-0.2, 5.5)		
	Pr >  t			
Week 192	n	1		
	LS Mean	0.468		
	SEM	1.435		
	95% CI	(-2.4, 3.3)		
	Pr >  t			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	Placebo qd + Fulv	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Other	Week 8	Pr >  t			
		n	16	5	
		LS Mean	0.840	0.677	0.163
		SEM	0.691	1.026	1.112
	Week 16	95% CI	(-0.6, 2.3)	(-1.4, 2.8)	(-2.1, 2.5)
		Pr >  t			0.8848
		n	13	4	
		LS Mean	0.877	0.848	0.028
	Week 24	SEM	0.711	1.113	1.181
		95% CI	(-0.6, 2.3)	(-1.4, 3.1)	(-2.4, 2.4)
		Pr >  t			0.9809
		n	9	2	
	Week 32	LS Mean	2.314	3.001	-0.687
		SEM	0.754	1.300	1.382
		95% CI	( 0.8, 3.9)	( 0.4, 5.6)	(-3.5, 2.1)
		Pr >  t			0.6215
	Week 40	n	6	3	
		LS Mean	1.089	0.847	0.241
		SEM	0.824	1.181	1.311
		95% CI	(-0.6, 2.8)	(-1.6, 3.2)	(-2.4, 2.9)
	Week 48	Pr >  t			0.8550
		n	6	2	
		LS Mean	0.856	0.079	0.777
		SEM	0.833	1.298	1.421
Week 56	95% CI	(-0.8, 2.5)	(-2.5, 2.7)	(-2.1, 3.6)	
	Pr >  t			0.5872	
	n	5	1		
	LS Mean	0.738	0.541	0.196	
Week 64	SEM	0.864	1.600	1.722	
	95% CI	(-1.0, 2.5)	(-2.7, 3.7)	(-3.2, 3.6)	
	Pr >  t			0.9096	
	n	5	1		
Week 64	LS Mean	0.708	0.541	0.166	
	SEM	0.864	1.600	1.722	
	95% CI	(-1.0, 2.4)	(-2.7, 3.7)	(-3.3, 3.6)	
	Pr >  t			0.9234	
Week 64	n	3	1		
	LS Mean	0.582	0.541	0.041	
	SEM	0.979	1.600	1.782	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	(-1.4, 2.5)	(-2.7, 3.7)	(-3.5, 3.6)
		Pr >  t			0.9818
	Week 72	n	4	1	
		LS Mean	0.990	0.541	0.449
		SEM	0.910	1.600	1.746
		95% CI	(-0.8, 2.8)	(-2.7, 3.7)	(-3.0, 3.9)
		Pr >  t			0.7977
	Week 84	n	4	1	
		LS Mean	0.525	0.541	-0.016
		SEM	0.910	1.600	1.746
		95% CI	(-1.3, 2.4)	(-2.7, 3.7)	(-3.5, 3.5)
		Pr >  t			0.9928
	Week 96	n	3	1	
		LS Mean	0.582	0.541	0.041
		SEM	0.979	1.600	1.782
		95% CI	(-1.4, 2.5)	(-2.7, 3.7)	(-3.5, 3.6)
		Pr >  t			0.9818
	Week 108	n	4		
		LS Mean	0.525		
		SEM	0.910		
		95% CI	(-1.3, 2.4)		
		Pr >  t			
	Week 120	n	3		
		LS Mean	0.582		
		SEM	0.979		
		95% CI	(-1.4, 2.5)		
		Pr >  t			
	Week 132	n	3		
		LS Mean	1.629		
		SEM	0.979		
		95% CI	(-0.3, 3.6)		
		Pr >  t			
	Week 144	n	3		
		LS Mean	0.511		
		SEM	0.978		
		95% CI	(-1.4, 2.5)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	0.589		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	1.398		
	95% CI	(-2.2, 3.4)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Baseline ECOG performance status	0 Week 8	n	98	88		
		LS Mean	-0.188	-0.028	-0.161	
		SEM	0.329	0.322	0.264	
		95% CI	(-0.8, 0.5)	(-0.7, 0.6)	(-0.7, 0.4)	
					Pr >  t	0.5421
	Week 16	n	88	70		
		LS Mean	-0.040	0.033	-0.073	
		SEM	0.336	0.345	0.283	
		95% CI	(-0.7, 0.6)	(-0.6, 0.7)	(-0.6, 0.5)	
					Pr >  t	0.7975
	Week 24	n	75	54		
		LS Mean	-0.042	0.385	-0.427	
		SEM	0.342	0.357	0.307	
		95% CI	(-0.7, 0.6)	(-0.3, 1.1)	(-1.0, 0.2)	
					Pr >  t	0.1640
	Week 32	n	62	52		
		LS Mean	0.102	-0.024	0.125	
		SEM	0.352	0.360	0.319	
		95% CI	(-0.6, 0.8)	(-0.7, 0.7)	(-0.5, 0.8)	
					Pr >  t	0.6951
	Week 40	n	51	46		
		LS Mean	0.376	-0.094	0.471	
		SEM	0.361	0.369	0.338	
		95% CI	(-0.3, 1.1)	(-0.8, 0.6)	(-0.2, 1.1)	
					Pr >  t	0.1642
	Week 48	n	50	37		
		LS Mean	0.618	0.088	0.530	
		SEM	0.362	0.383	0.354	
95% CI		(-0.1, 1.3)	(-0.7, 0.8)	(-0.2, 1.2)		
				Pr >  t	0.1350	
Week 56	n	43	33			
	LS Mean	0.097	-0.234	0.331		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.371	0.391	0.372
		95% CI	(-0.6, 0.8)	(-1.0, 0.5)	(-0.4, 1.1)
		Pr >  t			0.3745
	Week 64	n	35	33	
		LS Mean	0.189	-0.287	0.476
		SEM	0.384	0.391	0.386
		95% CI	(-0.6, 0.9)	(-1.1, 0.5)	(-0.3, 1.2)
		Pr >  t			0.2179
	Week 72	n	35	31	
		LS Mean	0.037	-0.095	0.132
		SEM	0.384	0.396	0.390
		95% CI	(-0.7, 0.8)	(-0.9, 0.7)	(-0.6, 0.9)
		Pr >  t			0.7355
	Week 84	n	31	29	
		LS Mean	0.489	0.448	0.041
		SEM	0.394	0.401	0.405
		95% CI	(-0.3, 1.3)	(-0.3, 1.2)	(-0.8, 0.8)
		Pr >  t			0.9199
	Week 96	n	27	22	
		LS Mean	0.148	0.025	0.123
		SEM	0.404	0.426	0.440
		95% CI	(-0.6, 0.9)	(-0.8, 0.9)	(-0.7, 1.0)
		Pr >  t			0.7792
	Week 108	n	19	20	
		LS Mean	0.495	-0.158	0.653
		SEM	0.440	0.436	0.481
		95% CI	(-0.4, 1.4)	(-1.0, 0.7)	(-0.3, 1.6)
		Pr >  t			0.1746
	Week 120	n	20	15	
		LS Mean	0.667	-0.345	1.012
		SEM	0.433	0.470	0.508
		95% CI	(-0.2, 1.5)	(-1.3, 0.6)	(0.0, 2.0)
		Pr >  t			0.0463
	Week 132	n	15	7	
		LS Mean	0.364	0.402	-0.038
		SEM	0.468	0.602	0.655
		95% CI	(-0.6, 1.3)	(-0.8, 1.6)	(-1.3, 1.2)
		Pr >  t			0.9538
	Week 144	n	10	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference	
		N=169	Placebo qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
1	Week 156	LS Mean	0.797	-0.436	1.233
		SEM	0.528	0.685	0.773
		95% CI	(-0.2, 1.8)	(-1.8, 0.9)	(-0.3, 2.7)
		Pr >  t			0.1112
	Week 168	n	5	3	
		LS Mean	0.270	0.405	-0.135
		SEM	0.682	0.845	1.014
		95% CI	(-1.1, 1.6)	(-1.3, 2.1)	(-2.1, 1.9)
	Week 180	Pr >  t			0.8941
		n	3	2	
		LS Mean	-0.845	-0.396	-0.450
		SEM	0.844	1.010	1.257
Week 192	95% CI	(-2.5, 0.8)	(-2.4, 1.6)	(-2.9, 2.0)	
	Pr >  t			0.7207	
	n	1	1		
	LS Mean	2.463	0.117	2.346	
Week 192	SEM	1.392	1.392	1.930	
	95% CI	(-0.3, 5.2)	(-2.6, 2.8)	(-1.4, 6.1)	
	Pr >  t			0.2244	
	n	1	1		
Week 8	LS Mean	0.313	-0.593	0.906	
	SEM	1.392	1.392	1.930	
	95% CI	(-2.4, 3.0)	(-3.3, 2.1)	(-2.9, 4.7)	
	Pr >  t			0.6388	
Week 16	n	43	49		
	LS Mean	0.043	0.035	0.007	
	SEM	0.398	0.416	0.412	
	95% CI	(-0.7, 0.8)	(-0.8, 0.9)	(-0.8, 0.8)	
Week 24	Pr >  t			0.9855	
	n	35	34		
	LS Mean	-0.222	0.305	-0.527	
	SEM	0.419	0.435	0.458	
Week 24	95% CI	(-1.0, 0.6)	(-0.6, 1.2)	(-1.4, 0.4)	
	Pr >  t			0.2509	
	n	29	24		
	LS Mean	0.149	-0.171	0.320	
Week 24	SEM	0.438	0.475	0.505	
	95% CI	(-0.7, 1.0)	(-1.1, 0.8)	(-0.7, 1.3)	
	Pr >  t			0.5270	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 32	n	23	20		
	LS Mean	0.271	0.703	-0.432	
	SEM	0.466	0.500	0.542	
	95% CI	(-0.6, 1.2)	(-0.3, 1.7)	(-1.5, 0.6)	
	Pr >  t			0.4258	
Week 40	n	23	15		
	LS Mean	0.019	1.075	-1.056	
	SEM	0.467	0.536	0.576	
	95% CI	(-0.9, 0.9)	( 0.0, 2.1)	(-2.2, 0.1)	
	Pr >  t			0.0676	
Week 48	n	18	13		
	LS Mean	0.651	1.022	-0.371	
	SEM	0.493	0.557	0.618	
	95% CI	(-0.3, 1.6)	(-0.1, 2.1)	(-1.6, 0.8)	
	Pr >  t			0.5487	
Week 56	n	15	12		
	LS Mean	-0.298	1.010	-1.308	
	SEM	0.517	0.569	0.649	
	95% CI	(-1.3, 0.7)	(-0.1, 2.1)	(-2.6,-0.0)	
	Pr >  t			0.0446	
Week 64	n	11	9		
	LS Mean	-0.126	2.405	-2.531	
	SEM	0.563	0.620	0.729	
	95% CI	(-1.2, 1.0)	( 1.2, 3.6)	(-4.0,-1.1)	
	Pr >  t			0.0006	
Week 72	n	12	4		
	LS Mean	0.290	0.237	0.053	
	SEM	0.550	0.824	0.902	
	95% CI	(-0.8, 1.4)	(-1.4, 1.9)	(-1.7, 1.8)	
	Pr >  t			0.9528	
Week 84	n	8	4		
	LS Mean	0.060	0.202	-0.142	
	SEM	0.627	0.824	0.948	
	95% CI	(-1.2, 1.3)	(-1.4, 1.8)	(-2.0, 1.7)	
	Pr >  t			0.8813	
Week 96	n	8	2		
	LS Mean	0.239	0.605	-0.367	
	SEM	0.627	1.095	1.191	
	95% CI	(-1.0, 1.5)	(-1.5, 2.8)	(-2.7, 2.0)	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.7585
	Week 108	n	6	1	
		LS Mean	0.460	-0.778	1.238
		SEM	0.692	1.495	1.593
		95% CI	(-0.9, 1.8)	(-3.7, 2.2)	(-1.9, 4.4)
		Pr >  t			0.4375
	Week 120	n	8	1	
		LS Mean	-0.112	-0.348	0.236
		SEM	0.628	1.495	1.566
		95% CI	(-1.3, 1.1)	(-3.3, 2.6)	(-2.8, 3.3)
		Pr >  t			0.8803
	Week 132	n	5	1	
		LS Mean	-0.640	0.362	-1.002
		SEM	0.740	1.495	1.614
		95% CI	(-2.1, 0.8)	(-2.6, 3.3)	(-4.2, 2.2)
		Pr >  t			0.5351
	Week 144	n	5		
		LS Mean	-0.326		
		SEM	0.740		
		95% CI	(-1.8, 1.1)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	-0.555		
		SEM	0.805		
		95% CI	(-2.1, 1.0)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-0.203		
		SEM	1.471		
		95% CI	(-3.1, 2.7)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Endocrine Status (L) Primary resistant	Week 8	n	21	15	
		LS Mean	-0.289	-0.096	-0.193
		SEM	0.479	0.563	0.570
		95% CI	(-1.3, 0.7)	(-1.2, 1.0)	(-1.3, 1.0)
		Pr >  t			0.7367
	Week 16	n	17	9	
		LS Mean	-0.024	0.984	-1.008
		SEM	0.504	0.636	0.650
		95% CI	(-1.0, 1.0)	(-0.3, 2.3)	(-2.3, 0.3)
		Pr >  t			0.1260
	Week 24	n	9	5	
		LS Mean	0.442	1.419	-0.978
		SEM	0.559	0.719	0.782
		95% CI	(-0.7, 1.6)	(-0.0, 2.9)	(-2.5, 0.6)
		Pr >  t			0.2142
	Week 32	n	8	4	
		LS Mean	-0.560	-0.053	-0.507
		SEM	0.574	0.760	0.831
		95% CI	(-1.7, 0.6)	(-1.6, 1.5)	(-2.2, 1.1)
		Pr >  t			0.5432
Week 40	n	5	4		
	LS Mean	-0.079	-0.376	0.296	
	SEM	0.638	0.760	0.882	
	95% CI	(-1.3, 1.2)	(-1.9, 1.1)	(-1.5, 2.0)	
	Pr >  t			0.7374	
Week 48	n	5	3		
	LS Mean	0.863	-0.651	1.514	
	SEM	0.638	0.818	0.932	
	95% CI	(-0.4, 2.1)	(-2.3, 1.0)	(-0.3, 3.4)	
	Pr >  t			0.1072	
Week 56	n	4	3		
	LS Mean	0.265	-0.411	0.676	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.676	0.818	0.961
	95% CI	(-1.1, 1.6)	(-2.0, 1.2)	(-1.2, 2.6)
	Pr >  t			0.4829
	n	4	3	
	LS Mean	0.405	-0.271	0.676
Week 72	SEM	0.676	0.818	0.961
	95% CI	(-0.9, 1.7)	(-1.9, 1.4)	(-1.2, 2.6)
	Pr >  t			0.4829
	n	4	3	
	LS Mean	0.655	0.446	0.210
Week 84	SEM	0.676	0.818	0.961
	95% CI	(-0.7, 2.0)	(-1.2, 2.1)	(-1.7, 2.1)
	Pr >  t			0.8276
	n	2	3	
	LS Mean	0.152	-0.174	0.327
Week 96	SEM	0.853	0.818	1.085
	95% CI	(-1.5, 1.8)	(-1.8, 1.4)	(-1.8, 2.5)
	Pr >  t			0.7639
	n	1	3	
	LS Mean	0.138	0.446	-0.307
Week 108	SEM	1.104	0.818	1.305
	95% CI	(-2.1, 2.3)	(-1.2, 2.1)	(-2.9, 2.3)
	Pr >  t			0.8143
	n		2	
	LS Mean		0.258	
Week 120	SEM		0.916	
	95% CI		(-1.6, 2.1)	
	Pr >  t			
	n	1	1	
	LS Mean	0.138	-1.391	1.530
Week 132	SEM	1.104	1.158	1.542
	95% CI	(-2.1, 2.3)	(-3.7, 0.9)	(-1.5, 4.6)
	Pr >  t			0.3236
	n		1	
	LS Mean		1.179	
Week 144	SEM		1.158	
	95% CI		(-1.1, 3.5)	
	Pr >  t			
	n	1		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Secondary resistant	Week 8	LS Mean	0.138		
		SEM	1.104		
		95% CI	(-2.1, 2.3)		
		Pr >  t			
	Week 16	n	98	104	
		LS Mean	0.292	0.464	-0.172
		SEM	0.306	0.307	0.262
		95% CI	(-0.3, 0.9)	(-0.1, 1.1)	(-0.7, 0.3)
	Week 24	n	83	80	0.5132
		LS Mean	0.232	0.578	-0.346
		SEM	0.315	0.323	0.286
		95% CI	(-0.4, 0.9)	(-0.1, 1.2)	(-0.9, 0.2)
	Week 32	n	75	60	0.2279
		LS Mean	0.335	0.557	-0.222
		SEM	0.322	0.340	0.310
		95% CI	(-0.3, 1.0)	(-0.1, 1.2)	(-0.8, 0.4)
	Week 40	n	59	55	0.4730
		LS Mean	0.659	0.748	-0.089
		SEM	0.340	0.346	0.329
		95% CI	(-0.0, 1.3)	(0.1, 1.4)	(-0.7, 0.6)
Week 48	n	52	47	0.7875	
	LS Mean	0.792	0.599	0.194	
	SEM	0.347	0.357	0.347	
	95% CI	(0.1, 1.5)	(-0.1, 1.3)	(-0.5, 0.9)	
Week 56	n	47	36	0.5767	
	LS Mean	1.270	1.016	0.254	
	SEM	0.354	0.377	0.374	
	95% CI	(0.6, 2.0)	(0.3, 1.8)	(-0.5, 1.0)	
	n	41	31	0.4963	
	LS Mean	0.438	0.781	-0.343	
	SEM	0.363	0.390	0.396	
	95% CI	(-0.3, 1.2)	(0.0, 1.5)	(-1.1, 0.4)	
				0.3863	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference
		N=169	Placebo qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n	32	28	
	LS Mean	0.482	1.015	-0.533
	SEM	0.383	0.400	0.423
	95% CI	(-0.3, 1.2)	( 0.2, 1.8)	(-1.4, 0.3)
	Pr >  t			0.2072
Week 72	n	29	22	
	LS Mean	0.380	0.406	-0.026
	SEM	0.392	0.425	0.455
	95% CI	(-0.4, 1.2)	(-0.4, 1.2)	(-0.9, 0.9)
	Pr >  t			0.9542
Week 84	n	26	21	
	LS Mean	0.676	0.626	0.050
	SEM	0.403	0.430	0.469
	95% CI	(-0.1, 1.5)	(-0.2, 1.5)	(-0.9, 1.0)
	Pr >  t			0.9151
Week 96	n	23	14	
	LS Mean	0.583	0.999	-0.416
	SEM	0.416	0.485	0.530
	95% CI	(-0.2, 1.4)	( 0.0, 2.0)	(-1.5, 0.6)
	Pr >  t			0.4319
Week 108	n	18	13	
	LS Mean	1.056	0.149	0.906
	SEM	0.445	0.497	0.564
	95% CI	( 0.2, 1.9)	(-0.8, 1.1)	(-0.2, 2.0)
	Pr >  t			0.1081
Week 120	n	19	10	
	LS Mean	1.015	0.469	0.546
	SEM	0.439	0.544	0.600
	95% CI	( 0.2, 1.9)	(-0.6, 1.5)	(-0.6, 1.7)
	Pr >  t			0.3629
Week 132	n	13	4	
	LS Mean	0.681	1.115	-0.434
	SEM	0.493	0.780	0.850
	95% CI	(-0.3, 1.6)	(-0.4, 2.6)	(-2.1, 1.2)
	Pr >  t			0.6095
Week 144	n	8	1	
	LS Mean	0.972	1.055	-0.082
	SEM	0.586	1.473	1.544
	95% CI	(-0.2, 2.1)	(-1.8, 3.9)	(-3.1, 2.9)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Sensitive	Week 156	Pr >  t			0.9575
		n	4	1	
		LS Mean	0.414	2.765	-2.351
		SEM	0.776	1.473	1.626
		95% CI	(-1.1, 1.9)	(-0.1, 5.7)	(-5.5, 0.8)
	Week 168	Pr >  t			0.1485
		n	3	1	
		LS Mean	-0.493	0.335	-0.828
		SEM	0.880	1.473	1.678
		95% CI	(-2.2, 1.2)	(-2.6, 3.2)	(-4.1, 2.5)
	Week 180	Pr >  t			0.6218
		n	1	1	
		LS Mean	2.822	0.905	1.917
		SEM	1.466	1.473	2.047
		95% CI	(-0.1, 5.7)	(-2.0, 3.8)	(-2.1, 5.9)
	Week 192	Pr >  t			0.3493
		n	1	1	
		LS Mean	0.672	0.195	0.477
		SEM	1.466	1.473	2.047
		95% CI	(-2.2, 3.5)	(-2.7, 3.1)	(-3.5, 4.5)
Week 8	Pr >  t			0.8158	
	n	17	16		
	LS Mean	-0.877	-1.038	0.161	
	SEM	0.456	0.471	0.646	
	95% CI	(-1.8, 0.0)	(-2.0, -0.1)	(-1.1, 1.4)	
Week 16	Pr >  t			0.8040	
	n	18	14		
	LS Mean	-0.529	-1.623	1.093	
	SEM	0.447	0.494	0.659	
	95% CI	(-1.4, 0.4)	(-2.6, -0.6)	(-0.2, 2.4)	
Week 24	Pr >  t			0.1005	
	n	16	13		
	LS Mean	-0.465	-0.748	0.283	
	SEM	0.467	0.506	0.681	
	95% CI	(-1.4, 0.5)	(-1.8, 0.3)	(-1.1, 1.6)	
Week 32	Pr >  t			0.6792	
	n	15	13		
	LS Mean	-0.523	-1.368	0.845	
		SEM	0.476	0.507	0.689

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	95% CI	(-1.5, 0.4)	(-2.4,-0.4)	(-0.5, 2.2)	
	Pr >  t			0.2226	
	n	14	10		
	LS Mean	-0.631	-0.426	-0.205	
	SEM	0.488	0.551	0.730	
Week 48	95% CI	(-1.6, 0.3)	(-1.5, 0.7)	(-1.6, 1.2)	
	Pr >  t			0.7789	
	n	14	11		
	LS Mean	-0.774	-1.300	0.526	
	SEM	0.488	0.535	0.718	
Week 56	95% CI	(-1.7, 0.2)	(-2.4,-0.2)	(-0.9, 1.9)	
	Pr >  t			0.4647	
	n	11	11		
	LS Mean	-0.755	-1.561	0.806	
	SEM	0.525	0.535	0.744	
Week 64	95% CI	(-1.8, 0.3)	(-2.6,-0.5)	(-0.7, 2.3)	
	Pr >  t			0.2804	
	n	8	11		
	LS Mean	-0.332	-1.314	0.981	
	SEM	0.582	0.535	0.786	
Week 72	95% CI	(-1.5, 0.8)	(-2.4,-0.3)	(-0.6, 2.5)	
	Pr >  t			0.2137	
	n	11	10		
	LS Mean	-0.455	-1.094	0.638	
	SEM	0.525	0.551	0.755	
Week 84	95% CI	(-1.5, 0.6)	(-2.2,-0.0)	(-0.9, 2.1)	
	Pr >  t			0.3994	
	n	9	9		
	LS Mean	0.250	0.334	-0.084	
	SEM	0.560	0.570	0.794	
Week 96	95% CI	(-0.9, 1.4)	(-0.8, 1.5)	(-1.7, 1.5)	
	Pr >  t			0.9157	
	n	8	7		
	LS Mean	-0.334	-1.841	1.506	
	SEM	0.583	0.620	0.846	
Week 108	95% CI	(-1.5, 0.8)	(-3.1,-0.6)	(-0.2, 3.2)	
	Pr >  t			0.0767	
	LS Mean	-0.483	-0.825	0.343	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	SEM	0.610	0.655	0.891
	95% CI	(-1.7, 0.7)	(-2.1, 0.5)	(-1.4, 2.1)
	Pr >  t			0.7010
	n	6	5	
	LS Mean	-0.413	-1.615	1.202
Week 132	SEM	0.646	0.702	0.949
	95% CI	(-1.7, 0.9)	(-3.0,-0.2)	(-0.7, 3.1)
	Pr >  t			0.2065
	n	5	3	
	LS Mean	-0.845	-1.188	0.343
Week 144	SEM	0.692	0.857	1.097
	95% CI	(-2.2, 0.5)	(-2.9, 0.5)	(-1.8, 2.5)
	Pr >  t			0.7546
	n	5	4	
	LS Mean	-0.187	-1.694	1.507
Week 156	SEM	0.692	0.764	1.026
	95% CI	(-1.5, 1.2)	(-3.2,-0.2)	(-0.5, 3.5)
	Pr >  t			0.1431
	n	4	2	
	LS Mean	-0.759	-1.526	0.767
Week 168	SEM	0.754	1.019	1.265
	95% CI	(-2.2, 0.7)	(-3.5, 0.5)	(-1.7, 3.3)
	Pr >  t			0.5449
	n	1	1	
	LS Mean	-0.635	-1.505	0.869
	SEM	1.391	1.397	1.970
	95% CI	(-3.4, 2.1)	(-4.3, 1.2)	(-3.0, 4.7)
	Pr >  t			0.6593

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	71	
			LS Mean	-0.632	-0.335	-0.297
		SEM	0.756	0.779	0.304	
		95% CI	(-2.1, 0.9)	(-1.9, 1.2)	(-0.9, 0.3)	
		Pr >  t			0.3285	
		Week 16	n	69	54	
			LS Mean	-0.525	-0.375	-0.149
			SEM	0.757	0.787	0.327
			95% CI	(-2.0, 1.0)	(-1.9, 1.2)	(-0.8, 0.5)
		Week 24	n	54	46	
			LS Mean	-0.637	-0.147	-0.490
			SEM	0.761	0.792	0.352
			95% CI	(-2.1, 0.9)	(-1.7, 1.4)	(-1.2, 0.2)
		Week 32	n	49	41	
			LS Mean	-0.257	-0.125	-0.132
			SEM	0.771	0.796	0.366
			95% CI	(-1.8, 1.3)	(-1.7, 1.4)	(-0.9, 0.6)
		Week 40	n	40	33	
			LS Mean	-0.266	-0.318	0.052
			SEM	0.778	0.803	0.396
			95% CI	(-1.8, 1.3)	(-1.9, 1.3)	(-0.7, 0.8)
		Week 48	n	38	28	
			LS Mean	-0.013	-0.384	0.371
			SEM	0.779	0.811	0.413
95% CI	(-1.6, 1.5)		(-2.0, 1.2)	(-0.4, 1.2)		
Week 56	n	32	28			
	LS Mean	-0.640	-0.449	-0.192		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.786	0.811	0.426	
	95% CI	(-2.2, 0.9)	(-2.0, 1.2)	(-1.0, 0.6)	
	Pr >  t			0.6528	
	n	23	26		
	LS Mean	-0.250	-0.201	-0.049	
Week 72	SEM	0.802	0.814	0.460	
	95% CI	(-1.8, 1.3)	(-1.8, 1.4)	(-1.0, 0.9)	
	Pr >  t			0.9159	
	n	27	25		
	LS Mean	-0.657	-0.434	-0.223	
Week 84	SEM	0.794	0.816	0.449	
	95% CI	(-2.2, 0.9)	(-2.0, 1.2)	(-1.1, 0.7)	
	Pr >  t			0.6192	
	n	23	22		
	LS Mean	-0.345	0.242	-0.586	
Week 96	SEM	0.801	0.822	0.475	
	95% CI	(-1.9, 1.2)	(-1.4, 1.9)	(-1.5, 0.3)	
	Pr >  t			0.2170	
	n	20	16		
	LS Mean	-0.425	-0.468	0.043	
Week 108	SEM	0.810	0.843	0.521	
	95% CI	(-2.0, 1.2)	(-2.1, 1.2)	(-1.0, 1.1)	
	Pr >  t			0.9335	
	n	20	14		
	LS Mean	-0.362	-0.217	-0.144	
Week 120	SEM	0.810	0.853	0.538	
	95% CI	(-2.0, 1.2)	(-1.9, 1.5)	(-1.2, 0.9)	
	Pr >  t			0.7888	
	n	17	11		
	LS Mean	-0.534	-0.712	0.178	
Week 132	SEM	0.820	0.875	0.587	
	95% CI	(-2.2, 1.1)	(-2.4, 1.0)	(-1.0, 1.3)	
	Pr >  t			0.7620	
	n	13	6		
	LS Mean	-0.722	0.207	-0.930	
Week 144	SEM	0.842	0.955	0.726	
	95% CI	(-2.4, 0.9)	(-1.7, 2.1)	(-2.4, 0.5)	
	Pr >  t			0.2005	
	n	10	5		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Second Line	Week 156	LS Mean	0.136	-0.715	0.851
		SEM	0.868	0.989	0.798
		95% CI	(-1.6, 1.8)	(-2.7, 1.2)	(-0.7, 2.4)
		Pr >  t			0.2866
		n	6	3	
	Week 168	LS Mean	-0.946	0.123	-1.070
		SEM	0.939	1.111	1.011
		95% CI	(-2.8, 0.9)	(-2.1, 2.3)	(-3.1, 0.9)
		Pr >  t			0.2902
		n	3	2	
	Week 180	LS Mean	-1.219	-0.675	-0.544
		SEM	1.097	1.247	1.290
		95% CI	(-3.4, 0.9)	(-3.1, 1.8)	(-3.1, 2.0)
		Pr >  t			0.6731
		n		1	
	Week 192	LS Mean		-0.164	
		SEM		1.586	
		95% CI		(-3.3, 2.9)	
		Pr >  t			
		n		1	
	Week 8	LS Mean		-0.874	
		SEM		1.586	
		95% CI		(-4.0, 2.2)	
		Pr >  t			
n		66	66		
Week 16	LS Mean	0.315	0.210	0.105	
	SEM	0.293	0.295	0.321	
	95% CI	(-0.3, 0.9)	(-0.4, 0.8)	(-0.5, 0.7)	
	Pr >  t			0.7442	
	n	54	51		
Week 24	LS Mean	0.244	0.535	-0.291	
	SEM	0.309	0.319	0.351	
	95% CI	(-0.4, 0.9)	(-0.1, 1.2)	(-1.0, 0.4)	
	Pr >  t			0.4084	
	n	49	33		
	LS Mean	0.591	0.555	0.036	
	SEM	0.318	0.355	0.390	
	95% CI	(-0.0, 1.2)	(-0.1, 1.3)	(-0.7, 0.8)	
	Pr >  t			0.9262	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	36	31	
	LS Mean	0.423	0.396	0.027
	SEM	0.344	0.363	0.415
	95% CI	(-0.3, 1.1)	(-0.3, 1.1)	(-0.8, 0.8)
	Pr >  t			0.9491
Week 40	n	33	28	
	LS Mean	0.580	0.676	-0.096
	SEM	0.351	0.375	0.430
	95% CI	(-0.1, 1.3)	(-0.1, 1.4)	(-0.9, 0.7)
	Pr >  t			0.8237
Week 48	n	29	22	
	LS Mean	1.225	1.055	0.170
	SEM	0.362	0.400	0.461
	95% CI	( 0.5, 1.9)	( 0.3, 1.8)	(-0.7, 1.1)
	Pr >  t			0.7131
Week 56	n	25	17	
	LS Mean	0.513	0.648	-0.135
	SEM	0.376	0.431	0.500
	95% CI	(-0.2, 1.3)	(-0.2, 1.5)	(-1.1, 0.8)
	Pr >  t			0.7870
Week 64	n	22	16	
	LS Mean	0.491	0.809	-0.318
	SEM	0.390	0.439	0.517
	95% CI	(-0.3, 1.3)	(-0.1, 1.7)	(-1.3, 0.7)
	Pr >  t			0.5392
Week 72	n	20	10	
	LS Mean	0.842	0.469	0.373
	SEM	0.401	0.514	0.590
	95% CI	( 0.1, 1.6)	(-0.5, 1.5)	(-0.8, 1.5)
	Pr >  t			0.5273
Week 84	n	16	11	
	LS Mean	1.172	0.520	0.652
	SEM	0.430	0.497	0.595
	95% CI	( 0.3, 2.0)	(-0.5, 1.5)	(-0.5, 1.8)
	Pr >  t			0.2735
Week 96	n	15	8	
	LS Mean	0.718	0.983	-0.265
	SEM	0.439	0.558	0.653
	95% CI	(-0.1, 1.6)	(-0.1, 2.1)	(-1.5, 1.0)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		Pr >  t			0.6852
	Week 108	n	6	7	
		LS Mean	1.864	-0.278	2.142
		SEM	0.616	0.587	0.803
		95% CI	( 0.7, 3.1)	( -1.4, 0.9)	( 0.6, 3.7)
		Pr >  t			0.0078
	Week 120	n	11	5	
		LS Mean	1.600	0.253	1.347
		SEM	0.489	0.672	0.782
		95% CI	( 0.6, 2.6)	( -1.1, 1.6)	( -0.2, 2.9)
		Pr >  t			0.0856
	Week 132	n	7	2	
		LS Mean	1.155	0.374	0.781
		SEM	0.579	1.003	1.123
		95% CI	( 0.0, 2.3)	( -1.6, 2.3)	( -1.4, 3.0)
		Pr >  t			0.4872
	Week 144	n	5		
		LS Mean	0.439		
		SEM	0.662		
		95% CI	( -0.9, 1.7)		
		Pr >  t			
	Week 156	n	3		
		LS Mean	1.160		
		SEM	0.828		
		95% CI	( -0.5, 2.8)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-0.355		
		SEM	1.383		
		95% CI	( -3.1, 2.4)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	2.935		
		SEM	1.383		
		95% CI	( 0.2, 5.7)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	0.785		
		SEM	1.383		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-1.9, 3.5)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	65		
			LS Mean	0.126	0.459	-0.333	
			SEM	0.423	0.415	0.316	
			95% CI	(-0.7, 1.0)	(-0.4, 1.3)	(-1.0, 0.3)	
					Pr >  t	0.2938	
		Week 16	n	60	51		
			LS Mean	-0.004	0.571	-0.575	
			SEM	0.430	0.434	0.335	
			95% CI	(-0.9, 0.8)	(-0.3, 1.4)	(-1.2, 0.1)	
					Pr >  t	0.0869	
		Week 24	n	51	42		
			LS Mean	0.158	0.831	-0.673	
			SEM	0.436	0.443	0.355	
			95% CI	(-0.7, 1.0)	(-0.0, 1.7)	(-1.4, 0.0)	
					Pr >  t	0.0590	
		Week 32	n	46	36		
			LS Mean	0.237	0.749	-0.511	
			SEM	0.443	0.454	0.371	
			95% CI	(-0.6, 1.1)	(-0.1, 1.6)	(-1.2, 0.2)	
					Pr >  t	0.1688	
		Week 40	n	40	33		
			LS Mean	0.511	0.672	-0.162	
			SEM	0.450	0.459	0.384	
			95% CI	(-0.4, 1.4)	(-0.2, 1.6)	(-0.9, 0.6)	
			Pr >  t	0.6744			
Week 48	n	37	28				
	LS Mean	0.663	0.947	-0.284			
	SEM	0.454	0.469	0.400			
	95% CI	(-0.2, 1.6)	( 0.0, 1.9)	(-1.1, 0.5)			
			Pr >  t	0.4781			
Week 56	n	33	23				
	LS Mean	0.225	0.640	-0.415			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.460	0.483	0.423
		95% CI	(-0.7, 1.1)	(-0.3, 1.6)	(-1.2, 0.4)
		Pr >  t			0.3274
	Week 64	n	26	20	
		LS Mean	0.225	0.393	-0.168
		SEM	0.474	0.494	0.450
		95% CI	(-0.7, 1.2)	(-0.6, 1.4)	(-1.1, 0.7)
		Pr >  t			0.7084
	Week 72	n	28	17	
		LS Mean	0.197	0.529	-0.332
		SEM	0.469	0.507	0.461
		95% CI	(-0.7, 1.1)	(-0.5, 1.5)	(-1.2, 0.6)
		Pr >  t			0.4710
	Week 84	n	23	17	
		LS Mean	0.321	0.591	-0.271
		SEM	0.482	0.508	0.474
		95% CI	(-0.6, 1.3)	(-0.4, 1.6)	(-1.2, 0.7)
		Pr >  t			0.5681
	Week 96	n	23	11	
		LS Mean	0.336	0.716	-0.380
		SEM	0.482	0.556	0.525
		95% CI	(-0.6, 1.3)	(-0.4, 1.8)	(-1.4, 0.7)
		Pr >  t			0.4698
	Week 108	n	15	13	
		LS Mean	0.762	0.674	0.088
		SEM	0.519	0.536	0.539
		95% CI	(-0.3, 1.8)	(-0.4, 1.7)	(-1.0, 1.1)
		Pr >  t			0.8697
	Week 120	n	16	9	
		LS Mean	0.955	0.472	0.483
		SEM	0.513	0.584	0.582
		95% CI	(-0.1, 2.0)	(-0.7, 1.6)	(-0.7, 1.6)
		Pr >  t			0.4065
	Week 132	n	14	5	
		LS Mean	0.714	1.269	-0.555
		SEM	0.526	0.692	0.700
		95% CI	(-0.3, 1.7)	(-0.1, 2.6)	(-1.9, 0.8)
		Pr >  t			0.4287
	Week 144	n	8	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Neoadjuvant	Week 156	LS Mean	0.194	0.660	-0.466
		SEM	0.600	0.829	0.884
		95% CI	(-1.0, 1.4)	(-1.0, 2.3)	(-2.2, 1.3)
		Pr >  t			0.5985
		n	7	2	
	Week 168	LS Mean	0.232	1.456	-1.224
		SEM	0.623	0.973	1.034
		95% CI	(-1.0, 1.5)	(-0.5, 3.4)	(-3.3, 0.8)
		Pr >  t			0.2370
		n	4	2	
	Week 180	LS Mean	-0.474	0.311	-0.785
		SEM	0.745	0.973	1.112
		95% CI	(-1.9, 1.0)	(-1.6, 2.2)	(-3.0, 1.4)
		Pr >  t			0.4805
		n	1	1	
	Week 192	LS Mean	2.591	0.829	1.762
		SEM	1.310	1.311	1.781
		95% CI	( 0.0, 5.2)	(-1.7, 3.4)	(-1.7, 5.3)
		Pr >  t			0.3228
		n	1	1	
	Week 8	LS Mean	0.441	0.119	0.322
		SEM	1.310	1.311	1.781
		95% CI	(-2.1, 3.0)	(-2.5, 2.7)	(-3.2, 3.8)
		Pr >  t			0.8566
n		18	17		
Week 16	LS Mean	0.477	0.670	-0.193	
	SEM	0.437	0.456	0.633	
	95% CI	(-0.4, 1.3)	(-0.2, 1.6)	(-1.5, 1.1)	
	Pr >  t			0.7619	
	n	17	11		
Week 24	LS Mean	0.566	0.349	0.217	
	SEM	0.445	0.544	0.703	
	95% CI	(-0.3, 1.5)	(-0.7, 1.4)	(-1.2, 1.6)	
	Pr >  t			0.7589	
	n	15	5		
	LS Mean	0.664	0.117	0.547	
	SEM	0.466	0.748	0.881	
	95% CI	(-0.3, 1.6)	(-1.4, 1.6)	(-1.2, 2.3)	
	Pr >  t			0.5358	

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32		n	13	5	
		LS Mean	0.769	0.089	0.681
		SEM	0.492	0.748	0.896
		95% CI	(-0.2, 1.7)	(-1.4, 1.6)	(-1.1, 2.5)
		Pr >  t			0.4487
Week 40		n	11	5	
		LS Mean	0.244	-0.169	0.413
		SEM	0.521	0.748	0.912
		95% CI	(-0.8, 1.3)	(-1.6, 1.3)	(-1.4, 2.2)
		Pr >  t			0.6511
Week 48		n	11	2	
		LS Mean	1.947	-0.307	2.253
		SEM	0.521	1.081	1.201
		95% CI	( 0.9, 3.0)	(-2.4, 1.8)	(-0.1, 4.6)
		Pr >  t			0.0623
Week 56		n	8	2	
		LS Mean	0.683	-0.307	0.990
		SEM	0.582	1.081	1.228
		95% CI	(-0.5, 1.8)	(-2.4, 1.8)	(-1.4, 3.4)
		Pr >  t			0.4214
Week 64		n	7	3	
		LS Mean	0.636	0.110	0.526
		SEM	0.612	0.916	1.102
		95% CI	(-0.6, 1.8)	(-1.7, 1.9)	(-1.6, 2.7)
		Pr >  t			0.6336
Week 72		n	7	3	
		LS Mean	0.254	-0.320	0.574
		SEM	0.613	0.916	1.102
		95% CI	(-1.0, 1.5)	(-2.1, 1.5)	(-1.6, 2.8)
		Pr >  t			0.6034
Week 84		n	7	2	
		LS Mean	1.315	0.048	1.267
		SEM	0.613	1.081	1.243
		95% CI	( 0.1, 2.5)	(-2.1, 2.2)	(-1.2, 3.7)
		Pr >  t			0.3096
Week 96		n	6	3	
		LS Mean	0.468	0.013	0.455
		SEM	0.650	0.916	1.123
		95% CI	(-0.8, 1.8)	(-1.8, 1.8)	(-1.8, 2.7)

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 108	Pr >  t			0.6862
		n	7	2	
		LS Mean	0.968	0.088	0.880
		SEM	0.613	1.079	1.241
		95% CI	(-0.2, 2.2)	(-2.0, 2.2)	(-1.6, 3.3)
		Pr >  t			0.4793
	Week 120	n	6	1	
		LS Mean	0.468	-0.346	0.814
		SEM	0.650	1.469	1.606
		95% CI	(-0.8, 1.8)	(-3.2, 2.6)	(-2.4, 4.0)
		Pr >  t			0.6127
	Week 132	n	4		
		LS Mean	0.226		
		SEM	0.763		
		95% CI	(-1.3, 1.7)		
		Pr >  t			
	Week 144	n	5		
		LS Mean	1.947		
		SEM	0.697		
		95% CI	( 0.6, 3.3)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	0.202		
		SEM	1.028		
		95% CI	(-1.8, 2.2)		
		Pr >  t			
No Prior Use	Week 8	n	59	55	
		LS Mean	-0.173	-0.348	0.174
		SEM	0.337	0.357	0.371
		95% CI	(-0.8, 0.5)	(-1.1, 0.4)	(-0.6, 0.9)
		Pr >  t			0.6391
	Week 16	n	47	42	
		LS Mean	0.037	-0.073	0.111
		SEM	0.357	0.384	0.413
		95% CI	(-0.7, 0.7)	(-0.8, 0.7)	(-0.7, 0.9)
		Pr >  t			0.7892
	Week 24	n	39	32	
		LS Mean	0.053	-0.086	0.139
		SEM	0.376	0.416	0.456



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169			Placebo qd + Fulv N=172			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv						
		95% CI	Pr >  t	n	LS Mean	SEM	95% CI	Pr >  t	n	LS Mean	SEM	95% CI	Pr >  t	
		(-0.7, 0.8)					(-0.9, 0.7)						(-0.8, 1.0)	0.7604
	Week 32			27	0.264	0.421	-0.089	0.420	31	0.353	0.493			
		(-0.6, 1.1)					(-0.9, 0.7)						(-0.6, 1.3)	0.4745
	Week 40			24	0.412	0.435	0.129	0.457	23	0.283	0.535			
		(-0.4, 1.3)					(-0.8, 1.0)						(-0.8, 1.3)	0.5977
	Week 48			21	0.442	0.453	0.032	0.476	20	0.409	0.566			
		(-0.4, 1.3)					(-0.9, 1.0)						(-0.7, 1.5)	0.4701
	Week 56			18	-0.132	0.474	-0.128	0.476	20	-0.004	0.585			
		(-1.1, 0.8)					(-1.1, 0.8)						(-1.2, 1.1)	0.9950
	Week 64			14	0.278	0.515	0.558	0.484	19	-0.280	0.625			
		(-0.7, 1.3)					(-0.4, 1.5)						(-1.5, 0.9)	0.6545
	Week 72			13	0.541	0.529	-0.118	0.520	15	0.659	0.665			
		(-0.5, 1.6)					(-1.1, 0.9)						(-0.6, 2.0)	0.3221
	Week 84			10	0.730	0.586	0.846	0.532	14	-0.117	0.716			
		(-0.4, 1.9)					(-0.2, 1.9)						(-1.5, 1.3)	0.8705
	Week 96			6	0.462		-0.061		10	0.524				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		SEM	0.714	0.596	0.870
		95% CI	(-0.9, 1.9)	(-1.2, 1.1)	(-1.2, 2.2)
		Pr >  t			0.5475
	Week 108	n	4	6	
		LS Mean	0.165	-0.900	1.064
		SEM	0.852	0.725	1.067
		95% CI	(-1.5, 1.8)	(-2.3, 0.5)	(-1.0, 3.2)
		Pr >  t			0.3188
	Week 120	n	6	6	
		LS Mean	0.123	-0.761	0.884
		SEM	0.714	0.725	0.963
		95% CI	(-1.3, 1.5)	(-2.2, 0.7)	(-1.0, 2.8)
		Pr >  t			0.3589
	Week 132	n	2	3	
		LS Mean	-1.901	-0.203	-1.698
		SEM	1.163	0.971	1.477
		95% CI	(-4.2, 0.4)	(-2.1, 1.7)	(-4.6, 1.2)
		Pr >  t			0.2508
	Week 144	n	2	2	
		LS Mean	-0.278	-1.255	0.976
		SEM	1.158	1.168	1.615
		95% CI	(-2.6, 2.0)	(-3.5, 1.0)	(-2.2, 4.1)
		Pr >  t			0.5458
	Week 156	n		1	
		LS Mean		-0.499	
		SEM		1.614	
		95% CI		(-3.7, 2.7)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	55	
		LS Mean	-0.159	0.338	-0.496
		SEM	0.710	0.743	0.333
		95% CI	(-1.6, 1.2)	(-1.1, 1.8)	(-1.2, 0.2)
		Pr >  t			0.1373
	Week 16	n	51	40	
		LS Mean	-0.119	0.488	-0.607
		SEM	0.713	0.756	0.366
		95% CI	(-1.5, 1.3)	(-1.0, 2.0)	(-1.3, 0.1)
		Pr >  t			0.0983
	Week 24	n	38	33	
		LS Mean	-0.331	0.463	-0.794
		SEM	0.719	0.763	0.404
		95% CI	(-1.8, 1.1)	(-1.0, 2.0)	(-1.6,-0.0)
		Pr >  t			0.0497
	Week 32	n	34	28	
		LS Mean	0.244	0.760	-0.516
		SEM	0.735	0.770	0.426
		95% CI	(-1.2, 1.7)	(-0.8, 2.3)	(-1.4, 0.3)
		Pr >  t			0.2268
Week 40	n	26	23		
	LS Mean	0.308	0.052	0.257	
	SEM	0.749	0.780	0.466	
	95% CI	(-1.2, 1.8)	(-1.5, 1.6)	(-0.7, 1.2)	
	Pr >  t			0.5822	
Week 48	n	24	17		
	LS Mean	0.806	0.379	0.427	
	SEM	0.753	0.801	0.507	
	95% CI	(-0.7, 2.3)	(-1.2, 2.0)	(-0.6, 1.4)	
	Pr >  t			0.4006	
Week 56	n	21	17		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	-0.208	0.438	-0.646
		SEM	0.762	0.802	0.520
		95% CI	(-1.7, 1.3)	(-1.1, 2.0)	(-1.7, 0.4)
		Pr >  t			0.2143
	Week 64	n	15	15	
		LS Mean	0.155	0.697	-0.542
		SEM	0.787	0.811	0.570
		95% CI	(-1.4, 1.7)	(-0.9, 2.3)	(-1.7, 0.6)
		Pr >  t			0.3424
	Week 72	n	16	15	
		LS Mean	-0.466	0.141	-0.607
		SEM	0.782	0.811	0.563
		95% CI	(-2.0, 1.1)	(-1.5, 1.7)	(-1.7, 0.5)
		Pr >  t			0.2812
	Week 84	n	14	13	
		LS Mean	-0.390	0.301	-0.691
		SEM	0.793	0.824	0.597
		95% CI	(-2.0, 1.2)	(-1.3, 1.9)	(-1.9, 0.5)
		Pr >  t			0.2477
	Week 96	n	12	9	
		LS Mean	-0.159	0.668	-0.827
		SEM	0.808	0.864	0.670
		95% CI	(-1.8, 1.4)	(-1.0, 2.4)	(-2.1, 0.5)
		Pr >  t			0.2179
	Week 108	n	13	8	
		LS Mean	0.045	0.338	-0.293
		SEM	0.800	0.880	0.682
		95% CI	(-1.5, 1.6)	(-1.4, 2.1)	(-1.6, 1.0)
		Pr >  t			0.6674
	Week 120	n	11	6	
		LS Mean	-0.266	0.104	-0.370
		SEM	0.818	0.926	0.759
		95% CI	(-1.9, 1.3)	(-1.7, 1.9)	(-1.9, 1.1)
		Pr >  t			0.6260
	Week 132	n	8	3	
		LS Mean	-0.326	1.550	-1.876
		SEM	0.858	1.092	0.989
		95% CI	(-2.0, 1.4)	(-0.6, 3.7)	(-3.8, 0.1)
		Pr >  t			0.0582

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		N=169	N=172		
First Line Endocrine Sensitive	Week 144	n	5	1	
		LS Mean	0.754	0.837	-0.083
		SEM	0.940	1.587	1.567
		95% CI	(-1.1, 2.6)	(-2.3, 4.0)	(-3.2, 3.0)
		Pr >  t			0.9576
	Week 156	n	2	1	
		LS Mean	-1.194	2.547	-3.741
		SEM	1.218	1.587	1.746
		95% CI	(-3.6, 1.2)	(-0.6, 5.7)	(-7.2,-0.3)
		Pr >  t			0.0326
	Week 168	n	2	1	
		LS Mean	-1.194	0.117	-1.311
		SEM	1.218	1.587	1.746
		95% CI	(-3.6, 1.2)	(-3.0, 3.2)	(-4.7, 2.1)
		Pr >  t			0.4530
	Week 180	n		1	
		LS Mean		0.687	
		SEM		1.587	
		95% CI		(-2.4, 3.8)	
		Pr >  t			
Week 192	n		1		
	LS Mean		-0.023		
	SEM		1.587		
	95% CI		(-3.1, 3.1)		
	Pr >  t				
Week 8	n	17	16		
	LS Mean	-0.877	-1.038	0.161	
	SEM	0.456	0.471	0.646	
	95% CI	(-1.8, 0.0)	(-2.0,-0.1)	(-1.1, 1.4)	
	Pr >  t			0.8040	
Week 16	n	18	14		
	LS Mean	-0.529	-1.623	1.093	
	SEM	0.447	0.494	0.659	
	95% CI	(-1.4, 0.4)	(-2.6,-0.6)	(-0.2, 2.4)	
	Pr >  t			0.1005	
Week 24	n	16	13		
	LS Mean	-0.465	-0.748	0.283	
	SEM	0.467	0.506	0.681	
	95% CI	(-1.4, 0.5)	(-1.8, 0.3)	(-1.1, 1.6)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		Pr >  t			0.6792
	Week 32	n	15	13	
		LS Mean	-0.523	-1.368	0.845
		SEM	0.476	0.507	0.689
		95% CI	(-1.5, 0.4)	(-2.4,-0.4)	(-0.5, 2.2)
		Pr >  t			0.2226
	Week 40	n	14	10	
		LS Mean	-0.631	-0.426	-0.205
		SEM	0.488	0.551	0.730
		95% CI	(-1.6, 0.3)	(-1.5, 0.7)	(-1.6, 1.2)
		Pr >  t			0.7789
	Week 48	n	14	11	
		LS Mean	-0.774	-1.300	0.526
		SEM	0.488	0.535	0.718
		95% CI	(-1.7, 0.2)	(-2.4,-0.2)	(-0.9, 1.9)
		Pr >  t			0.4647
	Week 56	n	11	11	
		LS Mean	-0.755	-1.561	0.806
		SEM	0.525	0.535	0.744
		95% CI	(-1.8, 0.3)	(-2.6,-0.5)	(-0.7, 2.3)
		Pr >  t			0.2804
	Week 64	n	8	11	
		LS Mean	-0.332	-1.314	0.981
		SEM	0.582	0.535	0.786
		95% CI	(-1.5, 0.8)	(-2.4,-0.3)	(-0.6, 2.5)
		Pr >  t			0.2137
	Week 72	n	11	10	
		LS Mean	-0.455	-1.094	0.638
		SEM	0.525	0.551	0.755
		95% CI	(-1.5, 0.6)	(-2.2,-0.0)	(-0.9, 2.1)
		Pr >  t			0.3994
	Week 84	n	9	9	
		LS Mean	0.250	0.334	-0.084
		SEM	0.560	0.570	0.794
		95% CI	(-0.9, 1.4)	(-0.8, 1.5)	(-1.7, 1.5)
		Pr >  t			0.9157
	Week 96	n	8	7	
		LS Mean	-0.334	-1.841	1.506
		SEM	0.583	0.620	0.846

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-1.5, 0.8)	(-3.1,-0.6)	(-0.2, 3.2)
		Pr >  t			0.0767
	Week 108	n	7	6	
		LS Mean	-0.483	-0.825	0.343
		SEM	0.610	0.655	0.891
		95% CI	(-1.7, 0.7)	(-2.1, 0.5)	(-1.4, 2.1)
		Pr >  t			0.7010
	Week 120	n	6	5	
		LS Mean	-0.413	-1.615	1.202
		SEM	0.646	0.702	0.949
		95% CI	(-1.7, 0.9)	(-3.0,-0.2)	(-0.7, 3.1)
		Pr >  t			0.2065
	Week 132	n	5	3	
		LS Mean	-0.845	-1.188	0.343
		SEM	0.692	0.857	1.097
		95% CI	(-2.2, 0.5)	(-2.9, 0.5)	(-1.8, 2.5)
		Pr >  t			0.7546
	Week 144	n	5	4	
		LS Mean	-0.187	-1.694	1.507
		SEM	0.692	0.764	1.026
		95% CI	(-1.5, 1.2)	(-3.2,-0.2)	(-0.5, 3.5)
		Pr >  t			0.1431
	Week 156	n	4	2	
		LS Mean	-0.759	-1.526	0.767
		SEM	0.754	1.019	1.265
		95% CI	(-2.2, 0.7)	(-3.5, 0.5)	(-1.7, 3.3)
		Pr >  t			0.5449
	Week 168	n	1	1	
		LS Mean	-0.635	-1.505	0.869
		SEM	1.391	1.397	1.970
		95% CI	(-3.4, 2.1)	(-4.3, 1.2)	(-3.0, 4.7)
		Pr >  t			0.6593
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	0.132	0.548	-0.416
		SEM	0.469	0.435	0.540
		95% CI	(-0.8, 1.1)	(-0.3, 1.4)	(-1.5, 0.7)
		Pr >  t			0.4429
	Week 16	n	15	17	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	LS Mean	0.129	0.526	-0.397
	SEM	0.500	0.458	0.566
	95% CI	(-0.9, 1.1)	(-0.4, 1.4)	(-1.5, 0.7)
	Pr >  t			0.4850
	n	14	11	
Week 32	LS Mean	0.003	0.523	-0.520
	SEM	0.509	0.515	0.627
	95% CI	(-1.0, 1.0)	(-0.5, 1.5)	(-1.8, 0.7)
	Pr >  t			0.4086
	n	12	9	
Week 40	LS Mean	0.165	-0.096	0.262
	SEM	0.537	0.553	0.672
	95% CI	(-0.9, 1.2)	(-1.2, 1.0)	(-1.1, 1.6)
	Pr >  t			0.6978
	n	11	7	
Week 48	LS Mean	0.307	0.486	-0.179
	SEM	0.553	0.611	0.723
	95% CI	(-0.8, 1.4)	(-0.7, 1.7)	(-1.6, 1.3)
	Pr >  t			0.8048
	n	8	6	
Week 56	LS Mean	0.935	0.655	0.280
	SEM	0.603	0.645	0.791
	95% CI	(-0.3, 2.1)	(-0.6, 1.9)	(-1.3, 1.8)
	Pr >  t			0.7238
	n	7	5	
Week 64	LS Mean	0.754	0.690	0.065
	SEM	0.626	0.685	0.844
	95% CI	(-0.5, 2.0)	(-0.7, 2.0)	(-1.6, 1.7)
	Pr >  t			0.9390
	n	5	3	
Week 72	LS Mean	-0.058	1.677	-1.735
	SEM	0.696	0.829	1.011
	95% CI	(-1.4, 1.3)	( 0.0, 3.3)	(-3.7, 0.3)
	Pr >  t			0.0879
	n	5	2	
Week 72	LS Mean	0.847	0.548	0.300
	SEM	0.698	0.980	1.140
	95% CI	(-0.5, 2.2)	(-1.4, 2.5)	(-1.9, 2.5)
	Pr >  t			0.7927
	n			



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172	
Week 84	n	4	2	
	LS Mean	0.391	1.048	-0.656
	SEM	0.750	0.980	1.173
	95% CI	(-1.1, 1.9)	(-0.9, 3.0)	(-3.0, 1.7)
	Pr >  t			0.5767
Week 96	n	4	2	
	LS Mean	0.376	0.548	-0.172
	SEM	0.751	0.980	1.174
	95% CI	(-1.1, 1.9)	(-1.4, 2.5)	(-2.5, 2.1)
	Pr >  t			0.8838
Week 108	n	1	2	
	LS Mean	0.278	-1.611	1.889
	SEM	1.318	0.979	1.597
	95% CI	(-2.3, 2.9)	(-3.5, 0.3)	(-1.3, 5.0)
	Pr >  t			0.2388
Week 120	n	5	1	
	LS Mean	3.045	1.412	1.634
	SEM	0.698	1.320	1.443
	95% CI	( 1.7, 4.4)	(-1.2, 4.0)	(-1.2, 4.5)
	Pr >  t			0.2592
Week 132	n	3	1	
	LS Mean	0.000	0.552	-0.552
	SEM	0.835	1.320	1.515
	95% CI	(-1.6, 1.6)	(-2.1, 3.2)	(-3.5, 2.4)
	Pr >  t			0.7161
Week 144	n	3		
	LS Mean	0.283		
	SEM	0.835		
	95% CI	(-1.4, 1.9)		
	Pr >  t			
Week 156	n	3		
	LS Mean	0.950		
	SEM	0.835		
	95% CI	(-0.7, 2.6)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-0.504		
	SEM	1.317		
	95% CI	(-3.1, 2.1)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		N=169	N=172		
Second Line (progression following metastatic treatment only)	Week 180	Pr >  t			
		n	1		
		LS Mean	2.786		
		SEM	1.317		
	Week 192	95% CI	( 0.2, 5.4)		
		Pr >  t			
		n	1		
		LS Mean	0.636		
	Week 8	SEM	1.317		
		95% CI	( -2.0, 3.2)		
		Pr >  t			
		n	37	38	
	Week 16	LS Mean	0.446	-0.037	0.483
		SEM	0.417	0.420	0.458
		95% CI	( -0.4, 1.3)	( -0.9, 0.8)	( -0.4, 1.4)
		Pr >  t			0.2934
	Week 24	n	30	28	
		LS Mean	0.379	0.451	-0.072
		SEM	0.433	0.459	0.505
		95% CI	( -0.5, 1.2)	( -0.5, 1.4)	( -1.1, 0.9)
	Week 32	Pr >  t			0.8872
		n	26	18	
		LS Mean	1.010	0.451	0.559
		SEM	0.450	0.517	0.566
Week 40	95% CI	( 0.1, 1.9)	( -0.6, 1.5)	( -0.6, 1.7)	
	Pr >  t			0.3240	
	n	18	19		
	LS Mean	0.590	0.557	0.033	
Week 48	SEM	0.494	0.511	0.594	
	95% CI	( -0.4, 1.6)	( -0.5, 1.6)	( -1.1, 1.2)	
	Pr >  t			0.9564	
	n	18	18		
Week 8	LS Mean	0.532	0.776	-0.244	
	SEM	0.494	0.518	0.600	
	95% CI	( -0.4, 1.5)	( -0.2, 1.8)	( -1.4, 0.9)	
	Pr >  t			0.6849	
Week 8	n	16	13		
	LS Mean	1.258	1.397	-0.139	
	SEM	0.508	0.561	0.649	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	( 0.3, 2.3)	( 0.3, 2.5)	( -1.4, 1.1)
		Pr >  t			0.8308
	Week 56	n	14	10	
		LS Mean	0.209	0.454	-0.245
		SEM	0.526	0.603	0.700
		95% CI	( -0.8, 1.2)	( -0.7, 1.6)	( -1.6, 1.1)
		Pr >  t			0.7269
	Week 64	n	13	11	
		LS Mean	0.654	0.508	0.145
		SEM	0.537	0.587	0.695
		95% CI	( -0.4, 1.7)	( -0.6, 1.7)	( -1.2, 1.5)
		Pr >  t			0.8346
	Week 72	n	10	6	
		LS Mean	0.706	0.345	0.361
		SEM	0.578	0.710	0.831
		95% CI	( -0.4, 1.8)	( -1.1, 1.7)	( -1.3, 2.0)
		Pr >  t			0.6642
	Week 84	n	8	7	
		LS Mean	1.569	0.269	1.300
		SEM	0.627	0.674	0.833
		95% CI	( 0.3, 2.8)	( -1.1, 1.6)	( -0.3, 2.9)
		Pr >  t			0.1193
	Week 96	n	6	5	
		LS Mean	1.155	1.217	-0.062
		SEM	0.689	0.756	0.948
		95% CI	( -0.2, 2.5)	( -0.3, 2.7)	( -1.9, 1.8)
		Pr >  t			0.9475
	Week 108	n	2	4	
		LS Mean	2.567	0.048	2.519
		SEM	1.077	0.823	1.298
		95% CI	( 0.4, 4.7)	( -1.6, 1.7)	( -0.0, 5.1)
		Pr >  t			0.0531
	Week 120	n	4	4	
		LS Mean	-0.059	-0.094	0.035
		SEM	0.803	0.823	1.084
		95% CI	( -1.6, 1.5)	( -1.7, 1.5)	( -2.1, 2.2)
		Pr >  t			0.9746
	Week 132	n	3	1	
		LS Mean	1.364	0.124	1.239

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		SEM	0.905	1.486	1.695
		95% CI	(-0.4, 3.1)	(-2.8, 3.0)	(-2.1, 4.6)
		Pr >  t			0.4652
	Week 144	n	2		
		LS Mean	0.364		
		SEM	1.071		
		95% CI	(-1.7, 2.5)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	93			
			LS Mean	0.031	0.229	-0.199		
			SEM	0.275	0.285	0.267		
			95% CI	(-0.5, 0.6)	(-0.3, 0.8)	(-0.7, 0.3)		
					Pr >  t			0.4568
		Week 16	n	90	73			
			LS Mean	-0.035	0.257	-0.292		
			SEM	0.282	0.300	0.288		
			95% CI	(-0.6, 0.5)	(-0.3, 0.8)	(-0.9, 0.3)		
					Pr >  t			0.3109
		Week 24	n	79	60			
			LS Mean	0.094	0.304	-0.210		
			SEM	0.289	0.313	0.306		
			95% CI	(-0.5, 0.7)	(-0.3, 0.9)	(-0.8, 0.4)		
					Pr >  t			0.4918
		Week 32	n	70	55			
			LS Mean	0.244	0.415	-0.171		
			SEM	0.298	0.320	0.317		
			95% CI	(-0.3, 0.8)	(-0.2, 1.0)	(-0.8, 0.5)		
					Pr >  t			0.5896
		Week 40	n	61	45			
			LS Mean	0.351	0.320	0.031		
			SEM	0.305	0.333	0.336		
			95% CI	(-0.2, 1.0)	(-0.3, 1.0)	(-0.6, 0.7)		
					Pr >  t			0.9256
		Week 48	n	56	37			
			LS Mean	0.566	0.399	0.167		
			SEM	0.310	0.348	0.355		
95% CI	(-0.0, 1.2)		(-0.3, 1.1)	(-0.5, 0.9)				
			Pr >  t			0.6374		
Week 56	n	49	33					
	LS Mean	0.154	0.142	0.012				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.318	0.357	0.371	
	95% CI	(-0.5, 0.8)	(-0.6, 0.8)	(-0.7, 0.7)	
	Pr >  t			0.9740	
	n	37	29		
	LS Mean	0.204	0.302	-0.098	
Week 72	SEM	0.337	0.369	0.398	
	95% CI	(-0.5, 0.9)	(-0.4, 1.0)	(-0.9, 0.7)	
	Pr >  t			0.8051	
	n	40	25		
	LS Mean	0.233	0.163	0.070	
Week 84	SEM	0.331	0.383	0.406	
	95% CI	(-0.4, 0.9)	(-0.6, 0.9)	(-0.7, 0.9)	
	Pr >  t			0.8630	
	n	32	23		
	LS Mean	0.502	0.816	-0.314	
Week 96	SEM	0.349	0.391	0.429	
	95% CI	(-0.2, 1.2)	( 0.0, 1.6)	(-1.2, 0.5)	
	Pr >  t			0.4641	
	n	29	17		
	LS Mean	0.289	0.119	0.170	
Week 108	SEM	0.357	0.427	0.468	
	95% CI	(-0.4, 1.0)	(-0.7, 1.0)	(-0.7, 1.1)	
	Pr >  t			0.7161	
	n	22	15		
	LS Mean	0.667	-0.240	0.907	
Week 120	SEM	0.386	0.444	0.504	
	95% CI	(-0.1, 1.4)	(-1.1, 0.6)	(-0.1, 1.9)	
	Pr >  t			0.0725	
	n	23	13		
	LS Mean	0.536	-0.212	0.748	
Week 132	SEM	0.381	0.466	0.520	
	95% CI	(-0.2, 1.3)	(-1.1, 0.7)	(-0.3, 1.8)	
	Pr >  t			0.1502	
	n	17	5		
	LS Mean	0.283	0.773	-0.490	
Week 144	SEM	0.417	0.667	0.726	
	95% CI	(-0.5, 1.1)	(-0.5, 2.1)	(-1.9, 0.9)	
	Pr >  t			0.4994	
	n	14	3		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.576	-0.337	0.912
		SEM	0.443	0.833	0.894
		95% CI	(-0.3, 1.4)	(-2.0, 1.3)	(-0.8, 2.7)
		Pr >  t			0.3077
	Week 156	n	8	2	
		LS Mean	-0.048	1.110	-1.158
		SEM	0.544	1.000	1.097
		95% CI	(-1.1, 1.0)	(-0.9, 3.1)	(-3.3, 1.0)
		Pr >  t			0.2916
	Week 168	n	4	1	
		LS Mean	-0.577	-0.194	-0.383
		SEM	0.726	1.387	1.536
		95% CI	(-2.0, 0.8)	(-2.9, 2.5)	(-3.4, 2.6)
		Pr >  t			0.8032
	Week 180	n	1	1	
		LS Mean	2.479	0.376	2.103
		SEM	1.382	1.387	1.934
		95% CI	(-0.2, 5.2)	(-2.3, 3.1)	(-1.7, 5.9)
		Pr >  t			0.2771
	Week 192	n	1	1	
		LS Mean	0.329	-0.334	0.663
		SEM	1.382	1.387	1.934
		95% CI	(-2.4, 3.0)	(-3.1, 2.4)	(-3.1, 4.5)
		Pr >  t			0.7318
>= 3	Week 8	n	37	44	
		LS Mean	0.023	-0.114	0.137
		SEM	0.691	0.685	0.400
		95% CI	(-1.3, 1.4)	(-1.5, 1.2)	(-0.7, 0.9)
		Pr >  t			0.7329
	Week 16	n	34	32	
		LS Mean	0.258	0.238	0.020
		SEM	0.713	0.720	0.437
		95% CI	(-1.1, 1.7)	(-1.2, 1.7)	(-0.8, 0.9)
		Pr >  t			0.9636
	Week 24	n	26	19	
		LS Mean	0.275	0.651	-0.376
		SEM	0.730	0.756	0.520
		95% CI	(-1.2, 1.7)	(-0.8, 2.1)	(-1.4, 0.6)
		Pr >  t			0.4704

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	16	17	
	LS Mean	0.355	0.015	0.339
	SEM	0.770	0.767	0.588
	95% CI	(-1.2, 1.9)	(-1.5, 1.5)	(-0.8, 1.5)
	Pr >  t			0.5645
Week 40	n	14	16	
	LS Mean	0.533	0.387	0.146
	SEM	0.784	0.772	0.613
	95% CI	(-1.0, 2.1)	(-1.1, 1.9)	(-1.1, 1.4)
	Pr >  t			0.8124
Week 48	n	13	13	
	LS Mean	1.455	0.654	0.801
	SEM	0.791	0.794	0.649
	95% CI	(-0.1, 3.0)	(-0.9, 2.2)	(-0.5, 2.1)
	Pr >  t			0.2183
Week 56	n	10	12	
	LS Mean	-0.104	0.514	-0.618
	SEM	0.825	0.804	0.699
	95% CI	(-1.7, 1.5)	(-1.1, 2.1)	(-2.0, 0.8)
	Pr >  t			0.3776
Week 64	n	10	13	
	LS Mean	0.325	0.772	-0.447
	SEM	0.825	0.795	0.689
	95% CI	(-1.3, 1.9)	(-0.8, 2.3)	(-1.8, 0.9)
	Pr >  t			0.5169
Week 72	n	8	10	
	LS Mean	0.165	0.227	-0.062
	SEM	0.858	0.827	0.763
	95% CI	(-1.5, 1.9)	(-1.4, 1.9)	(-1.6, 1.4)
	Pr >  t			0.9350
Week 84	n	8	10	
	LS Mean	0.564	0.273	0.291
	SEM	0.858	0.826	0.763
	95% CI	(-1.1, 2.3)	(-1.4, 1.9)	(-1.2, 1.8)
	Pr >  t			0.7029
Week 96	n	6	7	
	LS Mean	0.265	0.831	-0.566
	SEM	0.911	0.882	0.877
	95% CI	(-1.5, 2.1)	(-0.9, 2.6)	(-2.3, 1.2)



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.5191
	Week 108	n	4	6	
		LS Mean	0.181	0.905	-0.724
		SEM	1.005	0.910	1.001
		95% CI	(-1.8, 2.2)	(-0.9, 2.7)	(-2.7, 1.2)
		Pr >  t			0.4702
	Week 120	n	5	3	
		LS Mean	0.719	0.433	0.286
		SEM	0.949	1.091	1.120
		95% CI	(-1.1, 2.6)	(-1.7, 2.6)	(-1.9, 2.5)
		Pr >  t			0.7986
	Week 132	n	3	3	
		LS Mean	-0.049	0.423	-0.473
		SEM	1.090	1.091	1.242
		95% CI	(-2.2, 2.1)	(-1.7, 2.6)	(-2.9, 2.0)
		Pr >  t			0.7038
	Week 144	n	1	2	
		LS Mean	0.147	0.174	-0.027
		SEM	1.621	1.245	1.829
		95% CI	(-3.0, 3.3)	(-2.3, 2.6)	(-3.6, 3.6)
		Pr >  t			0.9883
	Week 156	n	1	1	
		LS Mean	0.857	-0.124	0.981
		SEM	1.621	1.622	2.103
		95% CI	(-2.3, 4.0)	(-3.3, 3.1)	(-3.2, 5.1)
		Pr >  t			0.6411
	Week 168	n		1	
		LS Mean		0.016	
		SEM		1.622	
		95% CI		(-3.2, 3.2)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation	E542K	Week 8	n	16	24			
			LS Mean	-0.818	-0.355	-0.463		
			SEM	0.765	0.854	0.732		
			95% CI	(-2.4, 0.7)	(-2.1, 1.4)	(-1.9, 1.0)		
					Pr >  t			0.5293
		Week 16	n	14	17			
			LS Mean	-0.758	0.012	-0.770		
			SEM	0.772	0.880	0.776		
			95% CI	(-2.3, 0.8)	(-1.8, 1.8)	(-2.3, 0.8)		
					Pr >  t			0.3242
		Week 24	n	14	11			
			LS Mean	-0.421	0.999	-1.420		
			SEM	0.772	0.919	0.819		
			95% CI	(-2.0, 1.1)	(-0.8, 2.8)	(-3.0, 0.2)		
					Pr >  t			0.0867
		Week 32	n	10	10			
			LS Mean	-0.590	-0.028	-0.562		
			SEM	0.830	0.930	0.860		
			95% CI	(-2.2, 1.1)	(-1.9, 1.8)	(-2.3, 1.1)		
					Pr >  t			0.5151
		Week 40	n	8	10			
			LS Mean	-0.723	0.812	-1.535		
			SEM	0.857	0.929	0.884		
			95% CI	(-2.4, 1.0)	(-1.0, 2.7)	(-3.3, 0.2)		
					Pr >  t			0.0854
		Week 48	n	7	11			
			LS Mean	-1.104	0.043	-1.147		
			SEM	0.875	0.921	0.894		
95% CI	(-2.8, 0.6)		(-1.8, 1.9)	(-2.9, 0.6)				
			Pr >  t			0.2026		
Week 56	n	6	9					
	LS Mean	-0.977	-0.045	-0.931				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.898	0.942	0.940	
	95% CI	(-2.8, 0.8)	(-1.9, 1.8)	(-2.8, 0.9)	
	Pr >  t			0.3235	
	n	5	8		
	LS Mean	-0.751	-0.831	0.080	
Week 72	SEM	0.928	0.955	0.982	
	95% CI	(-2.6, 1.1)	(-2.7, 1.1)	(-1.9, 2.0)	
	Pr >  t			0.9355	
	n	7	7		
	LS Mean	-0.899	0.159	-1.057	
Week 84	SEM	0.874	0.972	0.948	
	95% CI	(-2.6, 0.8)	(-1.8, 2.1)	(-2.9, 0.8)	
	Pr >  t			0.2670	
	n	7	7		
	LS Mean	-0.737	0.486	-1.223	
Week 96	SEM	0.874	0.972	0.948	
	95% CI	(-2.5, 1.0)	(-1.5, 2.4)	(-3.1, 0.7)	
	Pr >  t			0.1995	
	n	5	6		
	LS Mean	-0.595	-0.609	0.014	
Week 108	SEM	0.928	0.993	1.019	
	95% CI	(-2.4, 1.2)	(-2.6, 1.4)	(-2.0, 2.0)	
	Pr >  t			0.9891	
	n	4	6		
	LS Mean	-0.691	-0.061	-0.630	
Week 120	SEM	0.973	0.993	1.060	
	95% CI	(-2.6, 1.2)	(-2.0, 1.9)	(-2.7, 1.5)	
	Pr >  t			0.5528	
	n	4	4		
	LS Mean	0.454	-0.977	1.431	
Week 132	SEM	0.973	1.064	1.127	
	95% CI	(-1.5, 2.4)	(-3.1, 1.1)	(-0.8, 3.7)	
	Pr >  t			0.2061	
	n	3	1		
	LS Mean	-0.174	1.139	-1.313	
Week 144	SEM	1.042	1.540	1.627	
	95% CI	(-2.2, 1.9)	(-1.9, 4.2)	(-4.5, 1.9)	
	Pr >  t			0.4204	
	n	1	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
E545X	Week 8	LS Mean	4.207	-2.677	6.883
		SEM	1.480	1.549	1.945
		95% CI	( 1.3, 7.1)	( -5.7, 0.4)	( 3.0,10.7)
		Pr >  t			0.0005
	Week 16	n	35	36	
		LS Mean	0.679	0.369	0.309
		SEM	0.878	0.923	0.404
		95% CI	( -1.1, 2.4)	( -1.5, 2.2)	( -0.5, 1.1)
	Week 24	Pr >  t			0.4448
		n	34	30	
		LS Mean	0.767	0.707	0.059
		SEM	0.909	0.930	0.420
	Week 32	95% CI	( -1.0, 2.6)	( -1.1, 2.5)	( -0.8, 0.9)
		Pr >  t			0.8877
		n	32	22	
		LS Mean	0.414	0.787	-0.373
	Week 40	SEM	0.910	0.944	0.456
		95% CI	( -1.4, 2.2)	( -1.1, 2.6)	( -1.3, 0.5)
		Pr >  t			0.4145
		n	21	22	
	Week 48	LS Mean	0.770	0.673	0.096
		SEM	0.928	0.945	0.494
		95% CI	( -1.1, 2.6)	( -1.2, 2.5)	( -0.9, 1.1)
		Pr >  t			0.8458
Week 56	n	20	20		
	LS Mean	1.074	0.913	0.161	
	SEM	0.932	0.949	0.509	
	95% CI	( -0.8, 2.9)	( -1.0, 2.8)	( -0.8, 1.2)	
Week 8	Pr >  t			0.7526	
	n	19	12		
	LS Mean	1.279	1.361	-0.081	
	SEM	0.933	0.984	0.576	
Week 16	95% CI	( -0.6, 3.1)	( -0.6, 3.3)	( -1.2, 1.1)	
	Pr >  t			0.8876	
	n	16	8		
	LS Mean	0.812	0.671	0.141	
Week 24	SEM	0.944	1.027	0.658	
	95% CI	( -1.0, 2.7)	( -1.4, 2.7)	( -1.2, 1.4)	
	Pr >  t			0.8306	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	n	12	11		
	LS Mean	0.720	1.334		-0.614
	SEM	0.965	0.993		0.638
	95% CI	(-1.2, 2.6)	(-0.6, 3.3)		(-1.9, 0.6)
	Pr >  t				0.3367
Week 72	n	13	7		
	LS Mean	0.751	0.874		-0.123
	SEM	0.960	1.045		0.706
	95% CI	(-1.1, 2.6)	(-1.2, 2.9)		(-1.5, 1.3)
	Pr >  t				0.8613
Week 84	n	12	6		
	LS Mean	1.564	1.297		0.267
	SEM	0.965	1.068		0.746
	95% CI	(-0.3, 3.5)	(-0.8, 3.4)		(-1.2, 1.7)
	Pr >  t				0.7201
Week 96	n	7	6		
	LS Mean	0.574	1.682		-1.107
	SEM	1.023	1.067		0.819
	95% CI	(-1.4, 2.6)	(-0.4, 3.8)		(-2.7, 0.5)
	Pr >  t				0.1769
Week 108	n	5	3		
	LS Mean	1.585	1.466		0.120
	SEM	1.075	1.206		1.048
	95% CI	(-0.5, 3.7)	(-0.9, 3.8)		(-1.9, 2.2)
	Pr >  t				0.9092
Week 120	n	8	3		
	LS Mean	1.651	1.659		-0.008
	SEM	1.009	1.206		0.979
	95% CI	(-0.3, 3.6)	(-0.7, 4.0)		(-1.9, 1.9)
	Pr >  t				0.9937
Week 132	n	2	1		
	LS Mean	2.165	1.117		1.048
	SEM	1.312	1.650		1.710
	95% CI	(-0.4, 4.7)	(-2.1, 4.4)		(-2.3, 4.4)
	Pr >  t				0.5405
Week 144	n	2			
	LS Mean	0.299			
	SEM	1.313			
	95% CI	(-2.3, 2.9)			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 156	Pr >  t			
		n	1		
		LS Mean	0.274		
		SEM	1.632		
		95% CI	(-2.9, 3.5)		
		Pr >  t			
H1047X	Week 8	n	81	63	
		LS Mean	0.134	0.333	-0.199
		SEM	0.323	0.337	0.319
		95% CI	(-0.5, 0.8)	(-0.3, 1.0)	(-0.8, 0.4)
		Pr >  t			0.5332
	Week 16	n	70	51	
		LS Mean	0.074	0.182	-0.108
		SEM	0.332	0.356	0.342
		95% CI	(-0.6, 0.7)	(-0.5, 0.9)	(-0.8, 0.6)
		Pr >  t			0.7510
	Week 24	n	54	39	
		LS Mean	0.265	0.128	0.137
		SEM	0.346	0.377	0.375
		95% CI	(-0.4, 0.9)	(-0.6, 0.9)	(-0.6, 0.9)
		Pr >  t			0.7161
	Week 32	n	50	35	
		LS Mean	0.374	0.474	-0.100
		SEM	0.352	0.385	0.388
		95% CI	(-0.3, 1.1)	(-0.3, 1.2)	(-0.9, 0.7)
		Pr >  t			0.7968
	Week 40	n	42	27	
		LS Mean	0.321	0.052	0.269
		SEM	0.363	0.409	0.419
		95% CI	(-0.4, 1.0)	(-0.8, 0.9)	(-0.6, 1.1)
		Pr >  t			0.5206
	Week 48	n	38	23	
		LS Mean	0.995	0.439	0.556
		SEM	0.370	0.424	0.440
		95% CI	(0.3, 1.7)	(-0.4, 1.3)	(-0.3, 1.4)
		Pr >  t			0.2065
	Week 56	n	33	24	
		LS Mean	0.288	0.272	0.015
		SEM	0.380	0.420	0.445

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.5, 1.0)	(-0.6, 1.1)	(-0.9, 0.9)
		Pr >  t			0.9727
	Week 64	n	27	19	
		LS Mean	0.440	0.734	-0.293
		SEM	0.396	0.445	0.482
		95% CI	(-0.3, 1.2)	(-0.1, 1.6)	(-1.2, 0.7)
		Pr >  t			0.5428
	Week 72	n	26	17	
		LS Mean	0.537	0.015	0.522
		SEM	0.399	0.458	0.497
		95% CI	(-0.2, 1.3)	(-0.9, 0.9)	(-0.5, 1.5)
		Pr >  t			0.2936
	Week 84	n	18	16	
		LS Mean	0.641	0.664	-0.024
		SEM	0.440	0.466	0.535
		95% CI	(-0.2, 1.5)	(-0.3, 1.6)	(-1.1, 1.0)
		Pr >  t			0.9649
	Week 96	n	20	10	
		LS Mean	0.456	0.209	0.247
		SEM	0.427	0.536	0.588
		95% CI	(-0.4, 1.3)	(-0.8, 1.3)	(-0.9, 1.4)
		Pr >  t			0.6743
	Week 108	n	14	10	
		LS Mean	0.530	-0.286	0.816
		SEM	0.473	0.536	0.622
		95% CI	(-0.4, 1.5)	(-1.3, 0.8)	(-0.4, 2.0)
		Pr >  t			0.1897
	Week 120	n	14	7	
		LS Mean	0.387	-0.265	0.652
		SEM	0.471	0.606	0.683
		95% CI	(-0.5, 1.3)	(-1.5, 0.9)	(-0.7, 2.0)
		Pr >  t			0.3395
	Week 132	n	12	5	
		LS Mean	-0.084	0.624	-0.708
		SEM	0.495	0.688	0.771
		95% CI	(-1.1, 0.9)	(-0.7, 2.0)	(-2.2, 0.8)
		Pr >  t			0.3588
	Week 144	n	11	4	
		LS Mean	0.466	0.408	0.058



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.507	0.752	0.837
		95% CI	(-0.5, 1.5)	(-1.1, 1.9)	(-1.6, 1.7)
		Pr >  t			0.9443
	Week 156	n	8	3	
		LS Mean	0.185	0.700	-0.515
		SEM	0.567	0.848	0.958
		95% CI	(-0.9, 1.3)	(-1.0, 2.4)	(-2.4, 1.4)
		Pr >  t			0.5908
	Week 168	n	4	2	
		LS Mean	-0.494	-0.099	-0.396
		SEM	0.743	1.013	1.206
		95% CI	(-2.0, 1.0)	(-2.1, 1.9)	(-2.8, 2.0)
		Pr >  t			0.7429
	Week 180	n	1	1	
		LS Mean	2.586	0.410	2.176
		SEM	1.390	1.394	1.936
		95% CI	(-0.1, 5.3)	(-2.3, 3.1)	(-1.6, 6.0)
		Pr >  t			0.2615
	Week 192	n	1	1	
		LS Mean	0.436	-0.300	0.736
		SEM	1.390	1.394	1.936
		95% CI	(-2.3, 3.2)	(-3.0, 2.4)	(-3.1, 4.5)
		Pr >  t			0.7039

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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### 4.8.3.3 Gesundheitszustand: EQ-5D-VAS – 2. Datenschnitt

Tabelle 4H-34: Ergebnisse für den Endpunkt „Gesundheitszustand (EQ-5D VAS)“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73	
			LS Mean	-3.781	0.278	-4.059
			SEM	3.065	3.084	2.757
			95% CI	(-9.8, 2.3)	(-5.8, 6.4)	(-9.5, 1.4)
			Pr >  t			0.1419
	Week 16	n	67	56		
		LS Mean	-2.251	-1.013	-1.238	
		SEM	3.113	3.260	2.977	
		95% CI	(-8.4, 3.9)	(-7.4, 5.4)	(-7.1, 4.6)	
		Pr >  t			0.6778	
	Week 24	n	61	46		
		LS Mean	-3.510	-1.852	-1.658	
		SEM	3.170	3.359	3.139	
		95% CI	(-9.8, 2.7)	(-8.5, 4.8)	(-7.8, 4.5)	
		Pr >  t			0.5976	
	Week 32	n	52	41		
		LS Mean	-7.066	-1.105	-5.961	
		SEM	3.272	3.440	3.283	
		95% CI	(-13.5,-0.6)	(-7.9, 5.7)	(-12.4, 0.5)	
		Pr >  t			0.0700	
Week 40	n	45	36			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	LS Mean	-2.089	-2.948	0.858
	SEM	3.344	3.535	3.436
	95% CI	(-8.7, 4.5)	(-9.9, 4.0)	(-5.9, 7.6)
	Pr >  t			0.8029
	n	42	30	
Week 56	LS Mean	-4.219	-1.716	-2.503
	SEM	3.382	3.655	3.597
	95% CI	(-10.9, 2.4)	(-8.9, 5.5)	(-9.6, 4.6)
	Pr >  t			0.4867
	n	35	24	
Week 64	LS Mean	-3.331	-2.545	-0.786
	SEM	3.487	3.828	3.869
	95% CI	(-10.2, 3.5)	(-10.1, 5.0)	(-8.4, 6.8)
	Pr >  t			0.8392
	n	25	25	
Week 72	LS Mean	-5.595	-2.119	-3.476
	SEM	3.718	3.795	4.053
	95% CI	(-12.9, 1.7)	(-9.6, 5.3)	(-11.4, 4.5)
	Pr >  t			0.3913
	n	27	20	
Week 84	LS Mean	-5.356	1.045	-6.402
	SEM	3.661	3.988	4.183
	95% CI	(-12.6, 1.8)	(-6.8, 8.9)	(-14.6, 1.8)
	Pr >  t			0.1263
	n	23	19	
Week 96	LS Mean	-2.148	-0.705	-1.443
	SEM	3.800	4.038	4.341
	95% CI	(-9.6, 5.3)	(-8.6, 7.2)	(-10.0, 7.1)
	Pr >  t			0.7397
	n	20	13	
Week 108	LS Mean	-1.820	-3.415	1.596
	SEM	3.925	4.460	4.837
	95% CI	(-9.5, 5.9)	(-12.2, 5.3)	(-7.9, 11.1)
	Pr >  t			0.7415
	n	17	13	
Week 120	LS Mean	-1.194	-1.552	0.359
	SEM	4.087	4.461	4.970
	95% CI	(-9.2, 6.8)	(-10.3, 7.2)	(-9.4, 10.1)
	Pr >  t			0.9425
	n	18	12	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	-7.844	-0.304	-7.540
		SEM	4.028	4.566	5.017
		95% CI	(-15.8, 0.1)	(-9.3, 8.7)	(-17.4, 2.3)
		Pr >  t			0.1332
	Week 132	n	13	6	
		LS Mean	-0.892	-7.256	6.364
		SEM	4.397	5.738	6.352
		95% CI	(-9.5, 7.7)	(-18.5, 4.0)	(-6.1, 18.8)
		Pr >  t			0.3167
	Week 144	n	11	4	
		LS Mean	-3.063	-1.027	-2.036
		SEM	4.623	6.714	7.385
		95% CI	(-12.1, 6.0)	(-14.2, 12.1)	(-16.5, 12.5)
		Pr >  t			0.7828
	Week 156	n	7	2	
		LS Mean	-1.987	-6.498	4.511
		SEM	5.372	9.002	9.899
		95% CI	(-12.5, 8.6)	(-24.2, 11.2)	(-14.9, 23.9)
		Pr >  t			0.6487
	Week 168	n	3	1	
		LS Mean	0.588	4.621	-4.033
		SEM	7.497	12.37	14.05
		95% CI	(-14.1, 15.3)	(-19.7, 28.9)	(-31.6, 23.5)
		Pr >  t			0.7741
	Week 180	n	1	1	
		LS Mean	-4.672	-3.379	-1.293
		SEM	12.34	12.37	17.13
		95% CI	(-28.9, 19.6)	(-27.7, 20.9)	(-34.9, 32.3)
		Pr >  t			0.9399
	Week 192	n	1	1	
		LS Mean	-6.672	0.621	-7.293
		SEM	12.34	12.37	17.13
		95% CI	(-30.9, 17.6)	(-23.7, 24.9)	(-40.9, 26.3)
		Pr >  t			0.6705
Present	Week 8	n	65	68	
		LS Mean	-7.459	-5.058	-2.401
		SEM	3.178	3.270	2.807
		95% CI	(-13.7, -1.2)	(-11.5, 1.4)	(-7.9, 3.1)
		Pr >  t			0.3928
	Week 16	n	58	51	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	LS Mean	-2.645	-2.853	0.208
	SEM	3.319	3.455	3.058
	95% CI	(-9.2, 3.9)	(-9.7, 3.9)	(-5.8, 6.2)
	Pr >  t			0.9459
	n	44	36	
Week 32	LS Mean	-6.560	-4.463	-2.097
	SEM	3.463	3.730	3.489
	95% CI	(-13.4, 0.3)	(-11.8, 2.9)	(-9.0, 4.8)
	Pr >  t			0.5481
	n	34	32	
Week 40	LS Mean	-0.887	-3.581	2.694
	SEM	3.663	3.822	3.763
	95% CI	(-8.1, 6.3)	(-11.1, 3.9)	(-4.7, 10.1)
	Pr >  t			0.4743
	n	30	26	
Week 48	LS Mean	-2.603	-5.224	2.621
	SEM	3.762	3.995	4.035
	95% CI	(-10.0, 4.8)	(-13.1, 2.6)	(-5.3, 10.5)
	Pr >  t			0.5162
	n	27	21	
Week 56	LS Mean	-5.561	-4.357	-1.204
	SEM	3.843	4.203	4.314
	95% CI	(-13.1, 2.0)	(-12.6, 3.9)	(-9.7, 7.3)
	Pr >  t			0.7803
	n	24	21	
Week 64	LS Mean	-0.900	-1.643	0.742
	SEM	3.949	4.203	4.411
	95% CI	(-8.7, 6.9)	(-9.9, 6.6)	(-7.9, 9.4)
	Pr >  t			0.8664
	n	22	17	
Week 72	LS Mean	-0.941	-7.804	6.863
	SEM	4.032	4.435	4.707
	95% CI	(-8.9, 7.0)	(-16.5, 0.9)	(-2.4, 16.1)
	Pr >  t			0.1453
	n	21	15	
Week 84	LS Mean	0.336	-7.883	8.219
	SEM	4.081	4.588	4.894
	95% CI	(-7.7, 8.4)	(-16.9, 1.1)	(-1.4, 17.8)
	Pr >  t			0.0935
	n	17	14	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	LS Mean	-1.448	-9.329	7.881
	SEM	4.327	4.679	5.169
	95% CI	(-9.9, 7.1)	(-18.5,-0.1)	(-2.3,18.0)
	Pr >  t			0.1278
	n	16	11	
Week 108	LS Mean	0.371	-19.12	19.494
	SEM	4.378	5.030	5.549
	95% CI	(-8.2, 9.0)	(-29.0,-9.2)	( 8.6,30.4)
	Pr >  t			0.0005
	n	9	8	
Week 120	LS Mean	-6.372	-11.13	4.762
	SEM	5.264	5.591	6.714
	95% CI	(-16.7, 4.0)	(-22.1,-0.2)	(-8.4,17.9)
	Pr >  t			0.4784
	n	11	4	
Week 132	LS Mean	1.732	-7.921	9.653
	SEM	4.911	7.273	7.963
	95% CI	(-7.9,11.4)	(-22.2, 6.4)	(-6.0,25.3)
	Pr >  t			0.2258
	n	7	2	
Week 144	LS Mean	-5.874	-10.34	4.471
	SEM	5.756	9.768	10.71
	95% CI	(-17.2, 5.4)	(-29.5, 8.8)	(-16.6,25.5)
	Pr >  t			0.6765
	n	4	1	
Week 156	LS Mean	-9.337	3.034	-12.37
	SEM	7.114	13.46	14.79
	95% CI	(-23.3, 4.6)	(-23.4,29.5)	(-41.4,16.7)
	Pr >  t			0.4031
	n	3	1	
Week 168	LS Mean	-1.706	-6.966	5.260
	SEM	8.103	13.46	15.26
	95% CI	(-17.6,14.2)	(-33.4,19.5)	(-24.7,35.2)
	Pr >  t			0.7304
	n	1	1	
Week 168	LS Mean	-1.378	-6.966	5.588
	SEM	13.42	13.46	18.63
	95% CI	(-27.7,25.0)	(-33.4,19.5)	(-31.0,42.2)
	Pr >  t			0.7644

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	-5.372	-0.888	-4.483		
			SEM	2.473	2.624	2.470		
			95% CI	(-10.2, -0.5)	(-6.1, 4.3)	(-9.3, 0.4)		
					Pr >  t			0.0702
		Week 16	n	86	68			
			LS Mean	-1.798	-0.602	-1.196		
			SEM	2.536	2.741	2.647		
			95% CI	(-6.8, 3.2)	(-6.0, 4.8)	(-6.4, 4.0)		
					Pr >  t			0.6516
		Week 24	n	73	48			
			LS Mean	-3.372	-1.807	-1.565		
			SEM	2.614	2.958	2.932		
			95% CI	(-8.5, 1.8)	(-7.6, 4.0)	(-7.3, 4.2)		
					Pr >  t			0.5937
		Week 32	n	60	43			
			LS Mean	-5.144	-1.293	-3.852		
			SEM	2.742	3.042	3.092		
			95% CI	(-10.5, 0.2)	(-7.3, 4.7)	(-9.9, 2.2)		
					Pr >  t			0.2133
		Week 40	n	50	38			
			LS Mean	-1.592	0.129	-1.721		
			SEM	2.842	3.138	3.265		
			95% CI	(-7.2, 4.0)	(-6.0, 6.3)	(-8.1, 4.7)		
			Pr >  t			0.5983		
Week 48	n	48	31					
	LS Mean	-2.984	-0.515	-2.469				
	SEM	2.867	3.293	3.436				
	95% CI	(-8.6, 2.7)	(-7.0, 6.0)	(-9.2, 4.3)				
			Pr >  t			0.4726		
Week 56	n	41	25					
	LS Mean	-3.436	-2.993	-0.442				
	SEM	2.964	3.482	3.699				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.3, 2.4)	(-9.8, 3.8)	(-7.7, 6.8)
	Pr >  t			0.9048
	n	30	24	
	LS Mean	-4.341	-1.244	-3.097
	SEM	3.191	3.522	3.923
Week 72	95% CI	(-10.6, 1.9)	(-8.2, 5.7)	(-10.8, 4.6)
	Pr >  t			0.4301
	n	32	19	
	LS Mean	-4.540	1.346	-5.886
	SEM	3.141	3.763	4.101
Week 84	95% CI	(-10.7, 1.6)	(-6.0, 8.7)	(-13.9, 2.2)
	Pr >  t			0.1515
	n	26	19	
	LS Mean	-2.688	-0.077	-2.611
	SEM	3.331	3.763	4.238
Week 96	95% CI	(-9.2, 3.9)	(-7.5, 7.3)	(-10.9, 5.7)
	Pr >  t			0.5380
	n	24	14	
	LS Mean	-1.053	-9.500	8.446
	SEM	3.398	4.139	4.631
Week 108	95% CI	(-7.7, 5.6)	(-17.6,-1.4)	(-0.6,17.5)
	Pr >  t			0.0685
	n	19	13	
	LS Mean	-0.834	-0.684	-0.150
	SEM	3.652	4.243	4.902
Week 120	95% CI	(-8.0, 6.3)	(-9.0, 7.6)	(-9.8, 9.5)
	Pr >  t			0.9756
	n	20	11	
	LS Mean	-7.269	-0.291	-6.978
	SEM	3.585	4.495	5.082
Week 132	95% CI	(-14.3,-0.2)	(-9.1, 8.5)	(-16.9, 3.0)
	Pr >  t			0.1700
	n	15	5	
	LS Mean	-2.250	-5.600	3.350
	SEM	3.938	6.093	6.734
Week 144	95% CI	(-10.0, 5.5)	(-17.6, 6.4)	(-9.9,16.6)
	Pr >  t			0.6189
	n	12	3	
	LS Mean	-2.836	0.225	-3.061
	SEM	4.242	7.610	8.291

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.2, 5.5)	(-14.7,15.2)	(-19.3,13.2)
		Pr >  t			0.7121
	Week 156	n	7	2	
		LS Mean	-1.750	-6.232	4.482
		SEM	5.225	9.140	10.18
		95% CI	(-12.0, 8.5)	(-24.2,11.7)	(-15.5,24.5)
		Pr >  t			0.6597
	Week 168	n	3	1	
		LS Mean	0.750	4.879	-4.128
		SEM	7.522	12.68	14.49
		95% CI	(-14.0,15.5)	(-20.0,29.8)	(-32.6,24.3)
		Pr >  t			0.7758
	Week 180	n	1	1	
		LS Mean	-4.424	-3.121	-1.303
		SEM	12.63	12.68	17.69
		95% CI	(-29.2,20.4)	(-28.0,21.8)	(-36.0,33.4)
		Pr >  t			0.9413
	Week 192	n	1	1	
		LS Mean	-6.424	0.879	-7.303
		SEM	12.63	12.68	17.69
		95% CI	(-31.2,18.4)	(-24.0,25.8)	(-42.0,27.4)
		Pr >  t			0.6799
Yes	Week 8	n	44	57	
		LS Mean	-9.058	-8.412	-0.645
		SEM	5.226	4.986	3.264
		95% CI	(-19.4, 1.2)	(-18.2, 1.4)	(-7.1, 5.8)
		Pr >  t			0.8434
	Week 16	n	39	39	
		LS Mean	-7.325	-8.177	0.852
		SEM	5.383	5.325	3.603
		95% CI	(-17.9, 3.3)	(-18.7, 2.3)	(-6.2, 7.9)
		Pr >  t			0.8132
	Week 24	n	32	34	
		LS Mean	-11.50	-9.450	-2.054
		SEM	5.482	5.396	3.850
		95% CI	(-22.3,-0.7)	(-20.1, 1.2)	(-9.6, 5.5)
		Pr >  t			0.5940
	Week 32	n	26	30	
		LS Mean	-6.872	-8.274	1.403
		SEM	5.601	5.471	4.108

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-17.9, 4.2)	(-19.0, 2.5)	(-6.7, 9.5)
	Pr >  t			0.7329
	n	25	24	
	LS Mean	-7.449	-14.86	7.411
	SEM	5.627	5.599	4.314
Week 48	95% CI	(-18.5, 3.6)	(-25.9,-3.8)	(-1.1,15.9)
	Pr >  t			0.0865
	n	21	20	
	LS Mean	-12.30	-11.10	-1.197
	SEM	5.735	5.727	4.613
Week 56	95% CI	(-23.6,-1.0)	(-22.4, 0.2)	(-10.3, 7.9)
	Pr >  t			0.7954
	n	18	20	
	LS Mean	-3.341	-6.013	2.672
	SEM	5.849	5.726	4.754
Week 64	95% CI	(-14.8, 8.2)	(-17.3, 5.3)	(-6.7,12.0)
	Pr >  t			0.5744
	n	17	18	
	LS Mean	-5.515	-13.76	8.247
	SEM	5.894	5.805	4.907
Week 72	95% CI	(-17.1, 6.1)	(-25.2,-2.3)	(-1.4,17.9)
	Pr >  t			0.0935
	n	16	16	
	LS Mean	-3.221	-12.91	9.690
	SEM	5.949	5.905	5.085
Week 84	95% CI	(-14.9, 8.5)	(-24.5,-1.3)	(-0.3,19.7)
	Pr >  t			0.0572
	n	14	14	
	LS Mean	-4.044	-15.09	11.048
	SEM	6.067	6.029	5.357
Week 96	95% CI	(-16.0, 7.9)	(-26.9,-3.2)	( 0.5,21.6)
	Pr >  t			0.0397
	n	12	10	
	LS Mean	-4.204	-16.75	12.548
	SEM	6.225	6.399	5.935
Week 108	95% CI	(-16.4, 8.0)	(-29.3,-4.2)	( 0.9,24.2)
	Pr >  t			0.0349
	n	7	8	
	LS Mean	-12.18	-17.80	5.622
	SEM	6.942	6.705	6.979

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.8, 1.5)	(-31.0,-4.6)	( -8.1,19.3)
		Pr >  t			0.4208
	Week 120	n	9	5	
		LS Mean	-1.006	-12.08	11.077
		SEM	6.579	7.546	7.470
		95% CI	(-13.9,11.9)	(-26.9, 2.7)	( -3.6,25.8)
		Pr >  t			0.1387
	Week 132	n	5	3	
		LS Mean	-6.999	-18.49	11.491
		SEM	7.564	8.817	9.514
		95% CI	(-21.9, 7.9)	(-35.8,-1.2)	( -7.2,30.2)
		Pr >  t			0.2277
	Week 144	n	3	2	
		LS Mean	-15.64	-8.427	-7.209
		SEM	8.831	10.20	11.73
		95% CI	(-33.0, 1.7)	(-28.5,11.6)	(-30.3,15.8)
		Pr >  t			0.5392
	Week 156	n	3	1	
		LS Mean	-5.767	-12.93	7.164
		SEM	8.839	13.50	14.70
		95% CI	(-23.1,11.6)	(-39.5,13.6)	(-21.7,36.0)
		Pr >  t			0.6263
	Week 168	n	1	1	
		LS Mean	-5.588	-12.93	7.342
		SEM	13.55	13.50	17.93
		95% CI	(-32.2,21.0)	(-39.5,13.6)	(-27.9,42.6)
		Pr >  t			0.6823

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	99			
			LS Mean	-5.119	-1.692	-3.427		
			SEM	2.783	2.760	2.331		
			95% CI	(-10.6, 0.4)	(-7.1, 3.7)	(-8.0, 1.2)		
					Pr >  t			0.1423
		Week 16	n	93	77			
			LS Mean	-3.196	-3.372	0.176		
			SEM	2.814	2.913	2.501		
			95% CI	(-8.7, 2.3)	(-9.1, 2.4)	(-4.7, 5.1)		
					Pr >  t			0.9440
		Week 24	n	83	67			
			LS Mean	-4.904	-4.220	-0.684		
			SEM	2.865	2.969	2.618		
			95% CI	(-10.5, 0.7)	(-10.1, 1.6)	(-5.8, 4.5)		
					Pr >  t			0.7941
		Week 32	n	72	60			
			LS Mean	-6.034	-2.630	-3.404		
			SEM	2.927	3.030	2.732		
			95% CI	(-11.8, -0.3)	(-8.6, 3.3)	(-8.8, 2.0)		
					Pr >  t			0.2133
		Week 40	n	64	51			
			LS Mean	-3.425	-6.133	2.708		
			SEM	2.973	3.119	2.868		
			95% CI	(-9.3, 2.4)	(-12.3, -0.0)	(-2.9, 8.3)		
			Pr >  t			0.3454		
Week 48	n	58	45					
	LS Mean	-5.758	-3.069	-2.690				
	SEM	3.013	3.184	2.982				
	95% CI	(-11.7, 0.2)	(-9.3, 3.2)	(-8.5, 3.2)				
			Pr >  t			0.3673		
Week 56	n	49	38					
	LS Mean	-2.927	-2.788	-0.139				
	SEM	3.091	3.283	3.166				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.0, 3.1)	(-9.2, 3.7)	(-6.4, 6.1)
		Pr >  t			0.9649
	Week 64	n	39	37	
		LS Mean	-5.458	-4.623	-0.835
		SEM	3.211	3.300	3.305
		95% CI	(-11.8, 0.9)	(-11.1, 1.9)	(-7.3, 5.7)
		Pr >  t			0.8006
	Week 72	n	41	32	
		LS Mean	-4.257	-2.119	-2.139
		SEM	3.185	3.395	3.373
		95% CI	(-10.5, 2.0)	(-8.8, 4.6)	(-8.8, 4.5)
		Pr >  t			0.5262
	Week 84	n	33	29	
		LS Mean	-2.046	-4.283	2.237
		SEM	3.332	3.467	3.570
		95% CI	(-8.6, 4.5)	(-11.1, 2.5)	(-4.8, 9.2)
		Pr >  t			0.5310
	Week 96	n	31	21	
		LS Mean	-2.488	-6.079	3.590
		SEM	3.368	3.738	3.872
		95% CI	(-9.1, 4.1)	(-13.4, 1.3)	(-4.0, 11.2)
		Pr >  t			0.3540
	Week 108	n	23	18	
		LS Mean	-4.092	-5.206	1.114
		SEM	3.612	3.893	4.223
		95% CI	(-11.2, 3.0)	(-12.8, 2.4)	(-7.2, 9.4)
		Pr >  t			0.7919
	Week 120	n	26	15	
		LS Mean	-4.963	-3.634	-1.329
		SEM	3.502	4.098	4.329
		95% CI	(-11.8, 1.9)	(-11.7, 4.4)	(-9.8, 7.2)
		Pr >  t			0.7589
	Week 132	n	17	8	
		LS Mean	-2.069	-9.143	7.073
		SEM	3.909	5.026	5.493
		95% CI	(-9.7, 5.6)	(-19.0, 0.7)	(-3.7, 17.8)
		Pr >  t			0.1981
	Week 144	n	15	5	
		LS Mean	-5.456	-1.700	-3.757
		SEM	4.039	6.020	6.503

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.4, 2.5)	(-13.5,10.1)	(-16.5, 9.0)
		Pr >  t			0.5636
	Week 156	n	10	3	
		LS Mean	-2.634	-7.607	4.973
		SEM	4.611	7.451	8.149
		95% CI	(-11.7, 6.4)	(-22.2, 7.0)	(-11.0,21.0)
		Pr >  t			0.5418
	Week 168	n	4	2	
		LS Mean	-0.747	-1.498	0.751
		SEM	6.555	8.925	10.59
		95% CI	(-13.6,12.1)	(-19.0,16.0)	(-20.0,21.5)
		Pr >  t			0.9435
	Week 180	n	1	1	
		LS Mean	-5.235	-5.748	0.513
		SEM	12.31	12.32	17.11
		95% CI	(-29.4,18.9)	(-29.9,18.4)	(-33.1,34.1)
		Pr >  t			0.9761
	Week 192	n	1	1	
		LS Mean	-7.235	-1.748	-5.487
		SEM	12.31	12.32	17.11
		95% CI	(-31.4,16.9)	(-25.9,22.4)	(-39.1,28.1)
		Pr >  t			0.7485
Yes	Week 8	n	38	42	
		LS Mean	-7.340	-3.699	-3.641
		SEM	3.612	3.889	3.695
		95% CI	(-14.5,-0.2)	(-11.4, 4.0)	(-10.9, 3.6)
		Pr >  t			0.3256
	Week 16	n	32	30	
		LS Mean	-0.901	1.975	-2.877
		SEM	3.900	4.146	4.120
		95% CI	( -8.6, 6.8)	( -6.2,10.2)	(-11.0, 5.2)
		Pr >  t			0.4858
	Week 24	n	22	15	
		LS Mean	-5.939	0.431	-6.371
		SEM	4.224	5.031	5.266
		95% CI	(-14.3, 2.4)	( -9.5,10.3)	(-16.7, 4.0)
		Pr >  t			0.2274
	Week 32	n	14	13	
		LS Mean	-0.044	-2.141	2.097
		SEM	4.957	5.243	5.952

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.8, 9.7)	(-12.5, 8.2)	(-9.6,13.8)
		Pr >  t			0.7248
	Week 40	n	11	11	
		LS Mean	1.287	3.707	-2.420
		SEM	5.357	5.515	6.514
		95% CI	(-9.3,11.8)	(-7.2,14.6)	(-15.2,10.4)
		Pr >  t			0.7105
	Week 48	n	11	6	
		LS Mean	-1.349	-6.500	5.151
		SEM	5.357	6.774	7.607
		95% CI	(-11.9, 9.2)	(-19.8, 6.8)	(-9.8,20.1)
		Pr >  t			0.4989
	Week 56	n	10	7	
		LS Mean	-1.198	-1.242	0.044
		SEM	5.527	6.412	7.410
		95% CI	(-12.1, 9.7)	(-13.9,11.4)	(-14.5,14.6)
		Pr >  t			0.9953
	Week 64	n	8	5	
		LS Mean	4.700	-8.643	13.343
		SEM	5.956	7.231	8.431
		95% CI	(-7.0,16.4)	(-22.9, 5.6)	(-3.3,29.9)
		Pr >  t			0.1146
	Week 72	n	7	3	
		LS Mean	2.288	-17.63	19.917
		SEM	6.242	8.841	10.03
		95% CI	(-10.0,14.6)	(-35.0,-0.2)	( 0.2,39.7)
		Pr >  t			0.0480
	Week 84	n	7	4	
		LS Mean	-2.712	-9.680	6.968
		SEM	6.242	7.877	9.188
		95% CI	(-15.0, 9.6)	(-25.2, 5.8)	(-11.1,25.1)
		Pr >  t			0.4489
	Week 96	n	5	3	
		LS Mean	5.952	-46.96	52.914
		SEM	7.072	8.841	10.57
		95% CI	(-8.0,19.9)	(-64.4, -30)	(32.1,73.7)
		Pr >  t			<.0001
	Week 108	n	3	3	
		LS Mean	1.921	-10.55	12.476
		SEM	8.689	8.849	11.72



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.2,19.0)	(-28.0, 6.9)	(-10.6,35.5)
		Pr >  t			0.2879
	Week 120	n	3	1	
		LS Mean	-3.145	-1.410	-1.734
		SEM	8.691	14.34	16.27
		95% CI	(-20.3,14.0)	(-29.7,26.8)	(-33.8,30.3)
		Pr >  t			0.9152
	Week 132	n	3		
		LS Mean	-7.396		
		SEM	8.689		
		95% CI	(-24.5, 9.7)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	135			
			LS Mean	-3.041	0.552	-3.593		
			SEM	1.418	1.417	2.003		
			95% CI	(-5.8,-0.3)	(-2.2, 3.3)	(-7.5, 0.3)		
					Pr >  t			0.0732
		Week 16	n	119	104			
			LS Mean	-0.408	1.006	-1.413		
			SEM	1.485	1.573	2.161		
			95% CI	(-3.3, 2.5)	(-2.1, 4.1)	(-5.7, 2.8)		
					Pr >  t			0.5133
		Week 24	n	100	80			
			LS Mean	-2.404	-0.120	-2.283		
			SEM	1.585	1.740	2.352		
			95% CI	(-5.5, 0.7)	(-3.5, 3.3)	(-6.9, 2.3)		
					Pr >  t			0.3318
		Week 32	n	84	72			
			LS Mean	-2.546	0.504	-3.051		
			SEM	1.690	1.811	2.475		
			95% CI	(-5.9, 0.8)	(-3.0, 4.1)	(-7.9, 1.8)		
					Pr >  t			0.2180
		Week 40	n	73	62			
			LS Mean	-0.082	-1.207	1.125		
			SEM	1.781	1.914	2.612		
			95% CI	(-3.6, 3.4)	(-5.0, 2.5)	(-4.0, 6.2)		
					Pr >  t			0.6667
		Week 48	n	67	51			
			LS Mean	-2.554	-0.095	-2.459		
			SEM	1.837	2.061	2.758		
95% CI	(-6.2, 1.1)		(-4.1, 3.9)	(-7.9, 3.0)				
			Pr >  t			0.3728		
Week 56	n	57	45					
	LS Mean	0.078	0.682	-0.604				
	SEM	1.951	2.163	2.911				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-3.7, 3.9)	(-3.6, 4.9)	(-6.3, 5.1)
	Pr >  t			0.8358
Week 64	n	45	42	
	LS Mean	-1.227	-1.743	0.516
	SEM	2.134	2.223	3.080
	95% CI	(-5.4, 3.0)	(-6.1, 2.6)	(-5.5, 6.6)
	Pr >  t			0.8670
Week 72	n	46	35	
	LS Mean	-0.725	-0.013	-0.711
	SEM	2.118	2.389	3.191
	95% CI	(-4.9, 3.4)	(-4.7, 4.7)	(-7.0, 5.5)
	Pr >  t			0.8237
Week 84	n	40	33	
	LS Mean	0.417	-1.583	2.000
	SEM	2.236	2.446	3.313
	95% CI	(-4.0, 4.8)	(-6.4, 3.2)	(-4.5, 8.5)
	Pr >  t			0.5462
Week 96	n	35	24	
	LS Mean	1.675	-7.730	9.405
	SEM	2.360	2.790	3.653
	95% CI	(-3.0, 6.3)	(-13.2,-2.3)	( 2.2,16.6)
	Pr >  t			0.0101
Week 108	n	26	21	
	LS Mean	-0.647	-2.730	2.083
	SEM	2.669	2.954	3.980
	95% CI	(-5.9, 4.6)	(-8.5, 3.1)	(-5.7, 9.9)
	Pr >  t			0.6008
Week 120	n	28	16	
	LS Mean	-2.083	-0.204	-1.879
	SEM	2.590	3.327	4.214
	95% CI	(-7.2, 3.0)	(-6.7, 6.3)	(-10.1, 6.4)
	Pr >  t			0.6557
Week 132	n	20	8	
	LS Mean	-0.197	-6.074	5.877
	SEM	2.986	4.556	5.446
	95% CI	(-6.1, 5.7)	(-15.0, 2.9)	(-4.8,16.6)
	Pr >  t			0.2807
Week 144	n	14	5	
	LS Mean	-2.456	1.400	-3.856
	SEM	3.500	5.696	6.684

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.3, 4.4)	(-9.8, 12.6)	(-17.0, 9.3)
		Pr >  t			0.5641
	Week 156	n	10	3	
		LS Mean	0.393	-4.559	4.952
		SEM	4.083	7.280	8.346
		95% CI	(-7.6, 8.4)	(-18.8, 9.7)	(-11.4, 21.3)
		Pr >  t			0.5530
	Week 168	n	4	2	
		LS Mean	2.268	1.573	0.695
		SEM	6.310	8.874	10.89
		95% CI	(-10.1, 14.6)	(-15.8, 19.0)	(-20.7, 22.1)
		Pr >  t			0.9491
	Week 180	n	1	1	
		LS Mean	-2.225	-2.687	0.462
		SEM	12.47	12.47	17.64
		95% CI	(-26.7, 22.2)	(-27.2, 21.8)	(-34.1, 35.1)
		Pr >  t			0.9791
	Week 192	n	1	1	
		LS Mean	-4.225	1.313	-5.538
		SEM	12.47	12.47	17.64
		95% CI	(-28.7, 20.2)	(-23.2, 25.8)	(-40.1, 29.1)
		Pr >  t			0.7535
Prior use	Week 8	n	8	6	
		LS Mean	-5.319	-12.51	7.187
		SEM	7.620	8.863	11.82
		95% CI	(-21.9, 11.2)	(-31.4, 6.4)	(-18.2, 32.6)
		Pr >  t			0.5531
	Week 16	n	6	3	
		LS Mean	5.667	-14.67	20.340
		SEM	8.893	12.59	15.10
		95% CI	(-13.0, 24.4)	(-40.7, 11.3)	(-11.1, 51.8)
		Pr >  t			0.1930
	Week 24	n	5	2	
		LS Mean	-4.866	-21.67	16.803
		SEM	9.508	14.78	17.35
		95% CI	(-24.7, 15.0)	(-51.9, 8.6)	(-18.8, 52.4)
		Pr >  t			0.3415
	Week 32	n	2	1	
		LS Mean	5.643	-9.930	15.573
		SEM	13.79	19.79	23.90

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-22.6,33.9)	(-50.7,30.9)	(-33.6,64.7)
	Pr >  t			0.5205
Week 40	n	2		
	LS Mean	0.143		
	SEM	13.79		
	95% CI	(-28.1,28.4)		
	Pr >  t			
Week 48	n	2		
	LS Mean	2.143		
	SEM	13.79		
	95% CI	(-26.1,30.4)		
	Pr >  t			
Week 56	n	2		
	LS Mean	-2.857		
	SEM	13.79		
	95% CI	(-31.1,25.4)		
	Pr >  t			
Week 64	n	2		
	LS Mean	1.143		
	SEM	13.79		
	95% CI	(-27.1,29.4)		
	Pr >  t			
Week 72	n	2		
	LS Mean	1.643		
	SEM	13.79		
	95% CI	(-26.6,29.9)		
	Pr >  t			
Week 96	n	1		
	LS Mean	-7.627		
	SEM	18.18		
	95% CI	(-45.3,30.1)		
	Pr >  t			
Week 120	n	1		
	LS Mean	2.373		
	SEM	18.18		
	95% CI	(-35.3,40.1)		
	Pr >  t			
Week 144	n	1		
	LS Mean	-0.627		
	SEM	18.18		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-38.3,37.1)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-4.308	-2.716	-1.592		
			SEM	2.533	2.643	2.548		
			95% CI	(-9.3, 0.7)	(-7.9, 2.5)	(-6.6, 3.4)		
					Pr >  t			0.5325
		Week 16	n	70	52			
			LS Mean	-0.924	-1.732	0.808		
			SEM	2.597	2.865	2.770		
			95% CI	(-6.0, 4.2)	(-7.4, 3.9)	(-4.6, 6.3)		
					Pr >  t			0.7707
		Week 24	n	61	38			
			LS Mean	-4.018	-3.897	-0.121		
			SEM	2.669	3.086	3.031		
			95% CI	(-9.3, 1.2)	(-10.0, 2.2)	(-6.1, 5.8)		
					Pr >  t			0.9682
		Week 32	n	48	33			
			LS Mean	-1.946	-1.402	-0.544		
			SEM	2.813	3.182	3.235		
			95% CI	(-7.5, 3.6)	(-7.7, 4.9)	(-6.9, 5.8)		
					Pr >  t			0.8665
		Week 40	n	42	31			
			LS Mean	-0.622	-0.176	-0.446		
			SEM	2.887	3.228	3.346		
			95% CI	(-6.3, 5.1)	(-6.5, 6.2)	(-7.0, 6.1)		
			Pr >  t			0.8941		
Week 48	n	40	25					
	LS Mean	-1.980	-1.000	-0.980				
	SEM	2.916	3.391	3.528				
	95% CI	(-7.7, 3.8)	(-7.7, 5.7)	(-7.9, 5.9)				
			Pr >  t			0.7814		
Week 56	n	35	20					
	LS Mean	-0.417	-3.412	2.995				
	SEM	2.996	3.592	3.789				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-6.3, 5.5)	(-10.5, 3.6)	(-4.4,10.4)
	Pr >  t			0.4295
	n	29	18	
	LS Mean	0.697	-1.455	2.152
	SEM	3.122	3.699	3.991
Week 72	95% CI	(-5.4, 6.8)	(-8.7, 5.8)	(-5.7,10.0)
	Pr >  t			0.5899
	n	28	18	
	LS Mean	0.145	-0.370	0.515
	SEM	3.148	3.696	4.011
Week 84	95% CI	(-6.0, 6.3)	(-7.6, 6.9)	(-7.4, 8.4)
	Pr >  t			0.8979
	n	27	17	
	LS Mean	1.146	-1.669	2.815
	SEM	3.193	3.757	4.088
Week 96	95% CI	(-5.1, 7.4)	(-9.0, 5.7)	(-5.2,10.8)
	Pr >  t			0.4913
	n	24	14	
	LS Mean	1.502	-13.45	14.952
	SEM	3.281	3.974	4.361
Week 108	95% CI	(-4.9, 7.9)	(-21.3,-5.6)	( 6.4,23.5)
	Pr >  t			0.0006
	n	19	12	
	LS Mean	1.065	-4.993	6.058
	SEM	3.507	4.171	4.699
Week 120	95% CI	(-5.8, 8.0)	(-13.2, 3.2)	(-3.2,15.3)
	Pr >  t			0.1977
	n	18	8	
	LS Mean	-4.204	-1.234	-2.970
	SEM	3.549	4.789	5.290
Week 132	95% CI	(-11.2, 2.8)	(-10.6, 8.2)	(-13.4, 7.4)
	Pr >  t			0.5746
	n	11	4	
	LS Mean	-1.179	-5.294	4.115
	SEM	4.162	6.276	7.008
Week 144	95% CI	(-9.3, 7.0)	(-17.6, 7.0)	(-9.6,17.9)
	Pr >  t			0.5573
	n	11	4	
	LS Mean	0.281	0.097	0.184
	SEM	4.150	6.280	7.012



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.9, 8.4)	(-12.2,12.4)	(-13.6,13.9)
		Pr >  t			0.9791
	Week 156	n	5	2	
		LS Mean	1.651	-7.414	9.065
		SEM	5.625	8.493	9.807
		95% CI	(-9.4,12.7)	(-24.1, 9.3)	(-10.2,28.3)
		Pr >  t			0.3556
	Week 168	n	1	2	
		LS Mean	12.682	-0.414	13.097
		SEM	11.64	8.493	14.14
		95% CI	(-10.2,35.5)	(-17.1,16.3)	(-14.7,40.9)
		Pr >  t			0.3547
	Week 180	n		1	
		LS Mean		-4.675	
		SEM		11.71	
		95% CI		(-27.7,18.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.675	
		SEM		11.71	
		95% CI		(-23.7,22.3)	
		Pr >  t			
>= 65 Years	Week 8	n	63	72	
		LS Mean	-7.962	-2.377	-5.584
		SEM	4.083	4.054	3.023
		95% CI	(-16.0, 0.1)	(-10.4, 5.6)	(-11.5, 0.4)
		Pr >  t			0.0655
	Week 16	n	55	55	
		LS Mean	-5.470	-2.594	-2.876
		SEM	4.202	4.149	3.277
		95% CI	(-13.8, 2.8)	(-10.8, 5.6)	(-9.3, 3.6)
		Pr >  t			0.3806
	Week 24	n	44	44	
		LS Mean	-7.028	-2.999	-4.029
	SEM	4.318	4.252	3.580	
	95% CI	(-15.5, 1.5)	(-11.4, 5.4)	(-11.1, 3.0)	
	Pr >  t			0.2610	
Week 32	n	38	40		
	LS Mean	-9.256	-3.578	-5.678	
	SEM	4.446	4.346	3.753	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169			
Week 40	95% CI		(-18.0,-0.5)	(-12.1, 5.0)	(-13.0, 1.7)
	Pr >  t				0.1309
	n	33		31	
	LS Mean	-5.737		-8.462	2.725
	SEM	4.540		4.549	4.049
Week 48	95% CI		(-14.7, 3.2)	(-17.4, 0.5)	(-5.2,10.7)
	Pr >  t				0.5012
	n	29		26	
	LS Mean	-9.524		-5.397	-4.127
	SEM	4.629		4.688	4.303
Week 56	95% CI		(-18.6,-0.4)	(-14.6, 3.8)	(-12.6, 4.3)
	Pr >  t				0.3378
	n	24		25	
	LS Mean	-6.009		-1.852	-4.158
	SEM	4.780		4.718	4.498
Week 64	95% CI		(-15.4, 3.4)	(-11.1, 7.4)	(-13.0, 4.7)
	Pr >  t				0.3556
	n	18		24	
	LS Mean	-10.91		-7.582	-3.330
	SEM	5.053		4.755	4.826
Week 72	95% CI		(-20.8,-1.0)	(-16.9, 1.8)	(-12.8, 6.1)
	Pr >  t				0.4904
	n	20		17	
	LS Mean	-8.337		-5.938	-2.399
	SEM	4.951		5.095	5.058
Week 84	95% CI		(-18.1, 1.4)	(-16.0, 4.1)	(-12.3, 7.5)
	Pr >  t				0.6354
	n	13		16	
	LS Mean	-8.088		-7.763	-0.326
	SEM	5.440		5.163	5.603
Week 96	95% CI		(-18.8, 2.6)	(-17.9, 2.4)	(-11.3,10.7)
	Pr >  t				0.9537
	n	12		10	
	LS Mean	-5.810		-6.700	0.890
	SEM	5.554		5.819	6.311
Week 108	95% CI		(-16.7, 5.1)	(-18.1, 4.7)	(-11.5,13.3)
	Pr >  t				0.8879
	n	7		9	
	LS Mean	-12.48		-6.528	-5.956
	SEM	6.481		5.995	7.287

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.2, 0.2)	(-18.3, 5.2)	(-20.3, 8.4)
		Pr >  t			0.4140
	Week 120	n	11	8	
		LS Mean	-4.923	-5.235	0.312
		SEM	5.694	6.213	6.791
		95% CI	(-16.1, 6.3)	(-17.4, 7.0)	(-13.0,13.6)
		Pr >  t			0.9634
	Week 132	n	9	4	
		LS Mean	-5.750	-12.72	6.974
		SEM	6.007	7.870	8.552
		95% CI	(-17.5, 6.0)	(-28.2, 2.7)	(-9.8,23.8)
		Pr >  t			0.4151
	Week 144	n	4	1	
		LS Mean	-16.84	-5.022	-11.81
		SEM	7.873	14.21	15.45
		95% CI	(-32.3,-1.4)	(-32.9,22.9)	(-42.2,18.5)
		Pr >  t			0.4449
	Week 156	n	5	1	
		LS Mean	-7.673	-7.022	-0.652
		SEM	7.262	14.21	15.15
		95% CI	(-21.9, 6.6)	(-34.9,20.9)	(-30.4,29.1)
		Pr >  t			0.9657
	Week 168	n	3		
		LS Mean	-7.833		
		SEM	8.812		
		95% CI	(-25.1, 9.5)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-8.828		
		SEM	14.20		
		95% CI	(-36.7,19.1)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-10.83		
		SEM	14.20		
		95% CI	(-38.7,17.1)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	-5.782	4.554	-10.34		
			SEM	4.392	4.140	3.882		
			95% CI	(-14.5, 2.9)	(-3.7, 12.8)	(-18.0, -2.7)		
					Pr >  t			0.0084
		Week 16	n	30	30			
			LS Mean	-5.049	3.268	-8.317		
			SEM	4.428	4.374	4.097		
			95% CI	(-13.8, 3.7)	(-5.4, 11.9)	(-16.4, -0.2)		
					Pr >  t		0.0436	
		Week 24	n	21	26			
			LS Mean	-2.420	1.123	-3.544		
			SEM	4.727	4.474	4.552		
			95% CI	(-11.8, 6.9)	(-7.7, 10.0)	(-12.5, 5.4)		
					Pr >  t		0.4370	
		Week 32	n	19	24			
			LS Mean	-7.002	1.792	-8.795		
			SEM	4.822	4.543	4.730		
			95% CI	(-16.5, 2.5)	(-7.2, 10.8)	(-18.1, 0.5)		
					Pr >  t		0.0640	
		Week 40	n	16	19			
			LS Mean	-2.140	-0.107	-2.032		
			SEM	4.999	4.829	5.139		
			95% CI	(-12.0, 7.7)	(-9.6, 9.4)	(-12.1, 8.1)		
					Pr >  t		0.6928	
		Week 48	n	16	18			
			LS Mean	-5.202	0.404	-5.606		
			SEM	4.999	4.884	5.189		
95% CI	(-15.1, 4.7)		(-9.2, 10.0)	(-15.8, 4.6)				
			Pr >  t		0.2808			
Week 56	n	12	14					
	LS Mean	-5.485	1.870	-7.355				
	SEM	5.344	5.169	5.799				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.0, 5.1)	(-8.3,12.1)	(-18.8, 4.1)
		Pr >  t			0.2055
	Week 64	n	12	11	
		LS Mean	-5.318	-4.750	-0.569
		SEM	5.344	5.502	6.093
		95% CI	(-15.9, 5.2)	(-15.6, 6.1)	(-12.6,11.4)
		Pr >  t			0.9257
	Week 72	n	10	9	
		LS Mean	-12.56	-2.041	-10.51
		SEM	5.608	5.824	6.610
		95% CI	(-23.6,-1.5)	(-13.5, 9.4)	(-23.5, 2.5)
		Pr >  t			0.1125
	Week 84	n	8	8	
		LS Mean	-7.533	-8.256	0.723
		SEM	6.054	6.036	7.114
		95% CI	(-19.5, 4.4)	(-20.1, 3.6)	(-13.3,14.7)
		Pr >  t			0.9191
	Week 96	n	6	6	
		LS Mean	-2.775	-5.497	2.722
		SEM	6.630	6.620	8.082
		95% CI	(-15.8,10.3)	(-18.5, 7.5)	(-13.2,18.6)
		Pr >  t			0.7364
	Week 108	n	4	5	
		LS Mean	-15.20	-7.546	-7.654
		SEM	7.644	7.051	9.259
		95% CI	(-30.2,-0.2)	(-21.4, 6.3)	(-25.9,10.6)
		Pr >  t			0.4090
	Week 120	n	4	4	
		LS Mean	-2.450	-7.673	5.224
		SEM	7.644	7.651	9.722
		95% CI	(-17.5,12.6)	(-22.7, 7.4)	(-13.9,24.3)
		Pr >  t			0.5914
	Week 132	n	3	2	
		LS Mean	-16.81	-9.336	-7.477
		SEM	8.535	10.07	12.32
		95% CI	(-33.6,-0.0)	(-29.1,10.5)	(-31.7,16.8)
		Pr >  t			0.5443
	Week 144	n	3	1	
		LS Mean	-28.81	-1.645	-27.17
		SEM	8.535	13.70	15.42

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-45.6, -12)	(-28.6,25.3)	(-57.5, 3.2)
		Pr >  t			0.0790
	Week 156	n	2	1	
		LS Mean	-2.551	-3.645	1.094
		SEM	10.07	13.70	16.32
		95% CI	(-22.3,17.2)	(-30.6,23.3)	(-31.0,33.2)
		Pr >  t			0.9466
	Week 168	n	1		
		LS Mean	-7.671		
		SEM	13.67		
		95% CI	(-34.6,19.2)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	10.730	6.338	4.391
		SEM	9.391	9.071	5.801
		95% CI	(-8.0,29.5)	(-11.7,24.4)	(-7.2,16.0)
		Pr >  t			0.4517
	Week 16	n	15	14	
		LS Mean	14.469	6.941	7.528
		SEM	9.440	8.584	6.162
		95% CI	(-4.4,33.3)	(-10.2,24.1)	(-4.8,19.8)
		Pr >  t			0.2257
	Week 24	n	12	11	
		LS Mean	15.688	9.388	6.300
		SEM	9.604	9.323	6.656
		95% CI	(-3.5,34.8)	(-9.2,27.9)	(-6.9,19.5)
		Pr >  t			0.3465
	Week 32	n	8	9	
		LS Mean	13.920	10.941	2.979
		SEM	9.969	9.515	7.393
		95% CI	(-5.9,33.8)	(-8.0,29.9)	(-11.7,17.6)
		Pr >  t			0.6878
	Week 40	n	6	7	
		LS Mean	11.991	7.938	4.053
		SEM	10.31	9.766	8.132
		95% CI	(-8.5,32.5)	(-11.5,27.3)	(-12.0,20.1)
		Pr >  t			0.6191
	Week 48	n	4	6	
		LS Mean	-0.561	6.498	-7.059
		SEM	10.92	9.957	9.102

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 56	95% CI	(-22.2,21.1)	(-13.3,26.3)	(-25.1,10.9)	
	Pr >  t			0.4393	
	n	4	6		
	LS Mean	19.919	9.523	10.395	
	SEM	10.92	9.974	9.119	
Week 64	95% CI	(-1.8,41.6)	(-10.3,29.3)	(-7.6,28.4)	
	Pr >  t			0.2563	
	n	4	4		
	LS Mean	15.245	5.620	9.625	
	SEM	10.94	10.59	9.784	
Week 72	95% CI	(-6.5,37.0)	(-15.4,26.6)	(-9.7,29.0)	
	Pr >  t			0.3269	
	n	4	4		
	LS Mean	25.495	3.870	21.625	
	SEM	10.94	10.59	9.784	
Week 84	95% CI	( 3.8,47.2)	(-17.1,24.9)	( 2.3,41.0)	
	Pr >  t			0.0287	
	n	4	4		
	LS Mean	17.439	5.870	11.569	
	SEM	10.92	10.59	9.786	
Week 96	95% CI	(-4.2,39.1)	(-15.1,26.9)	(-7.8,30.9)	
	Pr >  t			0.2391	
	n	3	2		
	LS Mean	13.416	0.569	12.846	
	SEM	11.50	12.22	12.06	
Week 108	95% CI	(-9.4,36.2)	(-23.6,24.7)	(-11.0,36.7)	
	Pr >  t			0.2886	
	n	3	3		
	LS Mean	19.416	0.325	19.091	
	SEM	11.50	11.17	11.00	
Week 120	95% CI	(-3.4,42.2)	(-21.8,22.4)	(-2.6,40.8)	
	Pr >  t			0.0847	
	n	3	1		
	LS Mean	6.749	1.485	5.264	
	SEM	11.50	14.92	14.81	
Week 132	95% CI	(-16.0,29.5)	(-28.0,31.0)	(-24.0,34.5)	
	Pr >  t			0.7227	
	n	2	1		
	LS Mean	22.259	12.485	9.774	
	SEM	12.52	14.92	15.62	



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-2.5,47.0)	(-17.0,42.0)	(-21.1,40.7)
		Pr >  t			0.5326
	Week 156	n	1		
		LS Mean	19.647		
		SEM	15.21		
		95% CI	(-10.4,49.7)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	16.647		
		SEM	15.21		
		95% CI	(-13.4,46.7)		
		Pr >  t			
White	Week 8	n	93	86	
		LS Mean	-7.459	-5.777	-1.682
		SEM	2.641	2.779	2.498
		95% CI	(-12.7,-2.3)	(-11.2,-0.3)	(-6.6, 3.2)
		Pr >  t			0.5010
	Week 16	n	79	61	
		LS Mean	-3.928	-5.178	1.250
		SEM	2.736	3.007	2.767
		95% CI	(-9.3, 1.5)	(-11.1, 0.7)	(-4.2, 6.7)
		Pr >  t			0.6517
	Week 24	n	71	44	
		LS Mean	-8.002	-6.962	-1.040
		SEM	2.793	3.190	3.018
		95% CI	(-13.5,-2.5)	(-13.2,-0.7)	(-7.0, 4.9)
		Pr >  t			0.7305
	Week 32	n	59	39	
		LS Mean	-6.241	-5.694	-0.547
		SEM	2.913	3.284	3.177
		95% CI	(-12.0,-0.5)	(-12.1, 0.8)	(-6.8, 5.7)
		Pr >  t			0.8634
	Week 40	n	52	35	
		LS Mean	-3.912	-7.004	3.092
		SEM	2.977	3.358	3.312
		95% CI	(-9.8, 1.9)	(-13.6,-0.4)	(-3.4, 9.6)
		Pr >  t			0.3509
	Week 48	n	48	26	
		LS Mean	-5.317	-5.710	0.393
		SEM	3.020	3.585	3.578

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.3, 0.6)	(-12.8, 1.3)	(-6.6, 7.4)
		Pr >  t			0.9126
	Week 56	n	42	24	
		LS Mean	-4.843	-6.075	1.232
		SEM	3.094	3.655	3.712
		95% CI	(-10.9, 1.2)	(-13.3, 1.1)	(-6.1, 8.5)
		Pr >  t			0.7402
	Week 64	n	30	26	
		LS Mean	-4.909	-6.459	1.549
		SEM	3.317	3.587	3.840
		95% CI	(-11.4, 1.6)	(-13.5, 0.6)	(-6.0, 9.1)
		Pr >  t			0.6867
	Week 72	n	34	21	
		LS Mean	-3.798	-4.930	1.131
		SEM	3.230	3.778	3.946
		95% CI	(-10.1, 2.5)	(-12.3, 2.5)	(-6.6, 8.9)
		Pr >  t			0.7744
	Week 84	n	28	20	
		LS Mean	-3.062	-4.538	1.476
		SEM	3.378	3.826	4.108
		95% CI	(-9.7, 3.6)	(-12.1, 3.0)	(-6.6, 9.5)
		Pr >  t			0.7194
	Week 96	n	27	15	
		LS Mean	-2.362	-14.17	11.812
		SEM	3.400	4.142	4.428
		95% CI	(-9.0, 4.3)	(-22.3, -6.0)	(3.1, 20.5)
		Pr >  t			0.0078
	Week 108	n	19	12	
		LS Mean	-3.403	-7.079	3.676
		SEM	3.739	4.437	4.947
		95% CI	(-10.7, 3.9)	(-15.8, 1.6)	(-6.0, 13.4)
		Pr >  t			0.4577
	Week 120	n	22	10	
		LS Mean	-5.832	-3.458	-2.374
		SEM	3.586	4.710	5.091
		95% CI	(-12.9, 1.2)	(-12.7, 5.8)	(-12.4, 7.6)
		Pr >  t			0.6412
	Week 132	n	15	4	
		LS Mean	-2.805	-8.832	6.027
		SEM	4.005	6.672	7.168

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.7, 5.1)	(-21.9, 4.3)	(-8.0,20.1)
		Pr >  t			0.4007
	Week 144	n	12	4	
		LS Mean	-1.000	-3.414	2.413
		SEM	4.292	6.675	7.344
		95% CI	(-9.4, 7.4)	(-16.5, 9.7)	(-12.0,16.8)
		Pr >  t			0.7425
	Week 156	n	7	2	
		LS Mean	-4.704	-10.87	6.164
		SEM	5.229	9.027	9.983
		95% CI	(-15.0, 5.6)	(-28.6, 6.8)	(-13.4,25.8)
		Pr >  t			0.5371
	Week 168	n	2	2	
		LS Mean	1.057	-3.867	4.925
		SEM	8.941	9.027	12.34
		95% CI	(-16.5,18.6)	(-21.6,13.8)	(-19.3,29.1)
		Pr >  t			0.6899
	Week 180	n	1	1	
		LS Mean	-5.592	-8.056	2.465
		SEM	12.40	12.45	17.31
		95% CI	(-29.9,18.8)	(-32.5,16.4)	(-31.5,36.4)
		Pr >  t			0.8868
	Week 192	n	1	1	
		LS Mean	-7.592	-4.056	-3.535
		SEM	12.40	12.45	17.31
		95% CI	(-31.9,16.8)	(-28.5,20.4)	(-37.5,30.4)
		Pr >  t			0.8382

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	-5.616	4.465	-10.08		
			SEM	4.487	4.201	4.010		
			95% CI	(-14.5, 3.3)	(-3.9,12.8)	(-18.0,-2.2)		
					Pr >  t			0.0127
		Week 16	n	28	29			
			LS Mean	-5.734	2.948	-8.682		
			SEM	4.529	4.447	4.240		
			95% CI	(-14.7, 3.2)	(-5.9,11.8)	(-17.0,-0.3)		
					Pr >  t			0.0418
		Week 24	n	21	25			
			LS Mean	-2.520	0.813	-3.332		
			SEM	4.781	4.555	4.648		
			95% CI	(-12.0, 6.9)	(-8.2, 9.8)	(-12.5, 5.8)		
					Pr >  t			0.4741
		Week 32	n	19	23			
			LS Mean	-7.101	1.216	-8.317		
			SEM	4.877	4.631	4.831		
			95% CI	(-16.8, 2.5)	(-7.9,10.4)	(-17.8, 1.2)		
					Pr >  t			0.0863
		Week 40	n	16	18			
			LS Mean	-2.231	-0.716	-1.515		
			SEM	5.056	4.942	5.262		
			95% CI	(-12.2, 7.8)	(-10.5, 9.0)	(-11.9, 8.8)		
					Pr >  t			0.7736
		Week 48	n	16	17			
			LS Mean	-5.293	-0.365	-4.928		
			SEM	5.056	5.003	5.317		
95% CI	(-15.3, 4.7)		(-10.2, 9.5)	(-15.4, 5.5)				
			Pr >  t			0.3547		
Week 56	n	12	14					
	LS Mean	-5.574	1.472	-7.047				
	SEM	5.403	5.229	5.873				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-16.2, 5.1)	(-8.8, 11.8)	(-18.6, 4.5)
	Pr >  t			0.2310
	n	12	11	
	LS Mean	-5.408	-5.169	-0.239
	SEM	5.403	5.565	6.170
Week 72	95% CI	(-16.1, 5.3)	(-16.1, 5.8)	(-12.4, 11.9)
	Pr >  t			0.9691
	n	10	8	
	LS Mean	-12.64	-3.579	-9.062
	SEM	5.670	6.105	6.879
Week 84	95% CI	(-23.8, -1.5)	(-15.6, 8.4)	(-22.6, 4.5)
	Pr >  t			0.1886
	n	8	8	
	LS Mean	-7.614	-8.704	1.090
	SEM	6.119	6.105	7.199
Week 96	95% CI	(-19.7, 4.4)	(-20.7, 3.3)	(-13.1, 15.2)
	Pr >  t			0.8797
	n	6	6	
	LS Mean	-2.851	-5.943	3.092
	SEM	6.700	6.693	8.174
Week 108	95% CI	(-16.0, 10.3)	(-19.1, 7.2)	(-13.0, 19.2)
	Pr >  t			0.7055
	n	4	5	
	LS Mean	-15.27	-8.000	-7.271
	SEM	7.723	7.128	9.361
Week 120	95% CI	(-30.5, -0.1)	(-22.0, 6.0)	(-25.7, 11.1)
	Pr >  t			0.4378
	n	4	4	
	LS Mean	-2.522	-8.138	5.616
	SEM	7.723	7.733	9.828
Week 132	95% CI	(-17.7, 12.7)	(-23.3, 7.1)	(-13.7, 24.9)
	Pr >  t			0.5680
	n	3	2	
	LS Mean	-16.89	-9.789	-7.101
	SEM	8.622	10.17	12.45
Week 144	95% CI	(-33.8, 0.1)	(-29.8, 10.2)	(-31.6, 17.4)
	Pr >  t			0.5688
	n	3	1	
	LS Mean	-28.89	-2.128	-26.76
	SEM	8.622	13.84	15.58

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Europe	Week 156	95% CI	(-45.8, -12)	(-29.3,25.1)	(-57.4, 3.9)
		Pr >  t			0.0868
		n	2	1	
		LS Mean	-2.644	-4.128	1.484
		SEM	10.17	13.84	16.49
	Week 168	95% CI	(-22.6,17.4)	(-31.3,23.1)	(-30.9,33.9)
		Pr >  t			0.9283
		n	1		
		LS Mean	-7.798		
		SEM	13.81		
	Week 8	95% CI	(-34.9,19.4)		
		Pr >  t			
		n	66	69	
		LS Mean	-13.35	-9.668	-3.678
		SEM	5.091	5.091	2.855
	Week 16	95% CI	(-23.4,-3.3)	(-19.7, 0.4)	( -9.3, 1.9)
		Pr >  t			0.1985
		n	58	48	
		LS Mean	-4.930	-10.84	5.910
		SEM	5.130	5.190	3.170
	Week 24	95% CI	(-15.1, 5.2)	(-21.1,-0.6)	( -0.3,12.1)
		Pr >  t			0.0630
		n	51	36	
		LS Mean	-12.85	-11.73	-1.129
SEM		5.174	5.297	3.460	
Week 32	95% CI	(-23.1,-2.6)	(-22.2,-1.3)	( -7.9, 5.7)	
	Pr >  t			0.7443	
	n	43	30		
	LS Mean	-9.292	-9.726	0.434	
	SEM	5.291	5.457	3.707	
Week 40	95% CI	(-19.7, 1.1)	(-20.5, 1.0)	( -6.8, 7.7)	
	Pr >  t			0.9068	
	n	37	25		
	LS Mean	-8.251	-10.03	1.775	
	SEM	5.354	5.563	3.953	
Week 48	95% CI	(-18.8, 2.3)	(-21.0, 0.9)	( -6.0, 9.5)	
	Pr >  t			0.6535	
	n	33	21		
	LS Mean	-7.937	-9.974	2.037	
	SEM	5.408	5.684	4.188	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-18.6, 2.7)	(-21.2, 1.2)	(-6.2,10.3)
	Pr >  t			0.6268
Week 56	n	29	20	
	LS Mean	-3.394	-6.930	3.536
	SEM	5.469	5.721	4.322
	95% CI	(-14.2, 7.4)	(-18.2, 4.3)	(-5.0,12.0)
	Pr >  t			0.4136
Week 64	n	23	20	
	LS Mean	-9.001	-9.282	0.282
	SEM	5.606	5.723	4.496
	95% CI	(-20.0, 2.0)	(-20.6, 2.0)	(-8.5, 9.1)
	Pr >  t			0.9500
Week 72	n	25	19	
	LS Mean	-2.263	-9.895	7.632
	SEM	5.557	5.761	4.481
	95% CI	(-13.2, 8.7)	(-21.2, 1.5)	(-1.2,16.4)
	Pr >  t			0.0889
Week 84	n	22	17	
	LS Mean	-6.125	-7.750	1.625
	SEM	5.636	5.852	4.695
	95% CI	(-17.2, 5.0)	(-19.3, 3.8)	(-7.6,10.8)
	Pr >  t			0.7294
Week 96	n	20	13	
	LS Mean	-6.546	-19.43	12.888
	SEM	5.703	6.104	5.085
	95% CI	(-17.8, 4.7)	(-31.4,-7.4)	( 2.9,22.9)
	Pr >  t			0.0115
Week 108	n	15	11	
	LS Mean	-5.549	-11.12	5.572
	SEM	5.948	6.294	5.569
	95% CI	(-17.3, 6.2)	(-23.5, 1.3)	(-5.4,16.5)
	Pr >  t			0.3173
Week 120	n	17	8	
	LS Mean	-8.809	-7.099	-1.710
	SEM	5.841	6.730	5.951
	95% CI	(-20.3, 2.7)	(-20.3, 6.1)	(-13.4,10.0)
	Pr >  t			0.7739
Week 132	n	12	3	
	LS Mean	-2.073	-13.18	11.112
	SEM	6.170	8.929	8.595

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.2,10.1)	(-30.7, 4.3)	(-5.8,28.0)
		Pr >  t			0.1965
	Week 144	n	7	4	
		LS Mean	-3.619	-6.982	3.363
		SEM	6.918	8.125	8.364
		95% CI	(-17.2,10.0)	(-22.9, 9.0)	(-13.1,19.8)
		Pr >  t			0.6877
	Week 156	n	5	2	
		LS Mean	-5.876	-14.43	8.552
		SEM	7.565	10.35	10.98
		95% CI	(-20.7, 9.0)	(-34.7, 5.9)	(-13.0,30.1)
		Pr >  t			0.4361
	Week 168	n	2	2	
		LS Mean	0.444	-7.428	7.873
		SEM	10.32	10.35	13.03
		95% CI	(-19.8,20.7)	(-27.7,12.9)	(-17.7,33.5)
		Pr >  t			0.5459
	Week 180	n		1	
		LS Mean		-11.64	
		SEM		13.74	
		95% CI		(-38.6,15.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-7.644	
		SEM		13.74	
		95% CI		(-34.6,19.3)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	6.052	8.521	-2.469
		SEM	3.952	3.861	5.665
		95% CI	(-1.9,14.0)	( 0.7,16.3)	(-13.9, 9.0)
		Pr >  t			0.6653
	Week 16	n	13	12	
		LS Mean	5.022	14.068	-9.046
		SEM	4.010	3.965	5.772
		95% CI	(-3.1,13.1)	( 6.1,22.1)	(-20.7, 2.6)
		Pr >  t			0.1247
	Week 24	n	12	10	
		LS Mean	6.961	9.665	-2.704
		SEM	4.077	4.159	5.943



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-1.3,15.2)	( 1.3,18.0)	(-14.7, 9.3)
	Pr >  t			0.6513
	n	9	10	
	LS Mean	6.538	12.965	-6.427
	SEM	4.357	4.159	6.132
Week 40	95% CI	(-2.2,15.3)	( 4.6,21.3)	(-18.7, 5.9)
	Pr >  t			0.2996
	n	7	10	
	LS Mean	4.763	10.265	-5.501
	SEM	4.646	4.159	6.340
Week 48	95% CI	(-4.5,14.0)	( 1.9,18.6)	(-18.2, 7.2)
	Pr >  t			0.3892
	n	7	7	
	LS Mean	-5.522	9.545	-15.07
	SEM	4.646	4.558	6.604
Week 56	95% CI	(-14.8, 3.8)	( 0.5,18.6)	(-28.3,-1.9)
	Pr >  t			0.0258
	n	6	7	
	LS Mean	1.405	4.718	-3.314
	SEM	4.854	4.554	6.751
Week 64	95% CI	(-8.3,11.1)	(-4.4,13.8)	(-16.8,10.2)
	Pr >  t			0.6251
	n	4	7	
	LS Mean	9.050	8.058	0.992
	SEM	5.463	4.552	7.186
Week 72	95% CI	(-1.8,19.9)	(-1.0,17.1)	(-13.3,15.3)
	Pr >  t			0.8905
	n	4	4	
	LS Mean	8.300	8.062	0.238
	SEM	5.463	5.384	7.735
Week 84	95% CI	(-2.5,19.1)	(-2.6,18.7)	(-15.1,15.6)
	Pr >  t			0.9755
	n	4	5	
	LS Mean	8.440	5.859	2.581
	SEM	5.474	5.016	7.507
Week 96	95% CI	(-2.4,19.3)	(-4.1,15.8)	(-12.3,17.5)
	Pr >  t			0.7318
	n	4	2	
	LS Mean	13.300	3.444	9.856
	SEM	5.463	6.914	8.868

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	( 2.5,24.1)	(-10.2,17.1)	( -7.7,27.4)
		Pr >  t			0.2686
		n	2	3	
	Week 120	LS Mean	3.444	-0.803	4.247
		SEM	6.985	5.955	9.243
		95% CI	(-10.4,17.3)	(-12.6,11.0)	(-14.0,22.5)
	Week 120	Pr >  t			0.6466
		n	2	2	
		LS Mean	7.156	4.566	2.590
	Week 132	SEM	6.986	6.916	9.872
		95% CI	( -6.7,21.0)	( -9.1,18.2)	(-16.9,22.1)
		Pr >  t			0.7934
	Week 132	n	1	2	
		LS Mean	6.872	10.066	-3.193
		SEM	9.320	6.916	11.65
	Week 8	95% CI	(-11.5,25.3)	( -3.6,23.7)	(-26.2,19.8)
		Pr >  t			0.7843
		n	16	19	
	Week 8	LS Mean	1.469	-3.830	5.299
		SEM	5.306	5.153	6.283
		95% CI	( -9.3,12.2)	(-14.3, 6.6)	( -7.4,18.0)
	Week 16	Pr >  t			0.4039
		n	13	14	
		LS Mean	-1.296	-0.944	-0.352
Week 16	SEM	5.597	5.497	6.779	
	95% CI	(-12.6,10.0)	(-12.0,10.1)	(-14.0,13.3)	
	Pr >  t			0.9588	
Week 24	n	12	8		
	LS Mean	1.702	1.892	-0.190	
	SEM	5.679	6.482	7.585	
Week 24	95% CI	( -9.7,13.1)	(-11.0,14.8)	(-15.3,14.9)	
	Pr >  t			0.9801	
	n	9	7		
Week 32	LS Mean	-3.388	-2.992	-0.396	
	SEM	6.092	6.694	8.056	
	95% CI	(-15.6, 8.8)	(-16.3,10.3)	(-16.4,15.6)	
Week 32	Pr >  t			0.9609	
	n	9	7		
	LS Mean	0.282	-7.278	7.560	
Week 40	SEM	6.105	6.694	8.080	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-11.9,12.5)	(-20.6, 6.0)	(-8.5,23.6)
	Pr >  t			0.3521
	n	8	5	
	LS Mean	-7.211	-0.515	-6.696
	SEM	6.279	7.322	8.738
Week 56	95% CI	(-19.8, 5.3)	(-15.0,14.0)	(-24.0,10.6)
	Pr >  t			0.4452
	n	7	3	
	LS Mean	-3.135	-5.092	1.957
	SEM	6.482	8.582	9.962
Week 64	95% CI	(-16.1, 9.8)	(-22.1,11.9)	(-17.8,21.7)
	Pr >  t			0.8446
	n	5	3	
	LS Mean	-5.894	-7.758	1.864
	SEM	7.098	8.582	10.39
Week 72	95% CI	(-20.0, 8.2)	(-24.7, 9.2)	(-18.7,22.4)
	Pr >  t			0.8578
	n	5	3	
	LS Mean	-7.517	7.424	-14.94
	SEM	7.098	8.568	10.35
Week 84	95% CI	(-21.6, 6.6)	(-9.5,24.4)	(-35.4, 5.5)
	Pr >  t			0.1514
	n	2	2	
	LS Mean	-4.375	-1.747	-2.628
	SEM	9.738	9.895	13.26
Week 96	95% CI	(-23.6,14.9)	(-21.3,17.8)	(-28.8,23.6)
	Pr >  t			0.8432
	n	3	2	
	LS Mean	-8.825	-6.747	-2.078
	SEM	8.324	9.895	12.31
Week 108	95% CI	(-25.3, 7.6)	(-26.3,12.8)	(-26.4,22.2)
	Pr >  t			0.8661
	n	1	2	
	LS Mean	-4.810	10.753	-15.56
	SEM	12.86	9.895	15.70
Week 120	95% CI	(-30.2,20.6)	(-8.8,30.3)	(-46.6,15.5)
	Pr >  t			0.3234
	n	3	2	
	LS Mean	-14.83	6.253	-21.08
	SEM	8.324	9.895	12.31

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-31.3, 1.6)	(-13.3,25.8)	(-45.4, 3.2)
		Pr >  t			0.0889
	Week 132	n	1	1	
		LS Mean	-5.294	-24.23	18.933
		SEM	12.84	12.99	17.83
		95% CI	(-30.7,20.1)	(-49.9, 1.5)	(-16.3,54.2)
		Pr >  t			0.2902
	Week 144	n	2		
		LS Mean	-9.333		
		SEM	9.641		
		95% CI	(-28.4, 9.7)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	-9.294		
		SEM	12.84		
		95% CI	(-34.7,16.1)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-7.294		
		SEM	12.84		
		95% CI	(-32.7,18.1)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-6.294		
		SEM	12.84		
		95% CI	(-31.7,19.1)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-8.294		
		SEM	12.84		
		95% CI	(-33.7,17.1)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	-7.277	-4.186	-3.091
		SEM	3.920	6.075	6.826
		95% CI	(-15.2, 0.6)	(-16.3, 8.0)	(-16.8,10.6)
		Pr >  t			0.6524
	Week 16	n	13	4	
		LS Mean	-10.27	-6.965	-3.303
		SEM	4.257	7.086	7.562

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-18.8,-1.7)	(-21.1, 7.2)	(-18.4,11.8)
	Pr >  t			0.6637
	n	9	3	
	LS Mean	-9.055	-2.728	-6.327
	SEM	4.935	8.056	8.800
Week 32	95% CI	(-18.9, 0.8)	(-18.8,13.3)	(-23.9,11.2)
	Pr >  t			0.4746
	n	6	3	
	LS Mean	-8.056	-8.061	0.005
	SEM	5.949	8.056	9.272
Week 40	95% CI	(-19.9, 3.8)	(-24.1, 8.0)	(-18.5,18.5)
	Pr >  t			0.9996
	n	6	2	
	LS Mean	-3.887	-13.00	9.115
	SEM	6.074	9.664	10.75
Week 48	95% CI	(-16.0, 8.2)	(-32.2, 6.2)	(-12.3,30.5)
	Pr >  t			0.3993
	n	5	1	
	LS Mean	-1.973	-1.611	-0.362
	SEM	6.499	13.35	14.42
Week 56	95% CI	(-14.9,11.0)	(-28.2,24.9)	(-29.0,28.3)
	Pr >  t			0.9800
	n	5	1	
	LS Mean	-13.97	-5.611	-8.362
	SEM	6.499	13.35	14.42
Week 64	95% CI	(-26.9,-1.0)	(-32.2,20.9)	(-37.0,20.3)
	Pr >  t			0.5636
	n	3	1	
	LS Mean	2.468	-3.611	6.080
	SEM	7.984	13.35	15.14
Week 72	95% CI	(-13.4,18.4)	(-30.2,22.9)	(-24.0,36.2)
	Pr >  t			0.6891
	n	4	1	
	LS Mean	-14.15	3.389	-17.54
	SEM	7.126	13.35	14.71
Week 84	95% CI	(-28.3, 0.0)	(-23.2,29.9)	(-46.8,11.7)
	Pr >  t			0.2366
	n	4	1	
	LS Mean	2.101	-4.611	6.713
	SEM	7.126	13.35	14.71

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-12.1,16.3)	(-31.2,21.9)	(-22.6,36.0)
	Pr >  t			0.6494
	n	3	1	
	LS Mean	5.135	-5.611	10.746
	SEM	7.984	13.35	15.14
Week 108	95% CI	(-10.7,21.0)	(-32.2,20.9)	(-19.4,40.9)
	Pr >  t			0.4800
	n	4		
	LS Mean	0.851		
	SEM	7.126		
Week 120	95% CI	(-13.3,15.0)		
	Pr >  t			
	n	3		
	LS Mean	-1.532		
	SEM	7.984		
Week 132	95% CI	(-17.4,14.4)		
	Pr >  t			
	n	3		
	LS Mean	-10.20		
	SEM	7.984		
Week 144	95% CI	(-26.1, 5.7)		
	Pr >  t			
	n	3		
	LS Mean	4.623		
	SEM	8.009		
Week 156	95% CI	(-11.3,20.6)		
	Pr >  t			
	n	2		
	LS Mean	-4.289		
	SEM	9.501		
	95% CI	(-23.2,14.6)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	91		
		LS Mean	-7.083	-2.160	-4.923	
		SEM	2.921	2.852	2.361	
		95% CI	(-12.8, -1.3)	(-7.8, 3.5)	(-9.6, -0.3)	
			Pr >  t			0.0375
	Week 16	n	89	71		
		LS Mean	-2.254	-1.839	-0.414	
		SEM	2.984	3.069	2.548	
		95% CI	(-8.1, 3.6)	(-7.9, 4.2)	(-5.4, 4.6)	
			Pr >  t			0.8709
	Week 24	n	75	55		
		LS Mean	-4.542	-3.730	-0.812	
		SEM	3.044	3.192	2.782	
		95% CI	(-10.5, 1.4)	(-10.0, 2.5)	(-6.3, 4.7)	
			Pr >  t			0.7706
	Week 32	n	62	52		
		LS Mean	-5.578	-2.018	-3.560	
		SEM	3.141	3.222	2.910	
		95% CI	(-11.8, 0.6)	(-8.4, 4.3)	(-9.3, 2.2)	
			Pr >  t			0.2216
	Week 40	n	51	46		
		LS Mean	-2.461	-3.639	1.178	
		SEM	3.237	3.311	3.092	
		95% CI	(-8.8, 3.9)	(-10.1, 2.9)	(-4.9, 7.2)	
			Pr >  t			0.7033
	Week 48	n	50	37		
		LS Mean	-6.524	-1.200	-5.324	
		SEM	3.249	3.449	3.250	
95% CI		(-12.9, -0.1)	(-8.0, 5.6)	(-11.7, 1.1)		
		Pr >  t			0.1017	
Week 56	n	43	33			
	LS Mean	-1.362	-1.284	-0.078		
	SEM	3.333	3.532	3.422		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.9, 5.2)	(-8.2, 5.7)	(-6.8, 6.6)
	Pr >  t			0.9818
	n	35	33	
	LS Mean	-4.860	-2.344	-2.517
	SEM	3.464	3.532	3.553
Week 72	95% CI	(-11.7, 1.9)	(-9.3, 4.6)	(-9.5, 4.5)
	Pr >  t			0.4789
	n	35	31	
	LS Mean	-1.262	-2.008	0.746
	SEM	3.464	3.579	3.600
Week 84	95% CI	(-8.1, 5.5)	(-9.0, 5.0)	(-6.3, 7.8)
	Pr >  t			0.8358
	n	31	29	
	LS Mean	-2.521	-4.076	1.555
	SEM	3.562	3.632	3.736
Week 96	95% CI	(-9.5, 4.5)	(-11.2, 3.1)	(-5.8, 8.9)
	Pr >  t			0.6774
	n	27	22	
	LS Mean	-0.310	-10.39	10.079
	SEM	3.661	3.879	4.077
Week 108	95% CI	(-7.5, 6.9)	(-18.0, -2.8)	( 2.1, 18.1)
	Pr >  t			0.0136
	n	19	20	
	LS Mean	-3.276	-4.477	1.201
	SEM	4.014	3.976	4.473
Week 120	95% CI	(-11.2, 4.6)	(-12.3, 3.3)	(-7.6, 10.0)
	Pr >  t			0.7884
	n	21	15	
	LS Mean	-4.034	-2.243	-1.791
	SEM	3.891	4.312	4.686
Week 132	95% CI	(-11.7, 3.6)	(-10.7, 6.2)	(-11.0, 7.4)
	Pr >  t			0.7024
	n	15	7	
	LS Mean	-5.398	-10.06	4.664
	SEM	4.291	5.585	6.141
Week 144	95% CI	(-13.8, 3.0)	(-21.0, 0.9)	(-7.4, 16.7)
	Pr >  t			0.4477
	n	10	5	
Week 144	LS Mean	-11.31	-0.937	-10.37
	SEM	4.866	6.379	7.263

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.9,-1.8)	(-13.5,11.6)	(-24.6, 3.9)
		Pr >  t			0.1537
	Week 156	n	6	3	
		LS Mean	-1.146	-6.905	5.759
		SEM	5.913	7.913	9.257
		95% CI	(-12.7,10.5)	(-22.4, 8.6)	(-12.4,23.9)
		Pr >  t			0.5340
	Week 168	n	3	2	
		LS Mean	0.123	-0.775	0.898
		SEM	7.901	9.489	11.86
		95% CI	(-15.4,15.6)	(-19.4,17.8)	(-22.4,24.2)
		Pr >  t			0.9396
	Week 180	n	1	1	
		LS Mean	-5.765	-5.153	-0.612
		SEM	13.12	13.11	18.22
		95% CI	(-31.5,20.0)	(-30.9,20.6)	(-36.4,35.1)
		Pr >  t			0.9732
	Week 192	n	1	1	
		LS Mean	-7.765	-1.153	-6.612
		SEM	13.12	13.11	18.22
		95% CI	(-33.5,18.0)	(-26.9,24.6)	(-42.4,29.1)
		Pr >  t			0.7168
1	Week 8	n	43	50	
		LS Mean	-1.442	-0.245	-1.197
		SEM	3.401	3.558	3.490
		95% CI	(-8.2, 5.3)	(-7.3, 6.8)	(-8.1, 5.7)
		Pr >  t			0.7321
	Week 16	n	35	35	
		LS Mean	-2.727	-0.439	-2.288
		SEM	3.560	3.691	3.834
		95% CI	(-9.8, 4.3)	(-7.7, 6.9)	(-9.8, 5.3)
		Pr >  t			0.5514
	Week 24	n	29	26	
		LS Mean	-5.411	0.002	-5.413
		SEM	3.703	3.950	4.143
		95% CI	(-12.7, 1.9)	(-7.8, 7.8)	(-13.6, 2.7)
		Pr >  t			0.1926
	Week 32	n	23	21	
		LS Mean	-2.593	-0.992	-1.601
		SEM	3.914	4.155	4.445

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-10.3, 5.1)	(-9.2, 7.2)	(-10.3, 7.1)
	Pr >  t			0.7190
	n	23	16	
	LS Mean	-2.069	-3.319	1.250
	SEM	3.923	4.396	4.678
Week 48	95% CI	(-9.8, 5.7)	(-12.0, 5.3)	(-8.0,10.5)
	Pr >  t			0.7895
	n	18	14	
	LS Mean	-0.382	-5.926	5.544
	SEM	4.123	4.538	4.988
Week 56	95% CI	(-8.5, 7.7)	(-14.9, 3.0)	(-4.3,15.4)
	Pr >  t			0.2671
	n	15	12	
	LS Mean	-5.330	-3.035	-2.295
	SEM	4.305	4.712	5.303
Week 64	95% CI	(-13.8, 3.1)	(-12.3, 6.2)	(-12.7, 8.1)
	Pr >  t			0.6655
	n	11	9	
	LS Mean	0.154	-11.11	11.262
	SEM	4.652	5.100	5.924
Week 72	95% CI	(-9.0, 9.3)	(-21.1,-1.1)	(-0.4,22.9)
	Pr >  t			0.0580
	n	12	4	
	LS Mean	-8.580	-6.493	-2.088
	SEM	4.558	6.682	7.268
Week 84	95% CI	(-17.6, 0.4)	(-19.6, 6.6)	(-16.4,12.2)
	Pr >  t			0.7741
	n	8	4	
	LS Mean	-0.614	-3.993	3.378
	SEM	5.140	6.682	7.636
Week 96	95% CI	(-10.7, 9.5)	(-17.1, 9.1)	(-11.6,18.4)
	Pr >  t			0.6584
	n	8	2	
	LS Mean	-3.614	-8.512	4.898
	SEM	5.140	8.795	9.538
Week 108	95% CI	(-13.7, 6.5)	(-25.8, 8.8)	(-13.9,23.7)
	Pr >  t			0.6079
	n	6	1	
Week 108	LS Mean	-2.023	-20.08	18.061
	SEM	5.646	11.94	12.71

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.1, 9.1)	(-43.6, 3.4)	( -6.9,43.1)
		Pr >  t			0.1561
	Week 120	n	8	1	
		LS Mean	-4.818	-10.08	5.267
		SEM	5.154	11.94	12.50
		95% CI	(-15.0, 5.3)	(-33.6,13.4)	(-19.3,29.8)
		Pr >  t			0.6737
	Week 132	n	5	1	
		LS Mean	6.426	0.916	5.510
		SEM	6.014	11.94	12.88
		95% CI	( -5.4,18.2)	(-22.6,24.4)	(-19.8,30.8)
		Pr >  t			0.6689
	Week 144	n	5		
		LS Mean	9.026		
		SEM	6.014		
		95% CI	( -2.8,20.8)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	-2.178		
		SEM	6.522		
		95% CI	(-15.0,10.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-0.248		
		SEM	11.75		
		95% CI	(-23.3,22.8)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L)	Primary resistant	Week 8	n	21	16			
			LS Mean	-3.072	-1.518	-1.554		
			SEM	5.362	6.221	6.537		
			95% CI	(-14.0, 7.8)	(-14.1,11.1)	(-14.7,11.6)		
					Pr >  t			0.8130
		Week 16	n	17	10			
			LS Mean	-0.602	-6.338	5.736		
			SEM	5.735	7.254	7.655		
			95% CI	(-12.2,11.0)	(-20.9, 8.2)	( -9.5,21.0)		
					Pr >  t			0.4561
		Week 24	n	9	5			
			LS Mean	2.018	4.134	-2.117		
			SEM	6.657	8.802	9.902		
			95% CI	(-11.3,15.3)	(-13.4,21.6)	(-21.7,17.5)		
					Pr >  t			0.8312
		Week 32	n	8	4			
			LS Mean	5.783	-1.508	7.291		
			SEM	6.886	9.438	10.63		
			95% CI	( -7.9,19.5)	(-20.2,17.2)	(-13.8,28.4)		
					Pr >  t			0.4942
		Week 40	n	5	4			
			LS Mean	3.756	-3.758	7.514		
			SEM	7.912	9.438	11.41		
			95% CI	(-11.9,19.5)	(-22.5,15.0)	(-15.1,30.1)		
			Pr >  t			0.5117		
Week 48	n	5	3					
	LS Mean	-9.444	5.250	-14.69				
	SEM	7.912	10.34	12.17				
	95% CI	(-25.1, 6.3)	(-15.3,25.8)	(-38.8, 9.4)				
			Pr >  t			0.2297		
Week 56	n	4	3					
	LS Mean	-7.016	8.250	-15.27				
	SEM	8.503	10.34	12.59				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-23.9, 9.8)	(-12.3,28.8)	(-40.2, 9.7)
		Pr >  t			0.2280
		n	4	3	
		LS Mean	2.984	6.583	-3.600
		SEM	8.503	10.34	12.59
Week 72		95% CI	(-13.9,19.8)	(-13.9,27.1)	(-28.6,21.4)
		Pr >  t			0.7756
		n	4	3	
		LS Mean	0.234	8.250	-8.016
		SEM	8.503	10.34	12.59
Week 84		95% CI	(-16.6,17.1)	(-12.3,28.8)	(-33.0,16.9)
		Pr >  t			0.5257
		n	2	3	
		LS Mean	-16.44	1.917	-18.36
		SEM	11.21	10.34	14.44
Week 96		95% CI	(-38.6, 5.8)	(-18.6,22.4)	(-47.0,10.3)
		Pr >  t			0.2064
		n	1	3	
		LS Mean	-9.545	-2.083	-7.461
		SEM	14.89	10.34	17.65
Week 108		95% CI	(-39.1,20.0)	(-22.6,18.4)	(-42.5,27.6)
		Pr >  t			0.6735
		n		2	
		LS Mean		0.075	
		SEM		11.85	
Week 120		95% CI		(-23.4,23.5)	
		Pr >  t			
		n	1	1	
		LS Mean	0.455	12.540	-12.08
		SEM	14.89	15.48	21.09
Week 132		95% CI	(-29.1,30.0)	(-18.2,43.2)	(-54.0,29.8)
		Pr >  t			0.5682
		n		1	
		LS Mean		-20.46	
		SEM		15.48	
Week 144		95% CI		(-51.2,10.2)	
		Pr >  t			
		n	1		
		LS Mean	-2.545		
		SEM	14.89		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-32.1,27.0)		
		Pr >  t			
Secondary resistant	Week 8	n	98	107	
		LS Mean	-6.319	-2.875	-3.444
		SEM	2.618	2.615	2.217
		95% CI	(-11.5,-1.2)	(-8.0, 2.3)	(-7.8, 0.9)
		Pr >  t			0.1210
	Week 16	n	84	81	
		LS Mean	-2.732	-1.839	-0.893
		SEM	2.687	2.745	2.412
		95% CI	(-8.0, 2.6)	(-7.2, 3.6)	(-5.6, 3.8)
		Pr >  t			0.7113
	Week 24	n	75	63	
		LS Mean	-5.346	-3.495	-1.851
		SEM	2.744	2.872	2.587
		95% CI	(-10.7, 0.0)	(-9.1, 2.1)	(-6.9, 3.2)
		Pr >  t			0.4746
	Week 32	n	59	56	
		LS Mean	-4.601	-2.762	-1.839
		SEM	2.890	2.926	2.760
		95% CI	(-10.3, 1.1)	(-8.5, 3.0)	(-7.3, 3.6)
		Pr >  t			0.5055
	Week 40	n	52	48	
		LS Mean	-2.612	-3.300	0.689
		SEM	2.952	3.018	2.906
		95% CI	(-8.4, 3.2)	(-9.2, 2.6)	(-5.0, 6.4)
		Pr >  t			0.8127
	Week 48	n	47	37	
		LS Mean	-5.705	-3.995	-1.709
		SEM	3.004	3.171	3.114
		95% CI	(-11.6, 0.2)	(-10.2, 2.2)	(-7.8, 4.4)
		Pr >  t			0.5832
	Week 56	n	41	31	
		LS Mean	-0.388	-4.021	3.633
		SEM	3.080	3.292	3.311
		95% CI	(-6.4, 5.7)	(-10.5, 2.4)	(-2.9,10.1)
		Pr >  t			0.2728
	Week 64	n	32	28	
		LS Mean	-4.788	-5.763	0.975
		SEM	3.240	3.371	3.534

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-11.1, 1.6)	(-12.4, 0.9)	(-6.0, 7.9)	
	Pr >  t			0.7828	
	n	29	22		
	LS Mean	-1.214	-4.213	2.999	
	SEM	3.316	3.576	3.796	
Week 84	95% CI	(-7.7, 5.3)	(-11.2, 2.8)	(-4.4, 10.4)	
	Pr >  t			0.4296	
	n	26	21		
	LS Mean	-0.375	-3.912	3.537	
	SEM	3.398	3.621	3.910	
Week 96	95% CI	(-7.0, 6.3)	(-11.0, 3.2)	(-4.1, 11.2)	
	Pr >  t			0.3659	
	n	23	14		
	LS Mean	0.875	-8.962	9.837	
	SEM	3.504	4.068	4.412	
Week 108	95% CI	(-6.0, 7.8)	(-16.9, -1.0)	( 1.2, 18.5)	
	Pr >  t			0.0260	
	n	18	13		
	LS Mean	-1.049	-5.460	4.411	
	SEM	3.746	4.166	4.692	
Week 120	95% CI	(-8.4, 6.3)	(-13.6, 2.7)	(-4.8, 13.6)	
	Pr >  t			0.3474	
	n	20	10		
	LS Mean	-6.904	-3.676	-3.228	
	SEM	3.642	4.546	4.955	
Week 132	95% CI	(-14.1, 0.2)	(-12.6, 5.2)	(-12.9, 6.5)	
	Pr >  t			0.5149	
	n	13	4		
	LS Mean	-4.118	-4.021	-0.097	
	SEM	4.131	6.484	7.052	
Week 144	95% CI	(-12.2, 4.0)	(-16.7, 8.7)	(-13.9, 13.7)	
	Pr >  t			0.9891	
	n	8	1		
	LS Mean	-6.095	-6.882	0.787	
	SEM	4.891	12.20	12.78	
Week 156	95% CI	(-15.7, 3.5)	(-30.8, 17.1)	(-24.3, 25.9)	
	Pr >  t			0.9509	
	n	5	1		
	LS Mean	-1.880	-11.88	10.002	
	SEM	5.883	12.20	13.19	



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-13.4, 9.7)	(-35.8,12.1)	(-15.9,35.9)
		Pr >  t			0.4485
		n	3	1	
	Week 180	LS Mean	0.716	2.118	-1.402
		SEM	7.310	12.20	13.89
		95% CI	(-13.6,15.1)	(-21.8,26.1)	(-28.7,25.9)
	Week 180	Pr >  t			0.9196
		n	1	1	
		LS Mean	-4.850	-5.882	1.033
	Week 192	SEM	12.15	12.20	16.94
		95% CI	(-28.7,19.0)	(-29.8,18.1)	(-32.2,34.3)
		Pr >  t			0.9514
	Week 192	n	1	1	
		LS Mean	-6.850	-1.882	-4.967
		SEM	12.15	12.20	16.94
	Week 8	95% CI	(-30.7,17.0)	(-25.8,22.1)	(-38.2,28.3)
		Pr >  t			0.7694
		n	17	16	
	Week 8	LS Mean	-2.434	3.227	-5.661
		SEM	4.493	4.533	6.291
		95% CI	(-11.3, 6.5)	( -5.8,12.2)	(-18.1, 6.8)
	Week 16	Pr >  t			0.3702
		n	18	14	
		LS Mean	0.552	5.075	-4.523
	Week 16	SEM	4.408	4.779	6.480
		95% CI	( -8.2, 9.3)	( -4.4,14.5)	(-17.4, 8.3)
		Pr >  t			0.4866
	Week 24	n	16	13	
LS Mean		-6.256	0.274	-6.530	
SEM		4.618	4.904	6.709	
Week 24	95% CI	(-15.4, 2.9)	( -9.4,10.0)	(-19.8, 6.8)	
	Pr >  t			0.3323	
	n	15	13		
Week 32	LS Mean	-10.57	2.484	-13.06	
	SEM	4.689	4.916	6.779	
	95% CI	(-19.9,-1.3)	( -7.2,12.2)	(-26.5, 0.4)	
Week 32	Pr >  t			0.0563	
	n	14	10		
	LS Mean	-2.714	-4.708	1.994	
Week 40	SEM	4.819	5.387	7.218	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	95% CI	(-12.3, 6.8)	(-15.3, 5.9)	(-12.3,16.3)	
	Pr >  t			0.7827	
	n	14	11		
	LS Mean	-1.642	1.441	-3.083	
	SEM	4.819	5.222	7.094	
Week 56	95% CI	(-11.2, 7.9)	(-8.9,11.8)	(-17.1,10.9)	
	Pr >  t			0.6645	
	n	11	11		
	LS Mean	-4.328	3.532	-7.860	
	SEM	5.205	5.222	7.365	
Week 64	95% CI	(-14.6, 6.0)	(-6.8,13.8)	(-22.4, 6.7)	
	Pr >  t			0.2876	
	n	8	11		
	LS Mean	-1.585	-1.195	-0.390	
	SEM	5.811	5.222	7.811	
Week 72	95% CI	(-13.0, 9.9)	(-11.5, 9.1)	(-15.8,15.0)	
	Pr >  t			0.9603	
	n	11	10		
	LS Mean	-2.237	0.512	-2.749	
	SEM	5.205	5.402	7.498	
Week 84	95% CI	(-12.5, 8.0)	(-10.2,11.2)	(-17.6,12.1)	
	Pr >  t			0.7144	
	n	9	9		
	LS Mean	-4.015	-3.975	-0.040	
	SEM	5.568	5.603	7.905	
Week 96	95% CI	(-15.0, 7.0)	(-15.0, 7.1)	(-15.6,15.6)	
	Pr >  t			0.9959	
	n	9	7		
	LS Mean	-5.238	-13.02	7.787	
	SEM	5.568	6.129	8.290	
Week 108	95% CI	(-16.2, 5.8)	(-25.1,-0.9)	(-8.6,24.1)	
	Pr >  t			0.3487	
	n	7	6		
	LS Mean	-9.501	-3.812	-5.690	
	SEM	6.112	6.504	8.934	
Week 120	95% CI	(-21.6, 2.5)	(-16.6, 9.0)	(-23.3,11.9)	
	Pr >  t			0.5249	
	n	6	5		
	LS Mean	2.582	-1.600	4.182	
	SEM	6.489	6.996	9.544	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132		95% CI	(-10.2,15.4)	(-15.4,12.2)	(-14.6,23.0)
		Pr >  t			0.6616
		n	5	3	
		LS Mean	-0.945	-7.175	6.230
		SEM	6.965	8.626	11.09
Week 144		95% CI	(-14.7,12.8)	(-24.2, 9.8)	(-15.6,28.1)
		Pr >  t			0.5748
		n	5	4	
		LS Mean	-5.945	2.756	-8.701
		SEM	6.965	7.647	10.35
Week 156		95% CI	(-19.7, 7.8)	(-12.3,17.8)	(-29.1,11.7)
		Pr >  t			0.4011
		n	4	2	
		LS Mean	-2.288	-2.476	0.188
		SEM	7.613	10.31	12.82
Week 168		95% CI	(-17.3,12.7)	(-22.8,17.8)	(-25.1,25.4)
		Pr >  t			0.9883
		n	1	1	
		LS Mean	-2.901	-2.240	-0.661
		SEM	14.19	14.21	20.08
		95% CI	(-30.8,25.0)	(-30.2,25.7)	(-40.2,38.9)
		Pr >  t			0.9738

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	58	
		LS Mean	-8.735	-5.112	-3.623
		SEM	7.209	7.539	3.146
		95% CI	(-23.0, 5.6)	(-20.1, 9.8)	(-9.8, 2.6)
		Pr >  t			0.2509
	Week 16	n	51	41	
		LS Mean	-5.858	-6.041	0.182
		SEM	7.234	7.633	3.413
		95% CI	(-20.2, 8.5)	(-21.2, 9.1)	(-6.5, 6.9)
		Pr >  t			0.9574
	Week 24	n	38	33	
		LS Mean	-5.868	-9.796	3.928
		SEM	7.280	7.689	3.715
		95% CI	(-20.3, 8.6)	(-25.0, 5.5)	(-3.4, 11.2)
		Pr >  t			0.2913
	Week 32	n	34	28	
		LS Mean	-7.736	-7.301	-0.435
		SEM	7.398	7.736	3.891
		95% CI	(-22.4, 6.9)	(-22.6, 8.0)	(-8.1, 7.2)
		Pr >  t			0.9110
	Week 40	n	26	23	
		LS Mean	-2.121	-6.753	4.633
		SEM	7.497	7.806	4.207
		95% CI	(-17.0, 12.7)	(-22.2, 8.7)	(-3.6, 12.9)
		Pr >  t			0.2715
	Week 48	n	24	17	
		LS Mean	-8.121	-6.136	-1.985
		SEM	7.530	7.956	4.525
95% CI		(-23.0, 6.8)	(-21.9, 9.6)	(-10.9, 6.9)	
	Pr >  t			0.6610	
Week 56	n	21	17		
	LS Mean	-1.850	-4.867	3.017	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	7.590	7.958	4.623
	95% CI	(-16.9,13.2)	(-20.6,10.9)	( -6.1,12.1)
	Pr >  t			0.5142
Week 64	n	15	15	
	LS Mean	-6.584	-2.744	-3.840
	SEM	7.768	8.024	5.022
	95% CI	(-22.0, 8.8)	(-18.6,13.1)	(-13.7, 6.0)
	Pr >  t			0.4448
Week 72	n	16	15	
	LS Mean	0.474	-4.049	4.522
	SEM	7.732	8.024	4.964
	95% CI	(-14.8,15.8)	(-19.9,11.8)	( -5.2,14.3)
	Pr >  t			0.3627
Week 84	n	14	13	
	LS Mean	-3.232	-5.746	2.515
	SEM	7.812	8.114	5.232
	95% CI	(-18.7,12.2)	(-21.8,10.3)	( -7.8,12.8)
	Pr >  t			0.6310
Week 96	n	12	9	
	LS Mean	-0.473	-8.501	8.028
	SEM	7.915	8.404	5.824
	95% CI	(-16.1,15.2)	(-25.1, 8.1)	( -3.4,19.5)
	Pr >  t			0.1686
Week 108	n	13	8	
	LS Mean	-1.051	-3.570	2.519
	SEM	7.862	8.520	5.915
	95% CI	(-16.6,14.5)	(-20.4,13.3)	( -9.1,14.1)
	Pr >  t			0.6703
Week 120	n	11	6	
	LS Mean	-4.344	-4.402	0.058
	SEM	7.986	8.854	6.539
	95% CI	(-20.1,11.4)	(-21.9,13.1)	(-12.8,12.9)
	Pr >  t			0.9930
Week 132	n	8	3	
	LS Mean	-6.275	-10.80	4.523
	SEM	8.273	10.08	8.407
	95% CI	(-22.6,10.1)	(-30.6, 9.0)	(-12.0,21.0)
	Pr >  t			0.5908
Week 144	n	5	1	
	LS Mean	-5.961	-9.123	3.162

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	8.877	13.93	13.18
		95% CI	(-23.5,11.5)	(-36.5,18.2)	(-22.7,29.1)
		Pr >  t			0.8104
	Week 168	n	3	1	
		LS Mean	-1.273	-14.12	12.850
		SEM	9.870	13.93	13.86
	Week 180	95% CI	(-20.7,18.1)	(-41.5,13.2)	(-14.4,40.1)
		Pr >  t			0.3544
		n	2	1	
	Week 192	LS Mean	3.225	-0.123	3.349
		SEM	10.96	13.93	14.67
		95% CI	(-18.3,24.8)	(-27.5,27.2)	(-25.5,32.2)
	Week 8	Pr >  t			0.8195
		n		1	
		LS Mean		-8.123	
	Week 16	SEM		13.93	
		95% CI		(-35.5,19.2)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-4.123	
		SEM		13.93	
	Week 32	95% CI		(-31.5,23.2)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	-2.434	3.227	-5.661	
	SEM	4.493	4.533	6.291	
	95% CI	(-11.3, 6.5)	( -5.8,12.2)	(-18.1, 6.8)	
Week 16	Pr >  t			0.3702	
	n	18	14		
	LS Mean	0.552	5.075	-4.523	
Week 24	SEM	4.408	4.779	6.480	
	95% CI	( -8.2, 9.3)	( -4.4,14.5)	(-17.4, 8.3)	
	Pr >  t			0.4866	
Week 32	n	16	13		
	LS Mean	-6.256	0.274	-6.530	
	SEM	4.618	4.904	6.709	
Week 8	95% CI	(-15.4, 2.9)	( -9.4,10.0)	(-19.8, 6.8)	
	Pr >  t			0.3323	
	n	15	13		
Week 16	LS Mean	-10.57	2.484	-13.06	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	4.689	4.916	6.779
	95% CI	(-19.9,-1.3)	(-7.2,12.2)	(-26.5, 0.4)
	Pr >  t			0.0563
Week 40	n	14	10	
	LS Mean	-2.714	-4.708	1.994
	SEM	4.819	5.387	7.218
	95% CI	(-12.3, 6.8)	(-15.3, 5.9)	(-12.3,16.3)
	Pr >  t			0.7827
Week 48	n	14	11	
	LS Mean	-1.642	1.441	-3.083
	SEM	4.819	5.222	7.094
	95% CI	(-11.2, 7.9)	(-8.9,11.8)	(-17.1,10.9)
	Pr >  t			0.6645
Week 56	n	11	11	
	LS Mean	-4.328	3.532	-7.860
	SEM	5.205	5.222	7.365
	95% CI	(-14.6, 6.0)	(-6.8,13.8)	(-22.4, 6.7)
	Pr >  t			0.2876
Week 64	n	8	11	
	LS Mean	-1.585	-1.195	-0.390
	SEM	5.811	5.222	7.811
	95% CI	(-13.0, 9.9)	(-11.5, 9.1)	(-15.8,15.0)
	Pr >  t			0.9603
Week 72	n	11	10	
	LS Mean	-2.237	0.512	-2.749
	SEM	5.205	5.402	7.498
	95% CI	(-12.5, 8.0)	(-10.2,11.2)	(-17.6,12.1)
	Pr >  t			0.7144
Week 84	n	9	9	
	LS Mean	-4.015	-3.975	-0.040
	SEM	5.568	5.603	7.905
	95% CI	(-15.0, 7.0)	(-15.0, 7.1)	(-15.6,15.6)
	Pr >  t			0.9959
Week 96	n	9	7	
	LS Mean	-5.238	-13.02	7.787
	SEM	5.568	6.129	8.290
	95% CI	(-16.2, 5.8)	(-25.1,-0.9)	(-8.6,24.1)
	Pr >  t			0.3487
Week 108	n	7	6	
	LS Mean	-9.501	-3.812	-5.690

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	6.112	6.504	8.934
		95% CI	(-21.6, 2.5)	(-16.6, 9.0)	(-23.3, 11.9)
		Pr >  t			0.5249
	Week 120	n	6	5	
		LS Mean	2.582	-1.600	4.182
		SEM	6.489	6.996	9.544
		95% CI	(-10.2, 15.4)	(-15.4, 12.2)	(-14.6, 23.0)
		Pr >  t			0.6616
	Week 132	n	5	3	
		LS Mean	-0.945	-7.175	6.230
		SEM	6.965	8.626	11.09
		95% CI	(-14.7, 12.8)	(-24.2, 9.8)	(-15.6, 28.1)
		Pr >  t			0.5748
	Week 144	n	5	4	
		LS Mean	-5.945	2.756	-8.701
		SEM	6.965	7.647	10.35
		95% CI	(-19.7, 7.8)	(-12.3, 17.8)	(-29.1, 11.7)
		Pr >  t			0.4011
	Week 156	n	4	2	
		LS Mean	-2.288	-2.476	0.188
		SEM	7.613	10.31	12.82
		95% CI	(-17.3, 12.7)	(-22.8, 17.8)	(-25.1, 25.4)
		Pr >  t			0.9883
	Week 168	n	1	1	
		LS Mean	-2.901	-2.240	-0.661
		SEM	14.19	14.21	20.08
		95% CI	(-30.8, 25.0)	(-30.2, 25.7)	(-40.2, 38.9)
		Pr >  t			0.9738
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-4.055	-9.332	5.277
		SEM	4.601	4.231	5.228
		95% CI	(-13.3, 5.1)	(-17.8, -0.9)	(-5.1, 15.7)
		Pr >  t			0.3158
	Week 16	n	15	17	
		LS Mean	-3.234	-5.248	2.014
		SEM	4.883	4.472	5.491
		95% CI	(-13.0, 6.5)	(-14.2, 3.7)	(-8.9, 12.9)
		Pr >  t			0.7146
	Week 24	n	14	12	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	-5.056	-3.845	-1.212
	SEM	4.969	4.880	5.945
	95% CI	(-15.0, 4.8)	(-13.5, 5.9)	(-13.0,10.6)
	Pr >  t			0.8389
	n	12	9	
Week 40	LS Mean	-0.245	-1.538	1.293
	SEM	5.212	5.339	6.469
	95% CI	(-10.6,10.1)	(-12.1, 9.0)	(-11.5,14.1)
	Pr >  t			0.8419
	n	11	7	
Week 48	LS Mean	-1.265	-7.125	5.860
	SEM	5.355	5.866	6.940
	95% CI	(-11.9, 9.4)	(-18.7, 4.5)	( -7.9,19.6)
	Pr >  t			0.3999
	n	8	6	
Week 56	LS Mean	-11.29	-4.746	-6.545
	SEM	5.814	6.169	7.550
	95% CI	(-22.8, 0.2)	(-16.9, 7.4)	(-21.5, 8.4)
	Pr >  t			0.3874
	n	7	5	
Week 64	LS Mean	-11.39	-8.367	-3.027
	SEM	6.036	6.536	8.034
	95% CI	(-23.3, 0.6)	(-21.3, 4.5)	(-18.9,12.8)
	Pr >  t			0.7069
	n	5	3	
Week 72	LS Mean	-1.583	-16.73	15.145
	SEM	6.672	7.875	9.582
	95% CI	(-14.8,11.6)	(-32.3,-1.2)	( -3.8,34.1)
	Pr >  t			0.1158
	n	5	2	
Week 84	LS Mean	-15.32	-9.106	-6.217
	SEM	6.694	9.261	10.78
	95% CI	(-28.6,-2.1)	(-27.4, 9.2)	(-27.5,15.1)
	Pr >  t			0.5647
	n	4	2	
Week 96	LS Mean	0.074	-13.11	13.179
	SEM	7.177	9.261	11.08
	95% CI	(-14.1,14.2)	(-31.4, 5.2)	( -8.7,35.0)
	Pr >  t			0.2358
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	0.039	-11.61	11.645
		SEM	7.181	9.261	11.09
		95% CI	(-14.1,14.2)	(-29.9, 6.7)	(-10.2,33.5)
		Pr >  t			0.2950
	Week 108	n	1	2	
		LS Mean	6.044	-11.49	17.538
		SEM	12.46	9.235	15.04
		95% CI	(-18.6,30.6)	(-29.7, 6.7)	(-12.2,47.2)
		Pr >  t			0.2454
	Week 120	n	5	1	
		LS Mean	-6.323	-24.26	17.938
		SEM	6.694	12.45	13.62
		95% CI	(-19.6, 6.9)	(-48.8, 0.3)	( -8.9,44.8)
		Pr >  t			0.1895
	Week 132	n	3	1	
		LS Mean	0.019	-17.26	17.280
		SEM	7.962	12.45	14.28
		95% CI	(-15.7,15.7)	(-41.8, 7.3)	(-10.9,45.5)
		Pr >  t			0.2281
	Week 144	n	3		
		LS Mean	-1.981		
		SEM	7.962		
		95% CI	(-17.7,13.7)		
		Pr >  t			
	Week 156	n	3		
		LS Mean	-4.648		
		SEM	7.962		
		95% CI	(-20.4,11.1)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-7.044		
		SEM	12.44		
		95% CI	(-31.6,17.5)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-6.044		
		SEM	12.44		
		95% CI	(-30.6,18.5)		
		Pr >  t			
	Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	-8.044		
		SEM	12.44		
		95% CI	(-32.6,16.5)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	-5.501	1.385	-6.885
		SEM	3.593	3.586	3.956
		95% CI	(-12.6, 1.6)	(-5.7, 8.5)	(-14.7, 0.9)
		Pr >  t			0.0834
	Week 16	n	30	29	
		LS Mean	-2.028	0.152	-2.180
		SEM	3.748	3.948	4.400
		95% CI	(-9.4, 5.4)	(-7.6, 7.9)	(-10.9, 6.5)
		Pr >  t			0.6207
	Week 24	n	26	20	
		LS Mean	-4.579	3.831	-8.410
		SEM	3.918	4.423	4.903
		95% CI	(-12.3, 3.2)	(-4.9,12.5)	(-18.1, 1.2)
		Pr >  t			0.0875
	Week 32	n	18	20	
		LS Mean	-3.001	-0.219	-2.782
		SEM	4.347	4.423	5.242
		95% CI	(-11.6, 5.6)	(-8.9, 8.5)	(-13.1, 7.5)
		Pr >  t			0.5960
	Week 40	n	18	19	
		LS Mean	-4.939	-0.682	-4.257
		SEM	4.345	4.483	5.290
		95% CI	(-13.5, 3.6)	(-9.5, 8.2)	(-14.7, 6.2)
		Pr >  t			0.4216
	Week 48	n	16	14	
		LS Mean	-0.366	-2.307	1.941
		SEM	4.489	4.866	5.736
		95% CI	(-9.2, 8.5)	(-11.9, 7.3)	(-9.3,13.2)
		Pr >  t			0.7353
	Week 56	n	14	10	
		LS Mean	-2.711	-2.359	-0.352
		SEM	4.665	5.391	6.329
		95% CI	(-11.9, 6.5)	(-13.0, 8.2)	(-12.8,12.1)
		Pr >  t			0.9557

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	-6.715	-7.135	0.420
		SEM	4.773	5.232	6.276
		95% CI	(-16.1, 2.7)	(-17.4, 3.2)	(-11.9,12.8)
		Pr >  t			0.9467
Week 72		n	10	6	
		LS Mean	-8.452	-6.024	-2.428
		SEM	5.182	6.437	7.595
		95% CI	(-18.6, 1.7)	(-18.7, 6.6)	(-17.4,12.5)
		Pr >  t			0.7494
Week 84		n	8	7	
		LS Mean	-3.914	-1.973	-1.941
		SEM	5.657	6.086	7.607
		95% CI	(-15.0, 7.2)	(-13.9,10.0)	(-16.9,13.0)
		Pr >  t			0.7987
Week 96		n	6	5	
		LS Mean	-3.898	-13.08	9.182
		SEM	6.265	6.887	8.716
		95% CI	(-16.2, 8.4)	(-26.6, 0.5)	( -8.0,26.3)
		Pr >  t			0.2928
Week 108		n	2	4	
		LS Mean	-5.047	-4.931	-0.115
		SEM	9.975	7.521	12.04
		95% CI	(-24.7,14.6)	(-19.7, 9.9)	(-23.8,23.6)
		Pr >  t			0.9924
Week 120		n	5	4	
		LS Mean	-7.747	3.069	-10.82
		SEM	6.724	7.521	9.549
		95% CI	(-21.0, 5.5)	(-11.7,17.9)	(-29.6, 8.0)
		Pr >  t			0.2581
Week 132		n	3	1	
		LS Mean	3.409	-1.742	5.151
		SEM	8.344	13.84	15.81
		95% CI	(-13.0,19.8)	(-29.0,25.5)	(-25.9,36.3)
		Pr >  t			0.7447
Week 144		n	2		
		LS Mean	-8.566		
		SEM	9.924		
		95% CI	(-28.1,11.0)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	93			
			LS Mean	-6.964	-0.520	-6.444		
			SEM	3.119	3.126	2.566		
			95% CI	(-13.1,-0.8)	(-6.7, 5.6)	(-11.5,-1.4)		
					Pr >  t			0.0124
		Week 16	n	79	68			
			LS Mean	-2.466	-1.259	-1.206		
			SEM	3.160	3.313	2.807		
			95% CI	(-8.7, 3.8)	(-7.8, 5.3)	(-6.7, 4.3)		
					Pr >  t			0.6675
		Week 24	n	64	55			
			LS Mean	-7.007	-1.236	-5.772		
			SEM	3.270	3.457	3.051		
			95% CI	(-13.4,-0.6)	(-8.0, 5.6)	(-11.8, 0.2)		
					Pr >  t			0.0590
		Week 32	n	49	53			
			LS Mean	-7.009	-1.082	-5.926		
			SEM	3.448	3.479	3.230		
			95% CI	(-13.8,-0.2)	(-7.9, 5.8)	(-12.3, 0.4)		
					Pr >  t			0.0669
		Week 40	n	44	45			
			LS Mean	-3.840	-2.314	-1.526		
			SEM	3.514	3.572	3.400		
			95% CI	(-10.7, 3.1)	(-9.3, 4.7)	(-8.2, 5.1)		
			Pr >  t			0.6537		
Week 48	n	41	36					
	LS Mean	-4.650	-1.218	-3.432				
	SEM	3.558	3.719	3.597				
	95% CI	(-11.6, 2.3)	(-8.5, 6.1)	(-10.5, 3.6)				
			Pr >  t			0.3402		
Week 56	n	33	32					
	LS Mean	-2.828	-0.069	-2.759				
	SEM	3.706	3.806	3.836				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.1, 4.5)	(-7.5, 7.4)	(-10.3, 4.8)
		Pr >  t			0.4722
	Week 64	n	27	31	
		LS Mean	-5.472	-1.679	-3.794
		SEM	3.866	3.832	4.019
		95% CI	(-13.1, 2.1)	(-9.2, 5.8)	(-11.7, 4.1)
		Pr >  t			0.3454
	Week 72	n	26	26	
		LS Mean	-4.427	0.165	-4.592
		SEM	3.899	3.979	4.190
		95% CI	(-12.1, 3.2)	(-7.7, 8.0)	(-12.8, 3.6)
		Pr >  t			0.2735
	Week 84	n	22	23	
		LS Mean	-5.743	-1.436	-4.308
		SEM	4.076	4.092	4.445
		95% CI	(-13.7, 2.3)	(-9.5, 6.6)	(-13.0, 4.4)
		Pr >  t			0.3327
	Week 96	n	19	18	
		LS Mean	-3.314	-9.058	5.744
		SEM	4.233	4.353	4.823
		95% CI	(-11.6, 5.0)	(-17.6,-0.5)	(-3.7,15.2)
		Pr >  t			0.2339
	Week 108	n	14	14	
		LS Mean	-4.102	0.089	-4.191
		SEM	4.620	4.672	5.436
		95% CI	(-13.2, 5.0)	(-9.1, 9.3)	(-14.9, 6.5)
		Pr >  t			0.4409
	Week 120	n	13	12	
		LS Mean	-6.983	0.199	-7.182
		SEM	4.723	4.897	5.714
		95% CI	(-16.3, 2.3)	(-9.4, 9.8)	(-18.4, 4.0)
		Pr >  t			0.2090
	Week 132	n	9	5	
		LS Mean	-1.035	-8.515	7.481
		SEM	5.327	6.685	7.709
		95% CI	(-11.5, 9.4)	(-21.6, 4.6)	(-7.6,22.6)
		Pr >  t			0.3321
	Week 144	n	7	4	
		LS Mean	1.905	2.163	-0.258
		SEM	5.833	7.326	8.605

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.5,13.4)	(-12.2,16.5)	(-17.1,16.6)
		Pr >  t			0.9761
	Week 156	n	4	2	
		LS Mean	-4.356	-3.070	-1.286
		SEM	7.275	9.890	11.71
		95% CI	(-18.6, 9.9)	(-22.5,16.3)	(-24.3,21.7)
		Pr >  t			0.9126
	Week 168	n	2	1	
		LS Mean	2.940	-2.875	5.815
		SEM	9.845	13.65	16.42
		95% CI	(-16.4,22.3)	(-29.7,23.9)	(-26.4,38.0)
		Pr >  t			0.7233
Yes	Week 8	n	53	48	
		LS Mean	-2.039	-4.605	2.566
		SEM	2.954	3.070	2.951
		95% CI	(-7.9, 3.8)	(-10.7, 1.5)	(-3.2, 8.4)
		Pr >  t			0.3856
	Week 16	n	46	39	
		LS Mean	-1.613	-2.209	0.596
		SEM	3.088	3.223	3.158
		95% CI	(-7.7, 4.5)	(-8.6, 4.2)	(-5.6, 6.8)
		Pr >  t			0.8505
	Week 24	n	41	27	
		LS Mean	-0.698	-5.612	4.915
		SEM	3.144	3.459	3.478
		95% CI	(-6.9, 5.5)	(-12.4, 1.2)	(-1.9,11.8)
		Pr >  t			0.1585
	Week 32	n	37	20	
		LS Mean	-0.663	-3.148	2.485
		SEM	3.221	3.725	3.773
		95% CI	(-7.0, 5.7)	(-10.5, 4.2)	(-4.9, 9.9)
		Pr >  t			0.5105
	Week 40	n	31	17	
		LS Mean	0.420	-6.305	6.726
		SEM	3.325	3.911	4.016
		95% CI	(-6.1, 7.0)	(-14.0, 1.4)	(-1.2,14.6)
		Pr >  t			0.0947
	Week 48	n	28	15	
		LS Mean	-4.174	-5.132	0.958
		SEM	3.389	4.038	4.194



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-10.9, 2.5)	(-13.1, 2.8)	(-7.3, 9.2)
	Pr >  t			0.8195
Week 56	n	26	13	
	LS Mean	-0.891	-5.349	4.458
	SEM	3.439	4.196	4.388
	95% CI	(-7.7, 5.9)	(-13.6, 2.9)	(-4.2, 13.1)
	Pr >  t			0.3102
Week 64	n	20	11	
	LS Mean	-0.001	-9.995	9.994
	SEM	3.636	4.401	4.738
	95% CI	(-7.2, 7.2)	(-18.6, -1.3)	( 0.7, 19.3)
	Pr >  t			0.0354
Week 72	n	22	9	
	LS Mean	-0.257	-8.524	8.267
	SEM	3.565	4.673	4.938
	95% CI	(-7.3, 6.8)	(-17.7, 0.7)	(-1.4, 18.0)
	Pr >  t			0.0947
Week 84	n	18	10	
	LS Mean	3.731	-9.486	13.218
	SEM	3.741	4.528	4.924
	95% CI	(-3.6, 11.1)	(-18.4, -0.6)	( 3.5, 22.9)
	Pr >  t			0.0075
Week 96	n	17	6	
	LS Mean	2.810	-11.76	14.571
	SEM	3.781	5.347	5.723
	95% CI	(-4.6, 10.2)	(-22.3, -1.3)	( 3.3, 25.8)
	Pr >  t			0.0111
Week 108	n	12	7	
	LS Mean	-0.531	-15.63	15.099
	SEM	4.166	5.070	5.730
	95% CI	(-8.7, 7.7)	(-25.6, -5.7)	( 3.8, 26.4)
	Pr >  t			0.0086
Week 120	n	16	4	
	LS Mean	-0.611	-9.290	8.679
	SEM	3.843	6.221	6.583
	95% CI	(-8.2, 6.9)	(-21.5, 2.9)	(-4.3, 21.6)
	Pr >  t			0.1879
Week 132	n	11	3	
	LS Mean	-2.265	-9.183	6.919
	SEM	4.275	6.982	7.534

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.7, 6.1)	(-22.9, 4.5)	(-7.9,21.7)
		Pr >  t			0.3588
	Week 144	n	8	1	
		LS Mean	-9.090	-10.15	1.057
		SEM	4.707	11.35	11.87
		95% CI	(-18.3, 0.2)	(-32.4,12.2)	(-22.3,24.4)
		Pr >  t			0.9291
	Week 156	n	6	1	
		LS Mean	1.168	-15.15	16.315
		SEM	5.231	11.35	12.08
		95% CI	(-9.1,11.4)	(-37.4, 7.2)	(-7.4,40.0)
		Pr >  t			0.1775
	Week 168	n	2	1	
		LS Mean	-1.809	-1.147	-0.662
		SEM	8.205	11.35	13.64
		95% CI	(-17.9,14.3)	(-23.4,21.2)	(-27.5,26.1)
		Pr >  t			0.9613
	Week 180	n	1	1	
		LS Mean	-2.901	-9.147	6.246
		SEM	11.26	11.35	15.66
		95% CI	(-25.0,19.2)	(-31.4,13.2)	(-24.5,37.0)
		Pr >  t			0.6902
	Week 192	n	1	1	
		LS Mean	-4.901	-5.147	0.246
		SEM	11.26	11.35	15.66
		95% CI	(-27.0,17.2)	(-27.4,17.2)	(-30.5,31.0)
		Pr >  t			0.9875

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35			
			LS Mean	-3.618	-6.613	2.995		
			SEM	4.303	4.639	4.381		
			95% CI	(-12.2, 4.9)	(-15.8, 2.6)	(-5.7, 11.7)		
					Pr >  t			0.4957
		Week 16	n	35	22			
			LS Mean	-6.842	-4.746	-2.096		
			SEM	4.444	5.120	4.863		
			95% CI	(-15.7, 2.0)	(-14.9, 5.4)	(-11.7, 7.5)		
					Pr >  t			0.6672
		Week 24	n	28	16			
			LS Mean	-8.334	-7.789	-0.545		
			SEM	4.577	5.409	5.301		
			95% CI	(-17.4, 0.7)	(-18.5, 2.9)	(-11.0, 9.9)		
					Pr >  t			0.9182
		Week 32	n	22	16			
			LS Mean	-4.404	-7.700	3.297		
			SEM	4.786	5.425	5.448		
			95% CI	(-13.9, 5.1)	(-18.4, 3.0)	(-7.4, 14.0)		
					Pr >  t			0.5459
		Week 40	n	19	12			
			LS Mean	-5.507	-17.19	11.684		
			SEM	4.901	5.715	5.842		
			95% CI	(-15.2, 4.2)	(-28.5, -5.9)	(0.2, 23.2)		
			Pr >  t			0.0467		
Week 48	n	16	10					
	LS Mean	-11.42	-13.35	1.934				
	SEM	5.049	5.940	6.183				
	95% CI	(-21.4, -1.4)	(-25.1, -1.6)	(-10.2, 14.1)				
			Pr >  t			0.7547		
Week 56	n	14	7					
	LS Mean	-5.821	-5.820	-0.001				
		SEM	5.177	6.461	6.791			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-16.0, 4.4)	(-18.6, 6.9)	(-13.4,13.4)
		Pr >  t			0.9999
Week 64		n	8	7	
		LS Mean	-4.927	-13.29	8.366
		SEM	5.853	6.458	7.329
		95% CI	(-16.5, 6.6)	(-26.0,-0.6)	( -6.1,22.8)
		Pr >  t			0.2545
Week 72		n	12	6	
		LS Mean	-5.902	-14.12	8.218
		SEM	5.337	6.729	7.170
		95% CI	(-16.4, 4.6)	(-27.4,-0.9)	( -5.9,22.3)
		Pr >  t			0.2526
Week 84		n	8	5	
		LS Mean	-5.507	-16.22	10.716
		SEM	5.878	7.081	7.881
		95% CI	(-17.1, 6.1)	(-30.2,-2.3)	( -4.8,26.2)
		Pr >  t			0.1749
Week 96		n	6	5	
		LS Mean	-1.970	-13.82	11.853
		SEM	6.357	7.081	8.242
		95% CI	(-14.5,10.5)	(-27.8, 0.1)	( -4.4,28.1)
		Pr >  t			0.1513
Week 108		n	7	5	
		LS Mean	-8.142	-24.22	16.081
		SEM	6.091	7.081	8.042
		95% CI	(-20.1, 3.9)	(-38.2, -10)	( 0.3,31.9)
		Pr >  t			0.0463
Week 120		n	5	3	
		LS Mean	-14.05	-19.68	5.626
		SEM	6.716	8.311	9.569
		95% CI	(-27.3,-0.8)	(-36.0,-3.3)	(-13.2,24.4)
		Pr >  t			0.5569
Week 132		n	2	2	
		LS Mean	-1.540	-12.94	11.397
		SEM	9.311	9.554	12.46
		95% CI	(-19.9,16.8)	(-31.7, 5.9)	(-13.1,35.9)
		Pr >  t			0.3612
Week 144		n	2		
		LS Mean	-16.36		
		SEM	9.310		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-34.7, 2.0)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	-4.221		
		SEM	9.322		
		95% CI	(-22.6,14.1)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-4.906		
		SEM	12.50		
		95% CI	(-29.5,19.7)		
		Pr >  t			
Positive	Week 8	n	98	105	
		LS Mean	-6.671	-1.340	-5.331
		SEM	2.681	2.648	2.238
		95% CI	(-11.9,-1.4)	(-6.5, 3.9)	(-9.7,-0.9)
		Pr >  t	0.0175		
	Week 16	n	88	84	
		LS Mean	-1.212	-1.886	0.674
		SEM	2.743	2.744	2.399
		95% CI	(-6.6, 4.2)	(-7.3, 3.5)	(-4.0, 5.4)
		Pr >  t	0.7789		
	Week 24	n	76	66	
		LS Mean	-4.002	-2.703	-1.299
		SEM	2.818	2.869	2.596
		95% CI	(-9.5, 1.5)	(-8.3, 2.9)	(-6.4, 3.8)
		Pr >  t	0.6170		
	Week 32	n	62	57	
		LS Mean	-4.851	-1.751	-3.100
		SEM	2.922	2.956	2.777
		95% CI	(-10.6, 0.9)	(-7.6, 4.1)	(-8.5, 2.3)
		Pr >  t	0.2645		
	Week 40	n	54	50	
		LS Mean	-1.841	-1.717	-0.124
		SEM	2.992	3.041	2.927
		95% CI	(-7.7, 4.0)	(-7.7, 4.3)	(-5.9, 5.6)
		Pr >  t	0.9662		
	Week 48	n	52	41	
		LS Mean	-3.002	-1.229	-1.773
		SEM	3.012	3.162	3.070

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-8.9, 2.9)	(-7.4, 5.0)	(-7.8, 4.3)
	Pr >  t			0.5638
	n	44	38	
	LS Mean	-1.684	-1.922	0.238
	SEM	3.103	3.212	3.215
Week 64	95% CI	(-7.8, 4.4)	(-8.2, 4.4)	(-6.1, 6.5)
	Pr >  t			0.9410
	n	39	35	
	LS Mean	-3.305	-3.497	0.192
	SEM	3.179	3.271	3.347
Week 72	95% CI	(-9.5, 2.9)	(-9.9, 2.9)	(-6.4, 6.8)
	Pr >  t			0.9542
	n	36	29	
	LS Mean	-2.494	-1.153	-1.341
	SEM	3.233	3.415	3.539
Week 84	95% CI	(-8.8, 3.9)	(-7.9, 5.6)	(-8.3, 5.6)
	Pr >  t			0.7049
	n	32	28	
	LS Mean	-1.326	-2.799	1.473
	SEM	3.325	3.444	3.644
Week 96	95% CI	(-7.9, 5.2)	(-9.6, 4.0)	(-5.7, 8.6)
	Pr >  t			0.6862
	n	30	19	
	LS Mean	-0.873	-10.87	10.000
	SEM	3.367	3.819	4.044
Week 108	95% CI	(-7.5, 5.7)	(-18.4,-3.4)	( 2.1,17.9)
	Pr >  t			0.0135
	n	18	16	
	LS Mean	-1.630	-1.183	-0.448
	SEM	3.867	4.024	4.636
Week 120	95% CI	(-9.2, 6.0)	(-9.1, 6.7)	(-9.5, 8.6)
	Pr >  t			0.9231
	n	24	13	
	LS Mean	-2.427	-0.082	-2.345
	SEM	3.562	4.301	4.649
Week 132	95% CI	(-9.4, 4.6)	(-8.5, 8.4)	(-11.5, 6.8)
	Pr >  t			0.6141
	n	18	6	
Week 132	LS Mean	-2.514	-9.075	6.561
	SEM	3.867	5.722	6.169

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.1, 5.1)	(-20.3, 2.2)	(-5.5,18.7)
		Pr >  t			0.2878
	Week 144	n	13	5	
		LS Mean	-2.960	-0.267	-2.693
		SEM	4.265	6.169	6.839
		95% CI	(-11.3, 5.4)	(-12.4,11.8)	(-16.1,10.7)
		Pr >  t			0.6938
	Week 156	n	8	3	
		LS Mean	-1.804	-6.258	4.454
		SEM	5.091	7.686	8.681
		95% CI	(-11.8, 8.2)	(-21.3, 8.8)	(-12.6,21.5)
		Pr >  t			0.6080
	Week 168	n	3	2	
		LS Mean	0.831	-0.121	0.952
		SEM	7.662	9.240	11.59
		95% CI	(-14.2,15.9)	(-18.2,18.0)	(-21.8,23.7)
		Pr >  t			0.9346
	Week 180	n	1	1	
		LS Mean	-4.218	-4.429	0.212
		SEM	12.80	12.80	17.84
		95% CI	(-29.3,20.9)	(-29.5,20.7)	(-34.8,35.2)
		Pr >  t			0.9905
	Week 192	n	1	1	
		LS Mean	-6.218	-0.429	-5.788
		SEM	12.80	12.80	17.84
		95% CI	(-31.3,18.9)	(-25.5,24.7)	(-40.8,29.2)
		Pr >  t			0.7456

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	105			
			LS Mean	-6.776	-1.303	-5.473		
			SEM	2.693	2.652	2.254		
			95% CI	(-12.1, -1.5)	(-6.5, 3.9)	(-9.9, -1.0)		
					Pr >  t			0.0155
		Week 16	n	86	84			
			LS Mean	-1.397	-1.840	0.443		
			SEM	2.758	2.749	2.418		
			95% CI	(-6.8, 4.0)	(-7.2, 3.6)	(-4.3, 5.2)		
					Pr >  t			0.8548
		Week 24	n	75	66			
			LS Mean	-4.167	-2.656	-1.511		
			SEM	2.831	2.874	2.613		
			95% CI	(-9.7, 1.4)	(-8.3, 3.0)	(-6.6, 3.6)		
					Pr >  t			0.5631
		Week 32	n	61	57			
			LS Mean	-5.029	-1.703	-3.326		
			SEM	2.938	2.962	2.797		
			95% CI	(-10.8, 0.7)	(-7.5, 4.1)	(-8.8, 2.2)		
					Pr >  t			0.2347
		Week 40	n	53	50			
			LS Mean	-1.991	-1.668	-0.323		
			SEM	3.011	3.048	2.949		
			95% CI	(-7.9, 3.9)	(-7.7, 4.3)	(-6.1, 5.5)		
					Pr >  t			0.9127
		Week 48	n	51	41			
			LS Mean	-3.098	-1.181	-1.917		
			SEM	3.031	3.169	3.094		
95% CI	(-9.1, 2.9)		(-7.4, 5.0)	(-8.0, 4.2)				
			Pr >  t			0.5357		
Week 56	n	43	38					
	LS Mean	-1.744	-1.873	0.129				
	SEM	3.126	3.220	3.243				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.9, 4.4)	(-8.2, 4.4)	(-6.2, 6.5)
	Pr >  t			0.9683
	n	39	35	
	LS Mean	-3.409	-3.449	0.041
	SEM	3.189	3.279	3.362
Week 72	95% CI	(-9.7, 2.9)	(-9.9, 3.0)	(-6.6, 6.6)
	Pr >  t			0.9904
	n	35	29	
	LS Mean	-2.685	-1.103	-1.582
	SEM	3.264	3.423	3.572
Week 84	95% CI	(-9.1, 3.7)	(-7.8, 5.6)	(-8.6, 5.4)
	Pr >  t			0.6578
	n	31	28	
	LS Mean	-1.455	-2.748	1.293
	SEM	3.360	3.453	3.682
Week 96	95% CI	(-8.1, 5.1)	(-9.5, 4.0)	(-5.9, 8.5)
	Pr >  t			0.7254
	n	29	19	
	LS Mean	-0.851	-10.82	9.970
	SEM	3.405	3.830	4.084
Week 108	95% CI	(-7.5, 5.8)	(-18.3, -3.3)	( 2.0, 18.0)
	Pr >  t			0.0148
	n	18	16	
	LS Mean	-1.735	-1.133	-0.602
	SEM	3.881	4.036	4.656
Week 120	95% CI	(-9.4, 5.9)	(-9.1, 6.8)	(-9.7, 8.5)
	Pr >  t			0.8972
	n	24	13	
	LS Mean	-2.532	-0.035	-2.497
	SEM	3.574	4.314	4.669
Week 132	95% CI	(-9.5, 4.5)	(-8.5, 8.4)	(-11.7, 6.7)
	Pr >  t			0.5929
	n	18	6	
	LS Mean	-2.619	-9.024	6.405
	SEM	3.881	5.742	6.195
Week 144	95% CI	(-10.2, 5.0)	(-20.3, 2.2)	(-5.7, 18.6)
	Pr >  t			0.3014
	n	13	5	
	LS Mean	-3.068	-0.212	-2.856
	SEM	4.280	6.192	6.868

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	(-11.5, 5.3)	(-12.4, 11.9)	(-16.3, 10.6)
		Pr >  t			0.6776
		n	8	3	
	Week 168	LS Mean	-1.918	-6.201	4.283
		SEM	5.110	7.715	8.717
		95% CI	(-11.9, 8.1)	(-21.3, 8.9)	(-12.8, 21.4)
	Week 180	Pr >  t			0.6233
		n	3	2	
		LS Mean	0.706	-0.062	0.768
	Week 192	SEM	7.692	9.275	11.64
		95% CI	(-14.4, 15.8)	(-18.3, 18.1)	(-22.1, 23.6)
		Pr >  t			0.9474
	Week 8	n	1	1	
		LS Mean	-4.344	-4.380	0.035
		SEM	12.86	12.85	17.91
	Week 16	95% CI	(-29.6, 20.9)	(-29.6, 20.8)	(-35.1, 35.2)
		Pr >  t			0.9984
		n	1	1	
	Week 24	LS Mean	-6.344	-0.380	-5.965
		SEM	12.86	12.85	17.91
		95% CI	(-31.6, 18.9)	(-25.6, 24.8)	(-41.1, 29.2)
	Week 32	Pr >  t			0.7392
		n	42	35	
		LS Mean	-3.618	-6.613	2.995
Week 8	SEM	4.303	4.639	4.381	
	95% CI	(-12.2, 4.9)	(-15.8, 2.6)	(-5.7, 11.7)	
	Pr >  t			0.4957	
Week 16	n	35	22		
	LS Mean	-6.842	-4.746	-2.096	
	SEM	4.444	5.120	4.863	
Week 24	95% CI	(-15.7, 2.0)	(-14.9, 5.4)	(-11.7, 7.5)	
	Pr >  t			0.6672	
	n	28	16		
Week 32	LS Mean	-8.334	-7.789	-0.545	
	SEM	4.577	5.409	5.301	
	95% CI	(-17.4, 0.7)	(-18.5, 2.9)	(-11.0, 9.9)	
Week 8	Pr >  t			0.9182	
	n	22	16		
	LS Mean	-4.404	-7.700	3.297	
Week 16	SEM	4.786	5.425	5.448	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.9, 5.1)	(-18.4, 3.0)	(-7.4,14.0)
		Pr >  t			0.5459
	Week 40	n	19	12	
		LS Mean	-5.507	-17.19	11.684
		SEM	4.901	5.715	5.842
		95% CI	(-15.2, 4.2)	(-28.5,-5.9)	( 0.2,23.2)
		Pr >  t			0.0467
	Week 48	n	16	10	
		LS Mean	-11.42	-13.35	1.934
		SEM	5.049	5.940	6.183
		95% CI	(-21.4,-1.4)	(-25.1,-1.6)	(-10.2,14.1)
		Pr >  t			0.7547
	Week 56	n	14	7	
		LS Mean	-5.821	-5.820	-0.001
		SEM	5.177	6.461	6.791
		95% CI	(-16.0, 4.4)	(-18.6, 6.9)	(-13.4,13.4)
		Pr >  t			0.9999
	Week 64	n	8	7	
		LS Mean	-4.927	-13.29	8.366
		SEM	5.853	6.458	7.329
		95% CI	(-16.5, 6.6)	(-26.0,-0.6)	(-6.1,22.8)
		Pr >  t			0.2545
	Week 72	n	12	6	
		LS Mean	-5.902	-14.12	8.218
		SEM	5.337	6.729	7.170
		95% CI	(-16.4, 4.6)	(-27.4,-0.9)	(-5.9,22.3)
		Pr >  t			0.2526
	Week 84	n	8	5	
		LS Mean	-5.507	-16.22	10.716
		SEM	5.878	7.081	7.881
		95% CI	(-17.1, 6.1)	(-30.2,-2.3)	(-4.8,26.2)
		Pr >  t			0.1749
	Week 96	n	6	5	
		LS Mean	-1.970	-13.82	11.853
		SEM	6.357	7.081	8.242
		95% CI	(-14.5,10.5)	(-27.8, 0.1)	(-4.4,28.1)
		Pr >  t			0.1513
	Week 108	n	7	5	
		LS Mean	-8.142	-24.22	16.081
		SEM	6.091	7.081	8.042

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-20.1, 3.9)	(-38.2, -10)	(-0.3, 31.9)
		Pr >  t			0.0463
	Week 120	n	5	3	
		LS Mean	-14.05	-19.68	5.626
		SEM	6.716	8.311	9.569
		95% CI	(-27.3, -0.8)	(-36.0, -3.3)	(-13.2, 24.4)
		Pr >  t			0.5569
	Week 132	n	2	2	
		LS Mean	-1.540	-12.94	11.397
		SEM	9.311	9.554	12.46
		95% CI	(-19.9, 16.8)	(-31.7, 5.9)	(-13.1, 35.9)
		Pr >  t			0.3612
	Week 144	n	2		
		LS Mean	-16.36		
		SEM	9.310		
		95% CI	(-34.7, 2.0)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	-4.221		
		SEM	9.322		
		95% CI	(-22.6, 14.1)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-4.906		
		SEM	12.50		
		95% CI	(-29.5, 19.7)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60	
		LS Mean	0.698	6.454	-5.757	
	SEM	6.808	7.031	2.982		
	95% CI	(-12.8,14.2)	(-7.5,20.4)	(-11.6, 0.1)		
	Pr >  t			0.0546		
	Week 16	n	59	49		
		LS Mean	2.830	4.051	-1.220	
		SEM	6.831	7.083	3.177	
		95% CI	(-10.7,16.4)	(-10.0,18.1)	(-7.5, 5.0)	
	Week 24	n	54	41		
		LS Mean	3.564	3.742	-0.179	
		SEM	6.844	7.132	3.327	
		95% CI	(-10.0,17.1)	(-10.4,17.9)	(-6.7, 6.4)	
	Week 32	n	48	37		
		LS Mean	-0.304	4.725	-5.029	
		SEM	6.865	7.160	3.442	
		95% CI	(-13.9,13.3)	(-9.5,18.9)	(-11.8, 1.7)	
	Week 40	n	43	33		
		LS Mean	3.731	4.926	-1.195	
		SEM	6.887	7.193	3.564	
		95% CI	(-9.9,17.4)	(-9.3,19.2)	(-8.2, 5.8)	
	Week 48	n	41	28		
		LS Mean	2.593	3.857	-1.264	
		SEM	6.897	7.247	3.697	
95% CI		(-11.1,16.3)	(-10.5,18.2)	(-8.5, 6.0)		
Week 56	n	35	22			
	LS Mean	2.162	2.387	-0.225		
	SEM	6.934	7.344	3.960		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.6,15.9)	(-12.2,16.9)	(-8.0, 7.6)
		Pr >  t			0.9547
	Week 64	n	26	23	
		LS Mean	0.385	3.847	-3.462
		SEM	7.022	7.325	4.096
		95% CI	(-13.5,14.3)	(-10.7,18.4)	(-11.5, 4.6)
		Pr >  t			0.3984
	Week 72	n	28	18	
		LS Mean	0.767	6.827	-6.060
		SEM	6.998	7.439	4.253
		95% CI	(-13.1,14.6)	(-7.9,21.5)	(-14.4, 2.3)
		Pr >  t			0.1547
	Week 84	n	22	18	
		LS Mean	3.576	5.029	-1.453
		SEM	7.118	7.440	4.407
		95% CI	(-10.5,17.7)	(-9.7,19.8)	(-10.1, 7.2)
		Pr >  t			0.7418
	Week 96	n	21	13	
		LS Mean	3.570	2.435	1.134
		SEM	7.103	7.635	4.762
		95% CI	(-10.5,17.6)	(-12.7,17.5)	(-8.2,10.5)
		Pr >  t			0.8118
	Week 108	n	17	12	
		LS Mean	4.673	4.104	0.570
		SEM	7.245	7.692	5.007
		95% CI	(-9.7,19.0)	(-11.1,19.3)	(-9.3,10.4)
		Pr >  t			0.9095
	Week 120	n	19	11	
		LS Mean	-1.672	5.435	-7.108
		SEM	7.147	7.759	5.028
		95% CI	(-15.8,12.5)	(-9.9,20.8)	(-17.0, 2.8)
		Pr >  t			0.1579
	Week 132	n	13	5	
		LS Mean	4.966	-0.002	4.967
		SEM	7.408	8.653	6.574
		95% CI	(-9.7,19.6)	(-17.1,17.0)	(-7.9,17.9)
		Pr >  t			0.4501
	Week 144	n	12	3	
		LS Mean	2.657	5.872	-3.215
		SEM	7.409	9.639	7.884

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.0,17.3)	(-13.1,24.8)	(-18.7,12.3)
		Pr >  t			0.6835
	Week 156	n	7	2	
		LS Mean	3.942	-0.539	4.481
		SEM	7.983	10.73	9.608
		95% CI	(-11.8,19.7)	(-21.6,20.5)	(-14.4,23.3)
		Pr >  t			0.6410
	Week 168	n	3	1	
		LS Mean	6.575	10.585	-4.009
		SEM	9.439	13.49	13.59
		95% CI	(-12.0,25.1)	(-15.9,37.1)	(-30.7,22.7)
		Pr >  t			0.7680
	Week 180	n	1	1	
		LS Mean	1.284	2.585	-1.300
		SEM	13.35	13.49	16.55
		95% CI	(-24.9,27.5)	(-23.9,29.1)	(-33.8,31.2)
		Pr >  t			0.9374
	Week 192	n	1	1	
		LS Mean	-0.716	6.585	-7.300
		SEM	13.35	13.49	16.55
		95% CI	(-26.9,25.5)	(-19.9,33.1)	(-39.8,25.2)
		Pr >  t			0.6592
Yes	Week 8	n	73	81	
		LS Mean	-7.637	-6.308	-1.329
		SEM	3.368	3.416	2.645
		95% CI	(-14.3,-1.0)	(-13.0, 0.4)	( -6.5, 3.9)
		Pr >  t			0.6155
	Week 16	n	66	58	
		LS Mean	-3.914	-3.594	-0.320
		SEM	3.488	3.616	2.903
		95% CI	(-10.8, 2.9)	(-10.7, 3.5)	( -6.0, 5.4)
		Pr >  t			0.9123
	Week 24	n	51	41	
		LS Mean	-9.519	-5.672	-3.847
		SEM	3.597	3.857	3.307
		95% CI	(-16.6,-2.4)	(-13.3, 1.9)	(-10.3, 2.6)
		Pr >  t			0.2451
	Week 32	n	38	36	
		LS Mean	-4.691	-5.063	0.372
		SEM	3.844	3.949	3.605

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.2, 2.9)	(-12.8, 2.7)	(-6.7, 7.5)
		Pr >  t			0.9179
	Week 40	n	32	29	
		LS Mean	-4.582	-9.062	4.480
		SEM	3.981	4.116	3.915
		95% CI	(-12.4, 3.2)	(-17.2,-1.0)	(-3.2,12.2)
		Pr >  t			0.2529
	Week 48	n	28	23	
		LS Mean	-8.972	-5.564	-3.409
		SEM	4.086	4.328	4.232
		95% CI	(-17.0,-0.9)	(-14.1, 2.9)	(-11.7, 4.9)
		Pr >  t			0.4208
	Week 56	n	24	23	
		LS Mean	-2.419	-2.662	0.243
		SEM	4.229	4.327	4.364
		95% CI	(-10.7, 5.9)	(-11.2, 5.8)	(-8.3, 8.8)
		Pr >  t			0.9556
	Week 64	n	21	19	
		LS Mean	-2.933	-9.235	6.302
		SEM	4.365	4.520	4.681
		95% CI	(-11.5, 5.6)	(-18.1,-0.4)	(-2.9,15.5)
		Pr >  t			0.1786
	Week 72	n	20	17	
		LS Mean	-1.809	-8.698	6.889
		SEM	4.420	4.644	4.851
		95% CI	(-10.5, 6.9)	(-17.8, 0.4)	(-2.6,16.4)
		Pr >  t			0.1560
	Week 84	n	18	15	
		LS Mean	-3.305	-10.30	6.994
		SEM	4.521	4.803	5.098
		95% CI	(-12.2, 5.6)	(-19.7,-0.9)	(-3.0,17.0)
		Pr >  t			0.1705
	Week 96	n	15	11	
		LS Mean	-0.903	-20.51	19.610
		SEM	4.750	5.250	5.702
		95% CI	(-10.2, 8.4)	(-30.8, -10)	( 8.4,30.8)
		Pr >  t			0.0006
	Week 108	n	9	9	
		LS Mean	-8.347	-11.64	3.290
		SEM	5.536	5.590	6.658



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.2, 2.5)	(-22.6,-0.7)	( -9.8,16.4)
		Pr >  t			0.6213
	Week 120	n	10	5	
		LS Mean	-0.141	-8.365	8.224
		SEM	5.371	6.885	7.661
		95% CI	(-10.7,10.4)	(-21.9, 5.2)	( -6.8,23.3)
		Pr >  t			0.2835
	Week 132	n	7	3	
		LS Mean	-7.904	-14.54	6.634
		SEM	6.032	8.442	9.502
		95% CI	(-19.7, 3.9)	(-31.1, 2.0)	(-12.0,25.3)
		Pr >  t			0.4853
	Week 144	n	3	2	
		LS Mean	-13.72	-4.155	-9.570
		SEM	8.403	10.07	12.44
		95% CI	(-30.2, 2.8)	(-23.9,15.6)	(-34.0,14.8)
		Pr >  t			0.4419
	Week 156	n	3	1	
		LS Mean	-3.774	-8.729	4.954
		SEM	8.413	13.84	15.64
		95% CI	(-20.3,12.7)	(-35.9,18.4)	(-25.8,35.7)
		Pr >  t			0.7516
	Week 168	n	1	1	
		LS Mean	-3.187	-8.729	5.542
		SEM	13.84	13.84	19.12
		95% CI	(-30.4,24.0)	(-35.9,18.4)	(-32.0,43.1)
		Pr >  t			0.7720

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
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Final

**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-3.889	-0.617	-3.271
			SEM	5.992	6.696	5.753
			95% CI	(-15.9, 8.1)	(-14.1,12.8)	(-14.7, 8.2)
		Pr >  t			0.5711	
		Week 16	n	14	17	
			LS Mean	5.790	-4.380	10.169
			SEM	6.090	6.860	6.170
			95% CI	( -6.4,18.0)	(-18.1, 9.4)	( -2.1,22.4)
		Pr >  t			0.1026	
		Week 24	n	14	11	
			LS Mean	-6.210	1.794	-8.005
			SEM	6.090	7.243	6.611
			95% CI	(-18.4, 6.0)	(-12.7,16.3)	(-21.1, 5.1)
		Pr >  t			0.2285	
		Week 32	n	10	10	
			LS Mean	-2.537	-3.508	0.971
			SEM	6.737	7.355	7.044
			95% CI	(-15.9,10.9)	(-18.2,11.2)	(-13.0,14.9)
		Pr >  t			0.8905	
		Week 40	n	8	10	
			LS Mean	4.757	-3.554	8.311
			SEM	7.028	7.355	7.315
			95% CI	( -9.2,18.7)	(-18.2,11.1)	( -6.1,22.8)
		Pr >  t			0.2578	
		Week 48	n	7	11	
			LS Mean	6.315	-5.961	12.277
			SEM	7.215	7.259	7.419
			95% CI	( -8.0,20.6)	(-20.5, 8.5)	( -2.4,26.9)
		Pr >  t			0.1001	
		Week 56	n	6	9	
			LS Mean	6.008	-2.355	8.364
			SEM	7.450	7.480	7.875

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.8,20.8)	(-17.3,12.6)	(-7.2,23.9)
	Pr >  t			0.2898
	n	5	8	
	LS Mean	8.154	-5.468	13.621
	SEM	7.770	7.627	8.319
Week 72	95% CI	(-7.2,23.5)	(-20.7, 9.7)	(-2.8,30.0)
	Pr >  t			0.1033
	n	7	7	
	LS Mean	5.049	-8.729	13.778
	SEM	7.198	7.811	7.961
Week 84	95% CI	(-9.2,19.3)	(-24.3, 6.8)	(-1.9,29.5)
	Pr >  t			0.0854
	n	7	7	
	LS Mean	6.906	-11.73	18.635
	SEM	7.198	7.811	7.961
Week 96	95% CI	(-7.4,21.2)	(-27.3, 3.8)	( 2.9,34.4)
	Pr >  t			0.0204
	n	6	6	
	LS Mean	6.010	-10.51	16.522
	SEM	7.436	8.041	8.403
Week 108	95% CI	(-8.7,20.7)	(-26.5, 5.5)	(-0.1,33.1)
	Pr >  t			0.0508
	n	4	6	
	LS Mean	3.426	-11.35	14.771
	SEM	8.247	8.041	9.119
Week 120	95% CI	(-12.9,19.7)	(-27.3, 4.6)	(-3.2,32.8)
	Pr >  t			0.1069
	n	4	4	
	LS Mean	-3.935	-1.399	-2.536
	SEM	8.249	8.795	9.797
Week 132	95% CI	(-20.2,12.4)	(-18.8,16.0)	(-21.9,16.8)
	Pr >  t			0.7960
	n	3	1	
	LS Mean	3.660	-27.69	31.349
	SEM	8.956	13.72	14.80
Week 144	95% CI	(-14.0,21.3)	(-54.7,-0.6)	( 2.2,60.5)
	Pr >  t			0.0353
	n	1	1	
	LS Mean	-23.60	2.321	-25.92
	SEM	13.36	13.74	17.84

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-49.9, 2.7)	(-24.8,29.4)	(-61.1, 9.3)
		Pr >  t			0.1478
		n	35	37	
	Week 16	LS Mean	-16.55	-8.644	-7.911
		SEM	8.511	8.957	3.954
		95% CI	(-33.3, 0.2)	(-26.3, 9.0)	(-15.7,-0.1)
	Week 24	Pr >  t			0.0464
		n	35	30	
		LS Mean	-11.16	-9.601	-1.562
	Week 32	SEM	8.867	9.051	4.131
		95% CI	(-28.6, 6.3)	(-27.4, 8.2)	( -9.7, 6.6)
		Pr >  t			0.7056
	Week 40	n	32	24	
		LS Mean	-14.45	-11.41	-3.034
		SEM	8.907	9.163	4.458
	Week 48	95% CI	(-32.0, 3.1)	(-29.4, 6.6)	(-11.8, 5.7)
		Pr >  t			0.4967
		n	21	22	
	Week 56	LS Mean	-15.42	-9.972	-5.450
		SEM	9.118	9.211	4.975
		95% CI	(-33.4, 2.5)	(-28.1, 8.2)	(-15.2, 4.3)
	Week 64	Pr >  t			0.2740
		n	20	20	
		LS Mean	-14.76	-16.92	2.162
Week 8	SEM	9.157	9.268	5.139	
	95% CI	(-32.8, 3.3)	(-35.2, 1.3)	( -7.9,12.3)	
	Pr >  t			0.6742	
Week 16	n	19	12		
	LS Mean	-15.42	-11.57	-3.858	
	SEM	9.180	9.672	5.886	
Week 24	95% CI	(-33.5, 2.6)	(-30.6, 7.5)	(-15.4, 7.7)	
	Pr >  t			0.5126	
	n	16	8		
Week 32	LS Mean	-11.62	-9.919	-1.702	
	SEM	9.298	10.16	6.809	
	95% CI	(-29.9, 6.7)	(-29.9,10.1)	(-15.1,11.7)	
Week 40	Pr >  t			0.8028	
	n	12	11		
	LS Mean	-15.17	-16.56	1.388	
Week 48	SEM	9.548	9.773	6.584	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-34.0, 3.6)	(-11.6,14.3)
		Pr >  t		0.8331
	Week 72	n	13	7
		LS Mean	-16.28	-12.47
		SEM	9.484	10.35
		95% CI	(-34.9, 2.4)	(-32.8, 7.9)
		Pr >  t		(-18.2,10.6) 0.6031
	Week 84	n	12	6
		LS Mean	-16.59	-11.50
		SEM	9.541	10.61
		95% CI	(-35.4, 2.2)	(-32.4, 9.4)
		Pr >  t		(-20.4,10.2) 0.5127
	Week 96	n	7	6
		LS Mean	-7.886	-35.34
		SEM	10.21	10.61
		95% CI	(-28.0,12.2)	(-56.2, -14)
		Pr >  t		( 10.6,44.3) 0.0015
	Week 108	n	5	3
		LS Mean	-16.56	-16.74
		SEM	10.81	12.23
		95% CI	(-37.8, 4.7)	(-40.8, 7.3)
		Pr >  t		(-21.6,22.0) 0.9871
	Week 120	n	8	3
		LS Mean	-21.21	-16.74
		SEM	10.05	12.23
		95% CI	(-41.0,-1.4)	(-40.8, 7.3)
		Pr >  t		(-24.8,15.9) 0.6660
	Week 132	n	2	1
		LS Mean	-20.95	-23.50
		SEM	13.50	17.19
		95% CI	(-47.5, 5.6)	(-57.3,10.3)
		Pr >  t		(-33.4,38.5) 0.8893
	Week 144	n	2	
		LS Mean	-9.258	
		SEM	13.53	
		95% CI	(-35.8,17.3)	
		Pr >  t		
	Week 156	n	2	
		LS Mean	-11.76	
		SEM	13.53	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-38.3,14.8)		
		Pr >  t			
H1047X	Week 8	n	81	65	
		LS Mean	-1.741	-1.415	-0.326
		SEM	2.706	2.814	2.650
		95% CI	(-7.1, 3.6)	(-7.0, 4.1)	(-5.5, 4.9)
		Pr >  t			0.9021
	Week 16	n	70	52	
		LS Mean	-2.877	2.292	-5.169
		SEM	2.775	2.966	2.835
		95% CI	(-8.3, 2.6)	(-3.6, 8.1)	(-10.7, 0.4)
		Pr >  t			0.0691
	Week 24	n	54	40	
		LS Mean	-2.854	-1.607	-1.247
		SEM	2.893	3.136	3.098
		95% CI	(-8.6, 2.8)	(-7.8, 4.6)	(-7.3, 4.8)
		Pr >  t			0.6876
	Week 32	n	50	36	
		LS Mean	-2.236	-0.032	-2.204
		SEM	2.942	3.197	3.196
		95% CI	(-8.0, 3.6)	(-6.3, 6.3)	(-8.5, 4.1)
		Pr >  t			0.4907
	Week 40	n	42	28	
		LS Mean	-0.962	1.065	-2.027
		SEM	3.029	3.375	3.441
		95% CI	(-6.9, 5.0)	(-5.6, 7.7)	(-8.8, 4.7)
		Pr >  t			0.5560
	Week 48	n	38	24	
		LS Mean	-4.093	1.922	-6.015
		SEM	3.082	3.490	3.600
		95% CI	(-10.2, 2.0)	(-4.9, 8.8)	(-13.1, 1.1)
		Pr >  t			0.0952
	Week 56	n	33	24	
		LS Mean	-2.372	1.166	-3.538
		SEM	3.164	3.492	3.675
		95% CI	(-8.6, 3.9)	(-5.7, 8.0)	(-10.8, 3.7)
		Pr >  t			0.3361
	Week 64	n	27	19	
		LS Mean	-0.870	0.057	-0.928
		SEM	3.292	3.691	3.974

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.3, 5.6)	(-7.2, 7.3)	(-8.7, 6.9)
		Pr >  t			0.8155
	Week 72	n	26	17	
		LS Mean	-1.948	1.847	-3.795
		SEM	3.320	3.794	4.093
		95% CI	(-8.5, 4.6)	(-5.6, 9.3)	(-11.8, 4.2)
		Pr >  t			0.3541
	Week 84	n	18	16	
		LS Mean	-0.803	2.277	-3.080
		SEM	3.644	3.858	4.403
		95% CI	(-8.0, 6.4)	(-5.3, 9.9)	(-11.7, 5.6)
		Pr >  t			0.4844
	Week 96	n	20	10	
		LS Mean	-0.345	0.686	-1.031
		SEM	3.541	4.426	4.838
		95% CI	(-7.3, 6.6)	(-8.0, 9.4)	(-10.5, 8.5)
		Pr >  t			0.8312
	Week 108	n	14	10	
		LS Mean	-1.204	3.381	-4.585
		SEM	3.910	4.426	5.109
		95% CI	(-8.9, 6.5)	(-5.3, 12.1)	(-14.6, 5.4)
		Pr >  t			0.3697
	Week 120	n	14	7	
		LS Mean	3.814	2.019	1.794
		SEM	3.896	4.992	5.604
		95% CI	(-3.8, 11.5)	(-7.8, 11.8)	(-9.2, 12.8)
		Pr >  t			0.7489
	Week 132	n	12	5	
		LS Mean	-0.829	-1.577	0.749
		SEM	4.092	5.657	6.322
		95% CI	(-8.9, 7.2)	(-12.7, 9.5)	(-11.7, 13.2)
		Pr >  t			0.9057
	Week 144	n	11	4	
		LS Mean	-0.892	1.674	-2.567
		SEM	4.191	6.179	6.861
		95% CI	(-9.1, 7.3)	(-10.5, 13.8)	(-16.0, 10.9)
		Pr >  t			0.7084
	Week 156	n	8	3	
		LS Mean	0.190	-2.888	3.078
		SEM	4.676	6.958	7.842

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168		95% CI	(-9.0, 9.4)	(-16.5, 10.8)	(-12.3, 18.5)
		Pr >  t			0.6948
		n	4	2	
		LS Mean	2.148	3.230	-1.083
		SEM	6.100	8.299	9.865
Week 180		95% CI	(-9.8, 14.1)	(-13.1, 19.5)	(-20.4, 18.3)
		Pr >  t			0.9126
		n	1	1	
		LS Mean	-2.199	-0.953	-1.246
		SEM	11.37	11.40	15.82
Week 192		95% CI	(-24.5, 20.1)	(-23.3, 21.4)	(-32.3, 29.8)
		Pr >  t			0.9372
		n	1	1	
		LS Mean	-4.199	3.047	-7.246
		SEM	11.37	11.40	15.82
	95% CI	(-26.5, 18.1)	(-19.3, 25.4)	(-38.3, 23.8)	
	Pr >  t			0.6471	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	65			
			LS Mean	-1.741	-1.415	-0.326		
			SEM	2.706	2.814	2.650		
			95% CI	(-7.1, 3.6)	(-7.0, 4.1)	(-5.5, 4.9)		
					Pr >  t			0.9021
		Week 16	n	70	52			
			LS Mean	-2.877	2.292	-5.169		
			SEM	2.775	2.966	2.835		
			95% CI	(-8.3, 2.6)	(-3.6, 8.1)	(-10.7, 0.4)		
					Pr >  t			0.0691
		Week 24	n	54	40			
			LS Mean	-2.854	-1.607	-1.247		
			SEM	2.893	3.136	3.098		
			95% CI	(-8.6, 2.8)	(-7.8, 4.6)	(-7.3, 4.8)		
					Pr >  t			0.6876
		Week 32	n	50	36			
			LS Mean	-2.236	-0.032	-2.204		
			SEM	2.942	3.197	3.196		
			95% CI	(-8.0, 3.6)	(-6.3, 6.3)	(-8.5, 4.1)		
					Pr >  t			0.4907
		Week 40	n	42	28			
			LS Mean	-0.962	1.065	-2.027		
			SEM	3.029	3.375	3.441		
			95% CI	(-6.9, 5.0)	(-5.6, 7.7)	(-8.8, 4.7)		
			Pr >  t			0.5560		
Week 48	n	38	24					
	LS Mean	-4.093	1.922	-6.015				
	SEM	3.082	3.490	3.600				
	95% CI	(-10.2, 2.0)	(-4.9, 8.8)	(-13.1, 1.1)				
			Pr >  t			0.0952		
Week 56	n	33	24					
	LS Mean	-2.372	1.166	-3.538				
		SEM	3.164	3.492	3.675			

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-8.6, 3.9)	(-5.7, 8.0)	(-10.8, 3.7)
		Pr >  t			0.3361
		n	27	19	
		LS Mean	-0.870	0.057	-0.928
		SEM	3.292	3.691	3.974
Week 72		95% CI	(-7.3, 5.6)	(-7.2, 7.3)	(-8.7, 6.9)
		Pr >  t			0.8155
		n	26	17	
		LS Mean	-1.948	1.847	-3.795
		SEM	3.320	3.794	4.093
Week 84		95% CI	(-8.5, 4.6)	(-5.6, 9.3)	(-11.8, 4.2)
		Pr >  t			0.3541
		n	18	16	
		LS Mean	-0.803	2.277	-3.080
		SEM	3.644	3.858	4.403
Week 96		95% CI	(-8.0, 6.4)	(-5.3, 9.9)	(-11.7, 5.6)
		Pr >  t			0.4844
		n	20	10	
		LS Mean	-0.345	0.686	-1.031
		SEM	3.541	4.426	4.838
Week 108		95% CI	(-7.3, 6.6)	(-8.0, 9.4)	(-10.5, 8.5)
		Pr >  t			0.8312
		n	14	10	
		LS Mean	-1.204	3.381	-4.585
		SEM	3.910	4.426	5.109
Week 120		95% CI	(-8.9, 6.5)	(-5.3, 12.1)	(-14.6, 5.4)
		Pr >  t			0.3697
		n	14	7	
		LS Mean	3.814	2.019	1.794
		SEM	3.896	4.992	5.604
Week 132		95% CI	(-3.8, 11.5)	(-7.8, 11.8)	(-9.2, 12.8)
		Pr >  t			0.7489
		n	12	5	
		LS Mean	-0.829	-1.577	0.749
		SEM	4.092	5.657	6.322
Week 144		95% CI	(-8.9, 7.2)	(-12.7, 9.5)	(-11.7, 13.2)
		Pr >  t			0.9057
		n	11	4	
	LS Mean	-0.892	1.674	-2.567	
	SEM	4.191	6.179	6.861	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 156	95% CI	(-9.1, 7.3)	(-10.5,13.8)	(-16.0,10.9)
		Pr >  t			0.7084
		n	8	3	
	Week 168	LS Mean	0.190	-2.888	3.078
		SEM	4.676	6.958	7.842
		95% CI	(-9.0, 9.4)	(-16.5,10.8)	(-12.3,18.5)
		Pr >  t			0.6948
		n	4	2	
	Week 180	LS Mean	2.148	3.230	-1.083
		SEM	6.100	8.299	9.865
		95% CI	(-9.8,14.1)	(-13.1,19.5)	(-20.4,18.3)
		Pr >  t			0.9126
n		1	1		
Week 192	LS Mean	-2.199	-0.953	-1.246	
	SEM	11.37	11.40	15.82	
	95% CI	(-24.5,20.1)	(-23.3,21.4)	(-32.3,29.8)	
	Pr >  t			0.9372	
	n	1	1		
Exon 9	Week 8	LS Mean	-4.199	3.047	-7.246
		SEM	11.37	11.40	15.82
		95% CI	(-26.5,18.1)	(-19.3,25.4)	(-38.3,23.8)
	Week 16	Pr >  t			0.6471
		n	53	64	
		LS Mean	-7.564	-0.952	-6.612
		SEM	4.348	4.661	3.152
		95% CI	(-16.1, 1.0)	(-10.1, 8.2)	(-12.8,-0.4)
	Week 24	Pr >  t			0.0366
		n	49	48	
		LS Mean	-0.139	-2.252	2.113
		SEM	4.470	4.789	3.390
95% CI		(-8.9, 8.7)	(-11.7, 7.2)	(-4.6, 8.8)	
Week 32	Pr >  t			0.5335	
	n	46	37		
	LS Mean	-6.052	-1.327	-4.725	
	SEM	4.500	4.927	3.639	
	95% CI	(-14.9, 2.8)	(-11.0, 8.4)	(-11.9, 2.4)	
	Pr >  t			0.1948	
	n	31	33		
	LS Mean	-5.993	-2.068	-3.925	
	SEM	4.853	4.999	4.024	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-15.5, 3.6)	(-11.9, 7.8)	(-11.8, 4.0)
		Pr >  t			0.3298
		n	28	30	
		LS Mean	-3.308	-6.812	3.504
		SEM	4.930	5.063	4.189
Week 48		95% CI	(-13.0, 6.4)	(-16.8, 3.2)	(-4.7,11.7)
		Pr >  t			0.4032
		n	26	23	
		LS Mean	-3.411	-4.461	1.050
		SEM	4.981	5.266	4.494
Week 56		95% CI	(-13.2, 6.4)	(-14.8, 5.9)	(-7.8, 9.9)
		Pr >  t			0.8153
		n	22	17	
		LS Mean	-0.591	-2.044	1.453
		SEM	5.113	5.554	4.972
Week 64		95% CI	(-10.6, 9.5)	(-13.0, 8.9)	(-8.3,11.2)
		Pr >  t			0.7702
		n	17	19	
		LS Mean	-2.402	-7.305	4.903
		SEM	5.362	5.444	5.109
Week 72		95% CI	(-12.9, 8.1)	(-18.0, 3.4)	(-5.1,14.9)
		Pr >  t			0.3376
		n	20	14	
		LS Mean	-3.607	-6.295	2.687
		SEM	5.208	5.778	5.308
Week 84		95% CI	(-13.9, 6.6)	(-17.7, 5.1)	(-7.7,13.1)
		Pr >  t			0.6129
		n	19	13	
		LS Mean	-3.123	-7.842	4.719
		SEM	5.248	5.872	5.455
Week 96		95% CI	(-13.4, 7.2)	(-19.4, 3.7)	(-6.0,15.4)
		Pr >  t			0.3873
		n	13	12	
		LS Mean	1.854	-18.70	20.554
		SEM	5.680	5.977	5.979
Week 108		95% CI	(-9.3,13.0)	(-30.5,-6.9)	( 8.8,32.3)
		Pr >  t			0.0006
		n	9	9	
		LS Mean	-4.184	-10.33	6.148
		SEM	6.239	6.416	6.914

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.4, 8.1)	(-22.9, 2.3)	(-7.4, 19.7)
		Pr >  t			0.3743
	Week 120	n	12	7	
		LS Mean	-10.04	-4.315	-5.720
		SEM	5.809	6.883	6.980
		95% CI	(-21.5, 1.4)	(-17.8, 9.2)	(-19.4, 8.0)
		Pr >  t			0.4128
	Week 132	n	5	2	
		LS Mean	-5.318	-20.45	15.137
		SEM	7.475	10.76	11.81
		95% CI	(-20.0, 9.4)	(-41.6, 0.7)	(-8.1, 38.3)
		Pr >  t			0.2004
	Week 144	n	3	1	
		LS Mean	-9.124	2.557	-11.68
		SEM	9.041	14.58	16.19
		95% CI	(-26.9, 8.6)	(-26.1, 31.2)	(-43.5, 20.1)
		Pr >  t			0.4710
	Week 156	n	2		
		LS Mean	-2.095		
		SEM	10.68		
		95% CI	(-23.1, 18.9)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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#### 4.8.3.4 Gesundheitsbezogenen Lebensqualität: EORTC QLQ-C30 – 2. Datenschnitt

Tabelle 4H-35: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Allgemeiner Gesundheitszustand/Lebensqualität“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73	
			LS Mean	0.295	1.261	-0.966
			SEM	2.868	2.900	2.683
			95% CI	(-5.4, 5.9)	(-4.5, 7.0)	(-6.2, 4.3)
			Pr >  t			0.7189
	Week 16	n	67	56		
		LS Mean	0.057	-2.696	2.753	
		SEM	2.925	3.094	2.932	
		95% CI	(-5.7, 5.8)	(-8.8, 3.4)	(-3.0, 8.5)	
		Pr >  t			0.3483	
	Week 24	n	61	46		
		LS Mean	-0.658	2.991	-3.649	
		SEM	2.994	3.213	3.120	
		95% CI	(-6.6, 5.2)	(-3.3, 9.3)	(-9.8, 2.5)	
		Pr >  t			0.2427	
	Week 32	n	52	41		
		LS Mean	-1.781	-0.555	-1.225	
		SEM	3.122	3.312	3.291	
		95% CI	(-7.9, 4.4)	(-7.1, 6.0)	(-7.7, 5.2)	
		Pr >  t			0.7098	
Week 40	n	45	36			
	LS Mean	-0.889	-0.171	-0.718		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	SEM	3.211	3.429	3.473
	95% CI	(-7.2, 5.4)	(-6.9, 6.6)	(-7.5, 6.1)
	Pr >  t			0.8363
	n	42	30	
	LS Mean	-1.831	-1.123	-0.708
Week 56	SEM	3.258	3.577	3.662
	95% CI	(-8.2, 4.6)	(-8.2, 5.9)	(-7.9, 6.5)
	Pr >  t			0.8467
	n	35	24	
	LS Mean	-2.277	0.998	-3.275
Week 64	SEM	3.386	3.787	3.982
	95% CI	(-8.9, 4.4)	(-6.4, 8.4)	(-11.1, 4.5)
	Pr >  t			0.4110
	n	25	25	
	LS Mean	-2.854	3.408	-6.263
Week 72	SEM	3.671	3.748	4.197
	95% CI	(-10.1, 4.4)	(-4.0, 10.8)	(-14.5, 2.0)
	Pr >  t			0.1360
	n	27	20	
	LS Mean	-3.818	-3.192	-0.626
Week 84	SEM	3.602	3.981	4.348
	95% CI	(-10.9, 3.3)	(-11.0, 4.6)	(-9.2, 7.9)
	Pr >  t			0.8855
	n	23	19	
	LS Mean	-1.219	-0.743	-0.476
Week 96	SEM	3.772	4.041	4.531
	95% CI	(-8.6, 6.2)	(-8.7, 7.2)	(-9.4, 8.4)
	Pr >  t			0.9163
	n	20	13	
	LS Mean	-5.190	1.925	-7.116
Week 108	SEM	3.924	4.545	5.101
	95% CI	(-12.9, 2.5)	(-7.0, 10.8)	(-17.1, 2.9)
	Pr >  t			0.1634
	n	17	13	
	LS Mean	-0.306	0.213	-0.519
Week 120	SEM	4.121	4.546	5.254
	95% CI	(-8.4, 7.8)	(-8.7, 9.1)	(-10.8, 9.8)
	Pr >  t			0.9213
	n	17	12	
	LS Mean	-6.168	0.732	-6.901

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 132	SEM	4.120	4.670	5.361
		95% CI	(-14.3, 1.9)	(-8.4, 9.9)	(-17.4, 3.6)
		Pr >  t			0.1984
		n	13	6	
		LS Mean	-1.133	-10.40	9.270
		SEM	4.489	6.035	6.823
	Week 144	95% CI	(-9.9, 7.7)	(-22.2, 1.4)	(-4.1, 22.7)
		Pr >  t			0.1746
		n	11	4	
		LS Mean	-10.01	5.100	-15.11
		SEM	4.756	7.149	7.981
		95% CI	(-19.3, -0.7)	(-8.9, 19.1)	(-30.8, 0.6)
Week 156	Pr >  t			0.0587	
	n	7	2		
	LS Mean	-3.483	-4.070	0.588	
	SEM	5.630	9.730	10.79	
	95% CI	(-14.5, 7.6)	(-23.2, 15.0)	(-20.6, 21.8)	
	Pr >  t			0.9566	
Week 168	n	3	1		
	LS Mean	-1.858	3.345	-5.203	
	SEM	8.051	13.49	15.39	
	95% CI	(-17.7, 13.9)	(-23.1, 29.8)	(-35.4, 25.0)	
	Pr >  t			0.7353	
	n	1	1		
Week 180	LS Mean	-16.48	3.345	-19.83	
	SEM	13.46	13.49	18.79	
	95% CI	(-42.9, 9.9)	(-23.1, 29.8)	(-56.7, 17.1)	
	Pr >  t			0.2917	
	n	1	1		
	LS Mean	0.190	3.345	-3.155	
Week 192	SEM	13.46	13.49	18.79	
	95% CI	(-26.2, 26.6)	(-23.1, 29.8)	(-40.0, 33.7)	
	Pr >  t			0.8667	
	n	65	67		
	LS Mean	-6.403	-3.221	-3.182	
	SEM	3.645	3.739	3.140	
Week 8	95% CI	(-13.6, 0.8)	(-10.6, 4.2)	(-9.4, 3.0)	
	Pr >  t			0.3117	
	n	57	51		
	LS Mean	-4.799	-3.813	-0.986	
	SEM				
	95% CI				
Week 16	Pr >  t				
	LS Mean				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	SEM	3.779	3.909	3.388
	95% CI	(-12.2, 2.6)	(-11.5, 3.9)	(-7.7, 5.7)
	Pr >  t			0.7712
	n	44	35	
	LS Mean	-6.668	-5.865	-0.803
Week 32	SEM	3.903	4.181	3.798
	95% CI	(-14.4, 1.0)	(-14.1, 2.4)	(-8.3, 6.7)
	Pr >  t			0.8326
	n	34	32	
	LS Mean	-4.216	-2.512	-1.705
Week 40	SEM	4.083	4.249	4.035
	95% CI	(-12.3, 3.8)	(-10.9, 5.9)	(-9.6, 6.2)
	Pr >  t			0.6729
	n	30	26	
	LS Mean	-5.877	-5.185	-0.692
Week 48	SEM	4.170	4.405	4.287
	95% CI	(-14.1, 2.3)	(-13.9, 3.5)	(-9.1, 7.7)
	Pr >  t			0.8719
	n	27	21	
	LS Mean	-6.787	-2.950	-3.837
Week 56	SEM	4.243	4.592	4.549
	95% CI	(-15.1, 1.6)	(-12.0, 6.1)	(-12.8, 5.1)
	Pr >  t			0.3993
	n	24	21	
	LS Mean	-1.272	-1.970	0.698
Week 64	SEM	4.337	4.592	4.639
	95% CI	(-9.8, 7.3)	(-11.0, 7.1)	(-8.4, 9.8)
	Pr >  t			0.8805
	n	22	17	
	LS Mean	-1.774	-10.80	9.030
Week 72	SEM	4.412	4.804	4.918
	95% CI	(-10.5, 6.9)	(-20.2,-1.4)	(-0.6,18.7)
	Pr >  t			0.0668
	n	21	15	
	LS Mean	-1.478	-0.432	-1.046
Week 84	SEM	4.456	4.944	5.092
	95% CI	(-10.2, 7.3)	(-10.1, 9.3)	(-11.0, 9.0)
	Pr >  t			0.8373
	n	17	14	
	LS Mean	-1.672	-3.858	2.186

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	SEM	4.676	5.024	5.351
	95% CI	(-10.9, 7.5)	(-13.7, 6.0)	(-8.3,12.7)
	Pr >  t			0.6829
	n	15	11	
	LS Mean	-2.724	-8.773	6.049
Week 108	SEM	4.799	5.347	5.773
	95% CI	(-12.2, 6.7)	(-19.3, 1.7)	(-5.3,17.4)
	Pr >  t			0.2951
	n	9	8	
	LS Mean	-5.867	-5.969	0.102
Week 120	SEM	5.537	5.864	6.826
	95% CI	(-16.7, 5.0)	(-17.5, 5.5)	(-13.3,13.5)
	Pr >  t			0.9881
	n	11	4	
	LS Mean	1.492	-7.550	9.042
Week 132	SEM	5.213	7.456	8.033
	95% CI	(-8.7,11.7)	(-22.2, 7.1)	(-6.7,24.8)
	Pr >  t			0.2607
	n	7	2	
	LS Mean	-4.079	-1.107	-2.972
Week 144	SEM	5.996	9.851	10.70
	95% CI	(-15.9, 7.7)	(-20.5,18.2)	(-24.0,18.0)
	Pr >  t			0.7814
	n	4	1	
	LS Mean	-0.524	6.198	-6.722
Week 156	SEM	7.288	13.44	14.70
	95% CI	(-14.8,13.8)	(-20.2,32.6)	(-35.6,22.1)
	Pr >  t			0.6476
	n	3	1	
	LS Mean	2.904	-10.47	13.376
Week 168	SEM	8.226	13.44	15.16
	95% CI	(-13.2,19.1)	(-36.9,15.9)	(-16.4,43.2)
	Pr >  t			0.3780
	n	1	1	
	LS Mean	-7.361	6.198	-13.56
Week 168	SEM	13.40	13.44	18.48
	95% CI	(-33.7,19.0)	(-20.2,32.6)	(-49.9,22.7)
	Pr >  t			0.4635

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	-2.994	0.503	-3.496		
			SEM	2.443	2.604	2.494		
			95% CI	(-7.8, 1.8)	(-4.6, 5.6)	(-8.4, 1.4)		
					Pr >  t			0.1616
		Week 16	n	86	68			
			LS Mean	-1.854	-4.571	2.717		
			SEM	2.512	2.729	2.689		
			95% CI	(-6.8, 3.1)	(-9.9, 0.8)	(-2.6, 8.0)		
					Pr >  t			0.3126
		Week 24	n	73	48			
			LS Mean	-2.837	1.568	-4.406		
			SEM	2.601	2.976	3.009		
			95% CI	(-8.0, 2.3)	(-4.3, 7.4)	(-10.3, 1.5)		
					Pr >  t			0.1435
		Week 32	n	60	43			
			LS Mean	-2.264	-2.223	-0.041		
			SEM	2.750	3.072	3.189		
			95% CI	(-7.7, 3.1)	(-8.3, 3.8)	(-6.3, 6.2)		
					Pr >  t			0.9898
		Week 40	n	50	38			
			LS Mean	-2.398	-0.015	-2.383		
			SEM	2.866	3.182	3.385		
			95% CI	(-8.0, 3.2)	(-6.3, 6.2)	(-9.0, 4.3)		
					Pr >  t			0.4816
		Week 48	n	48	31			
			LS Mean	-3.751	-1.484	-2.267		
			SEM	2.895	3.361	3.577		
95% CI	(-9.4, 1.9)		(-8.1, 5.1)	(-9.3, 4.8)				
			Pr >  t			0.5263		
Week 56	n	41	25					
	LS Mean	-2.917	0.375	-3.291				
	SEM	3.008	3.578	3.873				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.8, 3.0)	(-6.6, 7.4)	(-10.9, 4.3)
	Pr >  t			0.3957
	n	30	24	
	LS Mean	-2.917	2.519	-5.436
	SEM	3.269	3.622	4.125
Week 72	95% CI	(-9.3, 3.5)	(-4.6, 9.6)	(-13.5, 2.7)
	Pr >  t			0.1878
	n	32	19	
	LS Mean	-4.077	-3.566	-0.511
	SEM	3.212	3.897	4.324
Week 84	95% CI	(-10.4, 2.2)	(-11.2, 4.1)	(-9.0, 8.0)
	Pr >  t			0.9060
	n	26	19	
	LS Mean	-2.260	-1.874	-0.386
	SEM	3.431	3.898	4.477
Week 96	95% CI	(-9.0, 4.5)	(-9.5, 5.8)	(-9.2, 8.4)
	Pr >  t			0.9313
	n	23	14	
	LS Mean	-6.163	0.954	-7.117
	SEM	3.555	4.325	4.949
Week 108	95% CI	(-13.1, 0.8)	(-7.5, 9.4)	(-16.8, 2.6)
	Pr >  t			0.1507
	n	19	13	
	LS Mean	-1.590	0.805	-2.395
	SEM	3.797	4.441	5.216
Week 120	95% CI	(-9.0, 5.9)	(-7.9, 9.5)	(-12.6, 7.8)
	Pr >  t			0.6462
	n	19	11	
	LS Mean	-7.032	0.397	-7.429
	SEM	3.784	4.725	5.460
Week 132	95% CI	(-14.5, 0.4)	(-8.9, 9.7)	(-18.1, 3.3)
	Pr >  t			0.1739
	n	15	5	
	LS Mean	-3.775	-9.147	5.372
	SEM	4.121	6.505	7.237
Week 144	95% CI	(-11.9, 4.3)	(-21.9, 3.6)	(-8.8, 19.6)
	Pr >  t			0.4581
	n	12	3	
	LS Mean	-10.65	7.236	-17.89
	SEM	4.462	8.177	8.945

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Yes	Week 156	95% CI	(-19.4,-1.9)	(-8.8,23.3)	(-35.4,-0.3)
		Pr >  t			0.0458
		n	7	2	
		LS Mean	-4.782	-4.484	-0.298
		SEM	5.561	9.856	11.01
	Week 168	95% CI	(-15.7, 6.1)	(-23.8,14.9)	(-21.9,21.3)
		Pr >  t			0.9784
		n	3	1	
		LS Mean	-3.179	2.894	-6.073
		SEM	8.096	13.72	15.71
	Week 180	95% CI	(-19.1,12.7)	(-24.0,29.8)	(-36.9,24.8)
		Pr >  t			0.6992
		n	1	1	
		LS Mean	-17.85	2.894	-20.74
		SEM	13.68	13.72	19.20
Week 192	95% CI	(-44.7, 9.0)	(-24.0,29.8)	(-58.4,16.9)	
	Pr >  t			0.2803	
	n	1	1		
	LS Mean	-1.177	2.894	-4.071	
	SEM	13.68	13.72	19.20	
Yes	Week 8	95% CI	(-28.0,25.7)	(-24.0,29.8)	(-41.8,33.6)
		Pr >  t			0.8321
		n	44	56	
		LS Mean	-6.339	-6.913	0.574
		SEM	5.752	5.479	3.587
	Week 16	95% CI	(-17.7, 5.0)	(-17.7, 3.9)	(-6.5, 7.6)
		Pr >  t			0.8730
		n	38	39	
		LS Mean	-6.449	-4.796	-1.653
		SEM	5.905	5.781	3.913
	Week 24	95% CI	(-18.1, 5.2)	(-16.2, 6.6)	(-9.4, 6.1)
		Pr >  t			0.6731
		n	32	33	
		LS Mean	-8.098	-8.711	0.613
		SEM	5.985	5.853	4.137
Week 32	95% CI	(-19.9, 3.7)	(-20.2, 2.8)	(-7.5, 8.8)	
	Pr >  t			0.8822	
	n	26	30		
	LS Mean	-8.558	-4.643	-3.915	
	SEM	6.088	5.907	4.354	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-20.6, 3.4)	(-16.3, 7.0)	(-12.5, 4.7)
	Pr >  t			0.3693
	n	25	24	
	LS Mean	-8.430	-10.43	1.999
	SEM	6.109	6.023	4.545
Week 48	95% CI	(-20.5, 3.6)	(-22.3, 1.4)	(-6.9, 10.9)
	Pr >  t			0.6604
	n	21	20	
	LS Mean	-8.279	-7.127	-1.152
	SEM	6.205	6.138	4.818
Week 56	95% CI	(-20.5, 3.9)	(-19.2, 5.0)	(-10.6, 8.3)
	Pr >  t			0.8112
	n	18	20	
	LS Mean	-3.668	-5.657	1.988
	SEM	6.306	6.137	4.948
Week 64	95% CI	(-16.1, 8.8)	(-17.7, 6.4)	(-7.7, 11.7)
	Pr >  t			0.6881
	n	17	18	
	LS Mean	-5.080	-13.69	8.609
	SEM	6.347	6.208	5.090
Week 72	95% CI	(-17.6, 7.4)	(-25.9, -1.5)	(-1.4, 18.6)
	Pr >  t			0.0915
	n	16	16	
	LS Mean	-4.256	-4.989	0.732
	SEM	6.396	6.300	5.253
Week 84	95% CI	(-16.9, 8.3)	(-17.4, 7.4)	(-9.6, 11.1)
	Pr >  t			0.8892
	n	14	14	
	LS Mean	-3.870	-6.966	3.097
	SEM	6.501	6.407	5.505
Week 96	95% CI	(-16.7, 8.9)	(-19.6, 5.6)	(-7.7, 13.9)
	Pr >  t			0.5741
	n	12	10	
	LS Mean	-4.463	-12.78	8.318
	SEM	6.642	6.742	6.046
Week 108	95% CI	(-17.5, 8.6)	(-26.0, 0.5)	(-3.6, 20.2)
	Pr >  t			0.1695
	n	7	8	
Week 108	LS Mean	-8.558	-11.80	3.242
	SEM	7.289	7.021	7.029

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.9, 5.8)	(-25.6, 2.0)	(-10.6,17.0)
		Pr >  t			0.6448
	Week 120	n	9	5	
		LS Mean	0.511	-11.23	11.741
		SEM	6.962	7.791	7.496
		95% CI	(-13.2,14.2)	(-26.5, 4.1)	( -3.0,26.5)
		Pr >  t			0.1178
	Week 132	n	5	3	
		LS Mean	-2.117	-12.77	10.653
		SEM	7.857	8.978	9.451
		95% CI	(-17.6,13.3)	(-30.4, 4.9)	( -7.9,29.2)
		Pr >  t			0.2602
	Week 144	n	3	2	
		LS Mean	-1.664	-4.579	2.915
		SEM	9.029	10.28	11.59
		95% CI	(-19.4,16.1)	(-24.8,15.6)	(-19.8,25.7)
		Pr >  t			0.8015
	Week 156	n	3	1	
		LS Mean	1.029	-15.23	16.255
		SEM	9.038	13.44	14.46
		95% CI	(-16.7,18.8)	(-41.6,11.2)	(-12.2,44.7)
		Pr >  t			0.2616
	Week 168	n	1	1	
		LS Mean	-9.480	1.444	-10.92
		SEM	13.50	13.44	17.60
		95% CI	(-36.0,17.0)	(-24.9,27.8)	(-45.5,23.7)
		Pr >  t			0.5351

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Bone Lesions Only (L)	No	Week 8	n	104	110		
			LS Mean	-2.991	-1.298	-1.694	
			SEM	2.771	2.759	2.469	
			95% CI	(-8.4, 2.5)	(-6.7, 4.1)	(-6.5, 3.2)	
					Pr >  t		0.4931
		Week 16	n	92	83		
			LS Mean	-2.206	-2.311	0.105	
			SEM	2.855	2.940	2.681	
			95% CI	(-7.8, 3.4)	(-8.1, 3.5)	(-5.2, 5.4)	
					Pr >  t		0.9687
		Week 24	n	77	59		
			LS Mean	-4.226	-0.594	-3.632	
			SEM	2.927	3.142	2.971	
			95% CI	(-10.0, 1.5)	(-6.8, 5.6)	(-9.5, 2.2)	
					Pr >  t		0.2219
		Week 32	n	57	53		
			LS Mean	-2.034	-1.074	-0.960	
			SEM	3.126	3.209	3.201	
			95% CI	(-8.2, 4.1)	(-7.4, 5.2)	(-7.2, 5.3)	
					Pr >  t		0.7643
		Week 40	n	50	44		
			LS Mean	-2.054	-1.399	-0.655	
			SEM	3.207	3.348	3.407	
			95% CI	(-8.4, 4.2)	(-8.0, 5.2)	(-7.3, 6.0)	
					Pr >  t		0.8475
		Week 48	n	47	37		
			LS Mean	-4.913	-3.491	-1.422	
			SEM	3.246	3.480	3.572	
95% CI	(-11.3, 1.5)		(-10.3, 3.3)	(-8.4, 5.6)			
			Pr >  t		0.6907		
Week 56	n	40	32				
	LS Mean	0.249	0.361	-0.112			
	SEM	3.359	3.602	3.791			

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-6.3, 6.8)	(-6.7, 7.4)	(-7.6, 7.3)
		Pr >  t			0.9764
		n	32	27	
		LS Mean	-1.356	-5.183	3.827
		SEM	3.537	3.760	4.097
Week 72		95% CI	(-8.3, 5.6)	(-12.6, 2.2)	(-4.2, 11.9)
		Pr >  t			0.3504
		n	31	23	
		LS Mean	-0.897	0.276	-1.173
		SEM	3.568	3.928	4.275
Week 84		95% CI	(-7.9, 6.1)	(-7.4, 8.0)	(-9.6, 7.2)
		Pr >  t			0.7839
		n	27	21	
		LS Mean	0.957	-1.432	2.389
		SEM	3.701	4.030	4.472
Week 96		95% CI	(-6.3, 8.2)	(-9.3, 6.5)	(-6.4, 11.2)
		Pr >  t			0.5933
		n	23	16	
		LS Mean	-2.819	-3.101	0.282
		SEM	3.857	4.375	4.916
Week 108		95% CI	(-10.4, 4.8)	(-11.7, 5.5)	(-9.4, 9.9)
		Pr >  t			0.9543
		n	15	14	
		LS Mean	-1.472	-1.618	0.146
		SEM	4.406	4.568	5.510
Week 120		95% CI	(-10.1, 7.2)	(-10.6, 7.3)	(-10.7, 11.0)
		Pr >  t			0.9788
		n	18	8	
		LS Mean	0.991	-1.900	2.891
		SEM	4.151	5.586	6.215
Week 132		95% CI	(-7.2, 9.1)	(-12.9, 9.1)	(-9.3, 15.1)
		Pr >  t			0.6419
		n	12	4	
		LS Mean	1.099	-14.69	15.785
		SEM	4.755	7.414	8.226
Week 144		95% CI	(-8.2, 10.4)	(-29.2, -0.1)	(-0.4, 31.9)
		Pr >  t			0.0553
		n	8	3	
		LS Mean	0.534	5.433	-4.899
		SEM	5.507	8.429	9.576

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.3,11.3)	(-11.1,22.0)	(-23.7,13.9)
		Pr >  t			0.6091
	Week 156	n	5	1	
		LS Mean	5.727	-8.884	14.612
		SEM	6.695	14.06	15.25
		95% CI	(-7.4,18.9)	(-36.5,18.7)	(-15.3,44.5)
		Pr >  t			0.3383
	Week 168	n	2	1	
		LS Mean	-1.449	7.786	-9.235
		SEM	10.11	14.06	17.03
		95% CI	(-21.3,18.4)	(-19.8,35.4)	(-42.7,24.2)
		Pr >  t			0.5877
	Week 180	n	1		
		LS Mean	-14.93		
		SEM	14.02		
		95% CI	(-42.4,12.6)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	1.742		
		SEM	14.02		
		95% CI	(-25.8,29.3)		
		Pr >  t			
Yes	Week 8	n	38	30	
		LS Mean	0.204	4.031	-3.826
		SEM	3.904	4.184	3.543
		95% CI	(-7.6, 8.0)	(-4.3,12.3)	(-10.8, 3.2)
		Pr >  t			0.2816
	Week 16	n	32	24	
		LS Mean	0.425	-2.914	3.339
		SEM	3.962	4.303	3.852
		95% CI	(-7.4, 8.3)	(-11.4, 5.6)	(-4.3,10.9)
		Pr >  t			0.3870
	Week 24	n	28	22	
		LS Mean	1.479	1.766	-0.287
		SEM	4.095	4.375	4.018
		95% CI	(-6.6, 9.6)	(-6.9,10.4)	(-8.2, 7.6)
		Pr >  t			0.9431
	Week 32	n	29	20	
		LS Mean	-2.778	1.092	-3.870
		SEM	4.078	4.509	4.084

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	95% CI	(-10.9, 5.3)	(-7.8,10.0)	(-11.9, 4.2)	
	Pr >  t			0.3443	
	n	25	18		
	LS Mean	-2.841	-1.572	-1.269	
Week 48	SEM	4.169	4.581	4.272	
	95% CI	(-11.1, 5.4)	(-10.6, 7.5)	(-9.7, 7.1)	
	Pr >  t			0.7666	
	n	22	14		
Week 56	LS Mean	0.392	5.273	-4.881	
	SEM	4.251	4.814	4.604	
	95% CI	(-8.0, 8.8)	(-4.2,14.8)	(-13.9, 4.2)	
	Pr >  t			0.2899	
Week 64	n	19	13		
	LS Mean	-4.248	1.257	-5.506	
	SEM	4.355	4.894	4.794	
	95% CI	(-12.9, 4.4)	(-8.4,10.9)	(-14.9, 3.9)	
Week 72	Pr >  t			0.2516	
	n	15	15		
	LS Mean	-1.708	5.328	-7.035	
	SEM	4.552	4.750	4.844	
Week 84	95% CI	(-10.7, 7.3)	(-4.1,14.7)	(-16.6, 2.5)	
	Pr >  t			0.1473	
	n	17	12		
	LS Mean	-4.145	-3.684	-0.461	
Week 96	SEM	4.445	4.978	4.966	
	95% CI	(-12.9, 4.6)	(-13.5, 6.1)	(-10.2, 9.3)	
	Pr >  t			0.9262	
	n	13	12		
Week 108	LS Mean	-4.133	-0.239	-3.894	
	SEM	4.740	4.980	5.202	
	95% CI	(-13.5, 5.2)	(-10.1, 9.6)	(-14.1, 6.3)	
	Pr >  t			0.4546	
Week 108	n	12	8		
	LS Mean	-4.347	0.499	-4.846	
	SEM	4.827	5.506	5.781	
	95% CI	(-13.9, 5.2)	(-10.3,11.3)	(-16.2, 6.5)	
Week 108	Pr >  t			0.4024	
	n	11	7		
	LS Mean	-1.873	-1.095	-0.777	
	SEM	4.933	5.713	6.065	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.6, 7.9)	(-12.3,10.2)	(-12.7,11.1)
		Pr >  t			0.8981
	Week 120	n	10	8	
		LS Mean	-8.700	0.294	-8.993
		SEM	5.047	5.504	5.968
		95% CI	(-18.6, 1.2)	(-10.6,11.1)	(-20.7, 2.7)
		Pr >  t			0.1326
	Week 132	n	8	4	
		LS Mean	-5.505	-0.535	-4.969
		SEM	5.354	6.824	7.427
		95% CI	(-16.0, 5.0)	(-14.0,12.9)	(-19.6, 9.6)
		Pr >  t			0.5038
	Week 144	n	7	2	
		LS Mean	-15.95	5.177	-21.13
		SEM	5.574	8.890	9.485
		95% CI	(-26.9,-5.0)	(-12.3,22.6)	(-39.8,-2.5)
		Pr >  t			0.0264
	Week 156	n	5	2	
		LS Mean	-8.070	-3.153	-4.916
		SEM	6.205	8.890	9.868
		95% CI	(-20.3, 4.1)	(-20.6,14.3)	(-24.3,14.5)
		Pr >  t			0.6186
	Week 168	n	2	1	
		LS Mean	-4.048	4.364	-8.412
		SEM	8.780	11.99	14.16
		95% CI	(-21.3,13.2)	(-19.2,27.9)	(-36.2,19.4)
		Pr >  t			0.5529
	Week 180	n		1	
		LS Mean		4.364	
		SEM		11.99	
		95% CI		(-19.2,27.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		4.364	
		SEM		11.99	
		95% CI		(-19.2,27.9)	
		Pr >  t			

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-2.826	-0.323	-2.503		
			SEM	2.308	2.363	2.118		
			95% CI	(-7.4, 1.7)	(-5.0, 4.3)	(-6.7, 1.7)		
					Pr >  t			0.2377
		Week 16	n	119	97			
			LS Mean	-2.337	-2.203	-0.134		
			SEM	2.376	2.512	2.314		
			95% CI	(-7.0, 2.3)	(-7.1, 2.7)	(-4.7, 4.4)		
					Pr >  t			0.9539
		Week 24	n	100	75			
			LS Mean	-3.323	-0.979	-2.344		
			SEM	2.447	2.645	2.516		
			95% CI	(-8.1, 1.5)	(-6.2, 4.2)	(-7.3, 2.6)		
					Pr >  t			0.3517
		Week 32	n	82	69			
			LS Mean	-2.957	-0.752	-2.204		
			SEM	2.556	2.698	2.647		
			95% CI	(-8.0, 2.1)	(-6.1, 4.5)	(-7.4, 3.0)		
					Pr >  t			0.4052
		Week 40	n	73	58			
			LS Mean	-3.208	-2.130	-1.079		
			SEM	2.611	2.801	2.796		
			95% CI	(-8.3, 1.9)	(-7.6, 3.4)	(-6.6, 4.4)		
					Pr >  t			0.6998
		Week 48	n	66	48			
			LS Mean	-4.392	-0.710	-3.682		
			SEM	2.661	2.918	2.959		
95% CI	(-9.6, 0.8)		(-6.4, 5.0)	(-9.5, 2.1)				
			Pr >  t			0.2135		
Week 56	n	56	43					
	LS Mean	-2.050	0.559	-2.609				
		SEM	2.749	2.994	3.114			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.4, 3.3)	(-5.3, 6.4)	(-8.7, 3.5)
	Pr >  t			0.4023
	n	45	41	
	LS Mean	-2.692	-1.962	-0.730
	SEM	2.884	3.029	3.269
Week 72	95% CI	(-8.4, 3.0)	(-7.9, 4.0)	(-7.1, 5.7)
	Pr >  t			0.8234
	n	46	34	
	LS Mean	-3.152	-1.353	-1.799
	SEM	2.871	3.172	3.391
Week 84	95% CI	(-8.8, 2.5)	(-7.6, 4.9)	(-8.5, 4.9)
	Pr >  t			0.5958
	n	37	32	
	LS Mean	-2.217	-1.849	-0.368
	SEM	3.037	3.223	3.570
Week 96	95% CI	(-8.2, 3.7)	(-8.2, 4.5)	(-7.4, 6.6)
	Pr >  t			0.9179
	n	33	23	
	LS Mean	-4.602	-2.126	-2.476
	SEM	3.125	3.540	3.934
Week 108	95% CI	(-10.7, 1.5)	(-9.1, 4.8)	(-10.2, 5.2)
	Pr >  t			0.5292
	n	24	20	
	LS Mean	-2.352	-0.756	-1.596
	SEM	3.432	3.698	4.312
Week 120	95% CI	(-9.1, 4.4)	(-8.0, 6.5)	(-10.1, 6.9)
	Pr >  t			0.7113
	n	25	16	
	LS Mean	-1.217	-1.578	0.360
	SEM	3.385	3.982	4.527
Week 132	95% CI	(-7.9, 5.4)	(-9.4, 6.2)	(-8.5, 9.2)
	Pr >  t			0.9366
	n	19	8	
	LS Mean	-2.453	-8.408	5.955
	SEM	3.696	5.156	5.778
Week 144	95% CI	(-9.7, 4.8)	(-18.5, 1.7)	(-5.4, 17.3)
	Pr >  t			0.3029
	n	14	5	
	LS Mean	-8.405	4.684	-13.09
	SEM	4.100	6.288	7.040



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.4,-0.4)	(-7.6,17.0)	(-26.9, 0.7)
		Pr >  t			0.0632
	Week 156	n	10	3	
		LS Mean	-1.873	-6.437	4.564
		SEM	4.669	7.893	8.789
		95% CI	(-11.0, 7.3)	(-21.9, 9.0)	(-12.7,21.8)
		Pr >  t			0.6036
	Week 168	n	4	2	
		LS Mean	-3.350	5.143	-8.494
		SEM	6.888	9.530	11.46
		95% CI	(-16.9,10.2)	(-13.6,23.8)	(-31.0,14.0)
		Pr >  t			0.4588
	Week 180	n	1	1	
		LS Mean	-16.86	1.899	-18.76
		SEM	13.25	13.26	18.56
		95% CI	(-42.9, 9.1)	(-24.1,27.9)	(-55.2,17.7)
		Pr >  t			0.3125
	Week 192	n	1	1	
		LS Mean	-0.190	1.899	-2.088
		SEM	13.25	13.26	18.56
		95% CI	(-26.2,25.8)	(-24.1,27.9)	(-38.5,34.3)
		Pr >  t			0.9105
Yes	Week 8	n	5	9	
		LS Mean	10.839	6.132	4.706
		SEM	7.365	5.403	9.213
		95% CI	(-4.3,25.9)	(-4.8,17.1)	(-14.1,23.5)
		Pr >  t			0.6131
	Week 16	n	5	9	
		LS Mean	15.839	-1.177	17.016
		SEM	7.365	5.347	9.177
		95% CI	( 0.7,30.9)	(-12.0, 9.7)	(-1.7,35.8)
		Pr >  t			0.0738
	Week 24	n	5	5	
		LS Mean	9.175	13.545	-4.370
		SEM	7.365	7.206	10.37
		95% CI	(-5.9,24.3)	(-1.0,28.0)	(-25.4,16.7)
		Pr >  t			0.6759
	Week 32	n	4	3	
		LS Mean	7.466	4.519	2.947
		SEM	8.133	9.185	12.34

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.1,24.0)	(-13.9,23.0)	(-21.9,27.8)
		Pr >  t			0.8124
	Week 40	n	2	3	
		LS Mean	11.123	7.356	3.768
		SEM	11.01	9.214	14.29
		95% CI	(-11.0,33.2)	(-11.2,25.9)	(-24.9,32.5)
		Pr >  t			0.7931
	Week 48	n	3	2	
		LS Mean	17.581	-12.82	30.402
		SEM	9.249	11.20	14.36
		95% CI	(-1.1,36.3)	(-35.3, 9.7)	( 1.6,59.3)
		Pr >  t			0.0393
	Week 56	n	3	1	
		LS Mean	12.028	6.039	5.989
		SEM	9.249	15.52	18.19
		95% CI	(-6.6,30.7)	(-25.2,37.3)	(-30.5,42.5)
		Pr >  t			0.7434
	Week 64	n	2		
		LS Mean	19.458		
		SEM	11.01		
		95% CI	(-2.7,41.6)		
		Pr >  t			
	Week 72	n	2		
		LS Mean	15.760		
		SEM	10.99		
		95% CI	(-6.3,37.8)		
		Pr >  t			
	Week 84	n	3		
		LS Mean	20.358		
		SEM	9.249		
		95% CI	( 1.7,39.0)		
		Pr >  t			
	Week 96	n	2		
		LS Mean	15.293		
		SEM	11.01		
		95% CI	(-6.8,37.4)		
		Pr >  t			
	Week 108	n	2		
		LS Mean	9.196		
		SEM	11.05		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-13.0,31.4)
		Pr >  t		
	Week 120	n	3	
		LS Mean	-7.419	
		SEM	9.249	
		95% CI		(-26.1,11.3)
		Pr >  t		
	Week 132	n	1	
		LS Mean	12.895	
		SEM	15.14	
		95% CI		(-17.5,43.3)
		Pr >  t		
	Week 144	n	1	
		LS Mean	12.895	
		SEM	15.14	
		95% CI		(-17.5,43.3)
		Pr >  t		

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-3.660	-2.901	-0.760		
			SEM	2.772	2.900	2.840		
			95% CI	(-9.1, 1.8)	(-8.6, 2.8)	(-6.3, 4.8)		
					Pr >  t			0.7892
		Week 16	n	70	52			
			LS Mean	-1.666	-5.573	3.907		
			SEM	2.851	3.171	3.108		
			95% CI	(-7.3, 3.9)	(-11.8, 0.7)	(-2.2, 10.0)		
					Pr >  t			0.2095
		Week 24	n	61	37			
			LS Mean	-3.468	-3.423	-0.045		
			SEM	2.942	3.468	3.451		
			95% CI	(-9.3, 2.3)	(-10.2, 3.4)	(-6.8, 6.7)		
					Pr >  t			0.9896
		Week 32	n	48	33			
			LS Mean	-3.359	-6.216	2.857		
			SEM	3.126	3.571	3.686		
			95% CI	(-9.5, 2.8)	(-13.2, 0.8)	(-4.4, 10.1)		
					Pr >  t			0.4385
		Week 40	n	42	31			
			LS Mean	-2.464	-2.739	0.274		
			SEM	3.220	3.629	3.825		
			95% CI	(-8.8, 3.9)	(-9.9, 4.4)	(-7.2, 7.8)		
			Pr >  t			0.9429		
Week 48	n	40	25					
	LS Mean	-4.102	-3.384	-0.719				
	SEM	3.257	3.834	4.050				
	95% CI	(-10.5, 2.3)	(-10.9, 4.1)	(-8.7, 7.2)				
			Pr >  t			0.8592		
Week 56	n	35	20					
	LS Mean	-1.631	-2.719	1.087				
	SEM	3.360	4.087	4.375				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.2, 5.0)	(-10.7, 5.3)	(-7.5, 9.7)
		Pr >  t			0.8038
	Week 64	n	29	18	
		LS Mean	-1.005	-1.571	0.566
		SEM	3.519	4.222	4.624
		95% CI	(-7.9, 5.9)	(-9.9, 6.7)	(-8.5, 9.6)
		Pr >  t			0.9026
	Week 72	n	28	18	
		LS Mean	-3.006	-2.945	-0.062
		SEM	3.553	4.219	4.648
		95% CI	(-10.0, 4.0)	(-11.2, 5.3)	(-9.2, 9.1)
		Pr >  t			0.9894
	Week 84	n	27	17	
		LS Mean	-0.611	-4.655	4.044
		SEM	3.611	4.295	4.743
		95% CI	(-7.7, 6.5)	(-13.1, 3.8)	(-5.3, 13.4)
		Pr >  t			0.3941
	Week 96	n	23	14	
		LS Mean	-6.562	-5.686	-0.876
		SEM	3.767	4.566	5.113
		95% CI	(-14.0, 0.8)	(-14.6, 3.3)	(-10.9, 9.2)
		Pr >  t			0.8640
	Week 108	n	19	12	
		LS Mean	-0.721	-4.108	3.387
		SEM	4.005	4.809	5.492
		95% CI	(-8.6, 7.1)	(-13.5, 5.3)	(-7.4, 14.2)
		Pr >  t			0.5376
	Week 120	n	18	8	
		LS Mean	-7.984	-1.534	-6.450
		SEM	4.058	5.573	6.215
		95% CI	(-16.0, -0.0)	(-12.5, 9.4)	(-18.6, 5.7)
		Pr >  t			0.2996
	Week 132	n	11	4	
		LS Mean	-0.798	-3.718	2.919
		SEM	4.821	7.391	8.299
		95% CI	(-10.3, 8.7)	(-18.2, 10.8)	(-13.4, 19.2)
		Pr >  t			0.7251
	Week 144	n	11	4	
		LS Mean	-8.820	2.998	-11.82
		SEM	4.804	7.396	8.304

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.2, 0.6)	(-11.5,17.5)	(-28.1, 4.5)
		Pr >  t			0.1550
	Week 156	n	5	2	
		LS Mean	-2.767	-9.279	6.512
		SEM	6.614	10.08	11.67
		95% CI	(-15.7,10.2)	(-29.1,10.5)	(-16.4,29.4)
		Pr >  t			0.5771
	Week 168	n	1	2	
		LS Mean	8.909	3.221	5.688
		SEM	13.88	10.08	16.88
		95% CI	(-18.3,36.1)	(-16.6,23.0)	(-27.5,38.8)
		Pr >  t			0.7363
	Week 180	n		1	
		LS Mean		0.048	
		SEM		13.95	
		95% CI		(-27.3,27.4)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		0.048	
		SEM		13.95	
		95% CI		(-27.3,27.4)	
		Pr >  t			
>= 65 Years	Week 8	n	63	71	
		LS Mean	-0.719	3.138	-3.857
		SEM	4.187	4.194	3.012
		95% CI	(-9.0, 7.5)	(-5.1,11.4)	(-9.8, 2.1)
		Pr >  t			0.2014
	Week 16	n	54	55	
		LS Mean	-1.890	1.010	-2.899
		SEM	4.295	4.268	3.242
		95% CI	(-10.4, 6.6)	(-7.4, 9.4)	(-9.3, 3.5)
		Pr >  t			0.3718
	Week 24	n	44	44	
		LS Mean	-2.437	3.611	-6.049
		SEM	4.386	4.356	3.499
		95% CI	(-11.1, 6.2)	(-5.0,12.2)	(-12.9, 0.8)
		Pr >  t			0.0846
	Week 32	n	38	40	
		LS Mean	-1.688	4.960	-6.648
		SEM	4.493	4.433	3.647

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.5, 7.2)	(-3.8, 13.7)	(-13.8, 0.5)
		Pr >  t			0.0690
	Week 40	n	33	31	
		LS Mean	-3.013	0.075	-3.087
		SEM	4.572	4.597	3.904
		95% CI	(-12.0, 6.0)	(-9.0, 9.1)	(-10.8, 4.6)
		Pr >  t			0.4294
	Week 48	n	29	26	
		LS Mean	-2.827	1.487	-4.314
		SEM	4.645	4.713	4.125
		95% CI	(-12.0, 6.3)	(-7.8, 10.8)	(-12.4, 3.8)
		Pr >  t			0.2961
	Week 56	n	24	25	
		LS Mean	-1.418	4.187	-5.605
		SEM	4.771	4.738	4.296
		95% CI	(-10.8, 8.0)	(-5.1, 13.5)	(-14.0, 2.8)
		Pr >  t			0.1925
	Week 64	n	18	24	
		LS Mean	-3.271	-0.545	-2.726
		SEM	5.001	4.771	4.584
		95% CI	(-13.1, 6.6)	(-9.9, 8.9)	(-11.7, 6.3)
		Pr >  t			0.5523
	Week 72	n	20	17	
		LS Mean	-1.521	0.867	-2.388
		SEM	4.916	5.051	4.786
		95% CI	(-11.2, 8.2)	(-9.1, 10.8)	(-11.8, 7.0)
		Pr >  t			0.6181
	Week 84	n	13	16	
		LS Mean	-2.430	2.710	-5.139
		SEM	5.325	5.107	5.266
		95% CI	(-12.9, 8.0)	(-7.3, 12.8)	(-15.5, 5.2)
		Pr >  t			0.3294
	Week 96	n	12	10	
		LS Mean	1.054	2.277	-1.223
		SEM	5.424	5.663	5.895
		95% CI	(-9.6, 11.7)	(-8.9, 13.4)	(-12.8, 10.3)
		Pr >  t			0.8357
	Week 108	n	7	9	
		LS Mean	-6.687	1.314	-8.002
		SEM	6.222	5.814	6.765

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-18.9, 5.5)	(-10.1,12.7)	(-21.3, 5.3)
	Pr >  t			0.2373
	n	10	8	
	LS Mean	6.087	-0.831	6.918
	SEM	5.678	6.001	6.437
Week 132	95% CI	(-5.1,17.2)	(-12.6,11.0)	(-5.7,19.6)
	Pr >  t			0.2829
	n	9	4	
	LS Mean	-3.222	-12.27	9.051
	SEM	5.812	7.442	7.899
Week 144	95% CI	(-14.6, 8.2)	(-26.9, 2.3)	(-6.5,24.6)
	Pr >  t			0.2522
	n	4	1	
	LS Mean	-4.501	6.318	-10.82
	SEM	7.439	13.09	14.14
Week 156	95% CI	(-19.1,10.1)	(-19.4,32.0)	(-38.6,16.9)
	Pr >  t			0.4445
	n	5	1	
	LS Mean	0.311	-2.012	2.324
	SEM	6.903	13.09	13.87
Week 168	95% CI	(-13.2,13.9)	(-27.7,23.7)	(-24.9,29.6)
	Pr >  t			0.8670
	n	3		
	LS Mean	-5.950		
	SEM	8.266		
Week 180	95% CI	(-22.2,10.3)		
	Pr >  t			
	n	1		
	LS Mean	-15.00		
	SEM	13.09		
Week 192	95% CI	(-40.7,10.7)		
	Pr >  t			
	n	1		
	LS Mean	1.673		
	SEM	13.09		
	95% CI	(-24.0,27.4)		
	Pr >  t			



-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	-2.462	7.508	-9.969		
			SEM	5.049	4.745	4.400		
			95% CI	(-12.5, 7.6)	(-1.9,16.9)	(-18.7,-1.3)		
					Pr >  t			0.0247
		Week 16	n	30	30			
			LS Mean	-4.918	7.530	-12.45		
			SEM	5.094	4.993	4.646		
			95% CI	(-15.0, 5.2)	(-2.4,17.4)	(-21.6,-3.3)		
					Pr >  t			0.0080
		Week 24	n	21	26			
			LS Mean	-0.466	6.188	-6.654		
			SEM	5.387	5.093	5.098		
			95% CI	(-11.1,10.2)	(-3.9,16.3)	(-16.7, 3.4)		
					Pr >  t			0.1931
		Week 32	n	19	24			
			LS Mean	-3.267	3.802	-7.069		
			SEM	5.486	5.163	5.286		
			95% CI	(-14.1, 7.6)	(-6.4,14.0)	(-17.5, 3.3)		
					Pr >  t			0.1824
		Week 40	n	16	19			
			LS Mean	1.827	1.044	0.783		
			SEM	5.659	5.451	5.699		
			95% CI	(-9.4,13.0)	(-9.7,11.8)	(-10.4,12.0)		
			Pr >  t			0.8909		
Week 48	n	16	18					
	LS Mean	-1.298	0.081	-1.379				
	SEM	5.659	5.507	5.756				
	95% CI	(-12.5, 9.9)	(-10.8,11.0)	(-12.7,10.0)				
			Pr >  t			0.8108		
Week 56	n	12	14					
	LS Mean	-4.352	5.479	-9.831				
	SEM	6.006	5.797	6.387				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.2, 7.5)	(-6.0, 16.9)	(-22.4, 2.7)
		Pr >  t			0.1247
	Week 64	n	12	11	
		LS Mean	-5.047	-3.282	-1.764
		SEM	6.006	6.134	6.696
		95% CI	(-16.9, 6.8)	(-15.4, 8.8)	(-14.9, 11.4)
		Pr >  t			0.7924
	Week 72	n	10	9	
		LS Mean	-7.725	2.895	-10.62
		SEM	6.271	6.453	7.212
		95% CI	(-20.1, 4.6)	(-9.8, 15.6)	(-24.8, 3.6)
		Pr >  t			0.1417
	Week 84	n	8	8	
		LS Mean	-0.623	0.192	-0.814
		SEM	6.724	6.670	7.742
		95% CI	(-13.9, 12.6)	(-12.9, 13.3)	(-16.0, 14.4)
		Pr >  t			0.9163
	Week 96	n	6	6	
		LS Mean	1.349	-2.287	3.636
		SEM	7.308	7.270	8.748
		95% CI	(-13.0, 15.7)	(-16.6, 12.0)	(-13.6, 20.8)
		Pr >  t			0.6780
	Week 108	n	4	5	
		LS Mean	-8.067	2.998	-11.07
		SEM	8.350	7.714	9.972
		95% CI	(-24.5, 8.4)	(-12.2, 18.2)	(-30.7, 8.5)
		Pr >  t			0.2679
	Week 120	n	4	4	
		LS Mean	4.433	-3.420	7.854
		SEM	8.350	8.334	10.46
		95% CI	(-12.0, 20.9)	(-19.8, 13.0)	(-12.7, 28.4)
		Pr >  t			0.4532
	Week 132	n	3	2	
		LS Mean	-3.265	-5.727	2.462
		SEM	9.270	10.85	13.19
		95% CI	(-21.5, 15.0)	(-27.1, 15.6)	(-23.5, 28.4)
		Pr >  t			0.8520
	Week 144	n	3	1	
		LS Mean	-17.15	7.385	-24.54
		SEM	9.270	14.66	16.45

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-35.4, 1.1)	(-21.4,36.2)	(-56.9, 7.8)
		Pr >  t			0.1368
	Week 156	n	2	1	
		LS Mean	-5.894	-0.945	-4.949
		SEM	10.87	14.66	17.40
		95% CI	(-27.3,15.5)	(-29.8,27.9)	(-39.2,29.3)
		Pr >  t			0.7763
	Week 168	n	1		
		LS Mean	-16.21		
		SEM	14.64		
		95% CI	(-45.0,12.6)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	8.083	8.470	-0.387
		SEM	9.199	8.813	5.699
		95% CI	(-10.3,26.5)	(-9.1,26.1)	(-11.8,11.0)
		Pr >  t			0.9461
	Week 16	n	15	14	
		LS Mean	15.840	3.785	12.055
		SEM	9.253	8.389	6.058
		95% CI	(-2.7,34.4)	(-13.0,20.6)	(-0.0,24.2)
		Pr >  t			0.0508
	Week 24	n	12	11	
		LS Mean	15.378	3.590	11.788
		SEM	9.404	9.039	6.498
		95% CI	(-3.4,34.2)	(-14.4,21.6)	(-1.1,24.7)
		Pr >  t			0.0735
	Week 32	n	8	9	
		LS Mean	7.851	9.006	-1.155
		SEM	9.729	9.210	7.152
		95% CI	(-11.6,27.3)	(-9.3,27.4)	(-15.3,13.0)
		Pr >  t			0.8720
	Week 40	n	6	7	
		LS Mean	-4.527	6.981	-11.51
		SEM	10.04	9.431	7.810
		95% CI	(-24.5,15.5)	(-11.8,25.7)	(-27.0, 4.0)
		Pr >  t			0.1434
	Week 48	n	4	6	
		LS Mean	13.897	9.972	3.925
		SEM	10.58	9.599	8.679

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.1,34.9)	(-9.1,29.1)	(-13.2,21.1)
		Pr >  t			0.6519
	Week 56	n	4	6	
		LS Mean	6.182	12.756	-6.574
		SEM	10.58	9.613	8.696
		95% CI	(-14.9,27.2)	(-6.4,31.9)	(-23.8,10.6)
		Pr >  t			0.4510
	Week 64	n	4	4	
		LS Mean	10.895	6.393	4.501
		SEM	10.59	10.16	9.285
		95% CI	(-10.2,31.9)	(-13.8,26.6)	(-13.9,22.9)
		Pr >  t			0.6286
	Week 72	n	4	4	
		LS Mean	6.730	6.391	0.339
		SEM	10.59	10.16	9.285
		95% CI	(-14.3,27.8)	(-13.8,26.6)	(-18.0,18.7)
		Pr >  t			0.9709
	Week 84	n	4	4	
		LS Mean	9.732	12.643	-2.911
		SEM	10.58	10.16	9.289
		95% CI	(-11.3,30.8)	(-7.5,32.8)	(-21.3,15.5)
		Pr >  t			0.7544
	Week 96	n	3	2	
		LS Mean	5.877	2.293	3.584
		SEM	11.08	11.62	11.34
		95% CI	(-16.1,27.9)	(-20.7,25.3)	(-18.8,26.0)
		Pr >  t			0.7525
	Week 108	n	3	3	
		LS Mean	5.874	-0.428	6.302
		SEM	11.08	10.68	10.38
		95% CI	(-16.1,27.9)	(-21.6,20.7)	(-14.2,26.8)
		Pr >  t			0.5449
	Week 120	n	2	1	
		LS Mean	14.311	5.259	9.053
		SEM	12.00	14.06	14.58
		95% CI	(-9.5,38.1)	(-22.5,33.1)	(-19.8,37.9)
		Pr >  t			0.5357
	Week 132	n	2	1	
		LS Mean	-8.145	5.259	-13.40
		SEM	12.00	14.06	14.59

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-31.9,15.6)	(-22.5,33.1)	(-42.3,15.5)
		Pr >  t			0.3600
	Week 156	n	1		
		LS Mean	11.382		
		SEM	14.42		
		95% CI	(-17.1,39.9)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	3.052		
		SEM	14.42		
		95% CI	(-25.5,31.6)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	-3.562	-3.795	0.232
		SEM	2.766	2.914	2.628
		95% CI	(-9.0, 1.9)	(-9.5, 1.9)	(-4.9, 5.4)
		Pr >  t			0.9296
	Week 16	n	79	61	
		LS Mean	-2.954	-7.315	4.361
		SEM	2.866	3.154	2.912
		95% CI	(-8.6, 2.7)	(-13.5,-1.1)	(-1.4,10.1)
		Pr >  t			0.1349
	Week 24	n	71	43	
		LS Mean	-6.299	-2.560	-3.739
		SEM	2.927	3.367	3.196
		95% CI	(-12.1,-0.5)	(-9.2, 4.1)	(-10.0, 2.5)
		Pr >  t			0.2425
	Week 32	n	59	39	
		LS Mean	-3.809	-3.293	-0.516
		SEM	3.059	3.455	3.355
		95% CI	(-9.8, 2.2)	(-10.1, 3.5)	(-7.1, 6.1)
		Pr >  t			0.8778
	Week 40	n	52	35	
		LS Mean	-3.912	-3.133	-0.779
		SEM	3.130	3.535	3.502
		95% CI	(-10.1, 2.2)	(-10.1, 3.8)	(-7.7, 6.1)
		Pr >  t			0.8241
	Week 48	n	48	26	
		LS Mean	-6.203	-2.352	-3.852
		SEM	3.176	3.782	3.789

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.4, 0.0)	(-9.8, 5.1)	(-11.3, 3.6)
		Pr >  t			0.3097
	Week 56	n	42	24	
		LS Mean	-1.813	-3.866	2.053
		SEM	3.256	3.857	3.935
		95% CI	(-8.2, 4.6)	(-11.4, 3.7)	(-5.7, 9.8)
		Pr >  t			0.6020
	Week 64	n	30	26	
		LS Mean	-2.181	-2.271	0.090
		SEM	3.499	3.784	4.073
		95% CI	(-9.1, 4.7)	(-9.7, 5.2)	(-7.9, 8.1)
		Pr >  t			0.9824
	Week 72	n	34	21	
		LS Mean	-2.097	-4.430	2.333
		SEM	3.404	3.991	4.187
		95% CI	(-8.8, 4.6)	(-12.3, 3.4)	(-5.9, 10.5)
		Pr >  t			0.5776
	Week 84	n	28	20	
		LS Mean	-2.521	-3.802	1.281
		SEM	3.565	4.041	4.361
		95% CI	(-9.5, 4.5)	(-11.7, 4.1)	(-7.3, 9.8)
		Pr >  t			0.7691
	Week 96	n	26	15	
		LS Mean	-6.215	-2.981	-3.234
		SEM	3.623	4.384	4.732
		95% CI	(-13.3, 0.9)	(-11.6, 5.6)	(-12.5, 6.1)
		Pr >  t			0.4945
	Week 108	n	19	12	
		LS Mean	-1.730	-3.988	2.258
		SEM	3.955	4.701	5.263
		95% CI	(-9.5, 6.0)	(-13.2, 5.2)	(-8.1, 12.6)
		Pr >  t			0.6680
	Week 120	n	22	10	
		LS Mean	-6.196	-1.969	-4.226
		SEM	3.789	4.996	5.417
		95% CI	(-13.6, 1.2)	(-11.8, 7.8)	(-14.9, 6.4)
		Pr >  t			0.4355
	Week 132	n	15	4	
		LS Mean	-0.837	-3.720	2.883
		SEM	4.243	7.106	7.648

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.2, 7.5)	(-17.7,10.2)	(-12.1,17.9)
		Pr >  t			0.7063
	Week 144	n	12	4	
		LS Mean	-6.222	3.040	-9.262
		SEM	4.552	7.110	7.836
		95% CI	(-15.2, 2.7)	(-10.9,17.0)	(-24.6, 6.1)
		Pr >  t			0.2375
	Week 156	n	7	2	
		LS Mean	-1.861	-9.191	7.330
		SEM	5.562	9.634	10.66
		95% CI	(-12.8, 9.1)	(-28.1, 9.7)	(-13.6,28.3)
		Pr >  t			0.4921
	Week 168	n	2	2	
		LS Mean	4.116	3.309	0.807
		SEM	9.545	9.634	13.19
		95% CI	(-14.6,22.8)	(-15.6,22.2)	(-25.1,26.7)
		Pr >  t			0.9512
	Week 180	n	1	1	
		LS Mean	-16.99	0.120	-17.11
		SEM	13.26	13.30	18.51
		95% CI	(-43.0, 9.0)	(-26.0,26.2)	(-53.4,19.2)
		Pr >  t			0.3555
	Week 192	n	1	1	
		LS Mean	-0.318	0.120	-0.439
		SEM	13.26	13.30	18.51
		95% CI	(-26.3,25.7)	(-26.0,26.2)	(-36.8,35.9)
		Pr >  t			0.9811

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	0.094	7.552	-7.458		
			SEM	5.157	4.808	4.511		
			95% CI	(-10.2,10.3)	(-2.0,17.1)	(-16.4, 1.5)		
					Pr >  t			0.1004
		Week 16	n	28	29			
			LS Mean	-6.104	7.519	-13.62		
			SEM	5.206	5.060	4.766		
			95% CI	(-16.4, 4.2)	(-2.5,17.6)	(-23.0,-4.2)		
					Pr >  t			0.0048
		Week 24	n	21	25			
			LS Mean	-0.023	5.775	-5.798		
			SEM	5.438	5.163	5.150		
			95% CI	(-10.8,10.8)	(-4.5,16.0)	(-16.0, 4.4)		
					Pr >  t			0.2616
		Week 32	n	19	23			
			LS Mean	-2.837	3.545	-6.382		
			SEM	5.533	5.235	5.336		
			95% CI	(-13.8, 8.1)	(-6.8,13.9)	(-16.9, 4.1)		
					Pr >  t			0.2330
		Week 40	n	16	18			
			LS Mean	2.284	0.603	1.681		
			SEM	5.697	5.531	5.750		
			95% CI	(-9.0,13.6)	(-10.3,11.5)	(-9.6,13.0)		
			Pr >  t			0.7702		
Week 48	n	16	17					
	LS Mean	-0.841	-1.409	0.569				
	SEM	5.697	5.591	5.811				
	95% CI	(-12.1,10.4)	(-12.5, 9.6)	(-10.9,12.0)				
			Pr >  t			0.9221		
Week 56	n	12	14					
	LS Mean	-3.925	4.884	-8.809				
	SEM	6.028	5.808	6.358				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-15.8, 8.0)	(-6.6,16.4)	(-21.3, 3.7)
	Pr >  t			0.1670
	n	12	11	
	LS Mean	-4.620	-3.957	-0.663
	SEM	6.028	6.131	6.656
Week 72	95% CI	(-16.5, 7.3)	(-16.1, 8.1)	(-13.8,12.4)
	Pr >  t			0.9207
	n	10	8	
	LS Mean	-7.273	0.516	-7.789
	SEM	6.281	6.647	7.343
Week 84	95% CI	(-19.7, 5.1)	(-12.6,13.6)	(-22.2, 6.7)
	Pr >  t			0.2895
	n	8	8	
	LS Mean	-0.182	-0.525	0.343
	SEM	6.713	6.647	7.666
Week 96	95% CI	(-13.4,13.1)	(-13.6,12.6)	(-14.7,15.4)
	Pr >  t			0.9643
	n	6	6	
	LS Mean	1.745	-3.057	4.802
	SEM	7.273	7.223	8.639
Week 108	95% CI	(-12.6,16.1)	(-17.3,11.2)	(-12.2,21.8)
	Pr >  t			0.5786
	n	4	5	
	LS Mean	-7.655	2.266	-9.921
	SEM	8.276	7.651	9.825
Week 120	95% CI	(-23.9, 8.6)	(-12.8,17.3)	(-29.2, 9.4)
	Pr >  t			0.3132
	n	4	4	
	LS Mean	4.845	-4.172	9.017
	SEM	8.276	8.250	10.30
Week 132	95% CI	(-11.4,21.1)	(-20.4,12.1)	(-11.2,29.3)
	Pr >  t			0.3818
	n	3	2	
	LS Mean	-2.851	-6.408	3.557
	SEM	9.164	10.69	12.95
Week 144	95% CI	(-20.9,15.2)	(-27.4,14.6)	(-21.9,29.0)
	Pr >  t			0.7837
	n	3	1	
	LS Mean	-16.74	6.678	-23.42
	SEM	9.164	14.39	16.13

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Europe	Week 156	95% CI	(-34.8, 1.3)	(-21.6,35.0)	(-55.1, 8.3)
		Pr >  t			0.1475
		n	2	1	
	Week 168	LS Mean	-5.427	-1.652	-3.775
		SEM	10.71	14.39	17.05
		95% CI	(-26.5,15.6)	(-29.9,26.6)	(-37.3,29.8)
	Week 8	Pr >  t			0.8250
		n	1		
		LS Mean	-15.79		
	Week 16	SEM	14.37		
		95% CI	(-44.1,12.5)		
		Pr >  t			
	Week 24	n	66	68	
		LS Mean	-6.892	-4.835	-2.057
		SEM	5.470	5.489	3.049
	Week 32	95% CI	(-17.7, 3.9)	(-15.7, 6.0)	( -8.1, 3.9)
		Pr >  t			0.5005
		n	58	48	
	Week 40	LS Mean	0.745	-8.830	9.575
		SEM	5.506	5.586	3.367
		95% CI	(-10.1,11.6)	(-19.9, 2.2)	( 3.0,16.2)
	Week 48	Pr >  t			0.0047
		n	51	36	
		LS Mean	-6.261	-2.030	-4.231
Week 8	SEM	5.549	5.697	3.665	
	95% CI	(-17.2, 4.7)	(-13.3, 9.2)	(-11.4, 3.0)	
	Pr >  t			0.2489	
Week 16	n	43	30		
	LS Mean	-5.260	-4.677	-0.582	
	SEM	5.671	5.858	3.920	
Week 24	95% CI	(-16.5, 5.9)	(-16.2, 6.9)	( -8.3, 7.1)	
	Pr >  t			0.8820	
	n	37	25		
Week 32	LS Mean	-5.495	-0.587	-4.908	
	SEM	5.737	5.964	4.174	
	95% CI	(-16.8, 5.8)	(-12.3,11.2)	(-13.1, 3.3)	
Week 40	Pr >  t			0.2402	
	n	33	21		
	LS Mean	-6.065	-2.947	-3.118	
Week 48	SEM	5.790	6.087	4.419	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-17.5, 5.4)	(-14.9, 9.1)	(-11.8, 5.6)
	Pr >  t			0.4807
	n	29	20	
	LS Mean	-1.237	-1.368	0.132
	SEM	5.854	6.124	4.560
Week 64	95% CI	(-12.8,10.3)	(-13.4,10.7)	( -8.8, 9.1)
	Pr >  t			0.9770
	n	23	20	
	LS Mean	-4.120	-0.705	-3.415
	SEM	5.994	6.126	4.739
Week 72	95% CI	(-15.9, 7.7)	(-12.8,11.4)	(-12.7, 5.9)
	Pr >  t			0.4714
	n	25	19	
	LS Mean	-2.467	-4.704	2.237
	SEM	5.944	6.164	4.724
Week 84	95% CI	(-14.2, 9.3)	(-16.9, 7.4)	( -7.0,11.5)
	Pr >  t			0.6359
	n	22	17	
	LS Mean	-3.895	-3.284	-0.611
	SEM	6.025	6.255	4.945
Week 96	95% CI	(-15.8, 8.0)	(-15.6, 9.0)	(-10.3, 9.1)
	Pr >  t			0.9017
	n	20	13	
	LS Mean	-8.175	-1.499	-6.676
	SEM	6.094	6.516	5.349
Week 108	95% CI	(-20.2, 3.8)	(-14.3,11.3)	(-17.2, 3.8)
	Pr >  t			0.2124
	n	15	11	
	LS Mean	-1.175	-5.480	4.305
	SEM	6.341	6.709	5.851
Week 120	95% CI	(-13.7,11.3)	(-18.7, 7.7)	( -7.2,15.8)
	Pr >  t			0.4621
	n	16	8	
	LS Mean	-4.640	-2.806	-1.834
	SEM	6.287	7.158	6.302
Week 132	95% CI	(-17.0, 7.7)	(-16.9,11.3)	(-14.2,10.5)
	Pr >  t			0.7711
	n	12	3	
	LS Mean	-2.930	-4.950	2.020
	SEM	6.570	9.423	9.004

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-15.9,10.0)	(-23.5,13.6)	(-15.7,19.7)
		Pr >  t			0.8226
	Week 144	n	7	4	
		LS Mean	-8.954	3.269	-12.22
		SEM	7.340	8.593	8.764
		95% CI	(-23.4, 5.5)	(-13.6,20.1)	(-29.4, 5.0)
		Pr >  t			0.1635
	Week 156	n	5	2	
		LS Mean	-3.773	-8.938	5.165
		SEM	8.009	10.90	11.49
		95% CI	(-19.5,12.0)	(-30.3,12.5)	(-17.4,27.7)
		Pr >  t			0.6531
	Week 168	n	2	2	
		LS Mean	0.261	3.562	-3.301
		SEM	10.86	10.90	13.63
		95% CI	(-21.1,21.6)	(-17.8,25.0)	(-30.1,23.5)
		Pr >  t			0.8088
	Week 180	n		1	
		LS Mean		0.281	
		SEM		14.42	
		95% CI		(-28.0,28.6)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		0.281	
		SEM		14.42	
		95% CI		(-28.0,28.6)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	3.464	4.648	-1.183
		SEM	4.072	4.102	5.795
		95% CI	( -4.8,11.7)	( -3.6,12.9)	(-12.9,10.5)
		Pr >  t			0.8392
	Week 16	n	13	12	
		LS Mean	6.493	3.974	2.519
		SEM	4.149	4.214	5.917
		95% CI	( -1.9,14.9)	( -4.5,12.4)	( -9.4,14.4)
		Pr >  t			0.6723
	Week 24	n	12	10	
		LS Mean	7.136	3.063	4.074
		SEM	4.233	4.427	6.127

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-1.4,15.6)	(-5.8,11.9)	(-8.2,16.4)
	Pr >  t			0.5091
	n	9	10	
	LS Mean	2.638	9.732	-7.094
	SEM	4.571	4.427	6.364
Week 40	95% CI	(-6.5,11.8)	( 0.9,18.6)	(-19.8, 5.6)
	Pr >  t			0.2696
	n	7	10	
	LS Mean	-3.630	6.397	-10.03
	SEM	4.895	4.427	6.605
Week 48	95% CI	(-13.4, 6.1)	(-2.5,15.3)	(-23.2, 3.2)
	Pr >  t			0.1339
	n	7	7	
	LS Mean	1.133	7.261	-6.128
	SEM	4.895	4.865	6.893
Week 56	95% CI	(-8.6,10.9)	(-2.4,17.0)	(-19.9, 7.6)
	Pr >  t			0.3769
	n	6	7	
	LS Mean	0.355	7.512	-7.157
	SEM	5.132	4.865	7.072
Week 64	95% CI	(-9.9,10.6)	(-2.2,17.2)	(-21.2, 6.9)
	Pr >  t			0.3146
	n	4	7	
	LS Mean	16.924	1.967	14.957
	SEM	5.833	4.869	7.586
Week 72	95% CI	( 5.4,28.5)	(-7.7,11.7)	(-0.1,30.0)
	Pr >  t			0.0516
	n	4	4	
	LS Mean	16.924	3.735	13.189
	SEM	5.833	5.791	8.210
Week 84	95% CI	( 5.4,28.5)	(-7.7,15.2)	(-3.1,29.5)
	Pr >  t			0.1110
	n	4	5	
	LS Mean	7.017	2.369	4.648
	SEM	5.823	5.390	7.934
Week 96	95% CI	(-4.5,18.6)	(-8.3,13.1)	(-11.1,20.4)
	Pr >  t			0.5593
	n	3	2	
	LS Mean	17.825	-3.167	20.992
	SEM	6.456	7.489	9.886

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	( 5.1,30.6)	(-18.0,11.6)	( 1.4,40.5)
		Pr >  t			0.0355
		n	2	3	
	Week 120	LS Mean	-6.053	4.483	-10.54
		SEM	7.533	6.424	9.894
		95% CI	(-20.9, 8.8)	( -8.2,17.2)	(-30.1, 9.0)
	Week 120	Pr >  t			0.2888
		n	2	2	
		LS Mean	-1.769	14.760	-16.53
	Week 132	SEM	7.529	7.494	10.61
		95% CI	(-16.6,13.1)	( -0.0,29.6)	(-37.5, 4.4)
		Pr >  t			0.1214
	Week 132	n	1	2	
		LS Mean	9.227	6.425	2.802
		SEM	10.09	7.494	12.56
	Week 8	95% CI	(-10.7,29.2)	( -8.4,21.2)	(-22.0,27.6)
		Pr >  t			0.8238
		n	16	19	
	Week 8	LS Mean	1.396	-2.787	4.183
		SEM	4.420	4.383	5.339
		95% CI	( -7.5,10.3)	(-11.6, 6.0)	( -6.5,14.9)
	Week 16	Pr >  t			0.4371
		n	12	14	
		LS Mean	-4.754	-9.719	4.965
Week 16	SEM	4.805	4.766	5.884	
	95% CI	(-14.4, 4.9)	(-19.3,-0.2)	( -6.8,16.7)	
	Pr >  t			0.4020	
Week 24	n	12	8		
	LS Mean	-1.577	-3.686	2.110	
	SEM	4.799	5.681	6.600	
Week 24	95% CI	(-11.2, 8.0)	(-15.0, 7.6)	(-11.0,15.2)	
	Pr >  t			0.7500	
	n	9	7		
Week 32	LS Mean	-1.269	-9.229	7.960	
	SEM	5.206	5.887	7.045	
	95% CI	(-11.7, 9.1)	(-20.9, 2.5)	( -6.0,21.9)	
Week 32	Pr >  t			0.2613	
	n	9	7		
	LS Mean	-7.249	-16.37	9.123	
Week 40	SEM	5.214	5.887	7.080	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-17.6, 3.2)	(-28.1,-4.7)	(-4.9,23.2)
	Pr >  t			0.2005
	n	8	5	
	LS Mean	-9.383	-0.163	-9.220
	SEM	5.384	6.478	7.705
Week 56	95% CI	(-20.1, 1.3)	(-13.0,12.7)	(-24.5, 6.0)
	Pr >  t			0.2338
	n	7	3	
	LS Mean	-9.955	-6.640	-3.315
	SEM	5.581	7.662	8.864
Week 64	95% CI	(-21.0, 1.1)	(-21.8, 8.5)	(-20.8,14.2)
	Pr >  t			0.7090
	n	5	3	
	LS Mean	-7.183	-1.080	-6.103
	SEM	6.181	7.662	9.265
Week 72	95% CI	(-19.4, 5.1)	(-16.2,14.1)	(-24.4,12.2)
	Pr >  t			0.5112
	n	5	3	
	LS Mean	-8.067	1.984	-10.05
	SEM	6.168	7.662	9.225
Week 84	95% CI	(-20.3, 4.2)	(-13.2,17.1)	(-28.3, 8.2)
	Pr >  t			0.2778
	n	2	2	
	LS Mean	-2.374	0.094	-2.468
	SEM	8.665	8.899	11.92
Week 96	95% CI	(-19.5,14.8)	(-17.5,17.7)	(-26.0,21.1)
	Pr >  t			0.8363
	n	3	2	
	LS Mean	-14.72	-4.076	-10.65
	SEM	7.340	8.899	11.05
Week 108	95% CI	(-29.2,-0.2)	(-21.7,13.5)	(-32.5,11.2)
	Pr >  t			0.3369
	n	1	2	
	LS Mean	-10.11	0.089	-10.20
	SEM	11.58	8.899	14.19
Week 120	95% CI	(-33.0,12.8)	(-17.5,17.7)	(-38.3,17.9)
	Pr >  t			0.4735
	n	3	2	
	LS Mean	-9.169	-8.241	-0.928
	SEM	7.340	8.899	11.05



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-23.7, 5.3)	(-22.8,20.9)
		Pr >  t		0.9331
	Week 132	n	1	1
		LS Mean	-2.361	-43.41
		SEM	11.57	11.77
		95% CI	(-25.2,20.5)	(-66.7, -20)
		Pr >  t		( 9.1,73.0)
	Week 144	n	2	
		LS Mean	-12.86	
		SEM	8.582	
		95% CI	(-29.8, 4.1)	
		Pr >  t		0.0123
	Week 156	n	1	
		LS Mean	-2.361	
		SEM	11.57	
		95% CI	(-25.2,20.5)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	-2.361	
		SEM	11.57	
		95% CI	(-25.2,20.5)	
		Pr >  t		
	Week 180	n	1	
		LS Mean	-19.03	
		SEM	11.57	
		95% CI	(-41.9, 3.9)	
		Pr >  t		
	Week 192	n	1	
		LS Mean	-2.361	
		SEM	11.57	
		95% CI	(-25.2,20.5)	
		Pr >  t		
Other	Week 8	n	16	5
		LS Mean	-4.408	1.618
		SEM	4.947	7.499
		95% CI	(-14.5, 5.7)	(-13.5,16.7)
		Pr >  t		(-23.0,10.9)
	Week 16	n	13	4
		LS Mean	-14.17	5.901
		SEM	5.306	8.745
				-20.07
				9.328

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-24.9,-3.4)	(-11.6,23.4)	(-38.8,-1.3)
	Pr >  t			0.0361
	n	9	2	
	LS Mean	-12.17	-24.60	12.434
	SEM	6.043	11.78	12.46
Week 32	95% CI	(-24.3,-0.1)	(-48.1,-1.1)	(-12.4,37.3)
	Pr >  t			0.3217
	n	6	3	
	LS Mean	0.192	7.031	-6.839
	SEM	7.220	9.888	11.33
Week 40	95% CI	(-14.2,14.6)	(-12.7,26.8)	(-29.5,15.8)
	Pr >  t			0.5482
	n	6	2	
	LS Mean	2.471	-4.996	7.467
	SEM	7.407	11.79	13.10
Week 48	95% CI	(-12.3,17.2)	(-28.5,18.5)	(-18.6,33.6)
	Pr >  t			0.5704
	n	5	1	
	LS Mean	2.036	11.967	-9.931
	SEM	7.913	16.22	17.54
Week 56	95% CI	(-13.7,17.8)	(-20.3,44.2)	(-44.8,25.0)
	Pr >  t			0.5727
	n	5	1	
	LS Mean	7.038	-13.03	20.071
	SEM	7.913	16.22	17.54
Week 64	95% CI	(-8.7,22.8)	(-45.3,19.2)	(-14.8,55.0)
	Pr >  t			0.2558
	n	3	1	
	LS Mean	3.706	-4.703	8.408
	SEM	9.639	16.22	18.38
Week 72	95% CI	(-15.5,22.9)	(-37.0,27.6)	(-28.2,45.0)
	Pr >  t			0.6486
	n	4	1	
	LS Mean	-8.405	11.967	-20.37
	SEM	8.622	16.22	17.87
Week 84	95% CI	(-25.6, 8.8)	(-20.3,44.2)	(-55.9,15.2)
	Pr >  t			0.2575
	n	4	1	
	LS Mean	2.013	11.967	-9.954
	SEM	8.622	16.22	17.87

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-15.1,19.2)	(-20.3,44.2)	(-45.5,25.6)
	Pr >  t			0.5790
	n	3	1	
	LS Mean	-1.848	-4.703	2.855
	SEM	9.639	16.22	18.38
Week 108	95% CI	(-21.0,17.3)	(-37.0,27.6)	(-33.7,39.4)
	Pr >  t			0.8770
	n	4		
	LS Mean	2.013		
	SEM	8.622		
Week 120	95% CI	(-15.1,19.2)		
	Pr >  t			
	n	3		
	LS Mean	-4.628		
	SEM	9.639		
Week 132	95% CI	(-23.8,14.6)		
	Pr >  t			
	n	3		
	LS Mean	-4.631		
	SEM	9.639		
Week 144	95% CI	(-23.8,14.5)		
	Pr >  t			
	n	3		
	LS Mean	3.186		
	SEM	9.637		
Week 156	95% CI	(-16.0,22.4)		
	Pr >  t			
	n	2		
	LS Mean	3.369		
	SEM	11.38		
	95% CI	(-19.3,26.0)		
	Pr >  t			

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	-5.610	-1.891	-3.719	
		SEM	3.192	3.119	2.543	
		95% CI	(-11.9, 0.7)	(-8.0, 4.2)	(-8.7, 1.3)	
			Pr >  t			0.1442
	Week 16	n	88	71		
		LS Mean	-3.919	-4.028	0.109	
		SEM	3.256	3.334	2.730	
		95% CI	(-10.3, 2.5)	(-10.6, 2.5)	(-5.3, 5.5)	
			Pr >  t			0.9682
	Week 24	n	75	54		
		LS Mean	-4.883	-2.311	-2.571	
		SEM	3.311	3.464	2.969	
		95% CI	(-11.4, 1.6)	(-9.1, 4.5)	(-8.4, 3.3)	
			Pr >  t			0.3867
	Week 32	n	62	52		
		LS Mean	-5.017	-3.794	-1.223	
		SEM	3.407	3.486	3.088	
		95% CI	(-11.7, 1.7)	(-10.6, 3.1)	(-7.3, 4.8)	
			Pr >  t			0.6922
	Week 40	n	51	46		
		LS Mean	-7.395	-2.244	-5.151	
		SEM	3.501	3.573	3.270	
		95% CI	(-14.3,-0.5)	(-9.3, 4.8)	(-11.6, 1.3)	
		Pr >  t			0.1156	
Week 48	n	50	37			
	LS Mean	-8.312	-3.248	-5.065		
	SEM	3.512	3.708	3.428		
	95% CI	(-15.2,-1.4)	(-10.5, 4.0)	(-11.8, 1.7)		
		Pr >  t			0.1399	
Week 56	n	43	33			
	LS Mean	-3.460	-0.573	-2.887		
	SEM	3.594	3.789	3.601		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.5, 3.6)	(-8.0, 6.9)	(-10.0, 4.2)
	Pr >  t			0.4228
	n	35	33	
	LS Mean	-6.076	-0.911	-5.165
	SEM	3.722	3.789	3.732
Week 72	95% CI	(-13.4, 1.2)	(-8.4, 6.5)	(-12.5, 2.2)
	Pr >  t			0.1666
	n	35	31	
	LS Mean	-5.039	-2.717	-2.322
	SEM	3.722	3.835	3.778
Week 84	95% CI	(-12.4, 2.3)	(-10.3, 4.8)	(-9.7, 5.1)
	Pr >  t			0.5390
	n	31	29	
	LS Mean	-4.147	-3.541	-0.606
	SEM	3.818	3.886	3.914
Week 96	95% CI	(-11.6, 3.4)	(-11.2, 4.1)	(-8.3, 7.1)
	Pr >  t			0.8769
	n	27	22	
	LS Mean	-6.135	-3.213	-2.922
	SEM	3.916	4.129	4.256
Week 108	95% CI	(-13.8, 1.6)	(-11.3, 4.9)	(-11.3, 5.4)
	Pr >  t			0.4925
	n	19	20	
	LS Mean	-5.603	-2.450	-3.153
	SEM	4.262	4.225	4.654
Week 120	95% CI	(-14.0, 2.8)	(-10.7, 5.8)	(-12.3, 6.0)
	Pr >  t			0.4983
	n	20	15	
	LS Mean	-5.496	-3.036	-2.460
	SEM	4.191	4.558	4.911
Week 132	95% CI	(-13.7, 2.7)	(-12.0, 5.9)	(-12.1, 7.2)
	Pr >  t			0.6165
	n	15	7	
	LS Mean	-7.148	-10.76	3.617
	SEM	4.537	5.830	6.344
Week 144	95% CI	(-16.1, 1.8)	(-22.2, 0.7)	(-8.8, 16.1)
	Pr >  t			0.5687
	n	10	5	
Week 144	LS Mean	-18.23	3.163	-21.39
	SEM	5.111	6.631	7.484

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-28.3,-8.2)	(-9.8,16.2)	(-36.1,-6.7)
		Pr >  t			0.0043
	Week 156	n	6	3	
		LS Mean	-3.282	-7.968	4.686
		SEM	6.161	8.183	9.517
		95% CI	(-15.4, 8.8)	(-24.0, 8.1)	(-14.0,23.4)
		Pr >  t			0.6225
	Week 168	n	3	2	
		LS Mean	-2.036	3.607	-5.643
		SEM	8.171	9.785	12.17
		95% CI	(-18.1,14.0)	(-15.6,22.8)	(-29.5,18.2)
		Pr >  t			0.6430
	Week 180	n	1	1	
		LS Mean	-19.86	0.292	-20.15
		SEM	13.48	13.48	18.68
		95% CI	(-46.3, 6.6)	(-26.2,26.7)	(-56.8,16.5)
		Pr >  t			0.2811
	Week 192	n	1	1	
		LS Mean	-3.186	0.292	-3.478
		SEM	13.48	13.48	18.68
		95% CI	(-29.6,23.3)	(-26.2,26.7)	(-40.1,33.2)
		Pr >  t			0.8523
1	Week 8	n	43	50	
		LS Mean	4.616	4.380	0.237
		SEM	3.430	3.572	3.558
		95% CI	(-2.2,11.4)	(-2.7,11.5)	(-6.8, 7.3)
		Pr >  t			0.9470
	Week 16	n	35	35	
		LS Mean	3.350	1.071	2.279
		SEM	3.619	3.739	3.967
		95% CI	(-3.8,10.5)	(-6.3, 8.5)	(-5.5,10.1)
		Pr >  t			0.5662
	Week 24	n	29	26	
		LS Mean	1.385	5.477	-4.091
		SEM	3.796	4.059	4.347
		95% CI	(-6.1, 8.9)	(-2.5,13.5)	(-12.6, 4.5)
		Pr >  t			0.3474
	Week 32	n	23	21	
		LS Mean	2.127	7.039	-4.912
		SEM	4.059	4.312	4.713

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-5.9,10.1)	(-1.5,15.5)	(-14.2, 4.4)
	Pr >  t			0.2981
	n	23	16	
Week 48	LS Mean	7.484	-0.759	8.243
	SEM	4.070	4.610	4.996
	95% CI	(-0.5,15.5)	(-9.8, 8.3)	(-1.6,18.1)
Week 56	Pr >  t			0.0999
	n	18	14	
	LS Mean	7.265	3.493	3.772
Week 64	SEM	4.314	4.783	5.364
	95% CI	(-1.2,15.8)	(-5.9,12.9)	(-6.8,14.3)
	Pr >  t			0.4824
Week 72	n	15	12	
	LS Mean	2.443	2.535	-0.092
	SEM	4.536	4.994	5.740
Week 84	95% CI	(-6.5,11.4)	(-7.3,12.4)	(-11.4,11.2)
	Pr >  t			0.9872
	n	11	9	
Week 96	LS Mean	7.739	-7.466	15.205
	SEM	4.957	5.461	6.473
	95% CI	(-2.0,17.5)	(-18.2, 3.3)	( 2.5,27.9)
Week 108	Pr >  t			0.0193
	n	12	4	
	LS Mean	2.750	-0.439	3.188
Week 84	SEM	4.841	7.333	8.043
	95% CI	(-6.8,12.3)	(-14.9,14.0)	(-12.6,19.0)
	Pr >  t			0.6920
Week 96	n	8	4	
	LS Mean	5.947	5.814	0.134
	SEM	5.545	7.333	8.470
Week 108	95% CI	(-5.0,16.8)	(-8.6,20.2)	(-16.5,16.8)
	Pr >  t			0.9874
	n	8	2	
Week 108	LS Mean	0.741	-6.048	6.790
	SEM	5.545	9.795	10.67
	95% CI	(-10.2,11.6)	(-25.3,13.2)	(-14.2,27.8)
Week 108	Pr >  t			0.5250
	n	6	1	
	LS Mean	7.594	-17.40	24.989
	SEM	6.146	13.41	14.31



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.5,19.7)	(-43.8, 9.0)	(-3.1,53.1)
		Pr >  t			0.0816
	Week 120	n	8	1	
		LS Mean	2.739	-0.735	3.474
		SEM	5.559	13.41	14.07
		95% CI	(-8.2,13.7)	(-27.1,25.6)	(-24.2,31.1)
		Pr >  t			0.8051
	Week 132	n	5	1	
		LS Mean	11.563	-0.735	12.298
		SEM	6.581	13.41	14.50
		95% CI	(-1.4,24.5)	(-27.1,25.6)	(-16.2,40.8)
		Pr >  t			0.3969
	Week 144	n	5		
		LS Mean	14.895		
		SEM	6.581		
		95% CI	( 2.0,27.8)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	4.253		
		SEM	7.177		
		95% CI	(-9.9,18.4)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-7.692		
		SEM	13.21		
		95% CI	(-33.7,18.3)		
		Pr >  t			

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status (L) Primary resistant		Week 8	n	21	16		
			LS Mean	-7.227	-0.863	-6.364	
			SEM	4.877	5.770	6.015	
			95% CI	(-17.1, 2.6)	(-12.5,10.8)	(-18.4, 5.7)	
				Pr >  t			0.2944
		Week 16	n	17	10		
			LS Mean	-9.453	-3.155	-6.298	
			SEM	5.243	6.683	7.002	
			95% CI	(-20.0, 1.1)	(-16.5,10.2)	(-20.2, 7.6)	
				Pr >  t			0.3712
		Week 24	n	9	5		
			LS Mean	-5.125	-10.40	5.271	
			SEM	6.045	8.061	8.994	
			95% CI	(-17.2, 6.9)	(-26.4, 5.6)	(-12.6,23.1)	
				Pr >  t			0.5591
		Week 32	n	8	4		
			LS Mean	-2.635	4.263	-6.898	
			SEM	6.253	8.614	9.650	
			95% CI	(-15.1, 9.8)	(-12.8,21.4)	(-26.0,12.2)	
				Pr >  t			0.4762
		Week 40	n	5	4		
			LS Mean	-5.646	4.266	-9.912	
			SEM	7.168	8.614	10.35	
			95% CI	(-19.9, 8.6)	(-12.8,21.4)	(-30.4,10.6)	
				Pr >  t			0.3402
		Week 48	n	5	3		
			LS Mean	-15.65	3.665	-19.31	
			SEM	7.168	9.421	11.02	
95% CI	(-29.9,-1.4)		(-15.0,22.3)	(-41.1, 2.5)			
		Pr >  t			0.0824		
Week 56	n	4	3				
	LS Mean	-16.30	6.438	-22.73			
	SEM	7.708	9.421	11.41			

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-31.6,-1.0)	(-12.2,25.1)	(-45.3,-0.1)
		Pr >  t			0.0487
		n	4	3	
		LS Mean	-3.800	3.661	-7.461
		SEM	7.708	9.421	11.41
Week 72		95% CI	(-19.1,11.5)	(-15.0,22.3)	(-30.1,15.1)
		Pr >  t			0.5145
		n	4	3	
		LS Mean	-12.13	3.661	-15.79
		SEM	7.708	9.421	11.41
Week 84		95% CI	(-27.4, 3.1)	(-15.0,22.3)	(-38.4, 6.8)
		Pr >  t			0.1690
		n	2	3	
		LS Mean	-21.92	3.665	-25.58
		SEM	10.15	9.421	13.08
Week 96		95% CI	(-42.0,-1.8)	(-15.0,22.3)	(-51.5, 0.3)
		Pr >  t			0.0530
		n	1	3	
		LS Mean	-35.10	-4.672	-30.43
		SEM	13.51	9.421	16.00
Week 108		95% CI	(-61.9,-8.3)	(-23.3,14.0)	(-62.2, 1.3)
		Pr >  t			0.0602
		n		2	
		LS Mean		-4.771	
		SEM		10.78	
Week 120		95% CI		(-26.1,16.6)	
		Pr >  t			
		n	1	1	
		LS Mean	-1.771	3.368	-5.139
		SEM	13.51	14.05	19.11
Week 132		95% CI	(-28.6,25.0)	(-24.5,31.2)	(-43.1,32.8)
		Pr >  t			0.7886
		n		1	
		LS Mean		-38.30	
		SEM		14.05	
Week 144		95% CI		(-66.2, -10)	
		Pr >  t			
		n	1		
		LS Mean	-10.10		
		SEM	13.51		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-36.9,16.7)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-2.607	-1.905	-0.702
		SEM	2.883	2.880	2.446
		95% CI	(-8.3, 3.1)	(-7.6, 3.8)	(-5.5, 4.1)
		Pr >  t			0.7744
	Week 16	n	83	81	
		LS Mean	-0.698	-4.079	3.380
		SEM	2.963	3.024	2.665
		95% CI	(-6.5, 5.1)	(-10.0, 1.9)	(-1.9, 8.6)
		Pr >  t			0.2051
	Week 24	n	75	62	
		LS Mean	-3.240	-0.682	-2.558
		SEM	3.021	3.171	2.860
		95% CI	(-9.2, 2.7)	(-6.9, 5.6)	(-8.2, 3.1)
		Pr >  t			0.3714
	Week 32	n	59	56	
		LS Mean	-3.190	-2.932	-0.258
		SEM	3.182	3.223	3.042
		95% CI	(-9.4, 3.1)	(-9.3, 3.4)	(-6.2, 5.7)
		Pr >  t			0.9324
	Week 40	n	52	48	
		LS Mean	-4.762	-3.623	-1.139
		SEM	3.250	3.325	3.202
		95% CI	(-11.1, 1.6)	(-10.2, 2.9)	(-7.4, 5.1)
		Pr >  t			0.7220
	Week 48	n	47	37	
		LS Mean	-3.936	-3.767	-0.170
		SEM	3.307	3.493	3.432
		95% CI	(-10.4, 2.6)	(-10.6, 3.1)	(-6.9, 6.6)
		Pr >  t			0.9606
	Week 56	n	41	31	
		LS Mean	0.239	-2.808	3.047
		SEM	3.392	3.627	3.649
		95% CI	(-6.4, 6.9)	(-9.9, 4.3)	(-4.1,10.2)
		Pr >  t			0.4040
	Week 64	n	32	28	
		LS Mean	-2.122	-5.093	2.971
		SEM	3.567	3.714	3.895

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	N=169	N=172	
Week 72		95% CI	(-9.1, 4.9)	(-12.4, 2.2)	(-4.7,10.6)
		Pr >  t			0.4457
		n	29	22	
		LS Mean	-2.148	-3.634	1.485
		SEM	3.650	3.940	4.183
Week 84		95% CI	(-9.3, 5.0)	(-11.4, 4.1)	(-6.7, 9.7)
		Pr >  t			0.7226
		n	26	21	
		LS Mean	1.475	-1.718	3.192
		SEM	3.742	3.988	4.308
Week 96		95% CI	(-5.9, 8.8)	(-9.5, 6.1)	(-5.3,11.6)
		Pr >  t			0.4589
		n	23	14	
		LS Mean	-0.599	-4.652	4.054
		SEM	3.859	4.482	4.861
Week 108		95% CI	(-8.2, 7.0)	(-13.4, 4.1)	(-5.5,13.6)
		Pr >  t			0.4045
		n	18	13	
		LS Mean	-1.735	-2.106	0.371
		SEM	4.125	4.589	5.169
Week 120		95% CI	(-9.8, 6.4)	(-11.1, 6.9)	(-9.8,10.5)
		Pr >  t			0.9428
		n	19	10	
		LS Mean	-6.780	-2.314	-4.466
		SEM	4.066	5.008	5.499
Week 132		95% CI	(-14.8, 1.2)	(-12.1, 7.5)	(-15.3, 6.3)
		Pr >  t			0.4169
		n	13	4	
		LS Mean	-4.628	-2.295	-2.334
		SEM	4.548	7.141	7.767
Week 144		95% CI	(-13.6, 4.3)	(-16.3,11.7)	(-17.6,12.9)
		Pr >  t			0.7639
		n	8	1	
		LS Mean	-11.00	0.395	-11.40
		SEM	5.386	13.43	14.08
Week 156		95% CI	(-21.6,-0.4)	(-26.0,26.8)	(-39.0,16.2)
		Pr >  t			0.4184
		n	5	1	
		LS Mean	-1.087	-7.935	6.848
		SEM	6.478	13.43	14.53

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-13.8,11.6)	(-34.3,18.4)	(-21.7,35.4)
		Pr >  t			0.6375
		n	3	1	
	Week 180	LS Mean	1.025	0.395	0.630
		SEM	8.050	13.43	15.29
		95% CI	(-14.8,16.8)	(-26.0,26.8)	(-29.4,30.6)
	Week 180	Pr >  t			0.9671
		n	1	1	
		LS Mean	-16.80	0.395	-17.20
	Week 192	SEM	13.38	13.43	18.66
		95% CI	(-43.1, 9.4)	(-26.0,26.8)	(-53.8,19.4)
		Pr >  t			0.3568
	Week 192	n	1	1	
		LS Mean	-0.135	0.395	-0.530
		SEM	13.38	13.43	18.66
	Week 8	95% CI	(-26.4,26.1)	(-26.0,26.8)	(-37.1,36.1)
		Pr >  t			0.9774
		n	17	16	
	Week 16	LS Mean	3.729	7.805	-4.076
		SEM	3.861	3.957	5.444
		95% CI	( -3.9,11.4)	( -0.0,15.6)	(-14.8, 6.7)
	Week 16	Pr >  t			0.4552
		n	18	14	
		LS Mean	2.833	8.735	-5.902
	Week 24	SEM	3.768	4.181	5.589
		95% CI	( -4.6,10.3)	( 0.5,17.0)	(-16.9, 5.1)
		Pr >  t			0.2926
	Week 24	n	16	13	
LS Mean		0.488	6.425	-5.937	
SEM		3.980	4.309	5.820	
Week 32	95% CI	( -7.4, 8.4)	( -2.1,14.9)	(-17.4, 5.6)	
	Pr >  t			0.3092	
	n	15	13		
Week 32	LS Mean	-0.444	8.093	-8.536	
	SEM	4.070	4.316	5.901	
	95% CI	( -8.5, 7.6)	( -0.4,16.6)	(-20.2, 3.1)	
Week 40	Pr >  t			0.1499	
	n	14	10		
	LS Mean	4.864	5.105	-0.241	
		SEM	4.203	4.798	6.355

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-3.4,13.2)	(-4.4,14.6)	(-12.8,12.3)
	Pr >  t			0.9698
	n	14	11	
	LS Mean	1.889	7.550	-5.662
	SEM	4.203	4.626	6.224
Week 56	95% CI	(-6.4,10.2)	(-1.6,16.7)	(-17.9, 6.6)
	Pr >  t			0.3642
	n	11	11	
	LS Mean	-2.206	10.580	-12.79
	SEM	4.609	4.626	6.509
Week 64	95% CI	(-11.3, 6.9)	( 1.5,19.7)	(-25.6, 0.1)
	Pr >  t			0.0509
	n	8	11	
	LS Mean	-1.532	8.308	-9.840
	SEM	5.230	4.626	6.967
Week 72	95% CI	(-11.8, 8.8)	(-0.8,17.4)	(-23.6, 3.9)
	Pr >  t			0.1593
	n	11	10	
	LS Mean	3.098	6.019	-2.922
	SEM	4.609	4.810	6.644
Week 84	95% CI	(-6.0,12.2)	(-3.5,15.5)	(-16.0,10.2)
	Pr >  t			0.6606
	n	9	9	
	LS Mean	0.557	1.437	-0.881
	SEM	4.987	5.016	7.067
Week 96	95% CI	(-9.3,10.4)	(-8.5,11.3)	(-14.8,13.0)
	Pr >  t			0.9009
	n	8	7	
	LS Mean	-7.107	8.215	-15.32
	SEM	5.238	5.553	7.632
Week 108	95% CI	(-17.4, 3.2)	(-2.7,19.2)	(-30.4,-0.3)
	Pr >  t			0.0458
	n	7	6	
	LS Mean	-0.351	4.124	-4.475
	SEM	5.534	5.934	8.112
Week 120	95% CI	(-11.3,10.5)	(-7.6,15.8)	(-20.4,11.5)
	Pr >  t			0.5817
	n	6	5	
	LS Mean	10.114	3.328	6.786
	SEM	5.915	6.424	8.719

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-1.5,21.8)	(-9.3,16.0)	(-10.4,24.0)
	Pr >  t			0.4371
	n	5	3	
	LS Mean	4.711	-1.014	5.725
	SEM	6.395	8.052	10.28
Week 144	95% CI	(-7.9,17.3)	(-16.9,14.8)	(-14.5,26.0)
	Pr >  t			0.5780
	n	5	4	
	LS Mean	-3.621	12.641	-16.26
	SEM	6.395	7.081	9.536
Week 156	95% CI	(-16.2, 9.0)	(-1.3,26.6)	(-35.0, 2.5)
	Pr >  t			0.0892
	n	4	2	
	LS Mean	-1.927	1.021	-2.947
	SEM	7.052	9.706	12.00
Week 168	95% CI	(-15.8,12.0)	(-18.1,20.1)	(-26.6,20.7)
	Pr >  t			0.8062
	n	1	1	
	LS Mean	-12.47	15.778	-28.25
	SEM	13.49	13.51	19.10
	95% CI	(-39.0,14.1)	(-10.8,42.4)	(-65.9, 9.4)
	Pr >  t			0.1402

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-7.480	-6.681	-0.799
		SEM	7.472	7.751	3.324
		95% CI	(-22.3, 7.3)	(-22.0, 8.7)	(-7.3, 5.8)
		Pr >  t			0.8103
	Week 16	n	51	41	
		LS Mean	-5.286	-9.514	4.228
		SEM	7.491	7.850	3.615
		95% CI	(-20.1, 9.6)	(-25.1, 6.0)	(-2.9, 11.3)
		Pr >  t			0.2432
	Week 24	n	38	33	
		LS Mean	-3.897	-8.184	4.287
		SEM	7.545	7.919	3.951
		95% CI	(-18.8, 11.1)	(-23.9, 7.5)	(-3.5, 12.1)
		Pr >  t			0.2787
	Week 32	n	34	28	
		LS Mean	-6.661	-8.977	2.316
		SEM	7.678	7.976	4.148
		95% CI	(-21.9, 8.5)	(-24.8, 6.8)	(-5.8, 10.5)
		Pr >  t			0.5769
	Week 40	n	26	23	
		LS Mean	-6.508	-5.250	-1.258
		SEM	7.789	8.060	4.500
		95% CI	(-21.9, 8.9)	(-21.2, 10.7)	(-10.1, 7.6)
		Pr >  t			0.7799
	Week 48	n	24	17	
		LS Mean	-6.604	-4.918	-1.686
		SEM	7.825	8.225	4.851
95% CI		(-22.1, 8.9)	(-21.2, 11.4)	(-11.2, 7.8)	
	Pr >  t			0.7283	
Week 56	n	21	17		
	LS Mean	-1.602	-5.014	3.412	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	7.892	8.226	4.959
	95% CI	(-17.2,14.0)	(-21.3,11.3)	(-6.3,13.2)
	Pr >  t			0.4918
Week 64	n	15	15	
	LS Mean	-6.492	-6.656	0.164
	SEM	8.094	8.306	5.403
	95% CI	(-22.5, 9.5)	(-23.1, 9.8)	(-10.4,10.8)
	Pr >  t			0.9758
Week 72	n	16	15	
	LS Mean	-4.545	-7.147	2.602
	SEM	8.051	8.306	5.339
	95% CI	(-20.5,11.4)	(-23.6, 9.3)	(-7.9,13.1)
	Pr >  t			0.6262
Week 84	n	14	13	
	LS Mean	-3.252	-3.081	-0.171
	SEM	8.142	8.407	5.633
	95% CI	(-19.3,12.8)	(-19.7,13.5)	(-11.2,10.9)
	Pr >  t			0.9757
Week 96	n	12	9	
	LS Mean	-6.901	-5.404	-1.496
	SEM	8.265	8.743	6.285
	95% CI	(-23.2, 9.4)	(-22.7,11.9)	(-13.8,10.8)
	Pr >  t			0.8119
Week 108	n	13	8	
	LS Mean	-1.409	-3.626	2.217
	SEM	8.201	8.874	6.387
	95% CI	(-17.6,14.8)	(-21.1,13.9)	(-10.3,14.8)
	Pr >  t			0.7286
Week 120	n	11	6	
	LS Mean	-9.040	-7.015	-2.025
	SEM	8.340	9.255	7.074
	95% CI	(-25.5, 7.4)	(-25.3,11.2)	(-15.9,11.9)
	Pr >  t			0.7747
Week 132	n	8	3	
	LS Mean	-1.337	-18.61	17.270
	SEM	8.672	10.64	9.119
	95% CI	(-18.4,15.8)	(-39.5, 2.3)	(-0.6,35.2)
	Pr >  t			0.0588
Week 144	n	5	1	
	LS Mean	-15.88	-3.940	-11.94

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	9.354	14.94	14.34
		95% CI	(-34.3, 2.5)	(-33.3,25.4)	(-40.1,16.2)
		Pr >  t			0.4053
	Week 168	n	3	1	
		LS Mean	-2.892	-12.27	9.378
		SEM	10.47	14.94	15.09
	Week 180	95% CI	(-23.5,17.7)	(-41.6,17.1)	(-20.3,39.0)
		Pr >  t			0.5345
		n	2	1	
	Week 192	LS Mean	-0.998	-3.940	2.942
		SEM	11.69	14.94	15.96
		95% CI	(-24.0,22.0)	(-33.3,25.4)	(-28.4,34.3)
	Week 8	Pr >  t			0.8539
		n		1	
		LS Mean		-3.940	
	Week 16	SEM		14.94	
		95% CI		(-33.3,25.4)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-3.940	
		SEM		14.94	
	Week 32	95% CI		(-33.3,25.4)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	3.729	7.805	-4.076	
	SEM	3.861	3.957	5.444	
	95% CI	(-3.9,11.4)	(-0.0,15.6)	(-14.8, 6.7)	
Week 16	Pr >  t			0.4552	
	n	18	14		
	LS Mean	2.833	8.735	-5.902	
Week 24	SEM	3.768	4.181	5.589	
	95% CI	(-4.6,10.3)	( 0.5,17.0)	(-16.9, 5.1)	
	Pr >  t			0.2926	
Week 32	n	16	13		
	LS Mean	0.488	6.425	-5.937	
	SEM	3.980	4.309	5.820	
Week 8	95% CI	(-7.4, 8.4)	(-2.1,14.9)	(-17.4, 5.6)	
	Pr >  t			0.3092	
	n	15	13		
Week 16	LS Mean	-0.444	8.093	-8.536	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.070	4.316	5.901
		95% CI	(-8.5, 7.6)	(-0.4, 16.6)	(-20.2, 3.1)
		Pr >  t			0.1499
	Week 40	n	14	10	
		LS Mean	4.864	5.105	-0.241
		SEM	4.203	4.798	6.355
		95% CI	(-3.4, 13.2)	(-4.4, 14.6)	(-12.8, 12.3)
		Pr >  t			0.9698
	Week 48	n	14	11	
		LS Mean	1.889	7.550	-5.662
		SEM	4.203	4.626	6.224
		95% CI	(-6.4, 10.2)	(-1.6, 16.7)	(-17.9, 6.6)
		Pr >  t			0.3642
	Week 56	n	11	11	
		LS Mean	-2.206	10.580	-12.79
		SEM	4.609	4.626	6.509
		95% CI	(-11.3, 6.9)	( 1.5, 19.7)	(-25.6, 0.1)
		Pr >  t			0.0509
	Week 64	n	8	11	
		LS Mean	-1.532	8.308	-9.840
		SEM	5.230	4.626	6.967
		95% CI	(-11.8, 8.8)	(-0.8, 17.4)	(-23.6, 3.9)
		Pr >  t			0.1593
	Week 72	n	11	10	
		LS Mean	3.098	6.019	-2.922
		SEM	4.609	4.810	6.644
		95% CI	(-6.0, 12.2)	(-3.5, 15.5)	(-16.0, 10.2)
		Pr >  t			0.6606
	Week 84	n	9	9	
		LS Mean	0.557	1.437	-0.881
		SEM	4.987	5.016	7.067
		95% CI	(-9.3, 10.4)	(-8.5, 11.3)	(-14.8, 13.0)
		Pr >  t			0.9009
	Week 96	n	8	7	
		LS Mean	-7.107	8.215	-15.32
		SEM	5.238	5.553	7.632
		95% CI	(-17.4, 3.2)	(-2.7, 19.2)	(-30.4, -0.3)
		Pr >  t			0.0458
	Week 108	n	7	6	
		LS Mean	-0.351	4.124	-4.475

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.534	5.934	8.112
		95% CI	(-11.3,10.5)	(-7.6,15.8)	(-20.4,11.5)
		Pr >  t			0.5817
	Week 120	n	6	5	
		LS Mean	10.114	3.328	6.786
		SEM	5.915	6.424	8.719
		95% CI	(-1.5,21.8)	(-9.3,16.0)	(-10.4,24.0)
		Pr >  t			0.4371
	Week 132	n	5	3	
		LS Mean	4.711	-1.014	5.725
		SEM	6.395	8.052	10.28
		95% CI	(-7.9,17.3)	(-16.9,14.8)	(-14.5,26.0)
		Pr >  t			0.5780
	Week 144	n	5	4	
		LS Mean	-3.621	12.641	-16.26
		SEM	6.395	7.081	9.536
		95% CI	(-16.2, 9.0)	(-1.3,26.6)	(-35.0, 2.5)
		Pr >  t			0.0892
	Week 156	n	4	2	
		LS Mean	-1.927	1.021	-2.947
		SEM	7.052	9.706	12.00
		95% CI	(-15.8,12.0)	(-18.1,20.1)	(-26.6,20.7)
		Pr >  t			0.8062
	Week 168	n	1	1	
		LS Mean	-12.47	15.778	-28.25
		SEM	13.49	13.51	19.10
		95% CI	(-39.0,14.1)	(-10.8,42.4)	(-65.9, 9.4)
		Pr >  t			0.1402
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-3.185	0.694	-3.878
		SEM	4.253	3.931	4.953
		95% CI	(-11.7, 5.3)	(-7.2, 8.5)	(-13.7, 6.0)
		Pr >  t			0.4359
	Week 16	n	15	17	
		LS Mean	-3.052	1.661	-4.713
		SEM	4.543	4.165	5.195
		95% CI	(-12.1, 6.0)	(-6.6,10.0)	(-15.0, 5.6)
		Pr >  t			0.3668
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	-1.086	1.777	-2.863
	SEM	4.636	4.699	5.764
	95% CI	(-10.3, 8.1)	(-7.6, 11.1)	(-14.3, 8.6)
	Pr >  t			0.6204
	n	12	9	
Week 40	LS Mean	4.980	7.888	-2.908
	SEM	4.904	5.076	6.202
	95% CI	(-4.8, 14.7)	(-2.2, 17.9)	(-15.2, 9.4)
	Pr >  t			0.6399
	n	11	7	
Week 48	LS Mean	-5.578	-4.565	-1.013
	SEM	5.061	5.645	6.696
	95% CI	(-15.6, 4.5)	(-15.7, 6.6)	(-14.2, 12.2)
	Pr >  t			0.8800
	n	8	6	
Week 56	LS Mean	-4.897	-0.393	-4.504
	SEM	5.553	5.968	7.350
	95% CI	(-15.9, 6.1)	(-12.2, 11.4)	(-19.0, 10.0)
	Pr >  t			0.5409
	n	7	5	
Week 64	LS Mean	-2.053	9.199	-11.25
	SEM	5.790	6.360	7.869
	95% CI	(-13.5, 9.4)	(-3.4, 21.8)	(-26.8, 4.3)
	Pr >  t			0.1546
	n	5	3	
Week 72	LS Mean	-0.716	-7.394	6.678
	SEM	6.466	7.764	9.476
	95% CI	(-13.5, 12.1)	(-22.7, 7.9)	(-12.0, 25.4)
	Pr >  t			0.4819
	n	5	2	
Week 84	LS Mean	-8.280	3.780	-12.06
	SEM	6.483	9.217	10.71
	95% CI	(-21.1, 4.5)	(-14.4, 22.0)	(-33.2, 9.1)
	Pr >  t			0.2619
	n	4	2	
Week 96	LS Mean	4.671	3.780	0.891
	SEM	6.996	9.217	11.05
	95% CI	(-9.1, 18.5)	(-14.4, 22.0)	(-20.9, 22.7)
	Pr >  t			0.9358
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	1.732	-4.555	6.286
	SEM	7.002	9.217	11.05
	95% CI	(-12.1,15.6)	(-22.7,13.6)	(-15.5,28.1)
	Pr >  t			0.5700
Week 108	n	1	2	
	LS Mean	2.599	6.498	-3.900
	SEM	12.46	9.184	15.10
	95% CI	(-22.0,27.2)	(-11.6,24.6)	(-33.7,25.9)
	Pr >  t			0.7966
Week 120	n	5	1	
	LS Mean	-3.278	-2.882	-0.395
	SEM	6.483	12.48	13.62
	95% CI	(-16.1, 9.5)	(-27.5,21.8)	(-27.3,26.5)
	Pr >  t			0.9769
Week 132	n	3	1	
	LS Mean	3.150	-2.882	6.032
	SEM	7.820	12.48	14.32
	95% CI	(-12.3,18.6)	(-27.5,21.8)	(-22.3,34.3)
	Pr >  t			0.6742
Week 144	n	3		
	LS Mean	-2.406		
	SEM	7.820		
	95% CI	(-17.8,13.0)		
	Pr >  t			
Week 156	n	3		
	LS Mean	3.150		
	SEM	7.820		
	95% CI	(-12.3,18.6)		
	Pr >  t			
Week 168	n	1		
	LS Mean	1.466		
	SEM	12.45		
	95% CI	(-23.1,26.1)		
	Pr >  t			
Week 180	n	1		
	LS Mean	-15.20		
	SEM	12.45		
	95% CI	(-39.8, 9.4)		
	Pr >  t			
Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	1.466		
		SEM	12.45		
		95% CI	(-23.1,26.1)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	0.908	4.797	-3.889
		SEM	4.069	4.067	4.453
		95% CI	(-7.1, 9.0)	(-3.2,12.8)	(-12.7, 4.9)
		Pr >  t			0.3837
	Week 16	n	30	29	
		LS Mean	-0.589	0.120	-0.709
		SEM	4.233	4.461	4.936
		95% CI	(-9.0, 7.8)	(-8.7, 8.9)	(-10.4, 9.0)
		Pr >  t			0.8859
	Week 24	n	26	20	
		LS Mean	-7.415	7.698	-15.11
		SEM	4.423	4.971	5.482
		95% CI	(-16.2, 1.3)	(-2.1,17.5)	(-25.9,-4.3)
		Pr >  t			0.0063
	Week 32	n	18	20	
		LS Mean	-3.573	2.697	-6.270
		SEM	4.890	4.971	5.857
		95% CI	(-13.2, 6.1)	(-7.1,12.5)	(-17.8, 5.3)
		Pr >  t			0.2853
	Week 40	n	18	19	
		LS Mean	-0.964	-0.578	-0.386
		SEM	4.889	5.037	5.913
		95% CI	(-10.6, 8.7)	(-10.5, 9.4)	(-12.0,11.3)
		Pr >  t			0.9480
	Week 48	n	16	14	
		LS Mean	-0.349	-3.243	2.894
		SEM	5.044	5.448	6.396
		95% CI	(-10.3, 9.6)	(-14.0, 7.5)	(-9.7,15.5)
		Pr >  t			0.6513
	Week 56	n	14	10	
		LS Mean	-2.128	-3.755	1.627
		SEM	5.234	6.016	7.042
		95% CI	(-12.4, 8.2)	(-15.6, 8.1)	(-12.2,15.5)
		Pr >  t			0.8175



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169			
Week 64	n	13		11	
	LS Mean	-2.986		-1.649	-1.337
	SEM	5.349		5.847	6.988
	95% CI	(-13.5, 7.5)		(-13.2, 9.9)	(-15.1,12.4)
	Pr >  t				0.8484
Week 72	n	10		6	
	LS Mean	-6.526		2.654	-9.180
	SEM	5.791		7.148	8.416
	95% CI	(-17.9, 4.9)		(-11.4,16.7)	(-25.7, 7.4)
	Pr >  t				0.2761
Week 84	n	8		7	
	LS Mean	-1.757		-4.347	2.591
	SEM	6.304		6.769	8.434
	95% CI	(-14.2,10.6)		(-17.7, 9.0)	(-14.0,19.2)
	Pr >  t				0.7589
Week 96	n	6		5	
	LS Mean	-5.205		-6.227	1.021
	SEM	6.962		7.637	9.636
	95% CI	(-18.9, 8.5)		(-21.2, 8.8)	(-17.9,20.0)
	Pr >  t				0.9156
Week 108	n	2		4	
	LS Mean	-16.14		-1.703	-14.44
	SEM	11.01		8.324	13.26
	95% CI	(-37.8, 5.5)		(-18.1,14.7)	(-40.5,11.6)
	Pr >  t				0.2770
Week 120	n	4		4	
	LS Mean	0.158		4.550	-4.392
	SEM	8.148		8.324	11.04
	95% CI	(-15.9,16.2)		(-11.8,20.9)	(-26.1,17.3)
	Pr >  t				0.6911
Week 132	n	3		1	
	LS Mean	-13.18		5.388	-18.57
	SEM	9.223		15.23	17.38
	95% CI	(-31.3, 5.0)		(-24.6,35.3)	(-52.8,15.6)
	Pr >  t				0.2862
Week 144	n	2			
	LS Mean	-2.265			
	SEM	10.94			
	95% CI	(-23.8,19.3)			
	Pr >  t				

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-2.089	0.663	-2.752		
			SEM	3.293	3.298	2.690		
			95% CI	(-8.6, 4.4)	(-5.8, 7.2)	(-8.0, 2.5)		
					Pr >  t			0.3068
		Week 16	n	79	68			
			LS Mean	-0.778	-2.294	1.517		
			SEM	3.332	3.482	2.928		
			95% CI	(-7.3, 5.8)	(-9.1, 4.6)	(-4.2, 7.3)		
					Pr >  t			0.6047
		Week 24	n	64	55			
			LS Mean	-4.978	2.166	-7.144		
			SEM	3.441	3.627	3.171		
			95% CI	(-11.7, 1.8)	(-5.0, 9.3)	(-13.4,-0.9)		
					Pr >  t			0.0247
		Week 32	n	49	53			
			LS Mean	-5.534	0.573	-6.107		
			SEM	3.617	3.650	3.350		
			95% CI	(-12.6, 1.6)	(-6.6, 7.8)	(-12.7, 0.5)		
					Pr >  t			0.0687
		Week 40	n	44	45			
			LS Mean	-2.422	0.520	-2.943		
			SEM	3.681	3.741	3.519		
			95% CI	(-9.7, 4.8)	(-6.8, 7.9)	(-9.9, 4.0)		
					Pr >  t			0.4033
		Week 48	n	41	36			
			LS Mean	-3.100	0.143	-3.243		
			SEM	3.724	3.885	3.714		
95% CI	(-10.4, 4.2)		(-7.5, 7.8)	(-10.5, 4.0)				
			Pr >  t			0.3829		
Week 56	n	33	32					
	LS Mean	-2.551	0.778	-3.329				
	SEM	3.871	3.971	3.953				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.2, 5.1)	(-7.0, 8.6)	(-11.1, 4.4)
	Pr >  t			0.3999
	n	27	31	
	LS Mean	-2.883	-0.362	-2.520
	SEM	4.028	3.997	4.135
Week 72	95% CI	(-10.8, 5.0)	(-8.2, 7.5)	(-10.6, 5.6)
	Pr >  t			0.5423
	n	26	26	
	LS Mean	-4.460	-0.505	-3.955
	SEM	4.060	4.143	4.306
Week 84	95% CI	(-12.4, 3.5)	(-8.6, 7.6)	(-12.4, 4.5)
	Pr >  t			0.3586
	n	22	23	
	LS Mean	-3.176	-1.777	-1.399
	SEM	4.234	4.254	4.560
Week 96	95% CI	(-11.5, 5.1)	(-10.1, 6.6)	(-10.3, 7.5)
	Pr >  t			0.7590
	n	18	18	
	LS Mean	-7.275	-0.612	-6.663
	SEM	4.450	4.511	4.992
Week 108	95% CI	(-16.0, 1.5)	(-9.5, 8.2)	(-16.5, 3.1)
	Pr >  t			0.1823
	n	14	14	
	LS Mean	-3.155	0.271	-3.426
	SEM	4.772	4.828	5.552
Week 120	95% CI	(-12.5, 6.2)	(-9.2, 9.7)	(-14.3, 7.5)
	Pr >  t			0.5373
	n	12	12	
	LS Mean	-2.126	-3.253	1.127
	SEM	4.993	5.051	5.931
Week 132	95% CI	(-11.9, 7.7)	(-13.2, 6.7)	(-10.5, 12.8)
	Pr >  t			0.8494
	n	9	5	
	LS Mean	-1.829	-12.34	10.510
	SEM	5.475	6.836	7.840
Week 144	95% CI	(-12.6, 8.9)	(-25.8, 1.1)	(-4.9, 25.9)
	Pr >  t			0.1804
	n	7	4	
	LS Mean	-0.881	6.358	-7.239
	SEM	5.980	7.480	8.743

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.6,10.9)	(-8.3,21.0)	(-24.4, 9.9)
		Pr >  t			0.4079
	Week 156	n	4	2	
		LS Mean	-6.444	-5.464	-0.979
		SEM	7.425	10.06	11.88
		95% CI	(-21.0, 8.1)	(-25.2,14.3)	(-24.3,22.3)
		Pr >  t			0.9343
	Week 168	n	2	1	
		LS Mean	-3.446	9.522	-12.97
		SEM	10.01	13.85	16.64
		95% CI	(-23.1,16.2)	(-17.7,36.7)	(-45.6,19.7)
		Pr >  t			0.4359
Yes	Week 8	n	53	48	
		LS Mean	-1.483	-0.552	-0.931
		SEM	3.043	3.186	3.118
		95% CI	(-7.5, 4.5)	(-6.8, 5.7)	(-7.1, 5.2)
		Pr >  t			0.7655
	Week 16	n	45	39	
		LS Mean	-2.077	-1.728	-0.349
		SEM	3.214	3.363	3.369
		95% CI	(-8.4, 4.3)	(-8.4, 4.9)	(-7.0, 6.3)
		Pr >  t			0.9176
	Week 24	n	41	26	
		LS Mean	1.469	-3.575	5.044
		SEM	3.271	3.667	3.761
		95% CI	(-5.0, 7.9)	(-10.8, 3.6)	(-2.4,12.4)
		Pr >  t			0.1806
	Week 32	n	37	20	
		LS Mean	2.177	-1.824	4.001
		SEM	3.368	3.955	4.077
		95% CI	(-4.5, 8.8)	(-9.6, 6.0)	(-4.0,12.0)
		Pr >  t			0.3269
	Week 40	n	31	17	
		LS Mean	-2.232	-5.240	3.008
		SEM	3.496	4.180	4.363
		95% CI	(-9.1, 4.7)	(-13.5, 3.0)	(-5.6,11.6)
		Pr >  t			0.4909
	Week 48	n	28	15	
		LS Mean	-3.239	-2.765	-0.474
		SEM	3.573	4.333	4.573

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.3, 3.8)	(-11.3, 5.8)	(-9.5, 8.5)
		Pr >  t			0.9175
	Week 56	n	26	13	
		LS Mean	0.749	1.630	-0.881
		SEM	3.634	4.522	4.803
		95% CI	(-6.4, 7.9)	(-7.3, 10.5)	(-10.3, 8.6)
		Pr >  t			0.8545
	Week 64	n	20	11	
		LS Mean	0.479	-3.415	3.894
		SEM	3.873	4.766	5.214
		95% CI	(-7.1, 8.1)	(-12.8, 6.0)	(-6.3, 14.1)
		Pr >  t			0.4554
	Week 72	n	22	9	
		LS Mean	1.102	-1.615	2.718
		SEM	3.785	5.090	5.447
		95% CI	(-6.3, 8.5)	(-11.6, 8.4)	(-8.0, 13.4)
		Pr >  t			0.6181
	Week 84	n	18	10	
		LS Mean	2.603	1.211	1.392
		SEM	3.998	4.917	5.432
		95% CI	(-5.3, 10.5)	(-8.4, 10.9)	(-9.3, 12.1)
		Pr >  t			0.7978
	Week 96	n	17	6	
		LS Mean	1.056	-4.663	5.719
		SEM	4.045	5.886	6.365
		95% CI	(-6.9, 9.0)	(-16.2, 6.9)	(-6.8, 18.2)
		Pr >  t			0.3693
	Week 108	n	12	7	
		LS Mean	0.414	-4.377	4.792
		SEM	4.509	5.560	6.370
		95% CI	(-8.4, 9.3)	(-15.3, 6.5)	(-7.7, 17.3)
		Pr >  t			0.4522
	Week 120	n	16	4	
		LS Mean	-2.050	6.179	-8.228
		SEM	4.121	6.906	7.358
		95% CI	(-10.2, 6.1)	(-7.4, 19.7)	(-22.7, 6.2)
		Pr >  t			0.2639
	Week 132	n	11	3	
		LS Mean	-0.632	-0.410	-0.222
		SEM	4.637	7.787	8.456

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.7, 8.5)	(-15.7,14.9)	(-16.8,16.4)
		Pr >  t			0.9790
	Week 144	n	8	1	
		LS Mean	-12.13	1.641	-13.77
		SEM	5.148	12.81	13.43
		95% CI	(-22.2,-2.0)	(-23.5,26.8)	(-40.1,12.6)
		Pr >  t			0.3054
	Week 156	n	6	1	
		LS Mean	3.188	-6.689	9.877
		SEM	5.766	12.81	13.66
		95% CI	(-8.1,14.5)	(-31.9,18.5)	(-17.0,36.7)
		Pr >  t			0.4701
	Week 168	n	2	1	
		LS Mean	-1.068	1.641	-2.709
		SEM	9.213	12.81	15.44
		95% CI	(-19.2,17.0)	(-23.5,26.8)	(-33.0,27.6)
		Pr >  t			0.8608
	Week 180	n	1	1	
		LS Mean	-15.19	1.641	-16.83
		SEM	12.71	12.81	17.75
		95% CI	(-40.2, 9.8)	(-23.5,26.8)	(-51.7,18.0)
		Pr >  t			0.3435
	Week 192	n	1	1	
		LS Mean	1.481	1.641	-0.160
		SEM	12.71	12.81	17.75
		95% CI	(-23.5,26.5)	(-23.5,26.8)	(-35.0,34.7)
		Pr >  t			0.9928

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	-6.922	-7.911	0.989
			SEM	4.185	4.537	4.427
			95% CI	(-15.2, 1.4)	(-16.9, 1.1)	(-7.8, 9.7)
		Pr >  t			0.8235	
		Week 16	n	35	22	
			LS Mean	-9.823	-8.716	-1.107
			SEM	4.391	5.210	5.092
			95% CI	(-18.5,-1.1)	(-19.0, 1.6)	(-11.1, 8.9)
		Pr >  t			0.8280	
		Week 24	n	28	16	
			LS Mean	-10.57	-6.565	-4.006
			SEM	4.589	5.625	5.707
			95% CI	(-19.6,-1.5)	(-17.7, 4.5)	(-15.2, 7.2)
		Pr >  t			0.4833	
		Week 32	n	22	16	
			LS Mean	-6.232	-9.639	3.407
			SEM	4.911	5.642	5.911
			95% CI	(-15.9, 3.5)	(-20.8, 1.5)	(-8.2,15.0)
		Pr >  t			0.5648	
		Week 40	n	19	12	
			LS Mean	-8.898	-9.381	0.484
			SEM	5.084	6.068	6.464
			95% CI	(-18.9, 1.1)	(-21.3, 2.6)	(-12.2,13.2)
		Pr >  t			0.9404	
		Week 48	n	16	10	
			LS Mean	-12.51	-17.17	4.656
			SEM	5.301	6.387	6.939
95% CI	(-23.0,-2.1)		(-29.7,-4.6)	(-9.0,18.3)		
Pr >  t			0.5027			
Week 56	n	14	7			
	LS Mean	-15.10	-4.196	-10.91		
		SEM	5.494	7.124	7.776	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-25.9,-4.3)	(-18.2, 9.8)	(-26.2, 4.4)
		Pr >  t			0.1616
	Week 64	n	8	7	
		LS Mean	-8.568	-9.533	0.965
		SEM	6.465	7.126	8.505
		95% CI	(-21.3, 4.2)	(-23.6, 4.5)	(-15.8,17.7)
		Pr >  t			0.9097
	Week 72	n	12	6	
		LS Mean	-9.148	-8.028	-1.120
		SEM	5.728	7.500	8.290
		95% CI	(-20.4, 2.1)	(-22.8, 6.7)	(-17.4,15.2)
		Pr >  t			0.8926
	Week 84	n	8	5	
		LS Mean	-7.312	-9.361	2.049
		SEM	6.513	7.989	9.245
		95% CI	(-20.1, 5.5)	(-25.1, 6.4)	(-16.1,20.2)
		Pr >  t			0.8248
	Week 96	n	5	5	
		LS Mean	-13.36	-12.70	-0.666
		SEM	7.672	7.989	10.09
		95% CI	(-28.5, 1.7)	(-28.4, 3.0)	(-20.5,19.2)
		Pr >  t			0.9475
	Week 108	n	7	5	
		LS Mean	-7.874	-12.69	4.821
		SEM	6.811	7.989	9.458
		95% CI	(-21.3, 5.5)	(-28.4, 3.0)	(-13.8,23.4)
		Pr >  t			0.6106
	Week 120	n	5	3	
		LS Mean	-24.00	-10.27	-13.74
		SEM	7.681	9.664	11.47
		95% CI	(-39.1,-8.9)	(-29.3, 8.7)	(-36.3, 8.8)
		Pr >  t			0.2321
	Week 132	n	2	2	
		LS Mean	-10.39	-11.71	1.321
		SEM	11.15	11.34	15.23
		95% CI	(-32.3,11.5)	(-34.0,10.6)	(-28.7,31.3)
		Pr >  t			0.9310
	Week 144	n	2		
		LS Mean	-34.07		
		SEM	11.15		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-56.0, -12)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	-8.731		
		SEM	11.16		
		95% CI	(-30.7,13.2)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-14.21		
		SEM	15.28		
		95% CI	(-44.3,15.9)		
		Pr >  t			
Positive	Week 8	n	98	104	
		LS Mean	-0.393	2.444	-2.837
		SEM	2.846	2.822	2.349
		95% CI	(-6.0, 5.2)	(-3.1, 8.0)	(-7.5, 1.8)
		Pr >  t			0.2278
	Week 16	n	87	84	
		LS Mean	1.485	-0.461	1.946
		SEM	2.907	2.911	2.510
		95% CI	(-4.2, 7.2)	(-6.2, 5.3)	(-3.0, 6.9)
		Pr >  t			0.4384
	Week 24	n	76	65	
		LS Mean	-0.072	1.948	-2.020
		SEM	2.976	3.040	2.705
		95% CI	(-5.9, 5.8)	(-4.0, 7.9)	(-7.3, 3.3)
		Pr >  t			0.4556
	Week 32	n	62	57	
		LS Mean	-1.220	2.105	-3.326
		SEM	3.077	3.117	2.876
		95% CI	(-7.3, 4.8)	(-4.0, 8.2)	(-9.0, 2.3)
		Pr >  t			0.2479
	Week 40	n	54	50	
		LS Mean	-0.144	0.781	-0.925
		SEM	3.146	3.198	3.022
		95% CI	(-6.3, 6.0)	(-5.5, 7.1)	(-6.9, 5.0)
		Pr >  t			0.7597
	Week 48	n	52	41	
		LS Mean	-0.313	3.172	-3.485
		SEM	3.164	3.314	3.164

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-6.5, 5.9)	(-3.3, 9.7)	(-9.7, 2.7)
	Pr >  t			0.2709
	n	44	38	
	LS Mean	3.008	2.328	0.679
	SEM	3.253	3.362	3.307
Week 64	95% CI	(-3.4, 9.4)	(-4.3, 8.9)	(-5.8, 7.2)
	Pr >  t			0.8373
	n	39	35	
	LS Mean	0.796	0.669	0.128
	SEM	3.327	3.420	3.436
Week 72	95% CI	(-5.7, 7.3)	(-6.0, 7.4)	(-6.6, 6.9)
	Pr >  t			0.9704
	n	36	29	
	LS Mean	0.106	0.842	-0.735
	SEM	3.379	3.557	3.625
Week 84	95% CI	(-6.5, 6.7)	(-6.1, 7.8)	(-7.8, 6.4)
	Pr >  t			0.8393
	n	32	28	
	LS Mean	1.406	1.096	0.310
	SEM	3.467	3.586	3.729
Week 96	95% CI	(-5.4, 8.2)	(-5.9, 8.1)	(-7.0, 7.6)
	Pr >  t			0.9337
	n	30	19	
	LS Mean	-0.680	0.979	-1.659
	SEM	3.508	3.952	4.125
Week 108	95% CI	(-7.6, 6.2)	(-6.8, 8.7)	(-9.8, 6.4)
	Pr >  t			0.6876
	n	18	16	
	LS Mean	0.458	1.730	-1.272
	SEM	3.994	4.151	4.712
Week 120	95% CI	(-7.4, 8.3)	(-6.4, 9.9)	(-10.5, 8.0)
	Pr >  t			0.7872
	n	23	13	
	LS Mean	2.810	1.200	1.610
	SEM	3.737	4.423	4.756
Week 132	95% CI	(-4.5, 10.1)	(-7.5, 9.9)	(-7.7, 10.9)
	Pr >  t			0.7350
	n	18	6	
	LS Mean	0.979	-7.310	8.288
	SEM	3.995	5.826	6.239

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.9, 8.8)	(-18.7, 4.1)	(-4.0,20.5)
		Pr >  t			0.1843
	Week 144	n	13	5	
		LS Mean	-1.677	7.204	-8.882
		SEM	4.386	6.270	6.909
		95% CI	(-10.3, 6.9)	(-5.1,19.5)	(-22.4, 4.7)
		Pr >  t			0.1988
	Week 156	n	8	3	
		LS Mean	1.436	-3.928	5.365
		SEM	5.200	7.780	8.752
		95% CI	(-8.8,11.6)	(-19.2,11.3)	(-11.8,22.5)
		Pr >  t			0.5400
	Week 168	n	3	2	
		LS Mean	1.182	7.648	-6.465
		SEM	7.755	9.332	11.67
		95% CI	(-14.0,16.4)	(-10.7,26.0)	(-29.4,16.4)
		Pr >  t			0.5798
	Week 180	n	1	1	
		LS Mean	-13.33	4.395	-17.72
		SEM	12.90	12.90	17.94
		95% CI	(-38.6,12.0)	(-20.9,29.7)	(-52.9,17.5)
		Pr >  t			0.3233
	Week 192	n	1	1	
		LS Mean	3.342	4.395	-1.053
		SEM	12.90	12.90	17.94
		95% CI	(-22.0,28.7)	(-20.9,29.7)	(-36.2,34.1)
		Pr >  t			0.9532

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	-0.500	2.521	-3.021		
			SEM	2.861	2.830	2.367		
			95% CI	(-6.1, 5.1)	(-3.0, 8.1)	(-7.7, 1.6)		
					Pr >  t			0.2025
		Week 16	n	85	84			
			LS Mean	1.210	-0.380	1.590		
			SEM	2.925	2.919	2.530		
			95% CI	(-4.5, 7.0)	(-6.1, 5.4)	(-3.4, 6.6)		
					Pr >  t			0.5299
		Week 24	n	75	65			
			LS Mean	-0.243	2.023	-2.267		
			SEM	2.992	3.048	2.722		
			95% CI	(-6.1, 5.6)	(-4.0, 8.0)	(-7.6, 3.1)		
					Pr >  t			0.4053
		Week 32	n	61	57			
			LS Mean	-1.150	2.182	-3.331		
			SEM	3.096	3.125	2.896		
			95% CI	(-7.2, 4.9)	(-4.0, 8.3)	(-9.0, 2.4)		
					Pr >  t			0.2503
		Week 40	n	53	50			
			LS Mean	-0.133	0.857	-0.990		
			SEM	3.167	3.206	3.045		
			95% CI	(-6.4, 6.1)	(-5.4, 7.2)	(-7.0, 5.0)		
					Pr >  t			0.7451
		Week 48	n	51	41			
			LS Mean	-0.633	3.249	-3.881		
			SEM	3.186	3.322	3.187		
95% CI	(-6.9, 5.6)		(-3.3, 9.8)	(-10.1, 2.4)				
			Pr >  t			0.2236		
Week 56	n	43	38					
	LS Mean	3.114	2.406	0.708				
	SEM	3.279	3.371	3.333				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-3.3, 9.6)	(-4.2, 9.0)	(-5.8, 7.2)
	Pr >  t			0.8319
	n	39	35	
	LS Mean	0.739	0.744	-0.006
	SEM	3.339	3.428	3.450
Week 72	95% CI	(-5.8, 7.3)	(-6.0, 7.5)	(-6.8, 6.8)
	Pr >  t			0.9987
	n	35	29	
	LS Mean	-0.151	0.918	-1.069
	SEM	3.410	3.566	3.657
Week 84	95% CI	(-6.9, 6.5)	(-6.1, 7.9)	(-8.2, 6.1)
	Pr >  t			0.7701
	n	31	28	
	LS Mean	1.710	1.172	0.539
	SEM	3.504	3.595	3.765
Week 96	95% CI	(-5.2, 8.6)	(-5.9, 8.2)	(-6.8, 7.9)
	Pr >  t			0.8863
	n	29	19	
	LS Mean	-0.715	1.055	-1.770
	SEM	3.548	3.962	4.161
Week 108	95% CI	(-7.7, 6.3)	(-6.7, 8.8)	(-9.9, 6.4)
	Pr >  t			0.6707
	n	18	16	
	LS Mean	0.403	1.804	-1.401
	SEM	4.008	4.161	4.727
Week 120	95% CI	(-7.5, 8.3)	(-6.4, 10.0)	(-10.7, 7.9)
	Pr >  t			0.7669
	n	23	13	
	LS Mean	2.754	1.272	1.482
	SEM	3.750	4.434	4.770
Week 132	95% CI	(-4.6, 10.1)	(-7.4, 10.0)	(-7.9, 10.8)
	Pr >  t			0.7561
	n	18	6	
	LS Mean	0.923	-7.237	8.161
	SEM	4.008	5.840	6.257
Week 144	95% CI	(-6.9, 8.8)	(-18.7, 4.2)	(-4.1, 20.4)
	Pr >  t			0.1924
	n	13	5	
	LS Mean	-1.736	7.277	-9.013
	SEM	4.400	6.285	6.928

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	(-10.4, 6.9)	(-5.1,19.6)	(-22.6, 4.6)
		Pr >  t			0.1935
		n	8	3	
	Week 168	LS Mean	1.376	-3.853	5.229
		SEM	5.215	7.799	8.775
		95% CI	(-8.9,11.6)	(-19.2,11.4)	(-12.0,22.4)
	Week 180	Pr >  t			0.5514
		n	3	2	
		LS Mean	1.114	7.725	-6.610
	Week 192	SEM	7.775	9.355	11.70
		95% CI	(-14.1,16.4)	(-10.6,26.1)	(-29.6,16.4)
		Pr >  t			0.5723
	Week 8	n	1	1	
		LS Mean	-13.41	4.465	-17.88
		SEM	12.93	12.93	17.98
	Week 16	95% CI	(-38.8,12.0)	(-20.9,29.8)	(-53.2,17.4)
		Pr >  t			0.3203
		n	1	1	
	Week 24	LS Mean	3.258	4.465	-1.207
		SEM	12.93	12.93	17.98
		95% CI	(-22.1,28.6)	(-20.9,29.8)	(-36.5,34.1)
	Week 32	Pr >  t			0.9465
		n	42	35	
		LS Mean	-6.922	-7.911	0.989
Week 8	SEM	4.185	4.537	4.427	
	95% CI	(-15.2, 1.4)	(-16.9, 1.1)	(-7.8, 9.7)	
	Pr >  t			0.8235	
Week 16	n	35	22		
	LS Mean	-9.823	-8.716	-1.107	
	SEM	4.391	5.210	5.092	
Week 24	95% CI	(-18.5,-1.1)	(-19.0, 1.6)	(-11.1, 8.9)	
	Pr >  t			0.8280	
	n	28	16		
Week 32	LS Mean	-10.57	-6.565	-4.006	
	SEM	4.589	5.625	5.707	
	95% CI	(-19.6,-1.5)	(-17.7, 4.5)	(-15.2, 7.2)	
Week 8	Pr >  t			0.4833	
	n	22	16		
	LS Mean	-6.232	-9.639	3.407	
Week 16	SEM	4.911	5.642	5.911	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-15.9, 3.5)	(-20.8, 1.5)	(-8.2,15.0)
		Pr >  t			0.5648
	Week 40	n	19	12	
		LS Mean	-8.898	-9.381	0.484
		SEM	5.084	6.068	6.464
		95% CI	(-18.9, 1.1)	(-21.3, 2.6)	(-12.2,13.2)
		Pr >  t			0.9404
	Week 48	n	16	10	
		LS Mean	-12.51	-17.17	4.656
		SEM	5.301	6.387	6.939
		95% CI	(-23.0,-2.1)	(-29.7,-4.6)	(-9.0,18.3)
		Pr >  t			0.5027
	Week 56	n	14	7	
		LS Mean	-15.10	-4.196	-10.91
		SEM	5.494	7.124	7.776
		95% CI	(-25.9,-4.3)	(-18.2, 9.8)	(-26.2, 4.4)
		Pr >  t			0.1616
	Week 64	n	8	7	
		LS Mean	-8.568	-9.533	0.965
		SEM	6.465	7.126	8.505
		95% CI	(-21.3, 4.2)	(-23.6, 4.5)	(-15.8,17.7)
		Pr >  t			0.9097
	Week 72	n	12	6	
		LS Mean	-9.148	-8.028	-1.120
		SEM	5.728	7.500	8.290
		95% CI	(-20.4, 2.1)	(-22.8, 6.7)	(-17.4,15.2)
		Pr >  t			0.8926
	Week 84	n	8	5	
		LS Mean	-7.312	-9.361	2.049
		SEM	6.513	7.989	9.245
		95% CI	(-20.1, 5.5)	(-25.1, 6.4)	(-16.1,20.2)
		Pr >  t			0.8248
	Week 96	n	5	5	
		LS Mean	-13.36	-12.70	-0.666
		SEM	7.672	7.989	10.09
		95% CI	(-28.5, 1.7)	(-28.4, 3.0)	(-20.5,19.2)
		Pr >  t			0.9475
	Week 108	n	7	5	
		LS Mean	-7.874	-12.69	4.821
		SEM	6.811	7.989	9.458



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.3, 5.5)	(-13.8,23.4)
		Pr >  t		0.6106
	Week 120	n	5	3
		LS Mean	-24.00	-10.27
		SEM	7.681	9.664
		95% CI	(-39.1,-8.9)	(-29.3, 8.7)
		Pr >  t		(-36.3, 8.8)
	Week 132	n	2	2
		LS Mean	-10.39	-11.71
		SEM	11.15	11.34
		95% CI	(-32.3,11.5)	(-34.0,10.6)
		Pr >  t		(-28.7,31.3)
	Week 144	n	2	
		LS Mean	-34.07	
		SEM	11.15	
		95% CI	(-56.0, -12)	
		Pr >  t		0.9310
	Week 156	n	2	
		LS Mean	-8.731	
		SEM	11.16	
		95% CI	(-30.7,13.2)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	-14.21	
		SEM	15.28	
		95% CI	(-44.3,15.9)	
		Pr >  t		

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-0.081	-0.938	0.857
			SEM	6.556	7.306	6.454
			95% CI	(-13.2,13.1)	(-15.7,13.8)	(-12.0,13.7)
			Pr >  t			0.8947
		Week 16	n	14	17	
			LS Mean	5.320	-8.173	13.493
			SEM	6.654	7.537	6.925
			95% CI	(-8.0,18.7)	(-23.3, 7.0)	(-0.3,27.3)
			Pr >  t			0.0547
		Week 24	n	14	11	
			LS Mean	-3.609	2.815	-6.424
			SEM	6.654	7.961	7.385
			95% CI	(-17.0, 9.7)	(-13.1,18.8)	(-21.1, 8.2)
			Pr >  t			0.3864
		Week 32	n	10	10	
			LS Mean	-0.094	-11.01	10.917
			SEM	7.387	8.085	7.849
			95% CI	(-14.8,14.6)	(-27.2, 5.2)	(-4.6,26.5)
			Pr >  t			0.1669
		Week 40	n	8	10	
			LS Mean	-2.347	-7.163	4.816
			SEM	7.721	8.087	8.149
			95% CI	(-17.7,13.0)	(-23.3, 9.0)	(-11.3,20.9)
			Pr >  t			0.5555
		Week 48	n	7	11	
			LS Mean	2.211	-11.03	13.238
			SEM	7.932	7.975	8.273
			95% CI	(-13.5,18.0)	(-27.0, 4.9)	(-3.1,29.6)
			Pr >  t			0.1119
		Week 56	n	6	9	
			LS Mean	1.994	-3.701	5.695
			SEM	8.205	8.225	8.796

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.3,18.3)	(-20.1,12.7)	(-11.7,23.1)
		Pr >  t			0.5183
	Week 64	n	5	8	
		LS Mean	6.718	-4.373	11.091
		SEM	8.575	8.390	9.290
		95% CI	(-10.3,23.7)	(-21.1,12.4)	(-7.2,29.4)
		Pr >  t			0.2342
	Week 72	n	7	7	
		LS Mean	2.587	-2.247	4.834
		SEM	7.920	8.595	8.892
		95% CI	(-13.1,18.3)	(-19.4,14.9)	(-12.7,22.4)
		Pr >  t			0.5874
	Week 84	n	7	7	
		LS Mean	-2.176	-8.197	6.021
		SEM	7.920	8.595	8.892
		95% CI	(-17.9,13.5)	(-25.3, 8.9)	(-11.5,23.6)
		Pr >  t			0.4993
	Week 96	n	5	6	
		LS Mean	4.166	-2.679	6.845
		SEM	8.571	8.859	9.721
		95% CI	(-12.8,21.1)	(-20.3,14.9)	(-12.3,26.0)
		Pr >  t			0.4823
	Week 108	n	4	6	
		LS Mean	2.126	-8.232	10.358
		SEM	9.107	8.859	10.19
		95% CI	(-15.9,20.1)	(-25.9, 9.4)	(-9.7,30.5)
		Pr >  t			0.3106
	Week 120	n	4	4	
		LS Mean	-14.43	-4.496	-9.938
		SEM	9.110	9.718	10.95
		95% CI	(-32.4, 3.6)	(-23.8,14.8)	(-31.5,11.7)
		Pr >  t			0.3653
	Week 132	n	3	1	
		LS Mean	-3.701	-44.03	40.326
		SEM	9.919	15.24	16.53
		95% CI	(-23.3,15.9)	(-74.1, -14)	( 7.7,72.9)
		Pr >  t			0.0156
	Week 144	n	1	1	
		LS Mean	-47.96	9.299	-57.26
		SEM	14.87	15.28	19.93

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-77.3, -19)	(-20.8, 39.4)	(-96.6, -18)
		Pr >  t			0.0045
	Week 16	n	35	37	
		LS Mean	-22.52	-19.02	-3.497
	Week 24	SEM	8.682	9.134	3.983
		95% CI	(-39.6, -5.4)	(-37.0, -1.0)	(-11.3, 4.4)
	Week 32	Pr >  t			0.3809
		n	34	30	
	Week 40	LS Mean	-21.93	-21.08	-0.850
		SEM	8.993	9.226	4.173
	Week 48	95% CI	(-39.7, -4.2)	(-39.3, -2.9)	(-9.1, 7.4)
		Pr >  t			0.8388
	Week 56	n	32	23	
		LS Mean	-20.48	-16.60	-3.883
	Week 64	SEM	9.018	9.343	4.487
		95% CI	(-38.3, -2.7)	(-35.0, 1.8)	(-12.7, 5.0)
	Week 8	Pr >  t			0.3876
		n	21	22	
	Week 16	LS Mean	-17.95	-13.85	-4.098
		SEM	9.193	9.364	4.914
	Week 24	95% CI	(-36.1, 0.2)	(-32.3, 4.6)	(-13.8, 5.6)
		Pr >  t			0.4050
	Week 32	n	20	20	
		LS Mean	-23.39	-19.68	-3.705
	Week 40	SEM	9.230	9.418	5.061
		95% CI	(-41.6, -5.2)	(-38.2, -1.1)	(-13.7, 6.3)
	Week 48	Pr >  t			0.4646
		n	19	12	
Week 56	LS Mean	-20.89	-18.71	-2.178	
	SEM	9.248	9.774	5.734	
Week 64	95% CI	(-39.1, -2.7)	(-38.0, 0.5)	(-13.5, 9.1)	
	Pr >  t			0.7042	
Week 8	n	16	8		
	LS Mean	-18.59	-15.63	-2.957	
Week 16	SEM	9.353	10.20	6.568	
	95% CI	(-37.0, -0.2)	(-35.7, 4.5)	(-15.9, 10.0)	
Week 24	Pr >  t			0.6529	
	n	12	11		
Week 32	LS Mean	-17.94	-21.14	3.199	
	SEM	9.571	9.868	6.364	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-36.8, 0.9)	(-40.6, -1.7)	(-9.3, 15.7)
		Pr >  t			0.6155
	Week 72	n	13	7	
		LS Mean	-21.41	-21.18	-0.230
		SEM	9.519	10.36	7.037
		95% CI	(-40.2, -2.7)	(-41.6, -0.8)	(-14.1, 13.6)
		Pr >  t			0.9740
	Week 84	n	12	6	
		LS Mean	-17.01	-28.57	11.560
		SEM	9.563	10.60	7.442
		95% CI	(-35.8, 1.8)	(-49.4, -7.7)	(-3.1, 26.2)
		Pr >  t			0.1211
	Week 96	n	7	6	
		LS Mean	-17.30	-24.10	6.801
		SEM	10.15	10.58	8.170
		95% CI	(-37.3, 2.7)	(-44.9, -3.3)	(-9.3, 22.9)
		Pr >  t			0.4057
	Week 108	n	5	3	
		LS Mean	-19.90	-18.60	-1.299
		SEM	10.68	12.01	10.47
		95% CI	(-40.9, 1.1)	(-42.2, 5.0)	(-21.9, 19.3)
		Pr >  t			0.9014
	Week 120	n	8	3	
		LS Mean	-29.43	-15.82	-13.61
		SEM	10.02	12.01	9.777
		95% CI	(-49.2, -9.7)	(-39.4, 7.8)	(-32.8, 5.6)
		Pr >  t			0.1647
	Week 132	n	2	1	
		LS Mean	-34.99	-24.49	-10.50
		SEM	13.06	16.46	17.10
		95% CI	(-60.7, -9.3)	(-56.8, 7.9)	(-44.1, 23.1)
		Pr >  t			0.5396
	Week 144	n	2		
		LS Mean	-22.30		
		SEM	13.08		
		95% CI	(-48.0, 3.4)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	-22.30		
		SEM	13.08		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-48.0, 3.4)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	-0.659	1.778	-2.437
		SEM	2.788	2.913	2.774
		95% CI	(-6.2, 4.8)	(-4.0, 7.5)	(-7.9, 3.0)
		Pr >  t			0.3803
	Week 16	n	70	52	
		LS Mean	-2.983	0.952	-3.935
		SEM	2.868	3.079	2.974
		95% CI	(-8.6, 2.7)	(-5.1, 7.0)	(-9.8, 1.9)
		Pr >  t			0.1866
	Week 24	n	54	40	
		LS Mean	-3.273	-2.277	-0.996
		SEM	3.003	3.273	3.272
		95% CI	(-9.2, 2.6)	(-8.7, 4.2)	(-7.4, 5.4)
		Pr >  t			0.7610
	Week 32	n	50	36	
		LS Mean	-3.638	-1.243	-2.395
		SEM	3.059	3.343	3.381
		95% CI	(-9.7, 2.4)	(-7.8, 5.3)	(-9.0, 4.2)
		Pr >  t			0.4791
	Week 40	n	42	28	
		LS Mean	-2.139	-0.507	-1.632
		SEM	3.158	3.547	3.656
		95% CI	(-8.4, 4.1)	(-7.5, 6.5)	(-8.8, 5.5)
		Pr >  t			0.6556
	Week 48	n	38	24	
		LS Mean	-5.293	1.877	-7.170
		SEM	3.219	3.679	3.836
		95% CI	(-11.6, 1.0)	(-5.4, 9.1)	(-14.7, 0.4)
		Pr >  t			0.0621
	Week 56	n	33	24	
		LS Mean	-3.178	0.388	-3.566
		SEM	3.312	3.681	3.921
		95% CI	(-9.7, 3.3)	(-6.8, 7.6)	(-11.3, 4.1)
		Pr >  t			0.3635
	Week 64	n	27	19	
		LS Mean	-3.778	-0.620	-3.157
		SEM	3.461	3.908	4.258

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.6, 3.0)	(-8.3, 7.1)	(-11.5, 5.2)
		Pr >  t			0.4587
	Week 72	n	26	17	
		LS Mean	-4.041	-0.172	-3.869
		SEM	3.492	4.026	4.392
		95% CI	(-10.9, 2.8)	(-8.1, 7.7)	(-12.5, 4.8)
		Pr >  t			0.3786
	Week 84	n	18	16	
		LS Mean	-2.911	3.468	-6.379
		SEM	3.863	4.097	4.738
		95% CI	(-10.5, 4.7)	(-4.6, 11.5)	(-15.7, 2.9)
		Pr >  t			0.1785
	Week 96	n	20	10	
		LS Mean	-5.874	-1.272	-4.602
		SEM	3.744	4.738	5.225
		95% CI	(-13.2, 1.5)	(-10.6, 8.0)	(-14.9, 5.7)
		Pr >  t			0.3787
	Week 108	n	14	10	
		LS Mean	-1.957	-0.424	-1.533
		SEM	4.165	4.738	5.527
		95% CI	(-10.1, 6.2)	(-9.7, 8.9)	(-12.4, 9.3)
		Pr >  t			0.7815
	Week 120	n	14	7	
		LS Mean	4.162	-2.637	6.799
		SEM	4.149	5.374	6.079
		95% CI	(-4.0, 12.3)	(-13.2, 7.9)	(-5.1, 18.7)
		Pr >  t			0.2637
	Week 132	n	12	5	
		LS Mean	3.278	-3.987	7.264
		SEM	4.371	6.117	6.875
		95% CI	(-5.3, 11.9)	(-16.0, 8.0)	(-6.2, 20.8)
		Pr >  t			0.2910
	Week 144	n	11	4	
		LS Mean	-4.766	3.771	-8.538
		SEM	4.481	6.699	7.472
		95% CI	(-13.6, 4.0)	(-9.4, 16.9)	(-23.2, 6.1)
		Pr >  t			0.2535
	Week 156	n	8	3	
		LS Mean	-0.384	-5.256	4.872
		SEM	5.027	7.564	8.557

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168		95% CI	(-10.3, 9.5)	(-20.1, 9.6)	(-11.9,21.7)
		Pr >  t			0.5693
		n	4	2	
		LS Mean	-2.562	6.387	-8.949
		SEM	6.617	9.049	10.79
Week 180		95% CI	(-15.5,10.4)	(-11.4,24.2)	(-30.1,12.2)
		Pr >  t			0.4072
		n	1	1	
		LS Mean	-15.97	2.980	-18.95
		SEM	12.44	12.47	17.35
Week 192		95% CI	(-40.4, 8.4)	(-21.5,27.5)	(-53.0,15.1)
		Pr >  t			0.2751
		n	1	1	
		LS Mean	0.698	2.980	-2.282
		SEM	12.44	12.47	17.35
	95% CI	(-23.7,25.1)	(-21.5,27.5)	(-36.3,31.8)	
	Pr >  t			0.8954	

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64	
			LS Mean	-0.659	1.778	-2.437
			SEM	2.788	2.913	2.774
			95% CI	(-6.2, 4.8)	(-4.0, 7.5)	(-7.9, 3.0)
		Pr >  t			0.3803	
		Week 16	n	70	52	
			LS Mean	-2.983	0.952	-3.935
			SEM	2.868	3.079	2.974
			95% CI	(-8.6, 2.7)	(-5.1, 7.0)	(-9.8, 1.9)
		Pr >  t			0.1866	
		Week 24	n	54	40	
			LS Mean	-3.273	-2.277	-0.996
			SEM	3.003	3.273	3.272
			95% CI	(-9.2, 2.6)	(-8.7, 4.2)	(-7.4, 5.4)
		Pr >  t			0.7610	
		Week 32	n	50	36	
			LS Mean	-3.638	-1.243	-2.395
			SEM	3.059	3.343	3.381
			95% CI	(-9.7, 2.4)	(-7.8, 5.3)	(-9.0, 4.2)
		Pr >  t			0.4791	
		Week 40	n	42	28	
			LS Mean	-2.139	-0.507	-1.632
			SEM	3.158	3.547	3.656
			95% CI	(-8.4, 4.1)	(-7.5, 6.5)	(-8.8, 5.5)
		Pr >  t			0.6556	
		Week 48	n	38	24	
			LS Mean	-5.293	1.877	-7.170
			SEM	3.219	3.679	3.836
95% CI	(-11.6, 1.0)		(-5.4, 9.1)	(-14.7, 0.4)		
Pr >  t			0.0621			
Week 56	n	33	24			
	LS Mean	-3.178	0.388	-3.566		
	SEM	3.312	3.681	3.921		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.7, 3.3)	(-6.8, 7.6)	(-11.3, 4.1)
		Pr >  t			0.3635
	Week 64	n	27	19	
		LS Mean	-3.778	-0.620	-3.157
		SEM	3.461	3.908	4.258
		95% CI	(-10.6, 3.0)	(-8.3, 7.1)	(-11.5, 5.2)
		Pr >  t			0.4587
	Week 72	n	26	17	
		LS Mean	-4.041	-0.172	-3.869
		SEM	3.492	4.026	4.392
		95% CI	(-10.9, 2.8)	(-8.1, 7.7)	(-12.5, 4.8)
		Pr >  t			0.3786
	Week 84	n	18	16	
		LS Mean	-2.911	3.468	-6.379
		SEM	3.863	4.097	4.738
		95% CI	(-10.5, 4.7)	(-4.6, 11.5)	(-15.7, 2.9)
		Pr >  t			0.1785
	Week 96	n	20	10	
		LS Mean	-5.874	-1.272	-4.602
		SEM	3.744	4.738	5.225
		95% CI	(-13.2, 1.5)	(-10.6, 8.0)	(-14.9, 5.7)
		Pr >  t			0.3787
	Week 108	n	14	10	
		LS Mean	-1.957	-0.424	-1.533
		SEM	4.165	4.738	5.527
		95% CI	(-10.1, 6.2)	(-9.7, 8.9)	(-12.4, 9.3)
		Pr >  t			0.7815
	Week 120	n	14	7	
		LS Mean	4.162	-2.637	6.799
		SEM	4.149	5.374	6.079
		95% CI	(-4.0, 12.3)	(-13.2, 7.9)	(-5.1, 18.7)
		Pr >  t			0.2637
	Week 132	n	12	5	
		LS Mean	3.278	-3.987	7.264
		SEM	4.371	6.117	6.875
		95% CI	(-5.3, 11.9)	(-16.0, 8.0)	(-6.2, 20.8)
		Pr >  t			0.2910
	Week 144	n	11	4	
		LS Mean	-4.766	3.771	-8.538
		SEM	4.481	6.699	7.472

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	(-13.6, 4.0)	(-9.4,16.9)	(-23.2, 6.1)
		Pr >  t			0.2535
		n	8	3	
		LS Mean	-0.384	-5.256	4.872
	Week 168	SEM	5.027	7.564	8.557
		95% CI	(-10.3, 9.5)	(-20.1, 9.6)	(-11.9,21.7)
		Pr >  t			0.5693
		n	4	2	
	Week 180	LS Mean	-2.562	6.387	-8.949
		SEM	6.617	9.049	10.79
		95% CI	(-15.5,10.4)	(-11.4,24.2)	(-30.1,12.2)
		Pr >  t			0.4072
Week 192	n	1	1		
	LS Mean	-15.97	2.980	-18.95	
	SEM	12.44	12.47	17.35	
	95% CI	(-40.4, 8.4)	(-21.5,27.5)	(-53.0,15.1)	
Week 8	Pr >  t			0.2751	
	n	1	1		
	LS Mean	0.698	2.980	-2.282	
	SEM	12.44	12.47	17.35	
Week 16	95% CI	(-23.7,25.1)	(-21.5,27.5)	(-36.3,31.8)	
	Pr >  t			0.8954	
	n	53	64		
	LS Mean	-6.106	-3.960	-2.146	
Week 24	SEM	4.724	5.070	3.341	
	95% CI	(-15.4, 3.2)	(-14.0, 6.1)	(-8.7, 4.4)	
	Pr >  t			0.5211	
	n	48	48		
Week 32	LS Mean	-3.058	-6.515	3.456	
	SEM	4.841	5.199	3.596	
	95% CI	(-12.6, 6.5)	(-16.8, 3.8)	(-3.6,10.5)	
	Pr >  t			0.3371	
Week 8	n	46	36		
	LS Mean	-4.739	0.409	-5.148	
	SEM	4.860	5.343	3.839	
	95% CI	(-14.3, 4.9)	(-10.1,11.0)	(-12.7, 2.4)	
Week 16	Pr >  t			0.1807	
	n	31	33		
	LS Mean	-2.231	-2.335	0.103	
Week 24	SEM	5.186	5.397	4.192	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-12.5, 8.0)	(-13.0, 8.3)	(-8.1, 8.3)
	Pr >  t			0.9804
	n	28	30	
	LS Mean	-6.681	-5.246	-1.435
	SEM	5.258	5.457	4.351
Week 48	95% CI	(-17.0, 3.7)	(-16.0, 5.5)	(-10.0, 7.1)
	Pr >  t			0.7417
	n	26	23	
	LS Mean	-3.576	-6.728	3.152
	SEM	5.306	5.647	4.649
Week 56	95% CI	(-14.0, 6.9)	(-17.9, 4.4)	(-6.0, 12.3)
	Pr >  t			0.4980
	n	22	17	
	LS Mean	-1.824	-1.601	-0.223
	SEM	5.433	5.917	5.112
Week 64	95% CI	(-12.5, 8.9)	(-13.3, 10.1)	(-10.3, 9.8)
	Pr >  t			0.9652
	n	17	19	
	LS Mean	0.158	-4.960	5.118
	SEM	5.668	5.814	5.245
Week 72	95% CI	(-11.0, 11.3)	(-16.4, 6.5)	(-5.2, 15.4)
	Pr >  t			0.3295
	n	20	14	
	LS Mean	-3.294	-3.525	0.231
	SEM	5.521	6.125	5.438
Week 84	95% CI	(-14.2, 7.6)	(-15.6, 8.5)	(-10.4, 10.9)
	Pr >  t			0.9661
	n	19	13	
	LS Mean	-2.344	-9.915	7.570
	SEM	5.560	6.214	5.581
Week 96	95% CI	(-13.3, 8.6)	(-22.1, 2.3)	(-3.4, 18.5)
	Pr >  t			0.1755
	n	12	12	
	LS Mean	0.066	-5.183	5.249
	SEM	6.071	6.313	6.192
Week 108	95% CI	(-11.9, 12.0)	(-17.6, 7.2)	(-6.9, 17.4)
	Pr >  t			0.3969
	n	9	9	
Week 108	LS Mean	-2.288	-5.834	3.545
	SEM	6.497	6.727	7.004

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.1,10.5)	(-19.1, 7.4)	(-10.2,17.3)
		Pr >  t			0.6129
	Week 120	n	12	7	
		LS Mean	-14.19	-2.171	-12.02
		SEM	6.087	7.172	7.069
		95% CI	(-26.2,-2.2)	(-16.3,11.9)	(-25.9, 1.9)
		Pr >  t			0.0897
	Week 132	n	5	2	
		LS Mean	-11.48	-25.98	14.494
		SEM	7.686	10.92	11.83
		95% CI	(-26.6, 3.6)	(-47.4,-4.5)	( -8.7,37.7)
		Pr >  t			0.2211
	Week 144	n	3	1	
		LS Mean	-21.09	10.813	-31.90
		SEM	9.203	14.68	16.18
		95% CI	(-39.2,-3.0)	(-18.0,39.6)	(-63.7,-0.1)
		Pr >  t			0.0492
	Week 156	n	2		
		LS Mean	-6.685		
		SEM	10.81		
		95% CI	(-27.9,14.5)		
		Pr >  t			

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-36: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Körperliche Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	-3.106	-0.784	-2.322		
			SEM	2.270	2.405	2.175		
			95% CI	(-7.6, 1.4)	(-5.5, 4.0)	(-6.6, 2.0)		
					Pr >  t			0.2865
		Week 16	n	86	68			
			LS Mean	-1.472	-2.133	0.661		
			SEM	2.310	2.480	2.297		
			95% CI	(-6.0, 3.1)	(-7.0, 2.7)	(-3.9, 5.2)		
					Pr >  t			0.7736
		Week 24	n	73	48			
			LS Mean	-3.819	-1.068	-2.751		
			SEM	2.359	2.621	2.489		
			95% CI	(-8.5, 0.8)	(-6.2, 4.1)	(-7.6, 2.1)		
					Pr >  t			0.2696
		Week 32	n	60	43			
			LS Mean	-2.249	-3.052	0.803		
			SEM	2.438	2.674	2.595		
			95% CI	(-7.0, 2.5)	(-8.3, 2.2)	(-4.3, 5.9)		
					Pr >  t			0.7571
		Week 40	n	50	38			
			LS Mean	-0.214	-2.121	1.907		
			SEM	2.502	2.733	2.709		
			95% CI	(-5.1, 4.7)	(-7.5, 3.3)	(-3.4, 7.2)		
			Pr >  t			0.4818		
Week 48	n	48	31					
	LS Mean	-4.047	-1.889	-2.158				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	2.517	2.832	2.824
	95% CI	(-9.0, 0.9)	(-7.5, 3.7)	(-7.7, 3.4)
	Pr >  t			0.4449
Week 56	n	41	25	
	LS Mean	-2.652	-2.402	-0.250
	SEM	2.579	2.953	3.000
	95% CI	(-7.7, 2.4)	(-8.2, 3.4)	(-6.1, 5.6)
	Pr >  t			0.9336
Week 64	n	30	24	
	LS Mean	-3.365	0.100	-3.465
	SEM	2.723	2.979	3.152
	95% CI	(-8.7, 2.0)	(-5.8, 6.0)	(-9.7, 2.7)
	Pr >  t			0.2720
Week 72	n	32	19	
	LS Mean	-3.390	-0.402	-2.988
	SEM	2.691	3.136	3.275
	95% CI	(-8.7, 1.9)	(-6.6, 5.8)	(-9.4, 3.4)
	Pr >  t			0.3618
Week 84	n	26	19	
	LS Mean	-4.696	-1.080	-3.616
	SEM	2.812	3.137	3.369
	95% CI	(-10.2, 0.8)	(-7.2, 5.1)	(-10.2, 3.0)
	Pr >  t			0.2834
Week 96	n	23	14	
	LS Mean	-2.525	-4.214	1.689
	SEM	2.884	3.386	3.662
	95% CI	(-8.2, 3.1)	(-10.9, 2.4)	(-5.5, 8.9)
	Pr >  t			0.6448
Week 108	n	19	13	
	LS Mean	-3.257	-4.032	0.775
	SEM	3.023	3.455	3.831
	95% CI	(-9.2, 2.7)	(-10.8, 2.8)	(-6.7, 8.3)
	Pr >  t			0.8397
Week 120	n	19	11	
	LS Mean	-3.120	0.729	-3.849
	SEM	3.016	3.626	3.985
	95% CI	(-9.0, 2.8)	(-6.4, 7.8)	(-11.7, 4.0)
	Pr >  t			0.3343
Week 132	n	15	5	
	LS Mean	-7.808	-7.532	-0.276

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	3.213	4.732	5.131
		95% CI	(-14.1,-1.5)	(-16.8, 1.8)	(-10.3, 9.8)
		Pr >  t			0.9570
	Week 144	n	12	3	
		LS Mean	-7.928	-1.658	-6.270
		SEM	3.419	5.811	6.254
		95% CI	(-14.6,-1.2)	(-13.1, 9.7)	(-18.5, 6.0)
		Pr >  t			0.3164
	Week 156	n	7	2	
		LS Mean	-3.131	-1.753	-1.378
		SEM	4.095	6.911	7.625
		95% CI	(-11.2, 4.9)	(-15.3,11.8)	(-16.3,13.6)
		Pr >  t			0.8566
	Week 168	n	3	1	
		LS Mean	-0.152	3.583	-3.735
		SEM	5.725	9.484	10.78
		95% CI	(-11.4,11.1)	(-15.0,22.2)	(-24.9,17.4)
		Pr >  t			0.7292
	Week 180	n	1	1	
		LS Mean	-6.791	-3.087	-3.704
		SEM	9.435	9.484	13.14
		95% CI	(-25.3,11.7)	(-21.7,15.5)	(-29.5,22.1)
		Pr >  t			0.7780
	Week 192	n	1	1	
		LS Mean	-20.13	-3.087	-17.04
		SEM	9.435	9.484	13.14
		95% CI	(-38.6,-1.6)	(-21.7,15.5)	(-42.8, 8.7)
		Pr >  t			0.1948
Yes	Week 8	n	44	56	
		LS Mean	-4.339	-6.472	2.133
		SEM	5.104	4.876	3.187
		95% CI	(-14.4, 5.7)	(-16.1, 3.2)	( -4.2, 8.4)
		Pr >  t			0.5043
	Week 16	n	38	39	
		LS Mean	-6.681	-5.568	-1.114
		SEM	5.231	5.127	3.460
		95% CI	(-17.0, 3.6)	(-15.7, 4.5)	( -7.9, 5.7)
		Pr >  t			0.7479
	Week 24	n	32	33	
		LS Mean	-4.552	-11.38	6.829



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	5.298	5.187	3.648
	95% CI	(-15.0, 5.9)	(-21.6,-1.1)	(-0.4,14.0)
	Pr >  t			0.0624
Week 32	n	26	30	
	LS Mean	-3.337	-7.872	4.535
	SEM	5.384	5.232	3.829
	95% CI	(-14.0, 7.3)	(-18.2, 2.4)	(-3.0,12.1)
	Pr >  t			0.2373
Week 40	n	25	24	
	LS Mean	-4.056	-10.96	6.908
	SEM	5.403	5.327	3.987
	95% CI	(-14.7, 6.6)	(-21.5,-0.5)	(-0.9,14.8)
	Pr >  t			0.0841
Week 48	n	21	20	
	LS Mean	-5.843	-12.31	6.469
	SEM	5.481	5.422	4.213
	95% CI	(-16.7, 5.0)	(-23.0,-1.6)	(-1.8,14.8)
	Pr >  t			0.1256
Week 56	n	18	20	
	LS Mean	-2.950	-8.372	5.422
	SEM	5.564	5.420	4.321
	95% CI	(-13.9, 8.0)	(-19.1, 2.3)	(-3.1,13.9)
	Pr >  t			0.2103
Week 64	n	17	18	
	LS Mean	-4.689	-9.786	5.098
	SEM	5.599	5.481	4.438
	95% CI	(-15.7, 6.3)	(-20.6, 1.0)	(-3.6,13.8)
	Pr >  t			0.2514
Week 72	n	16	16	
	LS Mean	-3.339	-9.156	5.818
	SEM	5.638	5.554	4.575
	95% CI	(-14.4, 7.8)	(-20.1, 1.8)	(-3.2,14.8)
	Pr >  t			0.2042
Week 84	n	14	14	
	LS Mean	-4.972	-7.565	2.592
	SEM	5.723	5.642	4.784
	95% CI	(-16.2, 6.3)	(-18.7, 3.5)	(-6.8,12.0)
	Pr >  t			0.5881
Week 96	n	12	10	
	LS Mean	-6.118	-9.553	3.435

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.839	5.917	5.235
		95% CI	(-17.6, 5.4)	(-21.2, 2.1)	(-6.8,13.7)
		Pr >  t			0.5120
	Week 108	n	7	8	
		LS Mean	-7.340	-12.23	4.890
		SEM	6.372	6.147	6.058
		95% CI	(-19.9, 5.2)	(-24.3,-0.1)	(-7.0,16.8)
		Pr >  t			0.4199
	Week 120	n	9	5	
		LS Mean	-7.275	-8.548	1.273
		SEM	6.105	6.786	6.451
		95% CI	(-19.3, 4.7)	(-21.9, 4.8)	(-11.4,13.9)
		Pr >  t			0.8436
	Week 132	n	5	3	
		LS Mean	-5.673	-6.284	0.611
		SEM	6.842	7.773	8.097
		95% CI	(-19.1, 7.8)	(-21.6, 9.0)	(-15.3,16.5)
		Pr >  t			0.9399
	Week 144	n	3	2	
		LS Mean	-11.83	-6.234	-5.594
		SEM	7.820	8.862	9.902
		95% CI	(-27.2, 3.5)	(-23.6,11.2)	(-25.0,13.9)
		Pr >  t			0.5724
	Week 156	n	3	1	
		LS Mean	-8.661	-4.332	-4.329
		SEM	7.827	11.51	12.34
		95% CI	(-24.0, 6.7)	(-26.9,18.3)	(-28.6,19.9)
		Pr >  t			0.7258
	Week 168	n	1	1	
		LS Mean	-4.547	-4.332	-0.216
		SEM	11.58	11.51	15.00
		95% CI	(-27.3,18.2)	(-26.9,18.3)	(-29.7,29.3)
		Pr >  t			0.9885

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	-2.049	-2.173	0.124		
			SEM	2.505	2.497	2.150		
			95% CI	(-7.0, 2.9)	(-7.1, 2.7)	(-4.1, 4.4)		
					Pr >  t			0.9539
				Week 16	n	92	83	
					LS Mean	-2.079	-2.225	0.146
					SEM	2.558	2.612	2.292
					95% CI	(-7.1, 3.0)	(-7.4, 2.9)	(-4.4, 4.7)
					Pr >  t			0.9492
				Week 24	n	77	59	
					LS Mean	-3.993	-5.100	1.107
					SEM	2.603	2.737	2.478
					95% CI	(-9.1, 1.1)	(-10.5, 0.3)	(-3.8, 6.0)
					Pr >  t			0.6551
				Week 32	n	57	53	
					LS Mean	-1.903	-5.058	3.155
					SEM	2.721	2.777	2.626
					95% CI	(-7.3, 3.4)	(-10.5, 0.4)	(-2.0, 8.3)
					Pr >  t			0.2300
				Week 40	n	50	44	
					LS Mean	-0.436	-5.935	5.499
					SEM	2.771	2.861	2.758
					95% CI	(-5.9, 5.0)	(-11.6,-0.3)	( 0.1,10.9)
			Pr >  t			0.0466		
		Week 48	n	47	37			
			LS Mean	-4.772	-6.926	2.154		
			SEM	2.794	2.942	2.865		
			95% CI	(-10.3, 0.7)	(-12.7,-1.1)	(-3.5, 7.8)		
			Pr >  t			0.4523		
		Week 56	n	40	32			
			LS Mean	-2.740	-4.737	1.997		
			SEM	2.862	3.017	3.007		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.4, 2.9)	(-10.7, 1.2)	(-3.9, 7.9)
	Pr >  t			0.5068
	n	32	27	
	LS Mean	-2.562	-3.907	1.345
Week 72	SEM	2.972	3.116	3.208
	95% CI	(-8.4, 3.3)	(-10.0, 2.2)	(-5.0, 7.6)
	Pr >  t			0.6752
	n	31	23	
Week 84	LS Mean	-3.210	-4.216	1.006
	SEM	2.991	3.220	3.326
	95% CI	(-9.1, 2.7)	(-10.5, 2.1)	(-5.5, 7.5)
	Pr >  t			0.7624
Week 96	n	27	21	
	LS Mean	-2.803	-4.077	1.274
	SEM	3.071	3.285	3.457
	95% CI	(-8.8, 3.2)	(-10.5, 2.4)	(-5.5, 8.1)
Week 108	Pr >  t			0.7125
	n	23	16	
	LS Mean	-3.476	-6.363	2.887
	SEM	3.170	3.505	3.755
Week 120	95% CI	(-9.7, 2.8)	(-13.2, 0.5)	(-4.5, 10.3)
	Pr >  t			0.4420
	n	15	14	
	LS Mean	-4.344	-8.402	4.057
Week 132	SEM	3.518	3.630	4.158
	95% CI	(-11.3, 2.6)	(-15.5, -1.3)	(-4.1, 12.2)
	Pr >  t			0.3293
	n	18	8	
Week 144	LS Mean	-5.063	-6.660	1.596
	SEM	3.358	4.301	4.642
	95% CI	(-11.7, 1.5)	(-15.1, 1.8)	(-7.5, 10.7)
	Pr >  t			0.7310
Week 132	n	12	4	
	LS Mean	-5.734	-8.740	3.006
	SEM	3.744	5.541	6.039
	95% CI	(-13.1, 1.6)	(-19.6, 2.1)	(-8.8, 14.9)
Week 144	Pr >  t			0.6187
	n	8	3	
	LS Mean	-8.806	-3.311	-5.495
	SEM	4.244	6.243	6.988

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.1,-0.5)	(-15.6, 8.9)	(-19.2, 8.2)
		Pr >  t			0.4318
	Week 156	n	5	1	
		LS Mean	-6.774	-0.651	-6.123
		SEM	5.044	10.20	11.01
		95% CI	(-16.7, 3.1)	(-20.7,19.4)	(-27.7,15.5)
		Pr >  t			0.5783
	Week 168	n	2	1	
		LS Mean	1.996	-0.651	2.647
		SEM	7.410	10.20	12.28
		95% CI	(-12.5,16.5)	(-20.7,19.4)	(-21.4,26.7)
		Pr >  t			0.8293
	Week 180	n	1		
		LS Mean	-7.000		
		SEM	10.17		
		95% CI	(-27.0,13.0)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-20.34		
		SEM	10.17		
		95% CI	(-40.3,-0.4)		
		Pr >  t			
Yes	Week 8	n	38	30	
		LS Mean	-4.310	-1.308	-3.002
		SEM	3.789	4.064	3.271
		95% CI	(-11.8, 3.2)	( -9.4, 6.8)	( -9.5, 3.5)
		Pr >  t			0.3603
	Week 16	n	32	24	
		LS Mean	-2.703	-3.433	0.729
		SEM	3.839	4.151	3.499
		95% CI	(-10.3, 4.9)	(-11.7, 4.8)	( -6.2, 7.6)
		Pr >  t			0.8351
	Week 24	n	28	22	
		LS Mean	-1.279	-1.752	0.473
		SEM	3.934	4.201	3.619
		95% CI	( -9.1, 6.5)	(-10.1, 6.6)	( -6.7, 7.6)
		Pr >  t			0.8961
	Week 32	n	29	20	
		LS Mean	-1.551	-0.892	-0.659
		SEM	3.922	4.296	3.666

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-9.3, 6.2)	(-9.4, 7.6)	(-7.9, 6.6)
	Pr >  t			0.8574
	n	25	18	
Week 48	LS Mean	-1.105	-1.334	0.229
	SEM	3.982	4.344	3.797
	95% CI	(-9.0, 6.8)	(-9.9, 7.3)	(-7.3, 7.7)
Week 56	Pr >  t			0.9520
	n	22	14	
	LS Mean	-1.745	-0.108	-1.637
Week 64	SEM	4.037	4.498	4.032
	95% CI	(-9.7, 6.3)	(-9.0, 8.8)	(-9.6, 6.3)
	Pr >  t			0.6851
Week 72	n	19	13	
	LS Mean	-0.367	-1.205	0.838
	SEM	4.105	4.551	4.167
Week 84	95% CI	(-8.5, 7.8)	(-10.2, 7.8)	(-7.4, 9.0)
	Pr >  t			0.8408
	n	15	15	
Week 96	LS Mean	-3.802	-0.537	-3.265
	SEM	4.237	4.456	4.203
	95% CI	(-12.2, 4.6)	(-9.4, 8.3)	(-11.5, 5.0)
Week 108	Pr >  t			0.4379
	n	17	12	
	LS Mean	-1.231	-0.155	-1.076
Week 84	SEM	4.165	4.607	4.290
	95% CI	(-9.5, 7.0)	(-9.3, 9.0)	(-9.5, 7.4)
	Pr >  t			0.8021
Week 96	n	13	12	
	LS Mean	-6.204	0.496	-6.700
	SEM	4.360	4.609	4.460
Week 108	95% CI	(-14.8, 2.4)	(-8.6, 9.6)	(-15.5, 2.1)
	Pr >  t			0.1340
	n	12	8	
Week 84	LS Mean	-1.782	-2.834	1.052
	SEM	4.421	4.964	4.880
	95% CI	(-10.5, 7.0)	(-12.6, 7.0)	(-8.5, 10.6)
Week 96	Pr >  t			0.8295
	n	11	7	
	LS Mean	-2.619	-1.754	-0.865
Week 108	SEM	4.490	5.104	5.089

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.5, 6.3)	(-11.8, 8.3)	(-10.9, 9.1)
		Pr >  t			0.8651
	Week 120	n	10	8	
		LS Mean	-1.053	4.525	-5.577
		SEM	4.572	4.961	5.018
		95% CI	(-10.1, 8.0)	(-5.3, 14.3)	(-15.4, 4.3)
		Pr >  t			0.2670
	Week 132	n	8	4	
		LS Mean	-7.866	-2.211	-5.655
		SEM	4.783	5.889	6.102
		95% CI	(-17.3, 1.6)	(-13.8, 9.4)	(-17.6, 6.3)
		Pr >  t			0.3546
	Week 144	n	7	2	
		LS Mean	-7.333	-0.547	-6.786
		SEM	4.931	7.396	7.663
		95% CI	(-17.1, 2.4)	(-15.1, 14.0)	(-21.8, 8.3)
		Pr >  t			0.3763
	Week 156	n	5	2	
		LS Mean	-1.178	-0.547	-0.631
		SEM	5.375	7.396	7.955
		95% CI	(-11.8, 9.4)	(-15.1, 14.0)	(-16.3, 15.0)
		Pr >  t			0.9368
	Week 168	n	2	1	
		LS Mean	-3.038	4.895	-7.933
		SEM	7.261	9.727	11.27
		95% CI	(-17.3, 11.2)	(-14.2, 24.0)	(-30.1, 14.2)
		Pr >  t			0.4817
	Week 180	n		1	
		LS Mean		-1.775	
		SEM		9.727	
		95% CI		(-20.9, 17.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-1.775	
		SEM		9.727	
		95% CI		(-20.9, 17.3)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis



-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-2.925	-2.051	-0.874		
			SEM	2.087	2.130	1.834		
			95% CI	(-7.0, 1.2)	(-6.2, 2.1)	(-4.5, 2.7)		
					Pr >  t			0.6340
		Week 16	n	119	97			
			LS Mean	-2.643	-2.917	0.274		
			SEM	2.129	2.225	1.965		
			95% CI	(-6.8, 1.5)	(-7.3, 1.5)	(-3.6, 4.1)		
					Pr >  t			0.8893
		Week 24	n	100	75			
			LS Mean	-3.858	-4.199	0.341		
			SEM	2.172	2.307	2.094		
			95% CI	(-8.1, 0.4)	(-8.7, 0.3)	(-3.8, 4.5)		
					Pr >  t			0.8708
		Week 32	n	82	69			
			LS Mean	-2.392	-3.494	1.103		
			SEM	2.236	2.339	2.178		
			95% CI	(-6.8, 2.0)	(-8.1, 1.1)	(-3.2, 5.4)		
					Pr >  t			0.6128
		Week 40	n	73	58			
			LS Mean	-1.201	-4.401	3.201		
			SEM	2.269	2.401	2.273		
			95% CI	(-5.7, 3.3)	(-9.1, 0.3)	(-1.3, 7.7)		
					Pr >  t			0.1596
		Week 48	n	66	48			
			LS Mean	-4.602	-5.058	0.456		
			SEM	2.299	2.471	2.377		
95% CI	(-9.1,-0.1)		(-9.9,-0.2)	(-4.2, 5.1)				
			Pr >  t			0.8478		
Week 56	n	56	43					
	LS Mean	-2.596	-3.257	0.661				
		SEM	2.352	2.518	2.478			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.2, 2.0)	(-8.2, 1.7)	(-4.2, 5.5)
		Pr >  t			0.7897
	Week 64	n	45	41	
		LS Mean	-3.463	-2.926	-0.537
		SEM	2.433	2.539	2.578
		95% CI	(-8.2, 1.3)	(-7.9, 2.1)	(-5.6, 4.5)
		Pr >  t			0.8350
	Week 72	n	46	34	
		LS Mean	-3.052	-3.009	-0.043
		SEM	2.426	2.628	2.658
		95% CI	(-7.8, 1.7)	(-8.2, 2.2)	(-5.3, 5.2)
		Pr >  t			0.9871
	Week 84	n	37	32	
		LS Mean	-4.933	-2.673	-2.261
		SEM	2.526	2.659	2.776
		95% CI	(-9.9, 0.0)	(-7.9, 2.5)	(-7.7, 3.2)
		Pr >  t			0.4155
	Week 96	n	33	23	
		LS Mean	-3.811	-5.478	1.667
		SEM	2.581	2.859	3.017
		95% CI	(-8.9, 1.3)	(-11.1, 0.1)	(-4.3, 7.6)
		Pr >  t			0.5806
	Week 108	n	24	20	
		LS Mean	-4.400	-4.489	0.090
		SEM	2.774	2.960	3.271
		95% CI	(-9.8, 1.0)	(-10.3, 1.3)	(-6.3, 6.5)
		Pr >  t			0.9782
	Week 120	n	25	16	
		LS Mean	-3.989	-1.557	-2.431
		SEM	2.745	3.143	3.417
		95% CI	(-9.4, 1.4)	(-7.7, 4.6)	(-9.1, 4.3)
		Pr >  t			0.4769
	Week 132	n	19	8	
		LS Mean	-7.771	-6.074	-1.697
		SEM	2.942	3.920	4.274
		95% CI	(-13.5,-2.0)	(-13.8, 1.6)	(-10.1, 6.7)
		Pr >  t			0.6914
	Week 144	n	14	5	
		LS Mean	-8.687	-2.386	-6.301
		SEM	3.205	4.690	5.153

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.0,-2.4)	(-11.6, 6.8)	(-16.4, 3.8)
		Pr >  t			0.2216
	Week 156	n	10	3	
		LS Mean	-4.631	-1.925	-2.706
		SEM	3.580	5.800	6.381
		95% CI	(-11.7, 2.4)	(-13.3, 9.5)	(-15.2, 9.8)
		Pr >  t			0.6716
	Week 168	n	4	2	
		LS Mean	-1.194	1.358	-2.552
		SEM	5.093	6.945	8.272
		95% CI	(-11.2, 8.8)	(-12.3,15.0)	(-18.8,13.7)
		Pr >  t			0.7577
	Week 180	n	1	1	
		LS Mean	-7.314	-4.463	-2.851
		SEM	9.565	9.578	13.32
		95% CI	(-26.1,11.4)	(-23.3,14.3)	(-29.0,23.3)
		Pr >  t			0.8306
	Week 192	n	1	1	
		LS Mean	-20.65	-4.463	-16.19
		SEM	9.565	9.578	13.32
		95% CI	(-39.4,-1.9)	(-23.3,14.3)	(-42.3, 9.9)
		Pr >  t			0.2244
Yes	Week 8	n	5	9	
		LS Mean	0.698	-1.488	2.186
		SEM	7.748	5.619	9.597
		95% CI	(-15.1,16.5)	(-12.9, 9.9)	(-17.3,21.7)
		Pr >  t			0.8212
	Week 16	n	5	9	
		LS Mean	3.364	0.552	2.812
		SEM	7.748	5.651	9.641
		95% CI	(-12.4,19.2)	(-10.9,12.0)	(-16.8,22.4)
		Pr >  t			0.7724
	Week 24	n	5	5	
		LS Mean	6.028	-4.536	10.564
		SEM	7.748	7.619	10.94
		95% CI	( -9.8,21.8)	(-19.9,10.8)	(-11.6,32.7)
		Pr >  t			0.3400
	Week 32	n	4	3	
		LS Mean	6.984	-15.41	22.393
		SEM	8.517	9.574	12.90

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-10.3,24.2)	(-34.6, 3.8)	( -3.6,48.4)
	Pr >  t			0.0892
Week 40	n	2	3	
	LS Mean	7.684	-12.14	19.829
	SEM	11.44	9.534	14.83
	95% CI	(-15.3,30.7)	(-31.3, 7.0)	(-10.0,49.6)
	Pr >  t			0.1873
Week 48	n	3	2	
	LS Mean	9.603	-0.561	10.163
	SEM	9.640	11.55	14.89
	95% CI	( -9.8,29.0)	(-23.8,22.6)	(-19.7,40.1)
	Pr >  t			0.4980
Week 56	n	3	1	
	LS Mean	7.379	-35.31	42.692
	SEM	9.640	16.07	18.86
	95% CI	(-12.1,26.8)	(-67.6,-3.0)	( 4.8,80.6)
	Pr >  t			0.0279
Week 64	n	2		
	LS Mean	4.349		
	SEM	11.44		
	95% CI	(-18.6,27.3)		
	Pr >  t			
Week 72	n	2		
	LS Mean	4.742		
	SEM	11.43		
	95% CI	(-18.2,27.7)		
	Pr >  t			
Week 84	n	3		
	LS Mean	9.599		
	SEM	9.640		
	95% CI	( -9.8,29.0)		
	Pr >  t			
Week 96	n	2		
	LS Mean	11.014		
	SEM	11.44		
	95% CI	(-12.0,34.0)		
	Pr >  t			
Week 108	n	2		
	LS Mean	6.382		
	SEM	11.49		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-16.7,29.5)
		Pr >  t		
	Week 120	n	3	
		LS Mean	2.936	
		SEM	9.640	
		95% CI		(-16.5,22.4)
		Pr >  t		
	Week 132	n	1	
		LS Mean	12.654	
		SEM	15.70	
		95% CI		(-18.9,44.2)
		Pr >  t		
	Week 144	n	1	
		LS Mean	-0.676	
		SEM	15.70	
		95% CI		(-32.2,30.9)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-4.551	-3.514	-1.036		
			SEM	2.423	2.518	2.358		
			95% CI	(-9.3, 0.2)	(-8.5, 1.5)	(-5.7, 3.6)		
					Pr >  t			0.6606
		Week 16	n	70	52			
			LS Mean	-2.745	-2.915	0.169		
			SEM	2.466	2.670	2.514		
			95% CI	(-7.6, 2.1)	(-8.2, 2.3)	(-4.8, 5.1)		
					Pr >  t			0.9463
		Week 24	n	61	37			
			LS Mean	-4.536	-5.243	0.707		
			SEM	2.512	2.824	2.699		
			95% CI	(-9.5, 0.4)	(-10.8, 0.3)	(-4.6, 6.0)		
					Pr >  t			0.7936
		Week 32	n	48	33			
			LS Mean	-2.163	-2.474	0.311		
			SEM	2.603	2.876	2.827		
			95% CI	(-7.3, 3.0)	(-8.1, 3.2)	(-5.2, 5.9)		
					Pr >  t			0.9125
		Week 40	n	42	31			
			LS Mean	-2.116	-1.866	-0.249		
			SEM	2.651	2.907	2.903		
			95% CI	(-7.3, 3.1)	(-7.6, 3.9)	(-6.0, 5.5)		
			Pr >  t			0.9316		
Week 48	n	40	25					
	LS Mean	-4.853	-1.849	-3.003				
	SEM	2.669	3.013	3.027				
	95% CI	(-10.1, 0.4)	(-7.8, 4.1)	(-9.0, 2.9)				
			Pr >  t			0.3216		
Week 56	n	35	20					
	LS Mean	-4.277	-3.402	-0.874				
	SEM	2.721	3.147	3.206				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.6, 1.1)	(-9.6, 2.8)	(-7.2, 5.4)
	Pr >  t			0.7852
	n	29	18	
	LS Mean	-4.640	-2.991	-1.650
	SEM	2.802	3.218	3.345
Week 72	95% CI	(-10.2, 0.9)	(-9.3, 3.3)	(-8.2, 4.9)
	Pr >  t			0.6221
	n	28	18	
	LS Mean	-3.383	-2.171	-1.213
	SEM	2.819	3.216	3.359
Week 84	95% CI	(-8.9, 2.2)	(-8.5, 4.2)	(-7.8, 5.4)
	Pr >  t			0.7182
	n	27	17	
	LS Mean	-5.772	-2.061	-3.710
	SEM	2.847	3.257	3.413
Week 96	95% CI	(-11.4,-0.2)	(-8.5, 4.3)	(-10.4, 3.0)
	Pr >  t			0.2774
	n	23	14	
	LS Mean	-5.460	-5.063	-0.398
	SEM	2.929	3.404	3.624
Week 108	95% CI	(-11.2, 0.3)	(-11.8, 1.6)	(-7.5, 6.7)
	Pr >  t			0.9127
	n	19	12	
	LS Mean	-4.334	-7.553	3.219
	SEM	3.054	3.538	3.844
Week 120	95% CI	(-10.3, 1.7)	(-14.5,-0.6)	(-4.3,10.8)
	Pr >  t			0.4026
	n	18	8	
	LS Mean	-6.198	-1.503	-4.695
	SEM	3.084	3.966	4.267
Week 132	95% CI	(-12.3,-0.1)	(-9.3, 6.3)	(-13.1, 3.7)
	Pr >  t			0.2715
	n	11	4	
	LS Mean	-7.212	-5.240	-1.972
	SEM	3.500	5.029	5.521
Week 144	95% CI	(-14.1,-0.3)	(-15.1, 4.6)	(-12.8, 8.9)
	Pr >  t			0.7210
	n	11	4	
	LS Mean	-7.774	-0.466	-7.308
	SEM	3.493	5.033	5.525



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.6,-0.9)	(-10.3, 9.4)	(-18.2, 3.5)
		Pr >  t			0.1862
	Week 156	n	5	2	
		LS Mean	-1.309	1.842	-3.152
		SEM	4.535	6.658	7.605
		95% CI	(-10.2, 7.6)	(-11.2,14.9)	(-18.1,11.8)
		Pr >  t			0.6787
	Week 168	n	1	2	
		LS Mean	-1.391	1.842	-3.234
		SEM	8.993	6.658	10.87
		95% CI	(-19.0,16.3)	(-11.2,14.9)	(-24.6,18.1)
		Pr >  t			0.7662
	Week 180	n		1	
		LS Mean		-3.988	
		SEM		9.060	
		95% CI		(-21.8,13.8)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-3.988	
		SEM		9.060	
		95% CI		(-21.8,13.8)	
		Pr >  t			
>= 65 Years	Week 8	n	63	71	
		LS Mean	0.358	0.456	-0.097
		SEM	3.881	3.869	2.727
		95% CI	(-7.3, 8.0)	(-7.2, 8.1)	(-5.5, 5.3)
		Pr >  t			0.9716
	Week 16	n	54	55	
		LS Mean	-1.020	-0.934	-0.086
		SEM	3.969	3.928	2.920
		95% CI	(-8.9, 6.8)	(-8.7, 6.8)	(-5.8, 5.7)
		Pr >  t			0.9766
	Week 24	n	44	44	
		LS Mean	-0.952	-2.226	1.274
		SEM	4.041	3.998	3.130
		95% CI	(-8.9, 7.0)	(-10.1, 5.7)	(-4.9, 7.4)
		Pr >  t			0.6843
	Week 32	n	38	40	
		LS Mean	-0.691	-4.025	3.334
		SEM	4.125	4.060	3.253

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.8, 7.4)	(-12.0, 4.0)	(-3.1, 9.7)
		Pr >  t			0.3060
	Week 40	n	33	31	
		LS Mean	1.886	-6.273	8.159
		SEM	4.189	4.191	3.465
		95% CI	(-6.4, 10.1)	(-14.5, 2.0)	(1.4, 15.0)
		Pr >  t			0.0189
	Week 48	n	29	26	
		LS Mean	-1.828	-6.957	5.129
		SEM	4.247	4.283	3.645
		95% CI	(-10.2, 6.5)	(-15.4, 1.5)	(-2.0, 12.3)
		Pr >  t			0.1600
	Week 56	n	24	25	
		LS Mean	1.789	-3.007	4.796
		SEM	4.347	4.303	3.786
		95% CI	(-6.8, 10.4)	(-11.5, 5.5)	(-2.6, 12.2)
		Pr >  t			0.2057
	Week 64	n	18	24	
		LS Mean	-0.016	-1.913	1.897
		SEM	4.531	4.327	4.023
		95% CI	(-8.9, 8.9)	(-10.4, 6.6)	(-6.0, 9.8)
		Pr >  t			0.6374
	Week 72	n	20	17	
		LS Mean	-0.818	-2.782	1.964
		SEM	4.463	4.555	4.193
		95% CI	(-9.6, 8.0)	(-11.7, 6.2)	(-6.3, 10.2)
		Pr >  t			0.6397
	Week 84	n	13	16	
		LS Mean	-0.478	-2.135	1.657
		SEM	4.792	4.600	4.589
		95% CI	(-9.9, 8.9)	(-11.2, 6.9)	(-7.4, 10.7)
		Pr >  t			0.7181
	Week 96	n	12	10	
		LS Mean	1.771	-4.408	6.180
		SEM	4.870	5.051	5.115
		95% CI	(-7.8, 11.4)	(-14.3, 5.5)	(-3.9, 16.2)
		Pr >  t			0.2274
	Week 108	n	7	9	
		LS Mean	-2.973	-3.418	0.445
		SEM	5.518	5.173	5.844

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.8, 7.9)	(-13.6, 6.8)	(-11.0,11.9)
		Pr >  t			0.9393
	Week 120	n	10	8	
		LS Mean	0.945	-0.964	1.909
		SEM	5.076	5.326	5.571
		95% CI	(-9.0,10.9)	(-11.4, 9.5)	(-9.0,12.8)
		Pr >  t			0.7320
	Week 132	n	9	4	
		LS Mean	-5.071	-6.232	1.160
		SEM	5.185	6.511	6.797
		95% CI	(-15.3, 5.1)	(-19.0, 6.6)	(-12.2,14.5)
		Pr >  t			0.8645
	Week 144	n	4	1	
		LS Mean	-10.53	-8.731	-1.798
		SEM	6.517	11.25	12.08
		95% CI	(-23.3, 2.3)	(-30.8,13.4)	(-25.5,21.9)
		Pr >  t			0.8817
	Week 156	n	5	1	
		LS Mean	-5.701	-8.731	3.030
		SEM	6.076	11.25	11.85
		95% CI	(-17.6, 6.2)	(-30.8,13.4)	(-20.2,26.3)
		Pr >  t			0.7983
	Week 168	n	3		
		LS Mean	1.464		
		SEM	7.204		
		95% CI	(-12.7,15.6)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-4.863		
		SEM	11.25		
		95% CI	(-26.9,17.2)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-18.20		
		SEM	11.25		
		95% CI	(-40.3, 3.9)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36		
			LS Mean	-3.300	1.796	-5.096	
			SEM	4.456	4.220	3.571	
			95% CI	(-12.2, 5.6)	(-6.6, 10.2)	(-12.2, 2.0)	
					Pr >  t		0.1566
		Week 16	n	30	30		
			LS Mean	-6.907	0.959	-7.866	
			SEM	4.474	4.361	3.713	
			95% CI	(-15.8, 2.0)	(-7.7, 9.6)	(-15.2, -0.5)	
					Pr >  t		0.0363
		Week 24	n	21	26		
			LS Mean	-4.800	-0.389	-4.411	
			SEM	4.634	4.417	3.988	
			95% CI	(-14.0, 4.4)	(-9.2, 8.4)	(-12.3, 3.5)	
					Pr >  t		0.2706
		Week 32	n	19	24		
			LS Mean	-6.460	0.469	-6.929	
			SEM	4.684	4.455	4.098	
			95% CI	(-15.8, 2.9)	(-8.4, 9.3)	(-15.0, 1.2)	
					Pr >  t		0.0929
		Week 40	n	16	19		
			LS Mean	-3.339	-4.416	1.077	
			SEM	4.781	4.604	4.344	
			95% CI	(-12.8, 6.2)	(-13.6, 4.7)	(-7.5, 9.6)	
					Pr >  t		0.8045
		Week 48	n	16	18		
			LS Mean	-5.839	-3.468	-2.371	
			SEM	4.781	4.636	4.376	
95% CI	(-15.3, 3.7)		(-12.7, 5.7)	(-11.0, 6.3)			
			Pr >  t		0.5887		
Week 56	n	12	14				
	LS Mean	-1.977	-2.312	0.334			
	SEM	4.969	4.792	4.753			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.8, 7.9)	(-11.8, 7.2)	(-9.0, 9.7)
		Pr >  t			0.9440
	Week 64	n	12	11	
		LS Mean	-6.421	-4.609	-1.812
		SEM	4.969	4.978	4.939
		95% CI	(-16.3, 3.4)	(-14.5, 5.2)	(-11.5, 7.9)
		Pr >  t			0.7140
	Week 72	n	10	9	
		LS Mean	-3.284	-3.694	0.410
		SEM	5.114	5.165	5.268
		95% CI	(-13.4, 6.8)	(-13.9, 6.5)	(-10.0, 10.8)
		Pr >  t			0.9380
	Week 84	n	8	8	
		LS Mean	-3.443	-6.583	3.140
		SEM	5.362	5.287	5.593
		95% CI	(-14.0, 7.2)	(-17.0, 3.9)	(-7.9, 14.1)
		Pr >  t			0.5749
	Week 96	n	6	6	
		LS Mean	-7.803	-3.824	-3.979
		SEM	5.696	5.630	6.225
		95% CI	(-19.0, 3.4)	(-14.9, 7.3)	(-16.2, 8.3)
		Pr >  t			0.5232
	Week 108	n	4	5	
		LS Mean	-9.965	-5.208	-4.756
		SEM	6.308	5.890	7.008
		95% CI	(-22.4, 2.5)	(-16.8, 6.4)	(-18.5, 9.0)
		Pr >  t			0.4978
	Week 120	n	4	4	
		LS Mean	-9.965	-2.224	-7.741
		SEM	6.308	6.257	7.320
		95% CI	(-22.4, 2.5)	(-14.5, 10.1)	(-22.1, 6.7)
		Pr >  t			0.2909
	Week 132	n	3	2	
		LS Mean	-3.085	2.968	-6.053
		SEM	6.860	7.797	9.082
		95% CI	(-16.6, 10.4)	(-12.4, 18.3)	(-23.9, 11.8)
		Pr >  t			0.5055
	Week 144	n	3	1	
		LS Mean	-18.64	-7.757	-10.88
		SEM	6.860	10.21	11.22

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-32.1,-5.1)	(-27.8,12.3)	(-33.0,11.2)
		Pr >  t			0.3330
	Week 156	n	2	1	
		LS Mean	-13.94	-7.757	-6.187
		SEM	7.841	10.21	11.85
		95% CI	(-29.4, 1.5)	(-27.8,12.3)	(-29.5,17.1)
		Pr >  t			0.6019
	Week 168	n	1		
		LS Mean	-10.16		
		SEM	10.23		
		95% CI	(-30.3, 9.9)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	1.644	1.911	-0.267
		SEM	10.77	10.12	6.649
		95% CI	(-20.0,23.3)	(-18.3,22.2)	(-13.6,13.1)
		Pr >  t			0.9681
	Week 16	n	15	14	
		LS Mean	1.979	0.039	1.940
		SEM	10.83	9.705	7.018
		95% CI	(-19.7,23.7)	(-19.4,19.5)	(-12.1,16.0)
		Pr >  t			0.7832
	Week 24	n	12	11	
		LS Mean	3.185	-7.585	10.770
		SEM	10.98	10.34	7.473
		95% CI	(-18.8,25.2)	(-28.2,13.1)	(-4.1,25.7)
		Pr >  t			0.1539
	Week 32	n	8	9	
		LS Mean	3.014	-12.49	15.502
		SEM	11.28	10.51	8.125
		95% CI	(-19.5,25.6)	(-33.5, 8.5)	(-0.6,31.6)
		Pr >  t			0.0596
	Week 40	n	6	7	
		LS Mean	4.805	-13.57	18.379
		SEM	11.57	10.73	8.777
		95% CI	(-18.3,27.9)	(-35.0, 7.8)	( 1.0,35.8)
		Pr >  t			0.0387
	Week 48	n	4	6	
		LS Mean	-1.649	-6.416	4.767
		SEM	12.11	10.89	9.664

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.8,22.5)	(-28.1,15.3)	(-14.4,23.9)
		Pr >  t			0.6227
	Week 56	n	4	6	
		LS Mean	1.868	-3.886	5.755
		SEM	12.11	10.91	9.662
		95% CI	(-22.3,26.0)	(-25.6,17.8)	(-13.4,24.9)
		Pr >  t			0.5526
	Week 64	n	4	4	
		LS Mean	0.057	2.929	-2.872
		SEM	12.12	11.45	10.26
		95% CI	(-24.1,24.2)	(-19.8,25.7)	(-23.2,17.4)
		Pr >  t			0.7800
	Week 72	n	4	4	
		LS Mean	1.722	-3.741	5.463
		SEM	12.12	11.45	10.26
		95% CI	(-22.4,25.9)	(-26.5,19.0)	(-14.8,25.8)
		Pr >  t			0.5954
	Week 84	n	4	4	
		LS Mean	1.683	-2.074	3.757
		SEM	12.11	11.45	10.26
		95% CI	(-22.4,25.8)	(-24.8,20.7)	(-16.5,24.1)
		Pr >  t			0.7149
	Week 96	n	3	2	
		LS Mean	13.370	1.052	12.317
		SEM	12.61	12.91	12.36
		95% CI	(-11.7,38.4)	(-24.5,26.6)	(-12.1,36.8)
		Pr >  t			0.3208
	Week 108	n	3	3	
		LS Mean	2.260	4.771	-2.512
		SEM	12.61	11.97	11.38
		95% CI	(-22.8,27.3)	(-19.0,28.5)	(-25.0,20.0)
		Pr >  t			0.8256
	Week 120	n	2	1	
		LS Mean	-1.362	3.082	-4.444
		SEM	13.52	15.39	15.71
		95% CI	(-28.2,25.5)	(-27.4,33.5)	(-35.5,26.6)
		Pr >  t			0.7777
	Week 132	n	2	1	
		LS Mean	-14.08	-3.588	-10.49
		SEM	13.51	15.39	15.71



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-40.9,12.7)	(-34.0,26.9)	(-41.6,20.6)
		Pr >  t			0.5055
	Week 156	n	1		
		LS Mean	2.343		
		SEM	15.94		
		95% CI	(-29.2,33.9)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	2.343		
		SEM	15.94		
		95% CI	(-29.2,33.9)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	-2.949	-3.754	0.806
		SEM	2.319	2.449	2.139
		95% CI	(-7.5, 1.6)	(-8.6, 1.1)	(-3.4, 5.0)
		Pr >  t			0.7067
	Week 16	n	79	61	
		LS Mean	-0.948	-3.245	2.297
		SEM	2.383	2.605	2.329
		95% CI	(-5.6, 3.7)	(-8.4, 1.9)	(-2.3, 6.9)
		Pr >  t			0.3246
	Week 24	n	71	43	
		LS Mean	-3.591	-3.981	0.390
		SEM	2.420	2.737	2.513
		95% CI	(-8.4, 1.2)	(-9.4, 1.4)	(-4.5, 5.3)
		Pr >  t			0.8767
	Week 32	n	59	39	
		LS Mean	-0.679	-2.842	2.162
		SEM	2.501	2.792	2.616
		95% CI	(-5.6, 4.2)	(-8.3, 2.6)	(-3.0, 7.3)
		Pr >  t			0.4089
	Week 40	n	52	35	
		LS Mean	0.361	-1.727	2.088
		SEM	2.545	2.840	2.711
		95% CI	(-4.6, 5.4)	(-7.3, 3.9)	(-3.2, 7.4)
		Pr >  t			0.4415
	Week 48	n	48	26	
		LS Mean	-3.422	-4.185	0.763
		SEM	2.573	2.996	2.899

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.5, 1.6)	(-10.1, 1.7)	(-4.9, 6.5)
		Pr >  t			0.7925
	Week 56	n	42	24	
		LS Mean	-2.294	-3.198	0.903
		SEM	2.623	3.044	2.995
		95% CI	(-7.5, 2.9)	(-9.2, 2.8)	(-5.0, 6.8)
		Pr >  t			0.7631
	Week 64	n	30	26	
		LS Mean	-2.037	-2.511	0.474
		SEM	2.775	2.998	3.085
		95% CI	(-7.5, 3.4)	(-8.4, 3.4)	(-5.6, 6.5)
		Pr >  t			0.8780
	Week 72	n	34	21	
		LS Mean	-2.544	-1.434	-1.110
		SEM	2.716	3.129	3.161
		95% CI	(-7.9, 2.8)	(-7.6, 4.7)	(-7.3, 5.1)
		Pr >  t			0.7256
	Week 84	n	28	20	
		LS Mean	-4.504	0.527	-5.031
		SEM	2.817	3.161	3.277
		95% CI	(-10.0, 1.0)	(-5.7, 6.7)	(-11.5, 1.4)
		Pr >  t			0.1251
	Week 96	n	26	15	
		LS Mean	-3.293	-4.556	1.264
		SEM	2.854	3.382	3.524
		95% CI	(-8.9, 2.3)	(-11.2, 2.1)	(-5.7, 8.2)
		Pr >  t			0.7200
	Week 108	n	19	12	
		LS Mean	-2.670	-8.295	5.625
		SEM	3.066	3.588	3.883
		95% CI	(-8.7, 3.4)	(-15.3, -1.3)	(-2.0, 13.2)
		Pr >  t			0.1477
	Week 120	n	22	10	
		LS Mean	-2.259	0.237	-2.496
		SEM	2.960	3.782	3.988
		95% CI	(-8.1, 3.6)	(-7.2, 7.7)	(-10.3, 5.3)
		Pr >  t			0.5314
	Week 132	n	15	4	
		LS Mean	-5.818	-4.889	-0.929
		SEM	3.253	5.202	5.518

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.2, 0.6)	(-15.1, 5.3)	(-11.8, 9.9)
		Pr >  t			0.8664
	Week 144	n	12	4	
		LS Mean	-5.736	-0.105	-5.631
		SEM	3.456	5.205	5.649
		95% CI	(-12.5, 1.0)	(-10.3,10.1)	(-16.7, 5.5)
		Pr >  t			0.3191
	Week 156	n	7	2	
		LS Mean	-1.782	2.193	-3.975
		SEM	4.127	6.942	7.618
		95% CI	(-9.9, 6.3)	(-11.4,15.8)	(-18.9,11.0)
		Pr >  t			0.6020
	Week 168	n	2	2	
		LS Mean	3.913	2.193	1.720
		SEM	6.861	6.942	9.385
		95% CI	(-9.6,17.4)	(-11.4,15.8)	(-16.7,20.1)
		Pr >  t			0.8546
	Week 180	n	1	1	
		LS Mean	-5.863	-3.646	-2.217
		SEM	9.450	9.493	13.12
		95% CI	(-24.4,12.7)	(-22.3,15.0)	(-28.0,23.5)
		Pr >  t			0.8659
	Week 192	n	1	1	
		LS Mean	-19.20	-3.646	-15.56
		SEM	9.450	9.493	13.12
		95% CI	(-37.7,-0.7)	(-22.3,15.0)	(-41.3,10.2)
		Pr >  t			0.2362

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	-2.885	1.832	-4.717		
			SEM	4.594	4.320	3.720		
			95% CI	(-12.1, 6.3)	(-6.8, 10.5)	(-12.1, 2.7)		
					Pr >  t			0.2079
		Week 16	n	28	29			
			LS Mean	-7.525	0.929	-8.453		
			SEM	4.613	4.466	3.870		
			95% CI	(-16.7, 1.7)	(-8.0, 9.8)	(-16.1, -0.8)		
					Pr >  t			0.0311
		Week 24	n	21	25			
			LS Mean	-4.853	-0.479	-4.374		
			SEM	4.746	4.527	4.113		
			95% CI	(-14.3, 4.6)	(-9.5, 8.5)	(-12.5, 3.8)		
					Pr >  t			0.2896
		Week 32	n	19	23			
			LS Mean	-6.525	0.396	-6.921		
			SEM	4.796	4.567	4.225		
			95% CI	(-16.1, 3.0)	(-8.7, 9.5)	(-15.3, 1.4)		
					Pr >  t			0.1036
		Week 40	n	16	18			
			LS Mean	-3.396	-4.774	1.379		
			SEM	4.892	4.728	4.480		
			95% CI	(-13.1, 6.3)	(-14.2, 4.6)	(-7.5, 10.2)		
					Pr >  t			0.7587
		Week 48	n	16	17			
			LS Mean	-5.895	-3.783	-2.112		
			SEM	4.892	4.763	4.516		
95% CI	(-15.6, 3.8)		(-13.2, 5.7)	(-11.0, 6.8)				
			Pr >  t			0.6406		
Week 56	n	12	14					
	LS Mean	-2.039	-2.452	0.414				
	SEM	5.078	4.886	4.854				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-12.1, 8.0)	(-12.1, 7.2)	(-9.2,10.0)
	Pr >  t			0.9322
	n	12	11	
	LS Mean	-6.483	-4.763	-1.720
	SEM	5.078	5.072	5.040
Week 72	95% CI	(-16.6, 3.6)	(-14.8, 5.3)	(-11.6, 8.2)
	Pr >  t			0.7332
	n	10	8	
	LS Mean	-3.341	-4.252	0.911
	SEM	5.222	5.380	5.487
Week 84	95% CI	(-13.7, 7.0)	(-14.9, 6.4)	(-9.9,11.7)
	Pr >  t			0.8682
	n	8	8	
	LS Mean	-3.503	-6.752	3.250
	SEM	5.468	5.380	5.692
Week 96	95% CI	(-14.3, 7.3)	(-17.4, 3.9)	(-8.0,14.5)
	Pr >  t			0.5685
	n	6	6	
	LS Mean	-7.864	-3.993	-3.871
	SEM	5.801	5.722	6.322
Week 108	95% CI	(-19.3, 3.6)	(-15.3, 7.3)	(-16.3, 8.6)
	Pr >  t			0.5408
	n	4	5	
	LS Mean	-10.03	-5.376	-4.653
	SEM	6.410	5.982	7.104
Week 120	95% CI	(-22.7, 2.6)	(-17.2, 6.4)	(-18.6, 9.3)
	Pr >  t			0.5129
	n	4	4	
	LS Mean	-10.03	-2.398	-7.632
	SEM	6.410	6.349	7.416
Week 132	95% CI	(-22.7, 2.6)	(-14.9,10.1)	(-22.2, 7.0)
	Pr >  t			0.3041
	n	3	2	
	LS Mean	-3.149	2.802	-5.951
	SEM	6.961	7.889	9.180
Week 144	95% CI	(-16.9,10.6)	(-12.7,18.3)	(-24.0,12.1)
	Pr >  t			0.5172
	n	3	1	
	LS Mean	-18.70	-7.930	-10.77
	SEM	6.961	10.31	11.33

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-32.4,-5.0)	(-28.2,12.3)	(-33.1,11.5)
		Pr >  t			0.3424
	Week 156	n	2	1	
		LS Mean	-14.01	-7.930	-6.084
		SEM	7.942	10.31	11.96
		95% CI	(-29.6, 1.6)	(-28.2,12.3)	(-29.6,17.4)
		Pr >  t			0.6112
	Week 168	n	1		
		LS Mean	-10.26		
		SEM	10.33		
		95% CI	(-30.6,10.1)		
		Pr >  t			
	Week 8	n	66	68	
		LS Mean	-1.028	-2.604	1.576
		SEM	5.008	5.030	2.630
		95% CI	(-10.9, 8.9)	(-12.6, 7.3)	( -3.6, 6.8)
		Pr >  t			0.5494
	Week 16	n	58	48	
		LS Mean	1.885	-0.390	2.275
		SEM	5.030	5.095	2.859
		95% CI	( -8.1,11.8)	(-10.5, 9.7)	( -3.4, 7.9)
		Pr >  t			0.4269
	Week 24	n	51	36	
		LS Mean	-3.759	-2.682	-1.077
		SEM	5.059	5.168	3.067
		95% CI	(-13.8, 6.2)	(-12.9, 7.5)	( -7.1, 5.0)
		Pr >  t			0.7255
	Week 32	n	43	30	
		LS Mean	0.392	-2.281	2.673
		SEM	5.135	5.271	3.244
		95% CI	( -9.8,10.5)	(-12.7, 8.1)	( -3.7, 9.0)
		Pr >  t			0.4103
	Week 40	n	37	25	
		LS Mean	1.060	1.937	-0.877
		SEM	5.177	5.337	3.418
		95% CI	( -9.2,11.3)	( -8.6,12.5)	( -7.6, 5.8)
		Pr >  t			0.7975
	Week 48	n	33	21	
		LS Mean	-3.505	-2.895	-0.610
		SEM	5.211	5.417	3.590

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-13.8, 6.8)	(-13.6, 7.8)	(-7.7, 6.4)
	Pr >  t			0.8652
	n	29	20	
	LS Mean	-0.116	0.804	-0.920
	SEM	5.251	5.440	3.688
Week 64	95% CI	(-10.5,10.3)	(-9.9,11.5)	(-8.2, 6.3)
	Pr >  t			0.8030
	n	23	20	
	LS Mean	-1.487	0.974	-2.461
	SEM	5.339	5.441	3.813
Week 72	95% CI	(-12.0, 9.1)	(-9.8,11.7)	(-9.9, 5.0)
	Pr >  t			0.5190
	n	25	19	
	LS Mean	0.186	0.043	0.143
	SEM	5.308	5.466	3.802
Week 84	95% CI	(-10.3,10.7)	(-10.7,10.8)	(-7.3, 7.6)
	Pr >  t			0.9701
	n	22	17	
	LS Mean	-3.614	1.844	-5.458
	SEM	5.359	5.525	3.958
Week 96	95% CI	(-14.2, 7.0)	(-9.1,12.7)	(-13.2, 2.3)
	Pr >  t			0.1684
	n	20	13	
	LS Mean	-1.187	-2.003	0.815
	SEM	5.403	5.691	4.245
Week 108	95% CI	(-11.9, 9.5)	(-13.2, 9.2)	(-7.5, 9.1)
	Pr >  t			0.8478
	n	15	11	
	LS Mean	0.058	-6.380	6.438
	SEM	5.562	5.816	4.603
Week 120	95% CI	(-10.9,11.0)	(-17.8, 5.1)	(-2.6,15.5)
	Pr >  t			0.1624
	n	16	8	
	LS Mean	-0.322	2.429	-2.751
	SEM	5.527	6.110	4.928
Week 132	95% CI	(-11.2,10.6)	(-9.6,14.5)	(-12.4, 6.9)
	Pr >  t			0.5768
	n	12	3	
	LS Mean	-5.100	-1.511	-3.589
	SEM	5.711	7.653	6.900

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-16.4, 6.2)	(-16.5,13.5)	(-17.1,10.0)
		Pr >  t			0.6032
	Week 144	n	7	4	
		LS Mean	-5.028	2.145	-7.173
		SEM	6.217	7.080	6.724
		95% CI	(-17.3, 7.2)	(-11.8,16.1)	(-20.4, 6.0)
		Pr >  t			0.2864
	Week 156	n	5	2	
		LS Mean	-1.046	4.469	-5.515
		SEM	6.667	8.686	8.737
		95% CI	(-14.2,12.1)	(-12.6,21.5)	(-22.7,11.6)
		Pr >  t			0.5281
	Week 168	n	2	2	
		LS Mean	0.739	4.469	-3.730
		SEM	8.650	8.686	10.33
		95% CI	(-16.2,17.7)	(-12.6,21.5)	(-24.0,16.6)
		Pr >  t			0.7181
	Week 180	n		1	
		LS Mean		-1.372	
		SEM		11.21	
		95% CI		(-23.4,20.6)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-1.372	
		SEM		11.21	
		95% CI		(-23.4,20.6)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	-2.721	1.257	-3.978
		SEM	4.903	4.866	7.055
		95% CI	(-12.7, 7.2)	(-8.6,11.1)	(-18.3,10.3)
		Pr >  t			0.5763
	Week 16	n	13	12	
		LS Mean	-1.000	-3.811	2.811
		SEM	4.969	4.980	7.169
		95% CI	(-11.1, 9.1)	(-13.9, 6.2)	(-11.7,17.3)
		Pr >  t			0.6972
	Week 24	n	12	10	
		LS Mean	1.212	-5.946	7.158
		SEM	5.052	5.192	7.377



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-9.0,11.4)	(-16.4, 4.5)	(-7.7,22.0)
	Pr >  t			0.3375
	n	9	10	
	LS Mean	4.094	-5.947	10.041
	SEM	5.359	5.192	7.584
Week 40	95% CI	(-6.7,14.9)	(-16.4, 4.5)	(-5.2,25.3)
	Pr >  t			0.1921
	n	7	10	
	LS Mean	0.889	-6.613	7.502
	SEM	5.676	5.192	7.814
Week 48	95% CI	(-10.5,12.2)	(-17.1, 3.8)	(-8.2,23.2)
	Pr >  t			0.3415
	n	7	7	
	LS Mean	-1.018	-1.659	0.642
	SEM	5.676	5.612	8.086
Week 56	95% CI	(-12.4,10.3)	(-12.9, 9.6)	(-15.6,16.8)
	Pr >  t			0.9370
	n	6	7	
	LS Mean	-3.911	-8.367	4.456
	SEM	5.901	5.619	8.263
Week 64	95% CI	(-15.7, 7.9)	(-19.6, 2.9)	(-12.1,21.0)
	Pr >  t			0.5917
	n	4	7	
	LS Mean	-1.301	-3.790	2.489
	SEM	6.577	5.599	8.720
Week 72	95% CI	(-14.4,11.8)	(-15.0, 7.4)	(-14.9,19.9)
	Pr >  t			0.7761
	n	4	4	
	LS Mean	-1.301	1.067	-2.368
	SEM	6.577	6.504	9.324
Week 84	95% CI	(-14.4,11.8)	(-11.9,14.0)	(-20.9,16.2)
	Pr >  t			0.8001
	n	4	5	
	LS Mean	-3.743	1.895	-5.638
	SEM	6.569	6.099	9.045
Week 96	95% CI	(-16.8, 9.3)	(-10.2,14.0)	(-23.6,12.4)
	Pr >  t			0.5349
	n	3	2	
	LS Mean	4.031	-2.595	6.626
	SEM	7.191	8.203	10.98

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-10.2,18.3)	(-18.8,13.6)	(-15.1,28.4)
		Pr >  t			0.5473
		n	2	3	
	Week 120	LS Mean	-4.175	7.564	-11.74
		SEM	8.273	7.148	11.02
		95% CI	(-20.5,12.2)	(-6.6,21.7)	(-33.6,10.1)
	Week 120	Pr >  t			0.2888
		n	2	2	
		LS Mean	-5.097	1.279	-6.376
	Week 132	SEM	8.265	8.210	11.71
		95% CI	(-21.4,11.3)	(-15.0,17.5)	(-29.5,16.8)
		Pr >  t			0.5870
	Week 132	n	1	2	
		LS Mean	1.082	-5.386	6.468
		SEM	10.88	8.210	13.69
	Week 8	95% CI	(-20.4,22.6)	(-21.6,10.9)	(-20.6,33.5)
		Pr >  t			0.6372
		n	16	19	
	Week 8	LS Mean	-0.403	-3.616	3.214
		SEM	3.359	3.276	4.104
		95% CI	(-7.1, 6.3)	(-10.2, 2.9)	(-5.0,11.4)
	Week 16	Pr >  t			0.4366
		n	12	14	
		LS Mean	-1.616	-8.476	6.860
Week 16	SEM	3.680	3.592	4.523	
	95% CI	(-9.0, 5.7)	(-15.6,-1.3)	(-2.1,15.9)	
	Pr >  t			0.1334	
Week 24	n	12	8		
	LS Mean	1.965	-8.995	10.960	
	SEM	3.681	4.334	5.096	
Week 24	95% CI	(-5.4, 9.3)	(-17.6,-0.4)	( 0.8,21.1)	
	Pr >  t			0.0340	
	n	9	7		
Week 32	LS Mean	-3.921	-10.23	6.310	
	SEM	4.012	4.502	5.452	
	95% CI	(-11.9, 4.1)	(-19.2,-1.3)	(-4.5,17.1)	
Week 32	Pr >  t			0.2496	
	n	9	7		
	LS Mean	-0.852	-16.90	16.046	
Week 40	SEM	4.025	4.502	5.476	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-8.9, 7.2)	(-25.8,-8.0)	(-5.2,26.9)
	Pr >  t			0.0041
	n	8	5	
	LS Mean	-0.199	-12.11	11.907
	SEM	4.165	4.996	5.985
Week 56	95% CI	(-8.5, 8.1)	(-22.0,-2.2)	(-0.1,23.8)
	Pr >  t			0.0488
	n	7	3	
	LS Mean	-1.726	-10.35	8.621
	SEM	4.328	5.953	6.912
Week 64	95% CI	(-10.3, 6.9)	(-22.1, 1.4)	(-5.0,22.3)
	Pr >  t			0.2144
	n	5	3	
	LS Mean	1.756	-3.676	5.432
	SEM	4.813	5.953	7.234
Week 72	95% CI	(-7.8,11.3)	(-15.4, 8.1)	(-8.9,19.7)
	Pr >  t			0.4540
	n	5	3	
	LS Mean	-6.275	-10.40	4.125
	SEM	4.797	5.953	7.208
Week 84	95% CI	(-15.8, 3.2)	(-22.2, 1.4)	(-10.1,18.4)
	Pr >  t			0.5680
	n	2	2	
	LS Mean	-0.683	-14.38	13.697
	SEM	6.800	6.950	9.374
Week 96	95% CI	(-14.1,12.8)	(-28.1,-0.6)	(-4.8,32.2)
	Pr >  t			0.1462
	n	3	2	
	LS Mean	-2.960	-21.05	18.091
	SEM	5.742	6.950	8.664
Week 108	95% CI	(-14.3, 8.4)	(-34.8,-7.3)	(-1.0,35.2)
	Pr >  t			0.0386
	n	1	2	
	LS Mean	-7.991	-17.71	9.720
	SEM	9.127	6.950	11.18
Week 120	95% CI	(-26.0,10.1)	(-31.5,-4.0)	(-12.4,31.8)
	Pr >  t			0.3860
	n	3	2	
	LS Mean	-5.183	-14.38	9.198
	SEM	5.742	6.950	8.664

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
		95% CI	(-16.5, 6.2)	(-28.1,-0.6)	(-7.9,26.3)	
		Pr >  t			0.2903	
	Week 132	n	1	1		
		LS Mean	-14.09	-35.36	21.273	
		SEM	9.126	9.248	12.74	
		95% CI	(-32.1, 4.0)	(-53.7, -17)	(-3.9,46.5)	
		Pr >  t			0.0973	
	Week 144	n	2			
		LS Mean	-13.78			
		SEM	6.738			
		95% CI	(-27.1,-0.5)			
		Pr >  t				
	Week 156	n	1			
		LS Mean	-14.09			
		SEM	9.126			
		95% CI	(-32.1, 4.0)			
		Pr >  t				
	Week 168	n	1			
		LS Mean	5.913			
		SEM	9.126			
		95% CI	(-12.1,24.0)			
		Pr >  t				
	Week 180	n	1			
		LS Mean	-7.417			
		SEM	9.126			
		95% CI	(-25.5,10.6)			
		Pr >  t				
	Week 192	n	1			
		LS Mean	-20.76			
		SEM	9.126			
		95% CI	(-38.8,-2.7)			
		Pr >  t				
	Other	Week 8	n	16	5	
			LS Mean	-9.401	0.959	-10.36
			SEM	5.188	7.410	7.903
			95% CI	(-20.3, 1.5)	(-14.5,16.4)	(-26.8, 6.1)
			Pr >  t			0.2048
		Week 16	n	13	4	
			LS Mean	-9.829	-0.693	-9.136
			SEM	5.307	7.861	8.260

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-20.9, 1.3)	(-16.9,15.5)	(-26.2, 7.9)
	Pr >  t			0.2801
	n	9	2	
	LS Mean	-5.891	-2.267	-3.624
	SEM	5.484	8.816	9.304
Week 32	95% CI	(-17.3, 5.5)	(-20.2,15.6)	(-22.5,15.3)
	Pr >  t			0.6993
	n	6	3	
	LS Mean	-3.720	-4.197	0.477
	SEM	5.839	8.200	8.935
Week 40	95% CI	(-15.7, 8.2)	(-21.0,12.6)	(-17.8,18.7)
	Pr >  t			0.9578
	n	6	2	
	LS Mean	-1.276	-2.752	1.476
	SEM	5.894	8.804	9.517
Week 48	95% CI	(-13.3,10.8)	(-20.6,15.1)	(-17.8,20.8)
	Pr >  t			0.8776
	n	5	1	
	LS Mean	-4.826	-1.397	-3.429
	SEM	6.039	10.41	11.14
Week 56	95% CI	(-17.1, 7.5)	(-22.3,19.5)	(-25.7,18.9)
	Pr >  t			0.7593
	n	5	1	
	LS Mean	-6.162	-1.397	-4.765
	SEM	6.039	10.41	11.14
Week 64	95% CI	(-18.5, 6.1)	(-22.3,19.5)	(-27.1,17.5)
	Pr >  t			0.6704
	n	3	1	
	LS Mean	-5.399	-1.397	-4.003
	SEM	6.620	10.41	11.47
Week 72	95% CI	(-18.8, 8.0)	(-22.3,19.5)	(-26.9,18.9)
	Pr >  t			0.7283
	n	4	1	
	LS Mean	-8.945	-1.397	-7.549
	SEM	6.266	10.41	11.27
Week 84	95% CI	(-21.7, 3.8)	(-22.3,19.5)	(-30.1,15.0)
	Pr >  t			0.5056
	n	4	1	
	LS Mean	-3.943	-1.397	-2.546
	SEM	6.266	10.41	11.27

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-16.7, 8.8)	(-22.3,19.5)	(-25.1,20.0)
	Pr >  t			0.8220
	n	3	1	
	LS Mean	-5.399	-1.397	-4.003
	SEM	6.620	10.41	11.47
Week 108	95% CI	(-18.8, 8.0)	(-22.3,19.5)	(-26.9,18.9)
	Pr >  t			0.7283
	n	4		
	LS Mean	-7.278		
	SEM	6.266		
Week 120	95% CI	(-20.0, 5.4)		
	Pr >  t			
	n	3		
	LS Mean	-5.403		
	SEM	6.620		
Week 132	95% CI	(-18.8, 8.0)		
	Pr >  t			
	n	3		
	LS Mean	-14.29		
	SEM	6.620		
Week 144	95% CI	(-27.6,-0.9)		
	Pr >  t			
	n	3		
	LS Mean	-2.597		
	SEM	6.618		
Week 156	95% CI	(-16.0,10.8)		
	Pr >  t			
	n	2		
	LS Mean	2.381		
	SEM	7.246		
	95% CI	(-12.1,16.9)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Baseline ECOG performance status	0 Week 8	n	98	90			
		LS Mean	-2.915	-1.577	-1.337		
		SEM	2.776	2.707	2.124		
		95% CI	(-8.4, 2.6)	(-6.9, 3.8)	(-5.5, 2.8)		
						Pr >  t	0.5294
	Week 16	n	88	71			
		LS Mean	-2.647	-1.691	-0.955		
		SEM	2.815	2.842	2.246		
		95% CI	(-8.2, 2.9)	(-7.3, 3.9)	(-5.4, 3.5)		
						Pr >  t	0.6709
	Week 24	n	75	54			
		LS Mean	-3.718	-2.810	-0.908		
		SEM	2.848	2.919	2.395		
		95% CI	(-9.3, 1.9)	(-8.6, 2.9)	(-5.6, 3.8)		
						Pr >  t	0.7048
	Week 32	n	62	52			
		LS Mean	-3.040	-1.215	-1.825		
		SEM	2.902	2.932	2.468		
		95% CI	(-8.8, 2.7)	(-7.0, 4.6)	(-6.7, 3.0)		
						Pr >  t	0.4599
	Week 40	n	51	46			
		LS Mean	-2.356	-0.662	-1.694		
		SEM	2.957	2.982	2.580		
		95% CI	(-8.2, 3.5)	(-6.5, 5.2)	(-6.8, 3.4)		
					Pr >  t	0.5117	
Week 48	n	50	37				
	LS Mean	-5.949	-1.946	-4.002			
	SEM	2.963	3.061	2.678			
	95% CI	(-11.8, -0.1)	(-8.0, 4.1)	(-9.3, 1.3)			
					Pr >  t	0.1356	
Week 56	n	43	33				
	LS Mean	-3.270	-1.471	-1.800			
	SEM	3.011	3.109	2.786			



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.2, 2.7)	(-7.6, 4.6)	(-7.3, 3.7)
	Pr >  t			0.5184
	n	35	33	
	LS Mean	-4.257	-1.084	-3.174
	SEM	3.085	3.109	2.868
Week 72	95% CI	(-10.3, 1.8)	(-7.2, 5.0)	(-8.8, 2.5)
	Pr >  t			0.2688
	n	35	31	
	LS Mean	-3.143	-1.004	-2.139
	SEM	3.085	3.136	2.897
Week 84	95% CI	(-9.2, 2.9)	(-7.2, 5.2)	(-7.8, 3.5)
	Pr >  t			0.4606
	n	31	29	
	LS Mean	-4.631	-0.860	-3.771
	SEM	3.140	3.166	2.982
Week 96	95% CI	(-10.8, 1.5)	(-7.1, 5.4)	(-9.6, 2.1)
	Pr >  t			0.2064
	n	27	22	
	LS Mean	-2.584	-3.647	1.063
	SEM	3.198	3.311	3.201
Week 108	95% CI	(-8.9, 3.7)	(-10.2, 2.9)	(-5.2, 7.3)
	Pr >  t			0.7397
	n	19	20	
	LS Mean	-5.633	-4.867	-0.766
	SEM	3.404	3.369	3.457
Week 120	95% CI	(-12.3, 1.1)	(-11.5, 1.8)	(-7.6, 6.0)
	Pr >  t			0.8247
	n	20	15	
	LS Mean	-5.896	-0.181	-5.715
	SEM	3.363	3.572	3.625
Week 132	95% CI	(-12.5, 0.7)	(-7.2, 6.8)	(-12.8, 1.4)
	Pr >  t			0.1152
	n	15	7	
	LS Mean	-9.329	-4.683	-4.645
	SEM	3.571	4.372	4.571
Week 144	95% CI	(-16.3, -2.3)	(-13.3, 3.9)	(-13.6, 4.3)
	Pr >  t			0.3097
	n	10	5	
Week 144	LS Mean	-14.57	-0.743	-13.83
	SEM	3.929	4.891	5.337

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.3,-6.9)	(-10.3, 8.9)	(-24.3,-3.4)
		Pr >  t			0.0097
	Week 156	n	6	3	
		LS Mean	-6.595	-0.301	-6.294
		SEM	4.595	5.914	6.717
		95% CI	(-15.6, 2.4)	(-11.9,11.3)	(-19.5, 6.9)
		Pr >  t			0.3489
	Week 168	n	3	2	
		LS Mean	-0.014	2.980	-2.994
		SEM	5.914	6.988	8.534
		95% CI	(-11.6,11.6)	(-10.7,16.7)	(-19.7,13.8)
		Pr >  t			0.7258
	Week 180	n	1	1	
		LS Mean	-8.206	-2.866	-5.339
		SEM	9.500	9.493	13.02
		95% CI	(-26.8,10.4)	(-21.5,15.8)	(-30.9,20.2)
		Pr >  t			0.6817
	Week 192	n	1	1	
		LS Mean	-21.55	-2.866	-18.68
		SEM	9.500	9.493	13.02
		95% CI	(-40.2,-2.9)	(-21.5,15.8)	(-44.2, 6.9)
		Pr >  t			0.1516
1	Week 8	n	43	50	
		LS Mean	-1.638	-1.723	0.085
		SEM	3.400	3.557	3.450
		95% CI	(-8.4, 5.1)	(-8.8, 5.3)	(-6.7, 6.9)
		Pr >  t			0.9804
	Week 16	n	35	35	
		LS Mean	-1.038	-2.602	1.564
		SEM	3.546	3.679	3.772
		95% CI	(-8.1, 6.0)	(-9.9, 4.7)	(-5.9, 9.0)
		Pr >  t			0.6789
	Week 24	n	29	26	
		LS Mean	-1.940	-5.762	3.822
		SEM	3.676	3.920	4.063
		95% CI	(-9.2, 5.3)	(-13.5, 2.0)	(-4.2,11.8)
		Pr >  t			0.3479
	Week 32	n	23	21	
		LS Mean	1.024	-9.054	10.077
		SEM	3.869	4.107	4.343

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.6, 8.7)	(-17.2,-0.9)	(-1.5,18.6)
		Pr >  t			0.0211
	Week 40	n	23	16	
		LS Mean	3.658	-13.63	17.293
		SEM	3.878	4.328	4.559
		95% CI	(-4.0,11.3)	(-22.2,-5.1)	(-8.3,26.3)
		Pr >  t			0.0002
	Week 48	n	18	14	
		LS Mean	1.602	-11.04	12.639
		SEM	4.059	4.457	4.845
		95% CI	(-6.4, 9.6)	(-19.8,-2.3)	(-3.1,22.2)
		Pr >  t			0.0095
	Week 56	n	15	12	
		LS Mean	1.663	-7.668	9.331
		SEM	4.226	4.617	5.137
		95% CI	(-6.7,10.0)	(-16.8, 1.4)	(-0.8,19.4)
		Pr >  t			0.0701
	Week 64	n	11	9	
		LS Mean	0.897	-5.786	6.683
		SEM	4.545	4.973	5.714
		95% CI	(-8.1, 9.8)	(-15.6, 4.0)	(-4.6,17.9)
		Pr >  t			0.2429
	Week 72	n	12	4	
		LS Mean	-0.809	-6.533	5.723
		SEM	4.459	6.441	6.971
		95% CI	(-9.6, 8.0)	(-19.2, 6.1)	(-8.0,19.4)
		Pr >  t			0.4121
	Week 84	n	8	4	
		LS Mean	-3.000	-4.865	1.865
		SEM	4.994	6.441	7.314
		95% CI	(-12.8, 6.8)	(-17.5, 7.8)	(-12.5,16.2)
		Pr >  t			0.7988
	Week 96	n	8	2	
		LS Mean	-4.666	-5.626	0.960
		SEM	4.994	8.420	9.105
		95% CI	(-14.5, 5.2)	(-22.2,10.9)	(-16.9,18.9)
		Pr >  t			0.9161
	Week 108	n	6	1	
		LS Mean	1.290	0.375	0.915
		SEM	5.463	11.38	12.09

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.5,12.0)	(-22.0,22.8)	(-22.9,24.7)
		Pr >  t			0.9397
	Week 120	n	8	1	
		LS Mean	2.217	0.375	1.842
		SEM	5.009	11.38	11.89
		95% CI	(-7.6,12.1)	(-22.0,22.8)	(-21.5,25.2)
		Pr >  t			0.8770
	Week 132	n	5	1	
		LS Mean	1.299	-6.295	7.594
		SEM	5.805	11.38	12.25
		95% CI	(-10.1,12.7)	(-28.7,16.1)	(-16.5,31.7)
		Pr >  t			0.5358
	Week 144	n	5		
		LS Mean	5.301		
		SEM	5.805		
		95% CI	(-6.1,16.7)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	1.310		
		SEM	6.279		
		95% CI	(-11.0,13.7)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-2.918		
		SEM	11.19		
		95% CI	(-24.9,19.1)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status (L) Primary resistant		Week 8	n	21	16		
			LS Mean	-3.808	-0.816	-2.993	
			SEM	5.488	6.629	6.692	
			95% CI	(-14.9, 7.3)	(-14.2,12.6)	(-16.5,10.5)	
				Pr >  t			0.6568
		Week 16	n	17	10		
			LS Mean	-8.278	-6.324	-1.953	
			SEM	5.737	7.188	7.279	
			95% CI	(-19.8, 3.3)	(-20.8, 8.1)	(-16.5,12.6)	
				Pr >  t			0.7894
		Week 24	n	9	5		
			LS Mean	-2.304	-14.24	11.940	
			SEM	6.280	8.142	8.738	
			95% CI	(-14.9,10.3)	(-30.5, 2.0)	( -5.4,29.3)	
				Pr >  t			0.1752
		Week 32	n	8	4		
			LS Mean	-2.577	-12.86	10.283	
			SEM	6.416	8.524	9.202	
			95% CI	(-15.4,10.2)	(-29.8, 4.1)	( -8.0,28.5)	
				Pr >  t			0.2665
		Week 40	n	5	4		
			LS Mean	-4.021	-6.192	2.171	
			SEM	7.061	8.524	9.729	
			95% CI	(-18.1,10.0)	(-23.1,10.8)	(-17.1,21.5)	
		Pr >  t			0.8238		
Week 48	n	5	3				
	LS Mean	-12.02	-7.348	-4.675			
	SEM	7.061	9.098	10.23			
	95% CI	(-26.1, 2.0)	(-25.4,10.7)	(-25.0,15.6)			
		Pr >  t			0.6487		
Week 56	n	4	3				
	LS Mean	-4.429	-5.125	0.696			
	SEM	7.447	9.098	10.52			

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-19.2,10.4)	(-23.2,12.9)	(-20.2,21.5)
		Pr >  t			0.9474
		n	4	3	
		LS Mean	-4.426	-0.678	-3.748
		SEM	7.447	9.098	10.52
Week 72		95% CI	(-19.2,10.4)	(-18.7,17.4)	(-24.6,17.1)
		Pr >  t			0.7224
		n	4	3	
		LS Mean	-1.094	-5.125	4.031
		SEM	7.447	9.098	10.52
Week 84		95% CI	(-15.9,13.7)	(-23.2,12.9)	(-16.8,24.9)
		Pr >  t			0.7024
		n	2	3	
		LS Mean	-4.158	-9.568	5.410
		SEM	9.243	9.098	11.80
Week 96		95% CI	(-22.5,14.2)	(-27.6, 8.5)	(-18.0,28.8)
		Pr >  t			0.6474
		n	1	3	
		LS Mean	-2.433	-14.01	11.582
		SEM	11.85	9.098	14.05
Week 108		95% CI	(-25.9,21.1)	(-32.1, 4.1)	(-16.3,39.4)
		Pr >  t			0.4115
		n		2	
		LS Mean		-27.85	
		SEM		10.08	
Week 120		95% CI		(-47.8,-7.9)	
		Pr >  t			
		n	1	1	
		LS Mean	-9.103	-19.29	10.190
		SEM	11.85	12.56	16.51
Week 132		95% CI	(-32.6,14.4)	(-44.2, 5.6)	(-22.6,42.9)
		Pr >  t			0.5384
		n		1	
		LS Mean		-32.62	
		SEM		12.56	
Week 144		95% CI		(-57.5,-7.7)	
		Pr >  t			
		n	1		
		LS Mean	-2.433		
		SEM	11.85		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.9,21.1)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-3.622	-3.789	0.167
		SEM	2.478	2.471	2.046
		95% CI	(-8.5, 1.3)	(-8.7, 1.1)	(-3.9, 4.2)
		Pr >  t			0.9351
	Week 16	n	83	81	
		LS Mean	-2.340	-4.431	2.091
		SEM	2.531	2.569	2.201
		95% CI	(-7.3, 2.6)	(-9.5, 0.6)	(-2.2, 6.4)
		Pr >  t			0.3427
	Week 24	n	75	62	
		LS Mean	-4.513	-5.765	1.251
		SEM	2.569	2.668	2.336
		95% CI	(-9.6, 0.5)	(-11.0,-0.5)	(-3.3, 5.8)
		Pr >  t			0.5924
	Week 32	n	59	56	
		LS Mean	-2.238	-5.309	3.071
		SEM	2.674	2.703	2.461
		95% CI	(-7.5, 3.0)	(-10.6, 0.0)	(-1.8, 7.9)
		Pr >  t			0.2126
	Week 40	n	52	48	
		LS Mean	-1.751	-6.853	5.102
		SEM	2.719	2.769	2.572
		95% CI	(-7.1, 3.6)	(-12.3,-1.4)	(0.1,10.2)
		Pr >  t			0.0477
	Week 48	n	47	37	
		LS Mean	-4.568	-6.966	2.398
		SEM	2.756	2.880	2.730
		95% CI	(-10.0, 0.9)	(-12.6,-1.3)	(-3.0, 7.8)
		Pr >  t			0.3800
	Week 56	n	41	31	
		LS Mean	-3.237	-6.884	3.647
		SEM	2.812	2.970	2.880
		95% CI	(-8.8, 2.3)	(-12.7,-1.0)	(-2.0, 9.3)
		Pr >  t			0.2058
	Week 64	n	32	28	
		LS Mean	-4.230	-5.333	1.103
		SEM	2.929	3.028	3.052

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-10.0, 1.5)	(-11.3, 0.6)	(-4.9, 7.1)	
	Pr >  t			0.7178	
	n	29	22		
	LS Mean	-3.462	-4.475	1.013	
	SEM	2.985	3.181	3.254	
Week 84	95% CI	(-9.3, 2.4)	(-10.7, 1.8)	(-5.4, 7.4)	
	Pr >  t			0.7556	
	n	26	21		
	LS Mean	-3.920	-3.741	-0.179	
	SEM	3.045	3.214	3.342	
Week 96	95% CI	(-9.9, 2.1)	(-10.1, 2.6)	(-6.7, 6.4)	
	Pr >  t			0.9573	
	n	23	14		
	LS Mean	-1.461	-6.442	4.982	
	SEM	3.124	3.552	3.734	
Week 108	95% CI	(-7.6, 4.7)	(-13.4, 0.5)	(-2.3, 12.3)	
	Pr >  t			0.1825	
	n	18	13		
	LS Mean	-4.779	-3.694	-1.085	
	SEM	3.305	3.626	3.954	
Week 120	95% CI	(-11.3, 1.7)	(-10.8, 3.4)	(-8.8, 6.7)	
	Pr >  t			0.7839	
	n	19	10		
	LS Mean	-6.571	-2.554	-4.017	
	SEM	3.266	3.917	4.192	
Week 132	95% CI	(-13.0, -0.2)	(-10.2, 5.1)	(-12.2, 4.2)	
	Pr >  t			0.3381	
	n	13	4		
	LS Mean	-10.25	-4.145	-6.107	
	SEM	3.596	5.433	5.832	
Week 144	95% CI	(-17.3, -3.2)	(-14.8, 6.5)	(-17.6, 5.3)	
	Pr >  t			0.2953	
	n	8	1		
	LS Mean	-13.33	1.674	-15.01	
	SEM	4.181	10.02	10.46	
Week 156	95% CI	(-21.5, -5.1)	(-18.0, 21.3)	(-35.5, 5.5)	
	Pr >  t			0.1516	
	n	5	1		
	LS Mean	-4.411	1.674	-6.085	
	SEM	4.956	10.02	10.79	



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-14.1, 5.3)	(-18.0,21.3)	(-27.3,15.1)
		Pr >  t			0.5730
		n	3	1	
	Week 180	LS Mean	0.208	1.674	-1.466
		SEM	6.087	10.02	11.35
		95% CI	(-11.7,12.2)	(-18.0,21.3)	(-23.7,20.8)
	Week 180	Pr >  t			0.8973
		n	1	1	
		LS Mean	-8.046	-4.996	-3.049
	Week 192	SEM	9.972	10.02	13.83
		95% CI	(-27.6,11.5)	(-24.7,14.7)	(-30.2,24.1)
		Pr >  t			0.8256
	Week 192	n	1	1	
		LS Mean	-21.39	-4.996	-16.39
		SEM	9.972	10.02	13.83
	Week 8	95% CI	(-41.0,-1.8)	(-24.7,14.7)	(-43.5,10.8)
		Pr >  t			0.2363
		n	17	16	
	Week 16	LS Mean	-1.452	-0.390	-1.062
		SEM	3.407	3.520	4.810
		95% CI	( -8.3, 5.4)	( -7.4, 6.6)	(-10.7, 8.5)
	Week 16	Pr >  t			0.8259
		n	18	14	
		LS Mean	-0.444	5.634	-6.079
	Week 24	SEM	3.350	3.660	4.898
		95% CI	( -7.1, 6.3)	( -1.7,12.9)	(-15.8, 3.7)
		Pr >  t			0.2187
	Week 24	n	16	13	
LS Mean		-2.089	4.804	-6.893	
SEM		3.475	3.733	5.033	
Week 32	95% CI	( -9.0, 4.8)	( -2.6,12.2)	(-16.9, 3.1)	
	Pr >  t			0.1748	
	n	15	13		
Week 32	LS Mean	-3.297	2.379	-5.676	
	SEM	3.527	3.741	5.079	
	95% CI	(-10.3, 3.7)	( -5.1, 9.8)	(-15.8, 4.4)	
Week 40	Pr >  t			0.2671	
	n	14	10		
	LS Mean	1.168	3.232	-2.064	
		SEM	3.604	4.009	5.330

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-6.0, 8.3)	(-4.7, 11.2)	(-12.6, 8.5)
	Pr >  t			0.6994
	n	14	11	
	LS Mean	-2.165	1.625	-3.790
	SEM	3.604	3.914	5.257
Week 56	95% CI	(-9.3, 5.0)	(-6.2, 9.4)	(-14.2, 6.7)
	Pr >  t			0.4729
	n	11	11	
	LS Mean	0.894	5.867	-4.972
	SEM	3.831	3.914	5.419
Week 64	95% CI	(-6.7, 8.5)	(-1.9, 13.6)	(-15.7, 5.8)
	Pr >  t			0.3611
	n	8	11	
	LS Mean	-0.612	3.442	-4.054
	SEM	4.185	3.914	5.678
Week 72	95% CI	(-8.9, 7.7)	(-4.3, 11.2)	(-15.3, 7.2)
	Pr >  t			0.4767
	n	11	10	
	LS Mean	-0.925	2.262	-3.186
	SEM	3.831	4.015	5.492
Week 84	95% CI	(-8.5, 6.7)	(-5.7, 10.2)	(-14.1, 7.7)
	Pr >  t			0.5630
	n	9	9	
	LS Mean	-6.441	3.252	-9.693
	SEM	4.045	4.130	5.730
Week 96	95% CI	(-14.5, 1.6)	(-4.9, 11.4)	(-21.0, 1.7)
	Pr >  t			0.0934
	n	8	7	
	LS Mean	-8.374	2.043	-10.42
	SEM	4.188	4.437	6.054
Week 108	95% CI	(-16.7, -0.1)	(-6.7, 10.8)	(-22.4, 1.6)
	Pr >  t			0.0876
	n	7	6	
	LS Mean	-1.712	-3.027	1.315
	SEM	4.362	4.660	6.338
Week 120	95% CI	(-10.3, 6.9)	(-12.2, 6.2)	(-11.2, 13.8)
	Pr >  t			0.8359
	n	6	5	
	LS Mean	2.055	5.973	-3.918
	SEM	4.586	4.955	6.701

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132		95% CI	(-7.0,11.1)	(-3.8,15.8)	(-17.1, 9.3)
		Pr >  t			0.5595
		n	5	3	
		LS Mean	-1.169	2.345	-3.514
		SEM	4.875	5.947	7.648
Week 144		95% CI	(-10.8, 8.4)	(-9.4,14.1)	(-18.6,11.6)
		Pr >  t			0.6463
		n	5	4	
		LS Mean	-3.833	2.548	-6.381
		SEM	4.875	5.347	7.191
Week 156		95% CI	(-13.4, 5.8)	(-8.0,13.1)	(-20.6, 7.8)
		Pr >  t			0.3759
		n	4	2	
		LS Mean	-4.776	1.951	-6.727
		SEM	5.274	6.994	8.727
Week 168		95% CI	(-15.2, 5.6)	(-11.8,15.7)	(-23.9,10.5)
		Pr >  t			0.4415
		n	1	1	
		LS Mean	-5.315	6.390	-11.70
		SEM	9.422	9.467	13.34
		95% CI	(-23.9,13.2)	(-12.2,25.0)	(-38.0,14.5)
		Pr >  t			0.3809

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-2.527	-1.981	-0.546		
			SEM	3.371	3.288	2.453		
			95% CI	(-9.2, 4.1)	(-8.5, 4.5)	(-5.4, 4.3)		
					Pr >  t			0.8241
		Week 16	n	60	51			
			LS Mean	-0.980	-3.443	2.463		
			SEM	3.417	3.417	2.584		
			95% CI	(-7.7, 5.8)	(-10.2, 3.3)	(-2.6, 7.6)		
					Pr >  t			0.3413
		Week 24	n	51	42			
			LS Mean	-3.047	-4.134	1.087		
			SEM	3.455	3.469	2.711		
			95% CI	(-9.9, 3.8)	(-11.0, 2.7)	(-4.2, 6.4)		
					Pr >  t			0.6887
		Week 32	n	46	36			
			LS Mean	0.406	-3.275	3.681		
			SEM	3.498	3.538	2.810		
			95% CI	(-6.5, 7.3)	(-10.2, 3.7)	(-1.8, 9.2)		
					Pr >  t			0.1911
		Week 40	n	40	33			
			LS Mean	-0.466	-3.574	3.108		
			SEM	3.539	3.570	2.898		
			95% CI	(-7.4, 6.5)	(-10.6, 3.5)	(-2.6, 8.8)		
			Pr >  t			0.2842		
Week 48	n	37	28					
	LS Mean	-1.477	-5.522	4.045				
	SEM	3.561	3.631	3.000				
	95% CI	(-8.5, 5.5)	(-12.7, 1.6)	(-1.9, 9.9)				
			Pr >  t			0.1783		
Week 56	n	33	23					
	LS Mean	-0.655	-1.834	1.179				
	SEM	3.599	3.716	3.146				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 64	95% CI	(-7.7, 6.4)	(-9.1, 5.5)	(-5.0, 7.4)
	Pr >  t			0.7080
	n	26	20	
	LS Mean	-1.836	-2.024	0.188
	SEM	3.685	3.785	3.325
Week 72	95% CI	(-9.1, 5.4)	(-9.5, 5.4)	(-6.3, 6.7)
	Pr >  t			0.9549
	n	28	17	
	LS Mean	-1.812	-2.164	0.352
	SEM	3.657	3.874	3.394
Week 84	95% CI	(-9.0, 5.4)	(-9.8, 5.5)	(-6.3, 7.0)
	Pr >  t			0.9174
	n	23	17	
	LS Mean	-3.131	-0.790	-2.341
	SEM	3.736	3.875	3.481
Week 96	95% CI	(-10.5, 4.2)	(-8.4, 6.8)	(-9.2, 4.5)
	Pr >  t			0.5016
	n	23	11	
	LS Mean	-0.373	-6.503	6.130
	SEM	3.738	4.181	3.819
Week 108	95% CI	(-7.7, 7.0)	(-14.7, 1.7)	(-1.4, 13.6)
	Pr >  t			0.1089
	n	15	13	
	LS Mean	-3.044	-6.260	3.216
	SEM	3.967	4.051	3.910
Week 120	95% CI	(-10.8, 4.8)	(-14.2, 1.7)	(-4.5, 10.9)
	Pr >  t			0.4110
	n	16	9	
	LS Mean	-2.136	-4.539	2.403
	SEM	3.930	4.360	4.194
Week 132	95% CI	(-9.9, 5.6)	(-13.1, 4.0)	(-5.8, 10.6)
	Pr >  t			0.5668
	n	14	5	
	LS Mean	-7.827	-9.662	1.835
	SEM	4.012	5.068	4.991
Week 144	95% CI	(-15.7, 0.1)	(-19.6, 0.3)	(-8.0, 11.6)
	Pr >  t			0.7132
	n	8	3	
	LS Mean	-2.580	-0.050	-2.530
	SEM	4.485	5.975	6.241

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-11.4, 6.2)	(-11.8,11.7)	(-14.8, 9.7)
		Pr >  t			0.6852
		n	7	2	
	Week 168	LS Mean	-3.768	1.472	-5.240
		SEM	4.631	6.940	7.263
		95% CI	(-12.9, 5.3)	(-12.2,15.1)	(-19.5, 9.0)
	Week 180	Pr >  t			0.4709
		n	4	2	
		LS Mean	0.454	1.472	-1.018
	Week 192	SEM	5.426	6.940	7.794
		95% CI	(-10.2,11.1)	(-12.2,15.1)	(-16.3,14.3)
		Pr >  t			0.8961
	Week 8	n	1	1	
		LS Mean	-5.537	-4.478	-1.059
		SEM	9.239	9.236	12.40
	Week 16	95% CI	(-23.7,12.6)	(-22.6,13.7)	(-25.4,23.3)
		Pr >  t			0.9320
		n	1	1	
	Week 24	LS Mean	-18.88	-4.478	-14.40
		SEM	9.239	9.236	12.40
		95% CI	(-37.0,-0.7)	(-22.6,13.7)	(-38.7, 9.9)
	Week 32	Pr >  t			0.2460
		n	18	17	
		LS Mean	-5.235	-11.46	6.222
Week 8	SEM	3.860	4.138	5.625	
	95% CI	(-13.0, 2.5)	(-19.8,-3.1)	(-5.1,17.5)	
	Pr >  t			0.2740	
Week 16	n	17	11		
	LS Mean	-2.332	-7.133	4.801	
	SEM	3.937	4.691	6.096	
Week 24	95% CI	(-10.2, 5.6)	(-16.5, 2.2)	(-7.4,17.0)	
	Pr >  t			0.4340	
	n	15	5		
Week 32	LS Mean	-6.148	-13.72	7.576	
	SEM	4.077	6.075	7.306	
	95% CI	(-14.3, 2.0)	(-25.7,-1.7)	(-6.9,22.1)	
Week 8	Pr >  t			0.3022	
	n	13	5		
	LS Mean	-3.805	-8.394	4.589	
Week 16	SEM	4.231	6.075	7.399	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-12.2, 4.6)	(-20.4, 3.6)	(-10.1,19.3)	
	Pr >  t			0.5364	
	n	11	5		
	LS Mean	-3.024	-8.392	5.368	
	SEM	4.423	6.075	7.510	
Week 48	95% CI	(-11.8, 5.8)	(-20.4, 3.6)	(-9.5,20.3)	
	Pr >  t			0.4762	
	n	11	2		
	LS Mean	-12.02	-9.426	-2.590	
	SEM	4.426	8.383	9.478	
Week 56	95% CI	(-20.8,-3.2)	(-26.0, 7.1)	(-21.3,16.1)	
	Pr >  t			0.7850	
	n	8	2		
	LS Mean	-8.059	-6.091	-1.968	
	SEM	4.829	8.383	9.672	
Week 64	95% CI	(-17.6, 1.5)	(-22.6,10.5)	(-21.1,17.1)	
	Pr >  t			0.8390	
	n	7	3		
	LS Mean	-6.417	-5.977	-0.440	
	SEM	5.019	7.227	8.797	
Week 72	95% CI	(-16.4, 3.5)	(-20.2, 8.3)	(-17.8,16.9)	
	Pr >  t			0.9601	
	n	7	3		
	LS Mean	-3.595	-8.200	4.605	
	SEM	5.031	7.227	8.804	
Week 84	95% CI	(-13.6, 6.4)	(-22.5, 6.1)	(-12.8,22.0)	
	Pr >  t			0.6017	
	n	7	2		
	LS Mean	-11.21	-6.091	-5.124	
	SEM	5.031	8.383	9.774	
Week 96	95% CI	(-21.2,-1.2)	(-22.6,10.5)	(-24.4,14.2)	
	Pr >  t			0.6008	
	n	6	3		
	LS Mean	-12.75	-8.200	-4.550	
	SEM	5.275	7.227	8.945	
Week 108	95% CI	(-23.2,-2.3)	(-22.5, 6.1)	(-22.2,13.1)	
	Pr >  t			0.6117	
	n	7	2		
	LS Mean	-7.405	-28.46	21.054	
	SEM	5.031	8.366	9.762	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	Pr >  t		
No Prior Use	Week 120	n	6	1	
		LS Mean	-10.53	-5.748	-4.778
		SEM	5.275	11.15	12.33
	Week 132	95% CI	(-21.0,-0.1)	(-27.8,16.3)	(-29.1,19.6)
		Pr >  t			0.6989
		n	4		
	Week 144	LS Mean	-7.549		
		SEM	6.040		
		95% CI	(-19.5, 4.4)		
	Week 156	Pr >  t			
		n	5		
		LS Mean	-21.11		
	Week 8	SEM	5.592		
		95% CI	(-32.2, -10)		
		Pr >  t			
Week 16	n	3			
	LS Mean	-6.602			
	SEM	6.721			
Week 24	95% CI	(-19.9, 6.7)			
	Pr >  t				
	n	59	57		
Week 32	LS Mean	-2.987	0.116	-3.104	
	SEM	2.794	2.933	2.933	
	95% CI	(-8.5, 2.5)	(-5.7, 5.9)	(-8.9, 2.7)	
Week 16	Pr >  t			0.2913	
	n	47	44		
	LS Mean	-4.776	-0.747	-4.029	
Week 24	SEM	2.914	3.085	3.196	
	95% CI	(-10.5, 1.0)	(-6.8, 5.3)	(-10.3, 2.3)	
	Pr >  t			0.2086	
Week 32	n	39	34		
	LS Mean	-3.343	-2.948	-0.395	
	SEM	3.029	3.266	3.450	
Week 32	95% CI	(-9.3, 2.6)	(-9.4, 3.5)	(-7.2, 6.4)	
	Pr >  t			0.9089	
	n	27	32		
Week 32	LS Mean	-5.607	-3.981	-1.626	
	SEM	3.290	3.303	3.698	



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-12.1, 0.9)	(-10.5, 2.5)	(-8.9, 5.6)
		Pr >  t			0.6605
		n	24	24	
		LS Mean	-0.722	-5.597	4.875
		SEM	3.378	3.511	3.951
Week 48		95% CI	(-7.4, 5.9)	(-12.5, 1.3)	(-2.9, 12.6)
		Pr >  t			0.2180
		n	21	21	
		LS Mean	-4.665	-3.541	-1.124
		SEM	3.483	3.617	4.139
Week 56		95% CI	(-11.5, 2.2)	(-10.7, 3.6)	(-9.3, 7.0)
		Pr >  t			0.7861
		n	18	20	
		LS Mean	-2.287	-5.325	3.038
		SEM	3.614	3.658	4.291
Week 64		95% CI	(-9.4, 4.8)	(-12.5, 1.9)	(-5.4, 11.5)
		Pr >  t			0.4793
		n	14	19	
		LS Mean	-3.996	-3.385	-0.612
		SEM	3.861	3.702	4.543
Week 72		95% CI	(-11.6, 3.6)	(-10.7, 3.9)	(-9.5, 8.3)
		Pr >  t			0.8930
		n	13	15	
		LS Mean	-4.260	-3.091	-1.169
		SEM	3.944	3.924	4.795
Week 84		95% CI	(-12.0, 3.5)	(-10.8, 4.6)	(-10.6, 8.2)
		Pr >  t			0.8074
		n	10	14	
		LS Mean	-1.695	-4.157	2.463
		SEM	4.297	3.994	5.124
Week 96		95% CI	(-10.1, 6.7)	(-12.0, 3.7)	(-7.6, 12.5)
		Pr >  t			0.6310
		n	6	10	
		LS Mean	-3.317	-3.748	0.430
		SEM	5.111	4.395	6.122
Week 108		95% CI	(-13.4, 6.7)	(-12.4, 4.9)	(-11.6, 12.5)
		Pr >  t			0.9440
		n	4	6	
		LS Mean	-3.089	0.367	-3.455
		SEM	5.999	5.204	7.411

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-14.9, 8.7)	(-9.9,10.6)	(-18.0,11.1)
	Pr >  t			0.6412
	n	6	6	
	LS Mean	-2.523	3.318	-5.841
	SEM	5.112	5.206	6.728
Week 132	95% CI	(-12.6, 7.5)	(-6.9,13.5)	(-19.1, 7.4)
	Pr >  t			0.3857
	n	2	3	
	LS Mean	2.448	0.972	1.477
	SEM	8.043	6.795	10.14
Week 144	95% CI	(-13.4,18.2)	(-12.4,14.3)	(-18.4,21.4)
	Pr >  t			0.8842
	n	2	2	
	LS Mean	-4.708	-5.066	0.357
	SEM	8.020	8.095	11.06
Week 156	95% CI	(-20.5,11.0)	(-21.0,10.8)	(-21.4,22.1)
	Pr >  t			0.9743
	n		1	
	LS Mean		-7.728	
	SEM		11.06	
	95% CI		(-29.5,14.0)	
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-0.699	-5.193	4.493
		SEM	7.555	7.846	3.090
		95% CI	(-15.7,14.3)	(-20.8,10.4)	(-1.6,10.6)
		Pr >  t			0.1477
	Week 16	n	51	41	
		LS Mean	-2.553	-6.432	3.879
		SEM	7.566	7.911	3.295
		95% CI	(-17.6,12.4)	(-22.1, 9.3)	(-2.6,10.4)
		Pr >  t			0.2405
	Week 24	n	38	33	
		LS Mean	-4.736	-11.14	6.404
		SEM	7.595	7.952	3.522
		95% CI	(-19.8,10.3)	(-26.9, 4.6)	(-0.5,13.3)
		Pr >  t			0.0702
	Week 32	n	34	28	
		LS Mean	-2.647	-8.202	5.556
		SEM	7.674	7.984	3.653
		95% CI	(-17.9,12.6)	(-24.0, 7.6)	(-1.6,12.7)
		Pr >  t			0.1294
	Week 40	n	26	23	
		LS Mean	-1.848	-8.115	6.267
		SEM	7.739	8.031	3.888
		95% CI	(-17.2,13.5)	(-24.0, 7.8)	(-1.4,13.9)
		Pr >  t			0.1080
	Week 48	n	24	17	
		LS Mean	-7.061	-11.03	3.973
		SEM	7.759	8.126	4.126
95% CI		(-22.4, 8.3)	(-27.1, 5.1)	(-4.1,12.1)	
	Pr >  t			0.3362	
Week 56	n	21	17		
	LS Mean	-3.724	-7.608	3.884	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	7.798	8.129	4.201
	95% CI	(-19.2,11.7)	(-23.7, 8.5)	(-4.4,12.1)
	Pr >  t			0.3557
Week 64	n	15	15	
	LS Mean	-5.908	-4.090	-1.818
	SEM	7.917	8.174	4.505
	95% CI	(-21.6, 9.8)	(-20.3,12.1)	(-10.7, 7.0)
	Pr >  t			0.6867
Week 72	n	16	15	
	LS Mean	-3.847	-7.112	3.265
	SEM	7.892	8.174	4.461
	95% CI	(-19.5,11.8)	(-23.3, 9.1)	(-5.5,12.0)
	Pr >  t			0.4646
Week 84	n	14	13	
	LS Mean	-6.661	-9.729	3.068
	SEM	7.946	8.234	4.664
	95% CI	(-22.4, 9.1)	(-26.0, 6.6)	(-6.1,12.2)
	Pr >  t			0.5110
Week 96	n	12	9	
	LS Mean	-4.672	-9.568	4.896
	SEM	8.019	8.432	5.120
	95% CI	(-20.5,11.2)	(-26.2, 7.1)	(-5.2,15.0)
	Pr >  t			0.3394
Week 108	n	13	8	
	LS Mean	-3.376	-8.258	4.881
	SEM	7.980	8.510	5.193
	95% CI	(-19.2,12.4)	(-25.1, 8.6)	(-5.3,15.1)
	Pr >  t			0.3476
Week 120	n	11	6	
	LS Mean	-9.741	-7.740	-2.001
	SEM	8.064	8.740	5.681
	95% CI	(-25.7, 6.2)	(-25.0, 9.5)	(-13.2, 9.2)
	Pr >  t			0.7248
Week 132	n	8	3	
	LS Mean	-6.633	-16.03	9.401
	SEM	8.262	9.603	7.165
	95% CI	(-23.0, 9.7)	(-35.0, 2.9)	(-4.7,23.5)
	Pr >  t			0.1900
Week 144	n	5	1	
	LS Mean	-13.15	-2.011	-11.14

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	8.679	12.47	11.03
		95% CI	(-30.3, 4.0)	(-26.5,22.5)	(-32.8,10.5)
		Pr >  t			0.3132
	Week 168	n	3	1	
		LS Mean	-1.301	-2.011	0.710
		SEM	9.382	12.47	11.59
	Week 180	95% CI	(-19.8,17.2)	(-26.5,22.5)	(-22.1,23.5)
		Pr >  t			0.9512
		n	2	1	
	Week 192	LS Mean	-2.588	-2.011	-0.577
		SEM	10.18	12.47	12.25
		95% CI	(-22.6,17.4)	(-26.5,22.5)	(-24.6,23.5)
	Week 8	Pr >  t			0.9624
		n		1	
		LS Mean		-8.681	
	Week 16	SEM		12.47	
		95% CI		(-33.2,15.8)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-8.681	
		SEM		12.47	
	Week 32	95% CI		(-33.2,15.8)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	-1.452	-0.390	-1.062	
	SEM	3.407	3.520	4.810	
	95% CI	(-8.3, 5.4)	(-7.4, 6.6)	(-10.7, 8.5)	
Week 16	Pr >  t			0.8259	
	n	18	14		
	LS Mean	-0.444	5.634	-6.079	
Week 24	SEM	3.350	3.660	4.898	
	95% CI	(-7.1, 6.3)	(-1.7,12.9)	(-15.8, 3.7)	
	Pr >  t			0.2187	
Week 32	n	16	13		
	LS Mean	-2.089	4.804	-6.893	
	SEM	3.475	3.733	5.033	
Week 8	95% CI	(-9.0, 4.8)	(-2.6,12.2)	(-16.9, 3.1)	
	Pr >  t			0.1748	
	n	15	13		
Week 16	LS Mean	-3.297	2.379	-5.676	
	SEM				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	3.527	3.741	5.079
		95% CI	(-10.3, 3.7)	(-5.1, 9.8)	(-15.8, 4.4)
		Pr >  t			0.2671
	Week 40	n	14	10	
		LS Mean	1.168	3.232	-2.064
		SEM	3.604	4.009	5.330
		95% CI	(-6.0, 8.3)	(-4.7, 11.2)	(-12.6, 8.5)
		Pr >  t			0.6994
	Week 48	n	14	11	
		LS Mean	-2.165	1.625	-3.790
		SEM	3.604	3.914	5.257
		95% CI	(-9.3, 5.0)	(-6.2, 9.4)	(-14.2, 6.7)
		Pr >  t			0.4729
	Week 56	n	11	11	
		LS Mean	0.894	5.867	-4.972
		SEM	3.831	3.914	5.419
		95% CI	(-6.7, 8.5)	(-1.9, 13.6)	(-15.7, 5.8)
		Pr >  t			0.3611
	Week 64	n	8	11	
		LS Mean	-0.612	3.442	-4.054
		SEM	4.185	3.914	5.678
		95% CI	(-8.9, 7.7)	(-4.3, 11.2)	(-15.3, 7.2)
		Pr >  t			0.4767
	Week 72	n	11	10	
		LS Mean	-0.925	2.262	-3.186
		SEM	3.831	4.015	5.492
		95% CI	(-8.5, 6.7)	(-5.7, 10.2)	(-14.1, 7.7)
		Pr >  t			0.5630
	Week 84	n	9	9	
		LS Mean	-6.441	3.252	-9.693
		SEM	4.045	4.130	5.730
		95% CI	(-14.5, 1.6)	(-4.9, 11.4)	(-21.0, 1.7)
		Pr >  t			0.0934
	Week 96	n	8	7	
		LS Mean	-8.374	2.043	-10.42
		SEM	4.188	4.437	6.054
		95% CI	(-16.7, -0.1)	(-6.7, 10.8)	(-22.4, 1.6)
		Pr >  t			0.0876
	Week 108	n	7	6	
		LS Mean	-1.712	-3.027	1.315

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.362	4.660	6.338
		95% CI	(-10.3, 6.9)	(-12.2, 6.2)	(-11.2,13.8)
		Pr >  t			0.8359
	Week 120	n	6	5	
		LS Mean	2.055	5.973	-3.918
		SEM	4.586	4.955	6.701
		95% CI	(-7.0,11.1)	(-3.8,15.8)	(-17.1, 9.3)
		Pr >  t			0.5595
	Week 132	n	5	3	
		LS Mean	-1.169	2.345	-3.514
		SEM	4.875	5.947	7.648
		95% CI	(-10.8, 8.4)	(-9.4,14.1)	(-18.6,11.6)
		Pr >  t			0.6463
	Week 144	n	5	4	
		LS Mean	-3.833	2.548	-6.381
		SEM	4.875	5.347	7.191
		95% CI	(-13.4, 5.8)	(-8.0,13.1)	(-20.6, 7.8)
		Pr >  t			0.3759
	Week 156	n	4	2	
		LS Mean	-4.776	1.951	-6.727
		SEM	5.274	6.994	8.727
		95% CI	(-15.2, 5.6)	(-11.8,15.7)	(-23.9,10.5)
		Pr >  t			0.4415
	Week 168	n	1	1	
		LS Mean	-5.315	6.390	-11.70
		SEM	9.422	9.467	13.34
		95% CI	(-23.9,13.2)	(-12.2,25.0)	(-38.0,14.5)
		Pr >  t			0.3809
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-3.669	-3.512	-0.157
		SEM	4.020	3.681	4.417
		95% CI	(-11.8, 4.4)	(-10.9, 3.9)	(-9.0, 8.7)
		Pr >  t			0.9718
	Week 16	n	15	17	
		LS Mean	-0.438	-4.766	4.328
		SEM	4.165	3.805	4.565
		95% CI	(-8.8, 7.9)	(-12.4, 2.9)	(-4.8,13.5)
		Pr >  t			0.3474
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	0.114	-6.751	6.865
	SEM	4.206	4.050	4.838
	95% CI	(-8.3, 8.6)	(-14.9, 1.3)	(-2.8, 16.5)
	Pr >  t			0.1606
	n	12	9	
Week 40	LS Mean	0.722	-5.044	5.766
	SEM	4.324	4.223	5.052
	95% CI	(-7.9, 9.4)	(-13.5, 3.4)	(-4.3, 15.8)
	Pr >  t			0.2573
	n	11	7	
Week 48	LS Mean	5.334	-8.382	13.716
	SEM	4.393	4.492	5.302
	95% CI	(-3.5, 14.1)	(-17.3, 0.5)	(3.2, 24.3)
	Pr >  t			0.0113
	n	8	6	
Week 56	LS Mean	3.506	-2.923	6.430
	SEM	4.608	4.651	5.616
	95% CI	(-5.7, 12.7)	(-12.2, 6.3)	(-4.7, 17.6)
	Pr >  t			0.2549
	n	7	5	
Week 64	LS Mean	-3.616	-8.413	4.796
	SEM	4.715	4.840	5.866
	95% CI	(-13.0, 5.8)	(-18.0, 1.2)	(-6.8, 16.4)
	Pr >  t			0.4153
	n	5	3	
Week 72	LS Mean	2.790	-3.383	6.173
	SEM	5.039	5.564	6.714
	95% CI	(-7.2, 12.8)	(-14.4, 7.6)	(-7.1, 19.4)
	Pr >  t			0.3594
	n	5	2	
Week 84	LS Mean	-4.258	-2.488	-1.770
	SEM	5.064	6.349	7.395
	95% CI	(-14.3, 5.8)	(-15.0, 10.0)	(-16.4, 12.8)
	Pr >  t			0.8112
	n	4	2	
Week 96	LS Mean	-2.470	-5.818	3.349
	SEM	5.297	6.349	7.561
	95% CI	(-13.0, 8.0)	(-18.4, 6.7)	(-11.6, 18.3)
	Pr >  t			0.6584
	n	4	2	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	LS Mean	-1.791	-2.488	0.698
	SEM	5.304	6.349	7.565
	95% CI	(-12.3, 8.7)	(-15.0,10.0)	(-14.2,15.6)
	Pr >  t			0.9266
	n	1	2	
Week 120	LS Mean	-4.836	5.926	-10.76
	SEM	8.250	6.319	9.838
	95% CI	(-21.1,11.5)	( -6.6,18.4)	(-30.2, 8.7)
	Pr >  t			0.2756
	n	5	1	
Week 132	LS Mean	-1.590	-0.554	-1.036
	SEM	5.064	8.175	9.012
	95% CI	(-11.6, 8.5)	(-16.7,15.6)	(-18.8,16.8)
	Pr >  t			0.9086
	n	3	1	
Week 144	LS Mean	-3.229	6.116	-9.346
	SEM	5.714	8.175	9.396
	95% CI	(-14.5, 8.1)	(-10.0,22.3)	(-27.9, 9.2)
	Pr >  t			0.3213
	n	3		
Week 156	LS Mean	-7.673		
	SEM	5.714		
	95% CI	(-19.0, 3.6)		
	Pr >  t			
	n	3		
Week 168	LS Mean	-3.229		
	SEM	5.714		
	95% CI	(-14.5, 8.1)		
	Pr >  t			
	n	3		
Week 180	LS Mean	9.302		
	SEM	8.243		
	95% CI	( -7.0,25.6)		
	Pr >  t			
	n	1		
Week 192	LS Mean	-4.028		
	SEM	8.243		
	95% CI	(-20.3,12.2)		
	Pr >  t			
	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	-17.37		
		SEM	8.243		
		95% CI	(-33.6,-1.1)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	-6.663	1.561	-8.224
		SEM	3.259	3.256	3.539
		95% CI	(-13.1,-0.2)	(-4.9, 8.0)	(-15.2,-1.2)
		Pr >  t			0.0216
	Week 16	n	30	29	
		LS Mean	-5.667	-0.414	-5.253
		SEM	3.381	3.552	3.904
		95% CI	(-12.4, 1.0)	(-7.4, 6.6)	(-13.0, 2.5)
		Pr >  t			0.1802
	Week 24	n	26	20	
		LS Mean	-5.708	1.827	-7.535
		SEM	3.521	3.931	4.309
		95% CI	(-12.7, 1.3)	(-5.9, 9.6)	(-16.0, 1.0)
		Pr >  t			0.0817
	Week 32	n	18	20	
		LS Mean	-3.719	-0.839	-2.880
		SEM	3.864	3.931	4.586
		95% CI	(-11.3, 3.9)	(-8.6, 6.9)	(-11.9, 6.2)
		Pr >  t			0.5307
	Week 40	n	18	19	
		LS Mean	-2.629	-2.911	0.282
		SEM	3.863	3.978	4.626
		95% CI	(-10.3, 5.0)	(-10.8, 4.9)	(-8.8, 9.4)
		Pr >  t			0.9515
	Week 48	n	16	14	
		LS Mean	-5.301	-2.674	-2.627
		SEM	3.977	4.281	4.984
		95% CI	(-13.1, 2.5)	(-11.1, 5.8)	(-12.4, 7.2)
		Pr >  t			0.5986
	Week 56	n	14	10	
		LS Mean	-1.797	-4.403	2.605
		SEM	4.117	4.702	5.464
		95% CI	(-9.9, 6.3)	(-13.7, 4.9)	(-8.1,13.4)
		Pr >  t			0.6338

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	-4.583	-4.715	0.133
		SEM	4.202	4.575	5.422
		95% CI	(-12.9, 3.7)	(-13.7, 4.3)	(-10.5,10.8)
		Pr >  t			0.9805
Week 72		n	10	6	
		LS Mean	-3.721	-0.013	-3.708
		SEM	4.528	5.544	6.493
		95% CI	(-12.6, 5.2)	(-10.9,10.9)	(-16.5, 9.1)
		Pr >  t			0.5683
Week 84		n	8	7	
		LS Mean	-1.358	5.909	-7.267
		SEM	4.908	5.261	6.505
		95% CI	(-11.0, 8.3)	( -4.4,16.3)	(-20.1, 5.5)
		Pr >  t			0.2647
Week 96		n	6	5	
		LS Mean	2.967	-6.827	9.794
		SEM	5.401	5.909	7.411
		95% CI	( -7.7,13.6)	(-18.4, 4.8)	( -4.8,24.4)
		Pr >  t			0.1872
Week 108		n	2	4	
		LS Mean	-9.674	-1.557	-8.117
		SEM	8.438	6.426	10.15
		95% CI	(-26.3, 6.9)	(-14.2,11.1)	(-28.1,11.8)
		Pr >  t			0.4245
Week 120		n	4	4	
		LS Mean	3.439	1.775	1.664
		SEM	6.288	6.426	8.474
		95% CI	( -8.9,15.8)	(-10.9,14.4)	(-15.0,18.3)
		Pr >  t			0.8445
Week 132		n	3	1	
		LS Mean	-11.25	-5.934	-5.318
		SEM	7.094	11.64	13.27
		95% CI	(-25.2, 2.7)	(-28.8,17.0)	(-31.4,20.8)
		Pr >  t			0.6889
Week 144		n	2		
		LS Mean	-4.893		
		SEM	8.395		
		95% CI	(-21.4,11.6)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-4.237	-3.175	-1.062		
			SEM	3.036	3.037	2.403		
			95% CI	(-10.2, 1.7)	(-9.2, 2.8)	(-5.8, 3.7)		
					Pr >  t			0.6588
		Week 16	n	79	68			
			LS Mean	-3.844	-3.208	-0.636		
			SEM	3.064	3.168	2.579		
			95% CI	(-9.9, 2.2)	(-9.4, 3.0)	(-5.7, 4.4)		
					Pr >  t			0.8055
		Week 24	n	64	55			
			LS Mean	-6.559	-4.321	-2.238		
			SEM	3.138	3.268	2.753		
			95% CI	(-12.7,-0.4)	(-10.8, 2.1)	(-7.6, 3.2)		
					Pr >  t			0.4166
		Week 32	n	49	53			
			LS Mean	-4.515	-4.357	-0.157		
			SEM	3.255	3.283	2.880		
			95% CI	(-10.9, 1.9)	(-10.8, 2.1)	(-5.8, 5.5)		
					Pr >  t			0.9564
		Week 40	n	44	45			
			LS Mean	-2.839	-5.435	2.596		
			SEM	3.300	3.345	3.001		
			95% CI	(-9.3, 3.7)	(-12.0, 1.1)	(-3.3, 8.5)		
					Pr >  t			0.3873
		Week 48	n	41	36			
			LS Mean	-7.097	-6.504	-0.593		
			SEM	3.329	3.443	3.140		
95% CI	(-13.6,-0.5)		(-13.3, 0.3)	(-6.8, 5.6)				
			Pr >  t			0.8504		
Week 56	n	33	32					
	LS Mean	-2.839	-4.997	2.158				
		SEM	3.429	3.502	3.311			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.6, 3.9)	(-11.9, 1.9)	(-4.3, 8.7)
		Pr >  t			0.5148
	Week 64	n	27	31	
		LS Mean	-5.571	-4.858	-0.713
		SEM	3.536	3.520	3.443
		95% CI	(-12.5, 1.4)	(-11.8, 2.1)	(-7.5, 6.0)
		Pr >  t			0.8360
	Week 72	n	26	26	
		LS Mean	-4.659	-4.184	-0.475
		SEM	3.558	3.620	3.568
		95% CI	(-11.7, 2.3)	(-11.3, 2.9)	(-7.5, 6.5)
		Pr >  t			0.8941
	Week 84	n	22	23	
		LS Mean	-6.280	-3.386	-2.894
		SEM	3.677	3.696	3.753
		95% CI	(-13.5, 0.9)	(-10.7, 3.9)	(-10.3, 4.5)
		Pr >  t			0.4408
	Week 96	n	18	18	
		LS Mean	-4.033	-7.068	3.035
		SEM	3.828	3.876	4.071
		95% CI	(-11.6, 3.5)	(-14.7, 0.5)	(-5.0, 11.0)
		Pr >  t			0.4561
	Week 108	n	14	14	
		LS Mean	-4.477	-7.734	3.257
		SEM	4.055	4.099	4.486
		95% CI	(-12.4, 3.5)	(-15.8, 0.3)	(-5.5, 12.1)
		Pr >  t			0.4680
	Week 120	n	12	12	
		LS Mean	-3.007	-2.410	-0.597
		SEM	4.211	4.258	4.769
		95% CI	(-11.3, 5.3)	(-10.8, 6.0)	(-10.0, 8.8)
		Pr >  t			0.9005
	Week 132	n	9	5	
		LS Mean	-9.717	-9.638	-0.079
		SEM	4.558	5.557	6.208
		95% CI	(-18.7, -0.8)	(-20.5, 1.3)	(-12.3, 12.1)
		Pr >  t			0.9899
	Week 144	n	7	4	
		LS Mean	-3.291	-4.964	1.673
		SEM	4.924	6.035	6.895

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.0, 6.4)	(-16.8, 6.9)	(-11.9,15.2)
		Pr >  t			0.8083
	Week 156	n	4	2	
		LS Mean	-5.717	-5.556	-0.161
		SEM	5.991	7.974	9.294
		95% CI	(-17.5, 6.0)	(-21.2,10.1)	(-18.4,18.1)
		Pr >  t			0.9862
	Week 168	n	2	1	
		LS Mean	-5.048	-1.076	-3.971
		SEM	7.936	10.86	12.96
		95% CI	(-20.6,10.5)	(-22.4,20.2)	(-29.4,21.5)
		Pr >  t			0.7593
Yes	Week 8	n	53	48	
		LS Mean	-0.795	-0.284	-0.510
		SEM	2.577	2.702	2.507
		95% CI	(-5.9, 4.3)	(-5.6, 5.1)	(-5.5, 4.4)
		Pr >  t			0.8389
	Week 16	n	45	39	
		LS Mean	-0.409	-1.638	1.229
		SEM	2.672	2.801	2.654
		95% CI	(-5.7, 4.9)	(-7.2, 3.9)	(-4.0, 6.5)
		Pr >  t			0.6438
	Week 24	n	41	26	
		LS Mean	1.208	-4.644	5.852
		SEM	2.702	2.962	2.874
		95% CI	(-4.1, 6.5)	(-10.5, 1.2)	( 0.2,11.5)
		Pr >  t			0.0428
	Week 32	n	37	20	
		LS Mean	1.567	-3.673	5.240
		SEM	2.752	3.118	3.053
		95% CI	(-3.9, 7.0)	(-9.8, 2.5)	(-0.8,11.2)
		Pr >  t			0.0871
	Week 40	n	31	17	
		LS Mean	1.935	-3.269	5.204
		SEM	2.820	3.236	3.215
		95% CI	(-3.6, 7.5)	(-9.6, 3.1)	(-1.1,11.5)
		Pr >  t			0.1064
	Week 48	n	28	15	
		LS Mean	0.447	-2.042	2.489
		SEM	2.859	3.320	3.337

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-5.2, 6.1)	(-8.6, 4.5)	(-4.1, 9.0)
	Pr >  t			0.4561
Week 56	n	26	13	
	LS Mean	-1.019	-1.227	0.207
	SEM	2.890	3.424	3.469
	95% CI	(-6.7, 4.7)	(-8.0, 5.5)	(-6.6, 7.0)
	Pr >  t			0.9524
Week 64	n	20	11	
	LS Mean	0.326	1.604	-1.278
	SEM	3.017	3.558	3.706
	95% CI	(-5.6, 6.3)	(-5.4, 8.6)	(-8.6, 6.0)
	Pr >  t			0.7304
Week 72	n	22	9	
	LS Mean	-0.025	-0.604	0.579
	SEM	2.970	3.739	3.844
	95% CI	(-5.9, 5.8)	(-8.0, 6.7)	(-7.0, 8.1)
	Pr >  t			0.8803
Week 84	n	18	10	
	LS Mean	-1.018	-1.394	0.376
	SEM	3.082	3.642	3.834
	95% CI	(-7.1, 5.1)	(-8.6, 5.8)	(-7.2, 7.9)
	Pr >  t			0.9219
Week 96	n	17	6	
	LS Mean	-1.372	-1.097	-0.274
	SEM	3.109	4.193	4.387
	95% CI	(-7.5, 4.8)	(-9.3, 7.1)	(-8.9, 8.3)
	Pr >  t			0.9501
Week 108	n	12	7	
	LS Mean	-2.471	-3.564	1.093
	SEM	3.360	4.006	4.391
	95% CI	(-9.1, 4.1)	(-11.4, 4.3)	(-7.5, 9.7)
	Pr >  t			0.8034
Week 120	n	16	4	
	LS Mean	-3.163	-0.782	-2.381
	SEM	3.151	4.791	4.987
	95% CI	(-9.4, 3.0)	(-10.2, 8.6)	(-12.2, 7.4)
	Pr >  t			0.6332
Week 132	n	11	3	
	LS Mean	-3.229	-0.462	-2.766
	SEM	3.432	5.320	5.659



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.0, 3.5)	(-10.9,10.0)	(-13.9, 8.3)
		Pr >  t			0.6251
	Week 144	n	8	1	
		LS Mean	-11.79	4.821	-16.61
		SEM	3.722	8.426	8.769
		95% CI	(-19.1,-4.5)	(-11.7,21.4)	(-33.8, 0.6)
		Pr >  t			0.0587
	Week 156	n	6	1	
		LS Mean	-1.908	4.821	-6.729
		SEM	4.077	8.426	8.920
		95% CI	(-9.9, 6.1)	(-11.7,21.4)	(-24.3,10.8)
		Pr >  t			0.4509
	Week 168	n	2	1	
		LS Mean	4.466	4.821	-0.355
		SEM	6.157	8.426	10.04
		95% CI	(-7.6,16.6)	(-11.7,21.4)	(-20.1,19.4)
		Pr >  t			0.9718
	Week 180	n	1	1	
		LS Mean	-4.622	-1.849	-2.773
		SEM	8.339	8.426	11.51
		95% CI	(-21.0,11.8)	(-18.4,14.7)	(-25.4,19.8)
		Pr >  t			0.8097
	Week 192	n	1	1	
		LS Mean	-17.96	-1.849	-16.11
		SEM	8.339	8.426	11.51
		95% CI	(-34.3,-1.6)	(-18.4,14.7)	(-38.7, 6.5)
		Pr >  t			0.1621

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	LS Mean			
		SEM			
		95% CI	( , )		
		Pr >  t			
		Week 8	n	2	
		Week 16	n	2	
		Week 24	n	1	
		Week 32	n	1	
		Week 40	n	1	
		Week 48	n	1	
	Week 56	n	1		
	Week 72	n	1		
	Week 84	n	1		
	Week 96	n	1		
	Positive	Week 8	n	140	140
		LS Mean	-2.879	-2.055	-0.823
		SEM	2.085	2.113	1.799
		95% CI	( -7.0, 1.2)	( -6.2, 2.1)	( -4.4, 2.7)
		Pr >  t			0.6474
		Week 16	n	122	107
LS Mean		-2.578	-2.535	-0.042	
SEM		2.127	2.200	1.921	
95% CI		( -6.8, 1.6)	( -6.9, 1.8)	( -3.8, 3.7)	
Pr >  t				0.9824	
Week 24	n	104	81		
LS Mean	-3.626	-4.266	0.640		
SEM	2.168	2.285	2.054		
95% CI	( -7.9, 0.6)	( -8.8, 0.2)	( -3.4, 4.7)		
Pr >  t			0.7554		
Week 32	n	85	73		
LS Mean	-2.161	-3.978	1.816		
SEM	2.234	2.323	2.147		
95% CI	( -6.6, 2.2)	( -8.5, 0.6)	( -2.4, 6.0)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.3978
Week 40	n	74	62	
	LS Mean	-1.053	-4.651	3.598
	SEM	2.275	2.381	2.247
	95% CI	(-5.5, 3.4)	(-9.3, 0.0)	(-0.8, 8.0)
	Pr >  t			0.1096
Week 48	n	68	51	
	LS Mean	-4.165	-5.040	0.874
	SEM	2.300	2.454	2.349
	95% CI	(-8.7, 0.4)	(-9.9,-0.2)	(-3.7, 5.5)
	Pr >  t			0.7099
Week 56	n	58	45	
	LS Mean	-2.528	-3.754	1.226
	SEM	2.352	2.506	2.456
	95% CI	(-7.1, 2.1)	(-8.7, 1.2)	(-3.6, 6.0)
	Pr >  t			0.6178
Week 64	n	47	42	
	LS Mean	-3.297	-2.953	-0.345
	SEM	2.431	2.538	2.564
	95% CI	(-8.1, 1.5)	(-7.9, 2.0)	(-5.4, 4.7)
	Pr >  t			0.8931
Week 72	n	47	35	
	LS Mean	-2.925	-3.009	0.084
	SEM	2.433	2.626	2.653
	95% CI	(-7.7, 1.9)	(-8.2, 2.1)	(-5.1, 5.3)
	Pr >  t			0.9748
Week 84	n	39	33	
	LS Mean	-4.373	-2.678	-1.695
	SEM	2.521	2.657	2.759
	95% CI	(-9.3, 0.6)	(-7.9, 2.5)	(-7.1, 3.7)
	Pr >  t			0.5391
Week 96	n	34	24	
	LS Mean	-3.134	-5.332	2.198
	SEM	2.588	2.853	3.008
	95% CI	(-8.2, 1.9)	(-10.9, 0.3)	(-3.7, 8.1)
	Pr >  t			0.4650
Week 108	n	26	21	
	LS Mean	-3.998	-6.296	2.298
	SEM	2.750	2.950	3.234
	95% CI	(-9.4, 1.4)	(-12.1,-0.5)	(-4.0, 8.6)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	Pr >  t			0.4775
	n	28	16	
	LS Mean	-3.971	-1.771	-2.200
	SEM	2.701	3.178	3.407
	95% CI	(-9.3, 1.3)	(-8.0, 4.5)	(-8.9, 4.5)
Week 132	Pr >  t			0.5185
	n	20	8	
	LS Mean	-6.944	-6.288	-0.656
	SEM	2.938	3.984	4.325
	95% CI	(-12.7,-1.2)	(-14.1, 1.5)	(-9.1, 7.8)
Week 144	Pr >  t			0.8794
	n	15	5	
	LS Mean	-8.515	-2.587	-5.929
	SEM	3.184	4.780	5.218
	95% CI	(-14.8,-2.3)	(-12.0, 6.8)	(-16.2, 4.3)
Week 156	Pr >  t			0.2560
	n	10	3	
	LS Mean	-4.386	-2.118	-2.268
	SEM	3.641	5.925	6.524
	95% CI	(-11.5, 2.8)	(-13.7, 9.5)	(-15.1,10.5)
Week 168	Pr >  t			0.7281
	n	4	2	
	LS Mean	-0.949	1.177	-2.127
	SEM	5.202	7.104	8.469
	95% CI	(-11.2, 9.3)	(-12.8,15.1)	(-18.7,14.5)
Week 180	Pr >  t			0.8018
	n	1	1	
	LS Mean	-7.117	-4.665	-2.453
	SEM	9.800	9.811	13.66
	95% CI	(-26.3,12.1)	(-23.9,14.6)	(-29.2,24.3)
Week 192	Pr >  t			0.8575
	n	1	1	
	LS Mean	-20.46	-4.665	-15.79
	SEM	9.800	9.811	13.66
	95% CI	(-39.7,-1.2)	(-23.9,14.6)	(-42.6,11.0)
	Pr >  t			0.2477

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
PIK3CA mutation	E542K	Week 8	n	16	24			
			LS Mean	-1.627	-5.636	4.009		
			SEM	5.732	6.359	5.356		
			95% CI	(-13.2, 9.9)	(-18.5, 7.2)	(-6.7, 14.7)		
					Pr >  t			0.4571
		Week 16	n	14	17			
			LS Mean	4.927	-10.09	15.014		
			SEM	5.795	6.518	5.678		
			95% CI	(-6.7, 16.6)	(-23.2, 3.0)	(3.7, 26.3)		
					Pr >  t			0.0101
		Week 24	n	14	11			
			LS Mean	-3.644	-7.628	3.984		
			SEM	5.795	6.794	5.994		
			95% CI	(-15.3, 8.0)	(-21.3, 6.0)	(-7.9, 15.9)		
					Pr >  t			0.5080
		Week 32	n	10	10			
			LS Mean	3.531	-9.143	12.674		
			SEM	6.235	6.883	6.307		
			95% CI	(-8.9, 16.0)	(-22.9, 4.7)	(0.2, 25.2)		
					Pr >  t			0.0472
		Week 40	n	8	10			
			LS Mean	2.590	-7.301	9.891		
			SEM	6.438	6.880	6.498		
			95% CI	(-10.3, 15.4)	(-21.1, 6.5)	(-3.0, 22.8)		
			Pr >  t			0.1309		
Week 48	n	7	11					
	LS Mean	4.237	-14.26	18.500				
	SEM	6.566	6.815	6.575				
	95% CI	(-8.8, 17.3)	(-27.9, -0.6)	(5.5, 31.5)				
			Pr >  t			0.0058		
Week 56	n	6	9					
	LS Mean	4.796	-5.606	10.402				
	SEM	6.733	6.968	6.905				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.6,18.2)	(-19.6, 8.3)	(-3.3,24.1)
	Pr >  t			0.1345
	n	5	8	
	LS Mean	3.623	-0.427	4.050
	SEM	6.963	7.069	7.226
Week 72	95% CI	(-10.2,17.5)	(-14.6,13.7)	(-10.2,18.3)
	Pr >  t			0.5760
	n	7	7	
	LS Mean	3.721	-8.058	11.779
	SEM	6.557	7.194	6.969
Week 84	95% CI	(-9.3,16.8)	(-22.4, 6.3)	(-2.0,25.6)
	Pr >  t			0.0934
	n	7	7	
	LS Mean	3.718	-6.153	9.871
	SEM	6.557	7.194	6.969
Week 96	95% CI	(-9.3,16.8)	(-20.5, 8.2)	(-3.9,23.7)
	Pr >  t			0.1590
	n	5	6	
	LS Mean	1.774	-12.09	13.861
	SEM	6.960	7.354	7.505
Week 108	95% CI	(-12.1,15.6)	(-26.8, 2.6)	(-1.0,28.7)
	Pr >  t			0.0667
	n	4	6	
	LS Mean	5.268	-16.53	21.799
	SEM	7.297	7.354	7.818
Week 120	95% CI	(-9.2,19.7)	(-31.2,-1.9)	( 6.4,37.2)
	Pr >  t			0.0059
	n	4	4	
	LS Mean	-0.390	-12.51	12.117
	SEM	7.299	7.883	8.322
Week 132	95% CI	(-14.9,14.1)	(-28.2, 3.2)	(-4.3,28.5)
	Pr >  t			0.1471
	n	3	1	
	LS Mean	0.366	-31.94	32.308
	SEM	7.815	11.48	12.11
Week 144	95% CI	(-15.1,15.8)	(-54.6,-9.3)	( 8.4,56.2)
	Pr >  t			0.0082
	n	1	1	
	LS Mean	-34.91	-8.679	-26.24
	SEM	11.10	11.52	14.48

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-56.8, -13)	(-31.4, 14.0)	(-54.8, 2.3)
		Pr >  t			0.0716
	Week 8	n	35	37	
		LS Mean	-3.184	-3.041	-0.143
	Week 8	SEM	7.732	8.095	3.478
		95% CI	(-18.5, 12.1)	(-19.1, 13.0)	(-7.0, 6.7)
	Week 16	Pr >  t			0.9673
		n	34	30	
	Week 16	LS Mean	-1.949	-2.185	0.235
		SEM	7.949	8.166	3.625
	Week 16	95% CI	(-17.7, 13.8)	(-18.3, 14.0)	(-6.9, 7.4)
		Pr >  t			0.9483
	Week 24	n	32	23	
		LS Mean	-2.737	-7.203	4.466
	Week 24	SEM	7.964	8.249	3.867
		95% CI	(-18.5, 13.0)	(-23.5, 9.1)	(-3.2, 12.1)
	Week 24	Pr >  t			0.2496
		n	21	22	
	Week 32	LS Mean	-1.874	-5.972	4.099
		SEM	8.100	8.266	4.190
	Week 32	95% CI	(-17.9, 14.1)	(-22.3, 10.4)	(-4.2, 12.4)
		Pr >  t			0.3290
	Week 40	n	20	20	
		LS Mean	-1.668	-8.614	6.946
	Week 40	SEM	8.126	8.301	4.302
		95% CI	(-17.7, 14.4)	(-25.0, 7.8)	(-1.5, 15.4)
	Week 40	Pr >  t			0.1077
		n	19	12	
Week 48	LS Mean	-2.863	-2.568	-0.295	
	SEM	8.137	8.555	4.808	
Week 48	95% CI	(-18.9, 13.2)	(-19.5, 14.3)	(-9.8, 9.2)	
	Pr >  t			0.9511	
Week 56	n	16	8		
	LS Mean	-0.925	-7.064	6.139	
Week 56	SEM	8.216	8.853	5.443	
	95% CI	(-17.2, 15.3)	(-24.5, 10.4)	(-4.6, 16.8)	
Week 56	Pr >  t			0.2601	
	n	12	11		
Week 64	LS Mean	-0.900	-6.779	5.879	
	SEM	8.374	8.609	5.288	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72	95% CI	(-17.4,15.6)	(-23.8,10.2)	(-4.5,16.3)
	Pr >  t			0.2670
	n	13	7	
	LS Mean	-2.670	-5.017	2.347
Week 84	SEM	8.335	8.979	5.808
	95% CI	(-19.1,13.8)	(-22.7,12.7)	(-9.1,13.8)
	Pr >  t			0.6863
	n	12	6	
Week 96	LS Mean	-3.219	-3.781	0.561
	SEM	8.364	9.148	6.113
	95% CI	(-19.7,13.3)	(-21.8,14.3)	(-11.5,12.6)
	Pr >  t			0.9269
Week 108	n	7	6	
	LS Mean	-1.291	-10.06	8.768
	SEM	8.790	9.144	6.681
	95% CI	(-18.6,16.0)	(-28.1, 8.0)	(-4.4,21.9)
Week 120	Pr >  t			0.1902
	n	5	3	
	LS Mean	-6.939	-7.411	0.472
	SEM	9.173	10.18	8.478
Week 132	95% CI	(-25.0,11.1)	(-27.5,12.6)	(-16.2,17.1)
	Pr >  t			0.9556
	n	8	3	
	LS Mean	-5.532	-5.188	-0.345
Week 144	SEM	8.699	10.18	7.938
	95% CI	(-22.7,11.6)	(-25.2,14.9)	(-16.0,15.3)
	Pr >  t			0.9654
	n	2	1	
Week 156	LS Mean	-16.91	4.438	-21.35
	SEM	10.95	13.55	13.69
	95% CI	(-38.5, 4.6)	(-22.2,31.1)	(-48.3, 5.6)
	Pr >  t			0.1198
Week 156	n	2		
	LS Mean	0.705		
	SEM	10.96		
	95% CI	(-20.9,22.3)		
Week 156	Pr >  t			
	n	2		
	LS Mean	4.040		
	SEM	10.96		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.5,25.6)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	-3.533	-1.504	-2.028
		SEM	2.494	2.587	2.397
		95% CI	(-8.5, 1.4)	(-6.6, 3.6)	(-6.7, 2.7)
		Pr >  t			0.3983
	Week 16	n	70	52	
		LS Mean	-4.767	0.026	-4.793
		SEM	2.545	2.696	2.532
		95% CI	(-9.8, 0.3)	(-5.3, 5.3)	(-9.8, 0.2)
		Pr >  t			0.0593
	Week 24	n	54	40	
		LS Mean	-4.434	-1.993	-2.441
		SEM	2.630	2.820	2.727
		95% CI	(-9.6, 0.7)	(-7.5, 3.6)	(-7.8, 2.9)
		Pr >  t			0.3713
	Week 32	n	50	36	
		LS Mean	-3.480	-2.298	-1.182
		SEM	2.664	2.864	2.799
		95% CI	(-8.7, 1.8)	(-7.9, 3.3)	(-6.7, 4.3)
		Pr >  t			0.6730
	Week 40	n	42	28	
		LS Mean	-1.778	-2.555	0.777
		SEM	2.725	2.992	2.979
		95% CI	(-7.1, 3.6)	(-8.4, 3.3)	(-5.1, 6.6)
		Pr >  t			0.7944
	Week 48	n	38	24	
		LS Mean	-7.155	-3.916	-3.239
		SEM	2.764	3.075	3.097
		95% CI	(-12.6,-1.7)	(-10.0, 2.1)	(-9.3, 2.8)
		Pr >  t			0.2961
	Week 56	n	33	24	
		LS Mean	-4.722	-2.648	-2.074
		SEM	2.822	3.077	3.154
		95% CI	(-10.3, 0.8)	(-8.7, 3.4)	(-8.3, 4.1)
		Pr >  t			0.5111
	Week 64	n	27	19	
		LS Mean	-5.591	-2.988	-2.603
		SEM	2.915	3.222	3.377

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.3, 0.1)	(-9.3, 3.3)	(-9.2, 4.0)
		Pr >  t			0.4411
	Week 72	n	26	17	
		LS Mean	-5.016	-1.444	-3.571
		SEM	2.935	3.298	3.466
		95% CI	(-10.8, 0.8)	(-7.9, 5.0)	(-10.4, 3.2)
		Pr >  t			0.3033
	Week 84	n	18	16	
		LS Mean	-7.980	-1.573	-6.408
		SEM	3.170	3.343	3.700
		95% CI	(-14.2,-1.7)	(-8.1, 5.0)	(-13.7, 0.9)
		Pr >  t			0.0837
	Week 96	n	20	10	
		LS Mean	-6.828	-0.140	-6.687
		SEM	3.095	3.765	4.032
		95% CI	(-12.9,-0.7)	(-7.5, 7.3)	(-14.6, 1.2)
		Pr >  t			0.0976
	Week 108	n	14	10	
		LS Mean	-5.251	-1.227	-4.023
		SEM	3.366	3.766	4.240
		95% CI	(-11.9, 1.4)	(-8.6, 6.2)	(-12.3, 4.3)
		Pr >  t			0.3429
	Week 120	n	14	7	
		LS Mean	-4.534	4.670	-9.204
		SEM	3.356	4.192	4.621
		95% CI	(-11.1, 2.1)	(-3.6,12.9)	(-18.3,-0.1)
		Pr >  t			0.0467
	Week 132	n	12	5	
		LS Mean	-6.623	-1.909	-4.713
		SEM	3.501	4.700	5.178
		95% CI	(-13.5, 0.3)	(-11.1, 7.3)	(-14.9, 5.4)
		Pr >  t			0.3630
	Week 144	n	11	4	
		LS Mean	-8.799	-0.135	-8.665
		SEM	3.575	5.101	5.598
		95% CI	(-15.8,-1.8)	(-10.1, 9.9)	(-19.7, 2.3)
		Pr >  t			0.1220
	Week 156	n	8	3	
		LS Mean	-7.855	0.165	-8.020
		SEM	3.939	5.705	6.366

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.6,-0.1)	(-11.0,11.4)	(-20.5, 4.5)
		Pr >  t			0.2081
	Week 168	n	4	2	
		LS Mean	-2.600	3.415	-6.015
		SEM	5.029	6.751	7.959
		95% CI	(-12.5, 7.3)	(-9.8,16.7)	(-21.6, 9.6)
		Pr >  t			0.4500
	Week 180	n	1	1	
		LS Mean	-8.699	-2.286	-6.414
		SEM	9.159	9.192	12.68
		95% CI	(-26.7, 9.3)	(-20.3,15.8)	(-31.3,18.5)
		Pr >  t			0.6132
	Week 192	n	1	1	
		LS Mean	-22.04	-2.286	-19.75
		SEM	9.159	9.192	12.68
		95% CI	(-40.0,-4.1)	(-20.3,15.8)	(-44.7, 5.1)
		Pr >  t			0.1198

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	-3.533	-1.504	-2.028		
			SEM	2.494	2.587	2.397		
			95% CI	(-8.5, 1.4)	(-6.6, 3.6)	(-6.7, 2.7)		
					Pr >  t			0.3983
		Week 16	n	70	52			
			LS Mean	-4.767	0.026	-4.793		
			SEM	2.545	2.696	2.532		
			95% CI	(-9.8, 0.3)	(-5.3, 5.3)	(-9.8, 0.2)		
					Pr >  t			0.0593
		Week 24	n	54	40			
			LS Mean	-4.434	-1.993	-2.441		
			SEM	2.630	2.820	2.727		
			95% CI	(-9.6, 0.7)	(-7.5, 3.6)	(-7.8, 2.9)		
					Pr >  t			0.3713
		Week 32	n	50	36			
			LS Mean	-3.480	-2.298	-1.182		
			SEM	2.664	2.864	2.799		
			95% CI	(-8.7, 1.8)	(-7.9, 3.3)	(-6.7, 4.3)		
					Pr >  t			0.6730
		Week 40	n	42	28			
			LS Mean	-1.778	-2.555	0.777		
			SEM	2.725	2.992	2.979		
			95% CI	(-7.1, 3.6)	(-8.4, 3.3)	(-5.1, 6.6)		
					Pr >  t			0.7944
		Week 48	n	38	24			
			LS Mean	-7.155	-3.916	-3.239		
			SEM	2.764	3.075	3.097		
95% CI	(-12.6, -1.7)		(-10.0, 2.1)	(-9.3, 2.8)				
			Pr >  t			0.2961		
Week 56	n	33	24					
	LS Mean	-4.722	-2.648	-2.074				
	SEM	2.822	3.077	3.154				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.3, 0.8)	(-8.7, 3.4)	(-8.3, 4.1)
	Pr >  t			0.5111
	n	27	19	
	LS Mean	-5.591	-2.988	-2.603
	SEM	2.915	3.222	3.377
Week 72	95% CI	(-11.3, 0.1)	(-9.3, 3.3)	(-9.2, 4.0)
	Pr >  t			0.4411
	n	26	17	
	LS Mean	-5.016	-1.444	-3.571
	SEM	2.935	3.298	3.466
Week 84	95% CI	(-10.8, 0.8)	(-7.9, 5.0)	(-10.4, 3.2)
	Pr >  t			0.3033
	n	18	16	
	LS Mean	-7.980	-1.573	-6.408
	SEM	3.170	3.343	3.700
Week 96	95% CI	(-14.2,-1.7)	(-8.1, 5.0)	(-13.7, 0.9)
	Pr >  t			0.0837
	n	20	10	
	LS Mean	-6.828	-0.140	-6.687
	SEM	3.095	3.765	4.032
Week 108	95% CI	(-12.9,-0.7)	(-7.5, 7.3)	(-14.6, 1.2)
	Pr >  t			0.0976
	n	14	10	
	LS Mean	-5.251	-1.227	-4.023
	SEM	3.366	3.766	4.240
Week 120	95% CI	(-11.9, 1.4)	(-8.6, 6.2)	(-12.3, 4.3)
	Pr >  t			0.3429
	n	14	7	
	LS Mean	-4.534	4.670	-9.204
	SEM	3.356	4.192	4.621
Week 132	95% CI	(-11.1, 2.1)	(-3.6,12.9)	(-18.3,-0.1)
	Pr >  t			0.0467
	n	12	5	
	LS Mean	-6.623	-1.909	-4.713
	SEM	3.501	4.700	5.178
Week 144	95% CI	(-13.5, 0.3)	(-11.1, 7.3)	(-14.9, 5.4)
	Pr >  t			0.3630
	n	11	4	
Week 144	LS Mean	-8.799	-0.135	-8.665
	SEM	3.575	5.101	5.598

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.8,-1.8)	(-10.1, 9.9)	(-19.7, 2.3)
		Pr >  t			0.1220
	Week 156	n	8	3	
		LS Mean	-7.855	0.165	-8.020
		SEM	3.939	5.705	6.366
		95% CI	(-15.6,-0.1)	(-11.0,11.4)	(-20.5, 4.5)
		Pr >  t			0.2081
	Week 168	n	4	2	
		LS Mean	-2.600	3.415	-6.015
		SEM	5.029	6.751	7.959
		95% CI	(-12.5, 7.3)	(-9.8,16.7)	(-21.6, 9.6)
		Pr >  t			0.4500
	Week 180	n	1	1	
		LS Mean	-8.699	-2.286	-6.414
		SEM	9.159	9.192	12.68
		95% CI	(-26.7, 9.3)	(-20.3,15.8)	(-31.3,18.5)
		Pr >  t			0.6132
	Week 192	n	1	1	
		LS Mean	-22.04	-2.286	-19.75
		SEM	9.159	9.192	12.68
		95% CI	(-40.0,-4.1)	(-20.3,15.8)	(-44.7, 5.1)
		Pr >  t			0.1198
Exon 9	Week 8	n	53	64	
		LS Mean	-2.666	-3.266	0.600
		SEM	4.455	4.788	2.982
		95% CI	(-11.5, 6.1)	(-12.7, 6.2)	(-5.3, 6.5)
		Pr >  t			0.8408
	Week 16	n	48	48	
		LS Mean	0.661	-3.975	4.636
		SEM	4.537	4.874	3.169
		95% CI	(-8.3, 9.6)	(-13.6, 5.7)	(-1.6,10.9)
		Pr >  t			0.1448
	Week 24	n	46	36	
		LS Mean	-2.422	-6.718	4.295
		SEM	4.549	4.967	3.343
		95% CI	(-11.4, 6.6)	(-16.5, 3.1)	(-2.3,10.9)
		Pr >  t			0.2000
	Week 32	n	31	33	
		LS Mean	0.325	-6.559	6.885
		SEM	4.761	5.005	3.591

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-9.1, 9.7)	(-16.5, 3.3)	(-0.2,13.9)
	Pr >  t			0.0561
	n	28	30	
	LS Mean	0.126	-7.540	7.666
	SEM	4.808	5.042	3.703
Week 48	95% CI	(-9.4, 9.6)	(-17.5, 2.4)	( 0.4,14.9)
	Pr >  t			0.0391
	n	26	23	
	LS Mean	-0.280	-7.196	6.916
	SEM	4.838	5.165	3.911
Week 56	95% CI	(-9.8, 9.3)	(-17.4, 3.0)	(-0.8,14.6)
	Pr >  t			0.0777
	n	22	17	
	LS Mean	1.291	-5.266	6.558
	SEM	4.920	5.340	4.238
Week 64	95% CI	(-8.4,11.0)	(-15.8, 5.3)	(-1.8,14.9)
	Pr >  t			0.1224
	n	17	19	
	LS Mean	1.021	-3.347	4.368
	SEM	5.075	5.272	4.333
Week 72	95% CI	(-9.0,11.0)	(-13.8, 7.1)	(-4.1,12.9)
	Pr >  t			0.3139
	n	20	14	
	LS Mean	-0.035	-5.645	5.609
	SEM	4.979	5.479	4.474
Week 84	95% CI	(-9.9, 9.8)	(-16.4, 5.2)	(-3.2,14.4)
	Pr >  t			0.2104
	n	19	13	
	LS Mean	-0.369	-4.021	3.652
	SEM	5.002	5.537	4.575
Week 96	95% CI	(-10.2, 9.5)	(-14.9, 6.9)	(-5.3,12.6)
	Pr >  t			0.4250
	n	12	12	
	LS Mean	0.224	-10.20	10.422
	SEM	5.342	5.604	5.018
Week 108	95% CI	(-10.3,10.7)	(-21.2, 0.8)	( 0.6,20.3)
	Pr >  t			0.0382
	n	9	9	
Week 108	LS Mean	-1.536	-12.20	10.664
	SEM	5.628	5.880	5.613



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.6, 9.5)	(-23.8,-0.6)	( -0.4,21.7)
		Pr >  t			0.0579
	Week 120	n	12	7	
		LS Mean	-3.310	-8.398	5.088
		SEM	5.356	6.181	5.664
		95% CI	(-13.9, 7.2)	(-20.6, 3.8)	( -6.0,16.2)
		Pr >  t			0.3693
	Week 132	n	5	2	
		LS Mean	-7.208	-13.19	5.984
		SEM	6.451	8.839	9.221
		95% CI	(-19.9, 5.5)	(-30.6, 4.2)	(-12.1,24.1)
		Pr >  t			0.5166
	Week 144	n	3	1	
		LS Mean	-10.79	-6.168	-4.626
		SEM	7.529	11.62	12.53
		95% CI	(-25.6, 4.0)	(-29.0,16.6)	(-29.2,20.0)
		Pr >  t			0.7121
	Week 156	n	2		
		LS Mean	5.361		
		SEM	8.693		
		95% CI	(-11.7,22.4)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-37: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Rollenfunktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference			
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv			
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73			
			LS Mean	-4.816	-2.743	-2.073		
			SEM	4.010	4.036	3.552		
			95% CI	(-12.7, 3.1)	(-10.7, 5.2)	(-9.1, 4.9)		
							Pr >  t	0.5599
		Week 16	n	67	56			
			LS Mean	-4.903	-5.826	0.923		
			SEM	4.066	4.241	3.813		
			95% CI	(-12.9, 3.1)	(-14.2, 2.5)	(-6.6, 8.4)		
							Pr >  t	0.8088
		Week 24	n	61	46			
			LS Mean	-6.317	-0.495	-5.823		
			SEM	4.130	4.355	4.002		
			95% CI	(-14.5, 1.8)	(-9.1, 8.1)	(-13.7, 2.0)		
							Pr >  t	0.1465
		Week 32	n	52	41			
			LS Mean	-5.599	-5.960	0.362		
			SEM	4.247	4.446	4.170		
			95% CI	(-14.0, 2.8)	(-14.7, 2.8)	(-7.8, 8.6)		
							Pr >  t	0.9309
		Week 40	n	45	36			
			LS Mean	-5.782	-4.571	-1.212		
			SEM	4.328	4.554	4.348		
			95% CI	(-14.3, 2.7)	(-13.5, 4.4)	(-9.8, 7.3)		
					Pr >  t	0.7806		
Week 48	n	42	30					
	LS Mean	-9.071	-2.280	-6.790				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	SEM	4.372	4.691	4.535
	95% CI	(-17.7,-0.5)	(-11.5, 7.0)	(-15.7, 2.1)
	Pr >  t			0.1349
	n	35	24	
	LS Mean	-9.991	-2.265	-7.726
Week 64	SEM	4.491	4.890	4.853
	95% CI	(-18.8,-1.1)	(-11.9, 7.4)	(-17.3, 1.8)
	Pr >  t			0.1119
	n	25	25	
	LS Mean	-7.196	-0.382	-6.814
Week 72	SEM	4.756	4.853	5.069
	95% CI	(-16.6, 2.2)	(-9.9, 9.2)	(-16.8, 3.1)
	Pr >  t			0.1793
	n	27	20	
	LS Mean	-12.20	-3.964	-8.235
Week 84	SEM	4.691	5.075	5.221
	95% CI	(-21.4,-3.0)	(-13.9, 6.0)	(-18.5, 2.0)
	Pr >  t			0.1152
	n	23	19	
	LS Mean	-10.16	-1.750	-8.414
Week 96	SEM	4.849	5.132	5.407
	95% CI	(-19.7,-0.6)	(-11.8, 8.3)	(-19.0, 2.2)
	Pr >  t			0.1201
	n	20	13	
	LS Mean	-8.584	-1.511	-7.072
Week 108	SEM	4.993	5.621	5.993
	95% CI	(-18.4, 1.2)	(-12.6, 9.5)	(-18.8, 4.7)
	Pr >  t			0.2383
	n	17	13	
	LS Mean	-9.254	-6.629	-2.625
Week 120	SEM	5.182	5.622	6.151
	95% CI	(-19.4, 0.9)	(-17.7, 4.4)	(-14.7, 9.4)
	Pr >  t			0.6697
	n	17	12	
	LS Mean	-8.358	-1.205	-7.152
Week 132	SEM	5.180	5.744	6.262
	95% CI	(-18.5, 1.8)	(-12.5,10.1)	(-19.4, 5.1)
	Pr >  t			0.2537
	n	13	6	
	LS Mean	-11.24	-10.28	-0.960

Subgroup	Time Window		Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
			N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 144	SEM	5.541	7.120	7.796
		95% CI	(-22.1,-0.4)	(-24.3, 3.7)	(-16.3,14.3)
		Pr >  t			0.9020
		n	11	4	
		LS Mean	-11.15	0.677	-11.82
		SEM	5.804	8.277	9.032
	Week 156	95% CI	(-22.5, 0.3)	(-15.6,16.9)	(-29.5, 5.9)
		Pr >  t			0.1909
		n	7	2	
		LS Mean	-2.931	-13.34	10.409
		SEM	6.684	11.01	12.05
		95% CI	(-16.1,10.2)	(-34.9, 8.3)	(-13.2,34.1)
	Week 168	Pr >  t			0.3881
		n	3	1	
		LS Mean	-7.012	10.051	-17.06
		SEM	9.206	15.06	17.06
		95% CI	(-25.1,11.1)	(-19.5,39.6)	(-50.5,16.4)
		Pr >  t			0.3175
	Week 180	n	1	1	
		LS Mean	-23.31	-23.28	-0.031
		SEM	15.02	15.06	20.78
		95% CI	(-52.8, 6.2)	(-52.8, 6.3)	(-40.8,40.8)
		Pr >  t			0.9988
		n	1	1	
Week 192	LS Mean	10.020	10.051	-0.031	
	SEM	15.02	15.06	20.78	
	95% CI	(-19.5,39.5)	(-19.5,39.6)	(-40.8,40.8)	
	Pr >  t			0.9988	
	n	65	67		
	LS Mean	-7.433	-7.565	0.133	
Week 8	SEM	4.396	4.515	3.746	
	95% CI	(-16.1, 1.2)	(-16.5, 1.3)	(-7.2, 7.5)	
	Pr >  t			0.9718	
	n	57	51		
	LS Mean	-5.034	-8.760	3.727	
	SEM	4.542	4.697	4.017	
Week 16	95% CI	(-14.0, 3.9)	(-18.0, 0.5)	(-4.2,11.6)	
	Pr >  t			0.3544	
	n	44	35		
	LS Mean	-5.569	-12.04	6.467	
	SEM				
	95% CI				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.677	4.992	4.467
		95% CI	(-14.8, 3.7)	(-21.9,-2.2)	( -2.3,15.3)
		Pr >  t			0.1486
	Week 32	n	34	32	
		LS Mean	-3.201	-8.615	5.414
		SEM	4.869	5.065	4.728
		95% CI	(-12.8, 6.4)	(-18.6, 1.4)	( -3.9,14.7)
		Pr >  t			0.2528
	Week 40	n	30	26	
		LS Mean	-1.780	-12.71	10.929
		SEM	4.965	5.232	5.006
		95% CI	(-11.6, 8.0)	(-23.0,-2.4)	( 1.1,20.8)
		Pr >  t			0.0295
	Week 48	n	27	21	
		LS Mean	-1.925	-12.86	10.931
		SEM	5.042	5.434	5.293
		95% CI	(-11.9, 8.0)	(-23.5,-2.2)	( 0.5,21.3)
		Pr >  t			0.0394
	Week 56	n	24	21	
		LS Mean	-0.479	-14.32	13.841
		SEM	5.145	5.434	5.392
		95% CI	(-10.6, 9.6)	(-25.0,-3.6)	( 3.2,24.4)
		Pr >  t			0.0105
	Week 64	n	22	17	
		LS Mean	-3.070	-14.79	11.716
		SEM	5.225	5.662	5.698
		95% CI	(-13.4, 7.2)	(-25.9,-3.7)	( 0.5,22.9)
		Pr >  t			0.0402
	Week 72	n	21	15	
		LS Mean	0.687	-7.934	8.622
		SEM	5.273	5.813	5.892
		95% CI	( -9.7,11.1)	(-19.4, 3.5)	( -2.9,20.2)
		Pr >  t			0.1439
	Week 84	n	17	14	
		LS Mean	-6.166	-11.01	4.846
		SEM	5.508	5.901	6.175
		95% CI	(-17.0, 4.7)	(-22.6, 0.6)	( -7.3,17.0)
		Pr >  t			0.4329
	Week 96	n	15	11	
		LS Mean	-2.064	-14.69	12.631

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	5.643	6.252	6.644
	95% CI	(-13.2, 9.0)	(-27.0,-2.4)	(-0.4,25.7)
	Pr >  t			0.0577
Week 108	n	9	8	
	LS Mean	-5.453	-11.75	6.297
	SEM	6.446	6.818	7.812
	95% CI	(-18.1, 7.2)	(-25.1, 1.6)	(-9.0,21.6)
	Pr >  t			0.4205
Week 120	n	11	4	
	LS Mean	-5.771	-16.43	10.655
	SEM	6.097	8.574	9.161
	95% CI	(-17.8, 6.2)	(-33.3, 0.4)	(-7.3,28.6)
	Pr >  t			0.2452
Week 132	n	7	2	
	LS Mean	-9.528	-7.118	-2.410
	SEM	6.950	11.24	12.15
	95% CI	(-23.2, 4.1)	(-29.2,14.9)	(-26.3,21.5)
	Pr >  t			0.8429
Week 144	n	4	1	
	LS Mean	-19.01	-9.136	-9.876
	SEM	8.380	15.26	16.64
	95% CI	(-35.5,-2.6)	(-39.1,20.8)	(-42.6,22.8)
	Pr >  t			0.5531
Week 156	n	3	1	
	LS Mean	-17.69	-9.136	-8.554
	SEM	9.420	15.26	17.17
	95% CI	(-36.2, 0.8)	(-39.1,20.8)	(-42.3,25.2)
	Pr >  t			0.6184
Week 168	n	1	1	
	LS Mean	-3.094	-9.136	6.042
	SEM	15.21	15.26	20.91
	95% CI	(-33.0,26.8)	(-39.1,20.8)	(-35.0,47.1)
	Pr >  t			0.7727

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	-5.417	-2.185	-3.232		
			SEM	3.224	3.410	3.146		
			95% CI	(-11.8, 0.9)	(-8.9, 4.5)	(-9.4, 3.0)		
					Pr >  t			0.3049
		Week 16	n	86	68			
			LS Mean	-4.692	-6.657	1.966		
			SEM	3.293	3.540	3.348		
			95% CI	(-11.2, 1.8)	(-13.6, 0.3)	(-4.6, 8.5)		
					Pr >  t			0.5574
		Week 24	n	73	48			
			LS Mean	-5.551	-1.620	-3.931		
			SEM	3.378	3.780	3.667		
			95% CI	(-12.2, 1.1)	(-9.1, 5.8)	(-11.1, 3.3)		
					Pr >  t			0.2841
		Week 32	n	60	43			
			LS Mean	-3.512	-5.763	2.250		
			SEM	3.515	3.871	3.844		
			95% CI	(-10.4, 3.4)	(-13.4, 1.8)	(-5.3, 9.8)		
					Pr >  t			0.5585
		Week 40	n	50	38			
			LS Mean	-4.922	-3.246	-1.676		
			SEM	3.623	3.974	4.037		
			95% CI	(-12.0, 2.2)	(-11.1, 4.6)	(-9.6, 6.3)		
					Pr >  t			0.6782
		Week 48	n	48	31			
			LS Mean	-7.654	-1.411	-6.243		
			SEM	3.651	4.143	4.227		
95% CI	(-14.8,-0.5)		(-9.6, 6.7)	(-14.5, 2.1)				
			Pr >  t			0.1402		
Week 56	n	41	25					
	LS Mean	-8.654	-2.560	-6.094				
	SEM	3.756	4.350	4.521				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-16.0,-1.3)	(-11.1, 6.0)	(-15.0, 2.8)
	Pr >  t			0.1781
	n	30	24	
	LS Mean	-5.336	-0.154	-5.182
	SEM	4.001	4.393	4.772
Week 72	95% CI	(-13.2, 2.5)	(-8.8, 8.5)	(-14.5, 4.2)
	Pr >  t			0.2778
	n	32	19	
	LS Mean	-9.606	-3.904	-5.702
	SEM	3.947	4.659	4.974
Week 84	95% CI	(-17.4,-1.8)	(-13.1, 5.2)	(-15.5, 4.1)
	Pr >  t			0.2519
	n	26	19	
	LS Mean	-10.03	-1.477	-8.548
	SEM	4.154	4.659	5.128
Week 96	95% CI	(-18.2,-1.9)	(-10.6, 7.7)	(-18.6, 1.5)
	Pr >  t			0.0959
	n	23	14	
	LS Mean	-7.406	-1.220	-6.186
	SEM	4.274	5.077	5.609
Week 108	95% CI	(-15.8, 1.0)	(-11.2, 8.7)	(-17.2, 4.8)
	Pr >  t			0.2703
	n	19	13	
	LS Mean	-7.739	-4.407	-3.332
	SEM	4.507	5.192	5.883
Week 120	95% CI	(-16.6, 1.1)	(-14.6, 5.8)	(-14.9, 8.2)
	Pr >  t			0.5712
	n	19	11	
	LS Mean	-8.744	-0.763	-7.980
	SEM	4.496	5.475	6.134
Week 132	95% CI	(-17.6, 0.1)	(-11.5,10.0)	(-20.0, 4.1)
	Pr >  t			0.1935
	n	15	5	
	LS Mean	-13.04	-8.172	-4.865
	SEM	4.825	7.286	7.982
Week 144	95% CI	(-22.5,-3.6)	(-22.5, 6.1)	(-20.5,10.8)
	Pr >  t			0.5424
	n	12	3	
Week 144	LS Mean	-9.971	1.991	-11.96
	SEM	5.167	9.028	9.782

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.1, 0.2)	(-15.7,19.7)	(-31.2, 7.2)
		Pr >  t			0.2217
	Week 156	n	7	2	
		LS Mean	-2.129	-12.78	10.655
		SEM	6.277	10.79	11.97
		95% CI	(-14.4,10.2)	(-34.0, 8.4)	(-12.8,34.1)
		Pr >  t			0.3735
	Week 168	n	3	1	
		LS Mean	-6.244	10.610	-16.85
		SEM	8.909	14.90	16.99
		95% CI	(-23.7,11.2)	(-18.6,39.8)	(-50.2,16.5)
		Pr >  t			0.3214
	Week 180	n	1	1	
		LS Mean	-22.52	-22.72	0.201
		SEM	14.83	14.90	20.72
		95% CI	(-51.6, 6.6)	(-52.0, 6.5)	(-40.5,40.9)
		Pr >  t			0.9923
	Week 192	n	1	1	
		LS Mean	10.811	10.610	0.201
		SEM	14.83	14.90	20.72
		95% CI	(-18.3,39.9)	(-18.6,39.8)	(-40.5,40.9)
		Pr >  t			0.9923
Yes	Week 8	n	44	56	
		LS Mean	-11.60	-14.30	2.696
		SEM	7.295	6.967	4.552
		95% CI	(-26.0, 2.8)	(-28.1,-0.5)	( -6.3,11.7)
		Pr >  t			0.5547
	Week 16	n	38	39	
		LS Mean	-9.711	-12.93	3.215
		SEM	7.470	7.317	4.928
		95% CI	(-24.5, 5.0)	(-27.4, 1.5)	( -6.5,12.9)
		Pr >  t			0.5150
	Week 24	n	32	33	
		LS Mean	-11.27	-16.90	5.626
		SEM	7.560	7.394	5.185
		95% CI	(-26.2, 3.7)	(-31.5,-2.3)	( -4.6,15.8)
		Pr >  t			0.2791
	Week 32	n	26	30	
		LS Mean	-11.54	-14.94	3.400
		SEM	7.676	7.456	5.434

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-26.7, 3.6)	(-29.7,-0.2)	( -7.3,14.1)
	Pr >  t			0.5321
	n	25	24	
	LS Mean	-7.352	-21.30	13.947
	SEM	7.703	7.587	5.650
Week 48	95% CI	(-22.6, 7.9)	(-36.3,-6.3)	( 2.8,25.1)
	Pr >  t			0.0142
	n	21	20	
	LS Mean	-7.567	-20.81	13.247
	SEM	7.810	7.715	5.961
Week 56	95% CI	(-23.0, 7.8)	(-36.0,-5.6)	( 1.5,25.0)
	Pr >  t			0.0269
	n	18	20	
	LS Mean	-4.872	-20.64	15.773
	SEM	7.923	7.713	6.108
Week 64	95% CI	(-20.5,10.8)	(-35.9,-5.4)	( 3.8,27.8)
	Pr >  t			0.0102
	n	17	18	
	LS Mean	-10.06	-21.15	11.094
	SEM	7.971	7.796	6.270
Week 72	95% CI	(-25.8, 5.7)	(-36.5,-5.8)	( -1.2,23.4)
	Pr >  t			0.0776
	n	16	16	
	LS Mean	-5.232	-14.76	9.530
	SEM	8.024	7.897	6.458
Week 84	95% CI	(-21.1,10.6)	(-30.3, 0.8)	( -3.2,22.2)
	Pr >  t			0.1408
	n	14	14	
	LS Mean	-10.25	-17.87	7.621
	SEM	8.140	8.018	6.745
Week 96	95% CI	(-26.3, 5.8)	(-33.7,-2.1)	( -5.6,20.9)
	Pr >  t			0.2592
	n	12	10	
	LS Mean	-7.405	-22.15	14.742
	SEM	8.298	8.394	7.368
Week 108	95% CI	(-23.8, 8.9)	(-38.7,-5.6)	( 0.3,29.2)
	Pr >  t			0.0460
	n	7	8	
	LS Mean	-12.49	-21.92	9.429
	SEM	9.028	8.709	8.505

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-30.3, 5.3)	(-39.1,-4.8)	( -7.3,26.1)
		Pr >  t			0.2681
	Week 120	n	9	5	
		LS Mean	-8.804	-22.14	13.338
		SEM	8.662	9.586	9.050
		95% CI	(-25.9, 8.3)	(-41.0,-3.3)	( -4.4,31.1)
		Pr >  t			0.1411
	Week 132	n	5	3	
		LS Mean	-7.736	-20.81	13.074
		SEM	9.673	10.94	11.33
		95% CI	(-26.8,11.3)	(-42.3, 0.7)	( -9.2,35.3)
		Pr >  t			0.2490
	Week 144	n	3	2	
		LS Mean	-29.43	-16.65	-12.78
		SEM	11.02	12.45	13.84
		95% CI	(-51.1,-7.8)	(-41.1, 7.8)	(-40.0,14.4)
		Pr >  t			0.3561
	Week 156	n	3	1	
		LS Mean	-22.89	-16.65	-6.234
		SEM	11.03	16.12	17.22
		95% CI	(-44.6,-1.2)	(-48.3,15.0)	(-40.1,27.6)
		Pr >  t			0.7175
	Week 168	n	1	1	
		LS Mean	-8.246	-16.65	8.404
		SEM	16.21	16.12	20.92
		95% CI	(-40.1,23.6)	(-48.3,15.0)	(-32.7,49.5)
		Pr >  t			0.6881

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	-4.881	-3.957	-0.925		
			SEM	3.814	3.782	3.109		
			95% CI	(-12.4, 2.6)	(-11.4, 3.5)	(-7.0, 5.2)		
					Pr >  t			0.7664
		Week 16	n	92	77			
			LS Mean	-4.552	-5.654	1.102		
			SEM	3.852	3.953	3.304		
			95% CI	(-12.1, 3.0)	(-13.4, 2.1)	(-5.4, 7.6)		
					Pr >  t			0.7389
		Week 24	n	83	66			
			LS Mean	-5.848	-4.996	-0.852		
			SEM	3.904	4.020	3.439		
			95% CI	(-13.5, 1.8)	(-12.9, 2.9)	(-7.6, 5.9)		
					Pr >  t			0.8045
		Week 32	n	72	60			
			LS Mean	-5.895	-6.789	0.895		
			SEM	3.970	4.080	3.560		
			95% CI	(-13.7, 1.9)	(-14.8, 1.2)	(-6.1, 7.9)		
					Pr >  t			0.8016
		Week 40	n	64	51			
			LS Mean	-4.748	-7.530	2.782		
			SEM	4.020	4.176	3.713		
			95% CI	(-12.7, 3.2)	(-15.7, 0.7)	(-4.5, 10.1)		
			Pr >  t			0.4541		
Week 48	n	58	45					
	LS Mean	-7.412	-4.210	-3.202				
	SEM	4.064	4.247	3.841				
	95% CI	(-15.4, 0.6)	(-12.6, 4.1)	(-10.7, 4.3)				
			Pr >  t			0.4047		
Week 56	n	49	38					
	LS Mean	-7.517	-4.642	-2.875				
	SEM	4.147	4.355	4.049				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-15.7, 0.6)	(-13.2, 3.9)	(-10.8, 5.1)
		Pr >  t			0.4778
	Week 64	n	39	37	
		LS Mean	-7.094	-5.106	-1.988
		SEM	4.278	4.374	4.206
		95% CI	(-15.5, 1.3)	(-13.7, 3.5)	(-10.2, 6.3)
		Pr >  t			0.6366
	Week 72	n	41	32	
		LS Mean	-8.244	-5.471	-2.773
		SEM	4.248	4.479	4.284
		95% CI	(-16.6, 0.1)	(-14.3, 3.3)	(-11.2, 5.6)
		Pr >  t			0.5176
	Week 84	n	33	29	
		LS Mean	-8.782	-5.605	-3.177
		SEM	4.408	4.556	4.507
		95% CI	(-17.4,-0.1)	(-14.6, 3.3)	(-12.0, 5.7)
		Pr >  t			0.4810
	Week 96	n	31	21	
		LS Mean	-6.999	-7.762	0.763
		SEM	4.448	4.856	4.854
		95% CI	(-15.7, 1.7)	(-17.3, 1.8)	(-8.8,10.3)
		Pr >  t			0.8751
	Week 108	n	23	18	
		LS Mean	-8.719	-9.409	0.690
		SEM	4.716	5.028	5.258
		95% CI	(-18.0, 0.5)	(-19.3, 0.5)	(-9.6,11.0)
		Pr >  t			0.8956
	Week 120	n	25	15	
		LS Mean	-6.290	-3.726	-2.564
		SEM	4.630	5.258	5.413
		95% CI	(-15.4, 2.8)	(-14.0, 6.6)	(-13.2, 8.1)
		Pr >  t			0.6358
	Week 132	n	17	8	
		LS Mean	-8.867	-10.07	1.198
		SEM	5.045	6.313	6.742
		95% CI	(-18.8, 1.0)	(-22.5, 2.3)	(-12.0,14.4)
		Pr >  t			0.8589
	Week 144	n	15	5	
		LS Mean	-13.22	-2.395	-10.82
		SEM	5.192	7.461	7.931

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-23.4,-3.0)	(-17.0,12.2)	(-26.4, 4.7)
		Pr >  t			0.1726
	Week 156	n	10	3	
		LS Mean	-7.366	-12.07	4.706
		SEM	5.837	9.135	9.883
		95% CI	(-18.8, 4.1)	(-30.0, 5.8)	(-14.7,24.1)
		Pr >  t			0.6340
	Week 168	n	4	2	
		LS Mean	-5.960	1.420	-7.379
		SEM	8.085	10.87	12.80
		95% CI	(-21.8, 9.9)	(-19.9,22.8)	(-32.5,17.7)
		Pr >  t			0.5643
	Week 180	n	1	1	
		LS Mean	-22.72	-26.08	3.354
		SEM	14.89	14.90	20.59
		95% CI	(-51.9, 6.5)	(-55.3, 3.2)	(-37.0,43.8)
		Pr >  t			0.8706
	Week 192	n	1	1	
		LS Mean	10.608	7.254	3.354
		SEM	14.89	14.90	20.59
		95% CI	(-18.6,39.8)	(-22.0,36.5)	(-37.0,43.8)
		Pr >  t			0.8706
Yes	Week 8	n	38	42	
		LS Mean	-8.469	-6.031	-2.438
		SEM	4.572	4.913	4.562
		95% CI	(-17.5, 0.6)	(-15.8, 3.7)	(-11.5, 6.6)
		Pr >  t			0.5940
	Week 16	n	32	30	
		LS Mean	-5.127	-9.752	4.624
		SEM	4.859	5.162	5.036
		95% CI	(-14.7, 4.5)	(-20.0, 0.5)	( -5.3,14.6)
		Pr >  t			0.3598
	Week 24	n	22	15	
		LS Mean	-5.849	-5.041	-0.808
		SEM	5.190	6.096	6.237
		95% CI	(-16.1, 4.4)	(-17.1, 7.0)	(-13.1,11.5)
		Pr >  t			0.8970
	Week 32	n	14	13	
		LS Mean	3.083	-5.679	8.763
		SEM	5.905	6.305	6.942

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.6,14.7)	(-18.1, 6.8)	(-4.9,22.4)
		Pr >  t			0.2080
	Week 40	n	11	11	
		LS Mean	0.071	-7.891	7.962
		SEM	6.309	6.570	7.518
		95% CI	(-12.4,12.5)	(-20.8, 5.1)	(-6.8,22.8)
		Pr >  t			0.2905
	Week 48	n	11	6	
		LS Mean	1.587	-21.06	22.650
		SEM	6.309	7.836	8.645
		95% CI	(-10.8,14.0)	(-36.5,-5.6)	( 5.6,39.7)
		Pr >  t			0.0093
	Week 56	n	10	7	
		LS Mean	2.591	-21.13	23.720
		SEM	6.479	7.471	8.444
		95% CI	(-10.2,15.4)	(-35.8,-6.4)	( 7.1,40.3)
		Pr >  t			0.0053
	Week 64	n	8	5	
		LS Mean	4.385	-10.74	15.130
		SEM	6.910	8.305	9.504
		95% CI	(-9.2,18.0)	(-27.1, 5.6)	(-3.6,33.8)
		Pr >  t			0.1125
	Week 72	n	7	3	
		LS Mean	4.124	0.152	3.972
		SEM	7.201	9.963	11.17
		95% CI	(-10.1,18.3)	(-19.5,19.8)	(-18.0,26.0)
		Pr >  t			0.7224
	Week 84	n	7	4	
		LS Mean	-5.401	-1.155	-4.245
		SEM	7.201	8.964	10.29
		95% CI	(-19.6, 8.8)	(-18.8,16.5)	(-24.5,16.0)
		Pr >  t			0.6802
	Week 96	n	4	3	
		LS Mean	3.630	0.152	3.478
		SEM	8.719	9.963	12.20
		95% CI	(-13.5,20.8)	(-19.5,19.8)	(-20.6,27.5)
		Pr >  t			0.7759
	Week 108	n	3	3	
		LS Mean	1.132	-3.115	4.247
		SEM	9.724	9.967	12.94



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.0,20.3)	(-22.7,16.5)	(-21.2,29.7)
		Pr >  t			0.7431
	Week 120	n	3	1	
		LS Mean	-15.22	-36.08	20.859
		SEM	9.725	15.75	17.78
		95% CI	(-34.4, 3.9)	(-67.1,-5.0)	(-14.2,55.9)
		Pr >  t			0.2421
	Week 132	n	3		
		LS Mean	-17.63		
		SEM	9.725		
		95% CI	(-36.8, 1.5)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Bone Lesions Only (L)	No	Week 8	n	104	110	
			LS Mean	-5.741	-5.427	-0.314
			SEM	3.431	3.419	2.955
			95% CI	(-12.5, 1.0)	(-12.2, 1.3)	(-6.1, 5.5)
		Pr >  t			0.9155	
		Week 16	n	92	83	
			LS Mean	-3.924	-5.517	1.594
			SEM	3.508	3.585	3.155
			95% CI	(-10.8, 3.0)	(-12.6, 1.5)	(-4.6, 7.8)
		Pr >  t			0.6138	
		Week 24	n	77	59	
			LS Mean	-5.921	-7.069	1.148
			SEM	3.572	3.764	3.422
			95% CI	(-13.0, 1.1)	(-14.5, 0.3)	(-5.6, 7.9)
		Pr >  t			0.7375	
		Week 32	n	57	53	
			LS Mean	-4.269	-8.817	4.548
			SEM	3.741	3.822	3.634
			95% CI	(-11.6, 3.1)	(-16.3,-1.3)	(-2.6,11.7)
		Pr >  t			0.2112	
		Week 40	n	50	44	
			LS Mean	-1.440	-9.058	7.618
			SEM	3.813	3.943	3.823
			95% CI	(-8.9, 6.1)	(-16.8,-1.3)	( 0.1,15.1)
		Pr >  t			0.0467	
		Week 48	n	47	37	
			LS Mean	-4.137	-10.22	6.079
			SEM	3.847	4.059	3.976
95% CI	(-11.7, 3.4)		(-18.2,-2.2)	(-1.7,13.9)		
Pr >  t			0.1267			
Week 56	n	40	32			
	LS Mean	-4.098	-10.85	6.755		
	SEM	3.945	4.166	4.179		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-11.9, 3.7)	(-19.0,-2.7)	(-1.4,15.0)
	Pr >  t			0.1063
	n	32	27	
	LS Mean	-3.488	-9.222	5.734
Week 72	SEM	4.102	4.308	4.464
	95% CI	(-11.5, 4.6)	(-17.7,-0.8)	(-3.0,14.5)
	Pr >  t			0.1993
	n	31	23	
Week 84	LS Mean	-2.292	-6.906	4.615
	SEM	4.129	4.458	4.632
	95% CI	(-10.4, 5.8)	(-15.7, 1.8)	(-4.5,13.7)
	Pr >  t			0.3194
Week 96	n	27	21	
	LS Mean	-6.250	-7.519	1.269
	SEM	4.245	4.550	4.818
	95% CI	(-14.6, 2.1)	(-16.5, 1.4)	(-8.2,10.7)
Week 108	Pr >  t			0.7923
	n	23	16	
	LS Mean	-3.758	-9.981	6.222
	SEM	4.387	4.864	5.241
Week 120	95% CI	(-12.4, 4.9)	(-19.5,-0.4)	(-4.1,16.5)
	Pr >  t			0.2354
	n	15	14	
	LS Mean	-3.291	-10.12	6.830
Week 132	SEM	4.884	5.042	5.813
	95% CI	(-12.9, 6.3)	(-20.0,-0.2)	(-4.6,18.2)
	Pr >  t			0.2403
	n	18	8	
Week 144	LS Mean	-5.748	-7.866	2.118
	SEM	4.655	5.998	6.499
	95% CI	(-14.9, 3.4)	(-19.6, 3.9)	(-10.6,14.9)
	Pr >  t			0.7446
Week 132	n	12	4	
	LS Mean	-7.611	-19.24	11.626
	SEM	5.207	7.756	8.473
	95% CI	(-17.8, 2.6)	(-34.5,-4.0)	(-5.0,28.3)
Week 144	Pr >  t			0.1703
	n	8	3	
	LS Mean	-12.44	-7.461	-4.976
	SEM	5.917	8.749	9.813

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-24.0,-0.8)	(-24.6, 9.7)	(-24.2,14.3)
		Pr >  t			0.6122
	Week 156	n	5	1	
		LS Mean	-8.584	-7.380	-1.204
		SEM	7.053	14.34	15.49
		95% CI	(-22.4, 5.3)	(-35.5,20.8)	(-31.6,29.2)
		Pr >  t			0.9381
	Week 168	n	2	1	
		LS Mean	-12.40	-7.380	-5.025
		SEM	10.40	14.34	17.27
		95% CI	(-32.8, 8.0)	(-35.5,20.8)	(-38.9,28.9)
		Pr >  t			0.7711
	Week 180	n	1		
		LS Mean	-21.49		
		SEM	14.29		
		95% CI	(-49.5, 6.6)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	11.843		
		SEM	14.29		
		95% CI	(-16.2,39.9)		
		Pr >  t			
Yes	Week 8	n	38	30	
		LS Mean	-7.081	-3.665	-3.416
		SEM	6.106	6.551	5.463
		95% CI	(-19.2, 5.0)	(-16.7, 9.3)	(-14.2, 7.4)
		Pr >  t			0.5327
	Week 16	n	32	24	
		LS Mean	-8.174	-13.80	5.622
		SEM	6.212	6.738	5.881
		95% CI	(-20.5, 4.2)	(-27.2,-0.4)	( -6.0,17.2)
		Pr >  t			0.3403
	Week 24	n	28	22	
		LS Mean	-6.763	-2.899	-3.864
		SEM	6.393	6.822	6.101
		95% CI	(-19.4, 5.9)	(-16.4,10.6)	(-15.9, 8.2)
		Pr >  t			0.5272
	Week 32	n	29	20	
		LS Mean	-6.463	-4.173	-2.290
		SEM	6.371	7.003	6.188

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-19.1, 6.2)	(-18.0, 9.7)	(-14.5, 9.9)
		Pr >  t			0.7117
		n	25	18	
		LS Mean	-10.73	-7.267	-3.466
		SEM	6.486	7.107	6.433
Week 48		95% CI	(-23.6, 2.1)	(-21.3, 6.8)	(-16.1, 9.2)
		Pr >  t			0.5905
		n	22	14	
		LS Mean	-11.54	0.416	-11.95
		SEM	6.593	7.399	6.867
Week 56		95% CI	(-24.6, 1.5)	(-14.2, 15.0)	(-25.5, 1.6)
		Pr >  t			0.0829
		n	19	13	
		LS Mean	-11.26	-1.415	-9.846
		SEM	6.728	7.504	7.116
Week 64		95% CI	(-24.6, 2.1)	(-16.2, 13.4)	(-23.9, 4.2)
		Pr >  t			0.1675
		n	15	15	
		LS Mean	-10.37	-2.137	-8.230
		SEM	6.982	7.322	7.182
Week 72		95% CI	(-24.2, 3.4)	(-16.6, 12.3)	(-22.4, 5.9)
		Pr >  t			0.2527
		n	17	12	
		LS Mean	-15.65	-4.388	-11.27
		SEM	6.843	7.613	7.343
Week 84		95% CI	(-29.2, -2.1)	(-19.4, 10.7)	(-25.7, 3.2)
		Pr >  t			0.1259
		n	13	12	
		LS Mean	-13.91	-3.223	-10.69
		SEM	7.216	7.615	7.656
Week 96		95% CI	(-28.2, 0.3)	(-18.3, 11.8)	(-25.7, 4.4)
		Pr >  t			0.1634
		n	12	8	
		LS Mean	-10.94	-3.180	-7.762
		SEM	7.326	8.291	8.426
Week 108		95% CI	(-25.4, 3.5)	(-19.5, 13.2)	(-24.3, 8.8)
		Pr >  t			0.3575
		n	11	7	
	LS Mean	-15.63	-7.873	-7.752	
	SEM	7.460	8.562	8.807	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-30.3,-0.9)	(-24.7, 9.0)	(-25.1, 9.6)
		Pr >  t			0.3793
	Week 120	n	10	8	
		LS Mean	-11.21	-4.355	-6.852
		SEM	7.612	8.292	8.678
		95% CI	(-26.2, 3.8)	(-20.7,12.0)	(-23.9,10.2)
		Pr >  t			0.4302
	Week 132	n	8	4	
		LS Mean	-16.27	-1.975	-14.30
		SEM	8.015	10.02	10.65
		95% CI	(-32.1,-0.5)	(-21.7,17.7)	(-35.2, 6.6)
		Pr >  t			0.1800
	Week 144	n	7	2	
		LS Mean	-15.41	2.890	-18.31
		SEM	8.294	12.80	13.46
		95% CI	(-31.8, 0.9)	(-22.3,28.0)	(-44.8, 8.1)
		Pr >  t			0.1745
	Week 156	n	5	2	
		LS Mean	-7.863	-13.77	5.912
		SEM	9.123	12.80	13.98
		95% CI	(-25.8,10.1)	(-38.9,11.4)	(-21.6,33.4)
		Pr >  t			0.6727
	Week 168	n	2	1	
		LS Mean	-1.598	9.612	-11.21
		SEM	12.58	17.02	19.91
		95% CI	(-26.3,23.1)	(-23.8,43.1)	(-50.3,27.9)
		Pr >  t			0.5737
	Week 180	n		1	
		LS Mean		-23.72	
		SEM		17.02	
		95% CI		(-57.2, 9.7)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		9.612	
		SEM		17.02	
		95% CI		(-23.8,43.1)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-7.988	-6.694	-1.294		
			SEM	3.602	3.748	3.544		
			95% CI	(-15.1,-0.9)	(-14.1, 0.7)	(-8.3, 5.7)		
					Pr >  t			0.7153
		Week 16	n	70	52			
			LS Mean	-5.545	-10.43	4.887		
			SEM	3.675	4.006	3.808		
			95% CI	(-12.8, 1.7)	(-18.3,-2.5)	(-2.6,12.4)		
					Pr >  t			0.2004
		Week 24	n	61	37			
			LS Mean	-7.339	-9.359	2.020		
			SEM	3.755	4.273	4.123		
			95% CI	(-14.7, 0.1)	(-17.8,-0.9)	(-6.1,10.1)		
					Pr >  t			0.6245
		Week 32	n	48	33			
			LS Mean	-5.721	-9.877	4.156		
			SEM	3.913	4.363	4.339		
			95% CI	(-13.4, 2.0)	(-18.5,-1.3)	(-4.4,12.7)		
					Pr >  t			0.3388
		Week 40	n	42	31			
			LS Mean	-7.746	-6.861	-0.885		
			SEM	3.995	4.415	4.468		
			95% CI	(-15.6, 0.1)	(-15.5, 1.8)	(-9.7, 7.9)		
			Pr >  t			0.8431		
Week 48	n	40	25					
	LS Mean	-7.550	-8.120	0.570				
	SEM	4.027	4.598	4.677				
	95% CI	(-15.5, 0.4)	(-17.2, 0.9)	(-8.6, 9.8)				
			Pr >  t			0.9030		
Week 56	n	35	20					
	LS Mean	-7.555	-9.021	1.466				
	SEM	4.116	4.825	4.978				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-15.7, 0.5)	(-18.5, 0.5)	(-8.3,11.2)
		Pr >  t			0.7685
	Week 64	n	29	18	
		LS Mean	-7.624	-6.666	-0.959
		SEM	4.256	4.947	5.212
		95% CI	(-16.0, 0.7)	(-16.4, 3.1)	(-11.2, 9.3)
		Pr >  t			0.8541
	Week 72	n	28	18	
		LS Mean	-9.814	-10.10	0.281
		SEM	4.286	4.944	5.235
		95% CI	(-18.2,-1.4)	(-19.8,-0.4)	(-10.0,10.6)
		Pr >  t			0.9572
	Week 84	n	27	17	
		LS Mean	-10.74	-7.520	-3.215
		SEM	4.334	5.013	5.326
		95% CI	(-19.3,-2.2)	(-17.4, 2.3)	(-13.7, 7.2)
		Pr >  t			0.5462
	Week 96	n	23	14	
		LS Mean	-5.745	-13.65	7.908
		SEM	4.475	5.262	5.677
		95% CI	(-14.5, 3.1)	(-24.0,-3.3)	(-3.2,19.1)
		Pr >  t			0.1641
	Week 108	n	19	12	
		LS Mean	-8.253	-12.27	4.017
		SEM	4.688	5.487	6.042
		95% CI	(-17.5, 1.0)	(-23.0,-1.5)	(-7.8,15.9)
		Pr >  t			0.5063
	Week 120	n	18	8	
		LS Mean	-13.06	-10.18	-2.872
		SEM	4.737	6.207	6.744
		95% CI	(-22.4,-3.7)	(-22.4, 2.0)	(-16.1,10.4)
		Pr >  t			0.6703
	Week 132	n	11	4	
		LS Mean	-12.02	-12.69	0.668
		SEM	5.442	7.968	8.806
		95% CI	(-22.7,-1.3)	(-28.3, 2.9)	(-16.6,18.0)
		Pr >  t			0.9395
	Week 144	n	11	4	
		LS Mean	-10.69	-4.954	-5.738
		SEM	5.429	7.974	8.812

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.4,-0.0)	(-20.6,10.7)	(-23.0,11.6)
		Pr >  t			0.5151
	Week 156	n	5	2	
		LS Mean	-2.829	-18.68	15.848
		SEM	7.165	10.64	12.21
		95% CI	(-16.9,11.2)	(-39.6, 2.2)	( -8.1,39.8)
		Pr >  t			0.1945
	Week 168	n	1	2	
		LS Mean	20.020	-2.013	22.033
		SEM	14.45	10.64	17.51
		95% CI	( -8.4,48.4)	(-22.9,18.9)	(-12.3,56.4)
		Pr >  t			0.2087
	Week 180	n		1	
		LS Mean		-29.48	
		SEM		14.55	
		95% CI		(-58.0,-0.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		3.851	
		SEM		14.55	
		95% CI		(-24.7,32.4)	
		Pr >  t			
>= 65 Years	Week 8	n	63	71	
		LS Mean	-1.590	-0.384	-1.206
		SEM	5.382	5.359	3.812
		95% CI	(-12.2, 9.0)	(-11.0,10.2)	( -8.7, 6.3)
		Pr >  t			0.7519
	Week 16	n	54	55	
		LS Mean	-2.068	-1.315	-0.753
		SEM	5.511	5.450	4.092
		95% CI	(-13.0, 8.8)	(-12.1, 9.5)	( -8.8, 7.3)
		Pr >  t			0.8541
	Week 24	n	44	44	
		LS Mean	-2.199	0.554	-2.753
		SEM	5.618	5.553	4.396
		95% CI	(-13.3, 8.9)	(-10.4,11.5)	(-11.4, 5.9)
		Pr >  t			0.5316
	Week 32	n	38	40	
		LS Mean	-1.218	-1.936	0.718
		SEM	5.742	5.644	4.575

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.5,10.1)	(-13.1, 9.2)	(-8.3, 9.7)
		Pr >  t			0.8754
	Week 40	n	33	31	
		LS Mean	2.269	-6.866	9.135
		SEM	5.834	5.838	4.883
		95% CI	(-9.2,13.8)	(-18.4, 4.6)	(-0.5,18.7)
		Pr >  t			0.0620
	Week 48	n	29	26	
		LS Mean	-2.543	-2.846	0.303
		SEM	5.920	5.974	5.146
		95% CI	(-14.2, 9.1)	(-14.6, 8.9)	(-9.8,10.4)
		Pr >  t			0.9531
	Week 56	n	24	25	
		LS Mean	-2.330	-3.631	1.302
		SEM	6.067	6.003	5.350
		95% CI	(-14.3, 9.6)	(-15.5, 8.2)	(-9.2,11.8)
		Pr >  t			0.8079
	Week 64	n	18	24	
		LS Mean	-0.690	-3.218	2.528
		SEM	6.336	6.039	5.693
		95% CI	(-13.2,11.8)	(-15.1, 8.7)	(-8.7,13.7)
		Pr >  t			0.6572
	Week 72	n	20	17	
		LS Mean	-0.330	1.438	-1.768
		SEM	6.237	6.373	5.939
		95% CI	(-12.6,12.0)	(-11.1,14.0)	(-13.4, 9.9)
		Pr >  t			0.7660
	Week 84	n	13	16	
		LS Mean	-3.365	-1.344	-2.021
		SEM	6.719	6.439	6.511
		95% CI	(-16.6, 9.9)	(-14.0,11.3)	(-14.8,10.8)
		Pr >  t			0.7563
	Week 96	n	12	10	
		LS Mean	-5.256	3.276	-8.532
		SEM	6.834	7.098	7.271
		95% CI	(-18.7, 8.2)	(-10.7,17.2)	(-22.8, 5.7)
		Pr >  t			0.2410
	Week 108	n	7	9	
		LS Mean	-6.792	-2.661	-4.130
		SEM	7.778	7.276	8.322

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.1, 8.5)	(-17.0,11.6)	(-20.5,12.2)
		Pr >  t			0.6198
	Week 120	n	10	8	
		LS Mean	4.247	0.195	4.052
		SEM	7.132	7.499	7.928
		95% CI	(-9.8,18.3)	(-14.5,14.9)	(-11.5,19.6)
		Pr >  t			0.6095
	Week 132	n	9	4	
		LS Mean	-6.561	-6.314	-0.247
		SEM	7.292	9.219	9.692
		95% CI	(-20.9, 7.8)	(-24.4,11.8)	(-19.3,18.8)
		Pr >  t			0.9796
	Week 144	n	4	1	
		LS Mean	-19.25	-0.953	-18.30
		SEM	9.227	16.05	17.27
		95% CI	(-37.4,-1.1)	(-32.5,30.6)	(-52.2,15.6)
		Pr >  t			0.2898
	Week 156	n	5	1	
		LS Mean	-8.917	-0.953	-7.964
		SEM	8.588	16.05	16.94
		95% CI	(-25.8, 7.9)	(-32.5,30.6)	(-41.2,25.3)
		Pr >  t			0.6384
	Week 168	n	3		
		LS Mean	-10.92		
		SEM	10.22		
		95% CI	(-31.0, 9.2)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-19.36		
		SEM	16.04		
		95% CI	(-50.9,12.1)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	13.966		
		SEM	16.04		
		95% CI	(-17.5,45.5)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	-5.905	2.978	-8.882		
			SEM	5.780	5.376	4.874		
			95% CI	(-17.4, 5.6)	(-7.7,13.7)	(-18.5, 0.8)		
					Pr >  t			0.0708
		Week 16	n	28	29			
			LS Mean	-4.648	-0.465	-4.183		
			SEM	5.824	5.621	5.095		
			95% CI	(-16.2, 7.0)	(-11.6,10.7)	(-14.3, 5.9)		
					Pr >  t			0.4131
		Week 24	n	21	25			
			LS Mean	-6.666	1.359	-8.024		
			SEM	6.038	5.722	5.475		
			95% CI	(-18.7, 5.3)	(-10.0,12.7)	(-18.8, 2.8)		
					Pr >  t			0.1446
		Week 32	n	19	23			
			LS Mean	-6.646	-2.033	-4.613		
			SEM	6.117	5.790	5.651		
			95% CI	(-18.8, 5.5)	(-13.5, 9.5)	(-15.8, 6.5)		
					Pr >  t			0.4154
		Week 40	n	16	18			
			LS Mean	1.708	-4.537	6.245		
			SEM	6.275	6.067	6.060		
			95% CI	(-10.7,14.2)	(-16.6, 7.5)	(-5.7,18.2)		
					Pr >  t			0.3039
		Week 48	n	16	17			
			LS Mean	1.707	-3.912	5.619		
			SEM	6.275	6.123	6.118		
95% CI	(-10.7,14.2)		(-16.0, 8.2)	(-6.4,17.7)				
			Pr >  t			0.3594		
Week 56	n	12	14					
	LS Mean	-4.237	-3.558	-0.680				
	SEM	6.589	6.329	6.659				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-17.3, 8.8)	(-16.1, 9.0)	(-13.8,12.4)
	Pr >  t			0.9188
	n	12	11	
	LS Mean	-4.238	-9.501	5.263
	SEM	6.589	6.638	6.951
Week 72	95% CI	(-17.3, 8.8)	(-22.6, 3.6)	(-8.4,18.9)
	Pr >  t			0.4496
	n	10	8	
	LS Mean	-7.040	-6.390	-0.650
	SEM	6.831	7.144	7.646
Week 84	95% CI	(-20.6, 6.5)	(-20.5, 7.7)	(-15.7,14.4)
	Pr >  t			0.9323
	n	8	8	
	LS Mean	1.213	-4.307	5.520
	SEM	7.240	7.144	7.964
Week 96	95% CI	(-13.1,15.5)	(-18.4, 9.8)	(-10.1,21.2)
	Pr >  t			0.4887
	n	6	6	
	LS Mean	-4.905	-16.92	12.012
	SEM	7.782	7.702	8.938
Week 108	95% CI	(-20.2,10.4)	(-32.1,-1.7)	(-5.6,29.6)
	Pr >  t			0.1798
	n	4	5	
	LS Mean	-10.55	-7.383	-3.168
	SEM	8.760	8.119	10.14
Week 120	95% CI	(-27.8, 6.7)	(-23.4, 8.6)	(-23.1,16.8)
	Pr >  t			0.7548
	n	4	4	
	LS Mean	-10.55	-13.41	2.858
	SEM	8.760	8.706	10.61
Week 132	95% CI	(-27.8, 6.7)	(-30.5, 3.7)	(-18.0,23.7)
	Pr >  t			0.7878
	n	3	2	
	LS Mean	-7.187	-1.361	-5.826
	SEM	9.631	11.12	13.28
Week 144	95% CI	(-26.1,11.8)	(-23.2,20.5)	(-31.9,20.3)
	Pr >  t			0.6611
	n	3	1	
	LS Mean	-29.41	-4.007	-25.40
	SEM	9.631	14.82	16.51

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Europe	Week 156	95% CI	(-48.4, -10)	(-33.2,25.1)	(-57.9, 7.1)
		Pr >  t			0.1248
		n	2	1	
	Week 168	LS Mean	-15.60	-4.007	-11.60
		SEM	11.17	14.82	17.45
		95% CI	(-37.6, 6.4)	(-33.2,25.1)	(-45.9,22.7)
	Week 8	Pr >  t			0.5067
		n	1		
		LS Mean	-16.06		
	Week 16	SEM	14.83		
		95% CI	(-45.2,13.1)		
		Pr >  t			
	Week 24	n	66	68	
		LS Mean	-12.32	-11.20	-1.113
		SEM	7.570	7.578	3.979
	Week 32	95% CI	(-27.3, 2.7)	(-26.2, 3.8)	(-9.0, 6.7)
		Pr >  t			0.7799
		n	58	48	
	Week 40	LS Mean	-9.795	-13.10	3.305
		SEM	7.606	7.683	4.334
		95% CI	(-24.8, 5.3)	(-28.3, 2.1)	(-5.2,11.8)
	Week 48	Pr >  t			0.4464
		n	51	36	
		LS Mean	-12.68	-11.64	-1.033
Week 8	SEM	7.651	7.798	4.653	
	95% CI	(-27.8, 2.5)	(-27.1, 3.8)	(-10.2, 8.1)	
	Pr >  t			0.8244	
Week 16	n	43	30		
	LS Mean	-9.441	-12.00	2.558	
	SEM	7.768	7.958	4.925	
Week 24	95% CI	(-24.8, 5.9)	(-27.7, 3.7)	(-7.1,12.2)	
	Pr >  t			0.6037	
	n	37	25		
Week 32	LS Mean	-7.679	-6.646	-1.033	
	SEM	7.832	8.063	5.195	
	95% CI	(-23.2, 7.8)	(-22.6, 9.3)	(-11.2, 9.2)	
Week 40	Pr >  t			0.8425	
	n	33	21		
	LS Mean	-14.93	-12.30	-2.631	
Week 48	SEM	7.882	8.185	5.457	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-30.5, 0.7)	(-28.5, 3.9)	(-13.4, 8.1)
	Pr >  t			0.6299
	n	29	20	
	LS Mean	-11.25	-11.42	0.174
	SEM	7.945	8.221	5.607
Week 64	95% CI	(-26.9, 4.5)	(-27.7, 4.8)	(-10.8,11.2)
	Pr >  t			0.9752
	n	23	20	
	LS Mean	-10.48	-8.200	-2.281
	SEM	8.081	8.221	5.799
Week 72	95% CI	(-26.4, 5.5)	(-24.4, 8.0)	(-13.7, 9.1)
	Pr >  t			0.6943
	n	25	19	
	LS Mean	-9.425	-8.762	-0.663
	SEM	8.033	8.259	5.783
Week 84	95% CI	(-25.3, 6.4)	(-25.1, 7.5)	(-12.0,10.7)
	Pr >  t			0.9087
	n	22	17	
	LS Mean	-18.39	-9.734	-8.658
	SEM	8.111	8.350	6.020
Week 96	95% CI	(-34.4,-2.4)	(-26.2, 6.7)	(-20.5, 3.2)
	Pr >  t			0.1509
	n	20	13	
	LS Mean	-14.24	-6.977	-7.265
	SEM	8.178	8.607	6.459
Week 108	95% CI	(-30.4, 1.9)	(-23.9,10.0)	(-19.9, 5.4)
	Pr >  t			0.2611
	n	15	11	
	LS Mean	-12.86	-17.19	4.335
	SEM	8.421	8.799	7.009
Week 120	95% CI	(-29.5, 3.8)	(-34.5, 0.1)	( -9.4,18.1)
	Pr >  t			0.5365
	n	16	8	
	LS Mean	-10.30	-9.295	-1.010
	SEM	8.368	9.252	7.505
Week 132	95% CI	(-26.8, 6.2)	(-27.5, 8.9)	(-15.7,13.7)
	Pr >  t			0.8930
	n	12	3	
	LS Mean	-12.06	-10.73	-1.334
	SEM	8.650	11.62	10.52

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-29.1, 5.0)	(-33.6,12.1)	(-22.0,19.3)
		Pr >  t			0.8991
	Week 144	n	7	4	
		LS Mean	-14.70	-6.298	-8.400
		SEM	9.428	10.74	10.25
		95% CI	(-33.3, 3.9)	(-27.4,14.8)	(-28.5,11.7)
		Pr >  t			0.4127
	Week 156	n	5	2	
		LS Mean	-14.31	-19.97	5.665
		SEM	10.12	13.21	13.32
		95% CI	(-34.2, 5.6)	(-45.9, 6.0)	(-20.5,31.8)
		Pr >  t			0.6708
	Week 168	n	2	2	
		LS Mean	3.559	-3.308	6.866
		SEM	13.16	13.21	15.76
		95% CI	(-22.3,29.4)	(-29.2,22.6)	(-24.1,37.8)
		Pr >  t			0.6631
	Week 180	n		1	
		LS Mean		-30.86	
		SEM		17.07	
		95% CI		(-64.4, 2.7)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		2.468	
		SEM		17.07	
		95% CI		(-31.1,36.0)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	-0.771	-6.401	5.630
		SEM	5.580	5.616	7.960
		95% CI	(-12.0,10.5)	(-17.7, 4.9)	(-10.4,21.7)
		Pr >  t			0.4830
	Week 16	n	13	12	
		LS Mean	0.390	-8.119	8.509
		SEM	5.693	5.769	8.124
		95% CI	(-11.1,11.8)	(-19.7, 3.5)	(-7.8,24.8)
		Pr >  t			0.3002
	Week 24	n	12	10	
		LS Mean	-2.409	-6.078	3.669
		SEM	5.808	6.084	8.427

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-14.1, 9.3)	(-18.3, 6.1)	(-13.2,20.6)
	Pr >  t			0.6650
	n	9	10	
	LS Mean	-1.435	-11.08	9.643
	SEM	6.282	6.084	8.761
Week 40	95% CI	(-14.0,11.1)	(-23.3, 1.1)	( -7.9,27.2)
	Pr >  t			0.2754
	n	7	10	
	LS Mean	-14.06	-12.75	-1.312
	SEM	6.741	6.084	9.102
Week 48	95% CI	(-27.5,-0.6)	(-24.9,-0.6)	(-19.5,16.9)
	Pr >  t			0.8858
	n	7	7	
	LS Mean	-9.296	3.843	-13.14
	SEM	6.741	6.702	9.507
Week 56	95% CI	(-22.7, 4.1)	( -9.5,17.2)	(-32.1, 5.8)
	Pr >  t			0.1710
	n	6	7	
	LS Mean	-7.435	-12.04	4.600
	SEM	7.072	6.710	9.762
Week 64	95% CI	(-21.5, 6.6)	(-25.4, 1.3)	(-14.8,24.0)
	Pr >  t			0.6387
	n	4	7	
	LS Mean	-6.335	-4.549	-1.786
	SEM	8.053	6.690	10.47
Week 72	95% CI	(-22.3, 9.6)	(-17.9, 8.8)	(-22.6,19.0)
	Pr >  t			0.8649
	n	4	4	
	LS Mean	-10.50	-2.559	-7.941
	SEM	8.053	7.996	11.35
Week 84	95% CI	(-26.5, 5.5)	(-18.4,13.3)	(-30.4,14.5)
	Pr >  t			0.4855
	n	4	5	
	LS Mean	-2.490	-3.352	0.863
	SEM	8.042	7.420	10.95
Week 96	95% CI	(-18.4,13.4)	(-18.1,11.4)	(-20.8,22.6)
	Pr >  t			0.9373
	n	3	2	
Week 96	LS Mean	9.981	-1.005	10.986
	SEM	8.924	10.37	13.69

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-7.7,27.6)	(-21.5,19.5)	(-16.1,38.0)
		Pr >  t			0.4235
		n	2	3	
		LS Mean	-9.483	0.999	-10.48
		SEM	10.43	8.891	13.71
	Week 120	95% CI	(-30.1,11.1)	(-16.6,18.6)	(-37.6,16.6)
		Pr >  t			0.4459
		n	2	2	
		LS Mean	-11.52	0.391	-11.91
		SEM	10.42	10.37	14.70
	Week 132	95% CI	(-32.1, 9.1)	(-20.1,20.9)	(-41.0,17.1)
		Pr >  t			0.4191
		n	1	2	
		LS Mean	-4.249	-7.944	3.695
		SEM	14.00	10.37	17.41
	Week 8	95% CI	(-31.9,23.4)	(-28.4,12.6)	(-30.7,38.1)
		Pr >  t			0.8322
		n	16	19	
		LS Mean	-0.468	-10.76	10.291
		SEM	6.618	6.539	8.054
	Week 16	95% CI	(-13.9,12.9)	(-24.0, 2.5)	(-6.0,26.6)
		Pr >  t			0.2085
		n	12	14	
		LS Mean	-9.009	-10.82	1.811
		SEM	7.130	7.060	8.749
	Week 24	95% CI	(-23.4, 5.3)	(-25.0, 3.4)	(-15.7,19.4)
		Pr >  t			0.8368
		n	12	8	
LS Mean		4.602	-9.825	14.427	
SEM		7.132	8.198	9.642	
Week 32	95% CI	(-9.7,19.0)	(-26.2, 6.5)	(-4.8,33.7)	
	Pr >  t			0.1390	
	n	9	7		
	LS Mean	-1.918	-10.18	8.264	
	SEM	7.641	8.458	10.21	
Week 40	95% CI	(-17.2,13.4)	(-27.0, 6.6)	(-12.0,28.6)	
	Pr >  t			0.4204	
	n	9	7		
	LS Mean	-13.19	-29.23	16.042	
	SEM	7.664	8.458	10.24	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-28.5, 2.1)	(-46.0, -12)	(-4.3,36.4)
	Pr >  t			0.1210
	n	8	5	
	LS Mean	-7.696	-19.85	12.158
	SEM	7.882	9.235	11.05
Week 56	95% CI	(-23.4, 8.0)	(-38.2,-1.5)	(-9.8,34.1)
	Pr >  t			0.2738
	n	7	3	
	LS Mean	-7.290	-10.63	3.336
	SEM	8.137	10.79	12.55
Week 64	95% CI	(-23.5, 8.9)	(-32.0,10.7)	(-21.5,28.2)
	Pr >  t			0.7909
	n	5	3	
	LS Mean	-3.606	-10.63	7.020
	SEM	8.910	10.79	13.06
Week 72	95% CI	(-21.3,14.1)	(-32.0,10.7)	(-18.8,32.9)
	Pr >  t			0.5919
	n	5	3	
	LS Mean	-9.700	-13.57	3.867
	SEM	8.886	10.79	13.02
Week 84	95% CI	(-27.3, 7.9)	(-34.9, 7.8)	(-21.9,29.6)
	Pr >  t			0.7669
	n	2	2	
	LS Mean	-19.55	-13.60	-5.953
	SEM	12.14	12.42	16.60
Week 96	95% CI	(-43.5, 4.5)	(-38.1,11.0)	(-38.8,26.9)
	Pr >  t			0.7203
	n	3	2	
	LS Mean	-2.998	-13.60	10.599
	SEM	10.41	12.42	15.41
Week 108	95% CI	(-23.6,17.6)	(-38.1,11.0)	(-19.9,41.1)
	Pr >  t			0.4928
	n	1	2	
	LS Mean	-14.86	-5.266	-9.590
	SEM	16.02	12.42	19.60
Week 120	95% CI	(-46.5,16.8)	(-29.8,19.3)	(-48.4,29.2)
	Pr >  t			0.6255
	n	3	2	
	LS Mean	-2.998	-5.266	2.269
	SEM	10.41	12.42	15.41

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-23.6,17.6)	(-28.2,32.7)	
		Pr >  t		0.8832	
	Week 132	n	1	1	
		LS Mean	-22.33	-48.65	
		SEM	16.01	16.24	
		95% CI	(-54.0, 9.3)	(-80.8, -17)	
		Pr >  t		0.2386	
	Week 144	n	2		
		LS Mean	-13.73		
		SEM	12.04		
		95% CI	(-37.5,10.1)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	11.004		
		SEM	16.01		
		95% CI	(-20.7,42.7)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-22.33		
		SEM	16.01		
		95% CI	(-54.0, 9.3)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-22.33		
		SEM	16.01		
		95% CI	(-54.0, 9.3)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	11.004		
		SEM	16.01		
		95% CI	(-20.7,42.7)		
		Pr >  t			
	Other	Week 8	n	16	5
			LS Mean	-5.728	5.118
			SEM	5.266	7.561
			95% CI	(-16.6, 5.2)	(-10.4,20.6)
			Pr >  t		(-27.8, 6.1)
					0.2010
		Week 16	n	13	4
			LS Mean	-1.862	-3.715
			SEM	5.516	8.515
					1.853
					8.989

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-13.2, 9.5)	(-21.0,13.5)	(-16.4,20.1)
	Pr >  t			0.8379
	n	9	2	
	LS Mean	-8.297	-8.405	0.108
	SEM	5.926	10.58	11.16
Week 32	95% CI	(-20.4, 3.8)	(-29.6,12.8)	(-22.2,22.4)
	Pr >  t			0.9923
	n	6	3	
	LS Mean	-2.010	0.070	-2.081
	SEM	6.677	9.275	10.39
Week 40	95% CI	(-15.4,11.4)	(-18.6,18.7)	(-23.0,18.8)
	Pr >  t			0.8421
	n	6	2	
	LS Mean	2.141	2.073	0.069
	SEM	6.829	10.52	11.62
Week 48	95% CI	(-11.6,15.9)	(-19.0,23.1)	(-23.2,23.3)
	Pr >  t			0.9953
	n	5	1	
	LS Mean	6.432	0.351	6.081
	SEM	7.157	13.66	14.74
Week 56	95% CI	(-7.9,20.8)	(-26.8,27.5)	(-23.3,35.4)
	Pr >  t			0.6811
	n	5	1	
	LS Mean	-0.234	0.351	-0.585
	SEM	7.157	13.66	14.74
Week 64	95% CI	(-14.6,14.1)	(-26.8,27.5)	(-29.9,28.8)
	Pr >  t			0.9684
	n	3	1	
	LS Mean	-4.304	0.351	-4.655
	SEM	8.326	13.66	15.35
Week 72	95% CI	(-20.9,12.3)	(-26.8,27.5)	(-35.2,25.9)
	Pr >  t			0.7625
	n	4	1	
	LS Mean	-5.295	0.351	-5.647
	SEM	7.617	13.66	14.98
Week 84	95% CI	(-20.5, 9.9)	(-26.8,27.5)	(-35.5,24.2)
	Pr >  t			0.7072
	n	4	1	
Week 84	LS Mean	3.037	0.351	2.686
	SEM	7.617	13.66	14.98

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-12.2,18.3)	(-26.8,27.5)	(-27.1,32.5)
	Pr >  t			0.8582
	n	3	1	
	LS Mean	1.249	0.351	0.898
	SEM	8.326	13.66	15.35
Week 108	95% CI	(-15.4,17.9)	(-26.8,27.5)	(-29.7,31.5)
	Pr >  t			0.9535
	n	4		
	LS Mean	3.037		
	SEM	7.617		
Week 120	95% CI	(-12.2,18.3)		
	Pr >  t			
	n	3		
	LS Mean	-9.861		
	SEM	8.326		
Week 132	95% CI	(-26.5, 6.7)		
	Pr >  t			
	n	3		
	LS Mean	-20.97		
	SEM	8.326		
Week 144	95% CI	(-37.6,-4.4)		
	Pr >  t			
	n	3		
	LS Mean	2.440		
	SEM	8.337		
Week 156	95% CI	(-14.2,19.1)		
	Pr >  t			
	n	2		
	LS Mean	4.351		
	SEM	9.551		
	95% CI	(-14.7,23.4)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	-8.371	-5.040	-3.331	
		SEM	3.870	3.778	3.003	
		95% CI	(-16.0,-0.7)	(-12.5, 2.4)	(-9.2, 2.6)	
			Pr >  t			0.2682
	Week 16	n	88	71		
		LS Mean	-7.047	-7.376	0.329	
		SEM	3.934	3.994	3.196	
		95% CI	(-14.8, 0.7)	(-15.2, 0.5)	(-6.0, 6.6)	
			Pr >  t			0.9181
	Week 24	n	75	54		
		LS Mean	-7.592	-7.120	-0.472	
		SEM	3.988	4.121	3.437	
		95% CI	(-15.4, 0.3)	(-15.2, 1.0)	(-7.2, 6.3)	
			Pr >  t			0.8909
	Week 32	n	62	52		
		LS Mean	-7.540	-5.961	-1.579	
		SEM	4.079	4.143	3.556	
		95% CI	(-15.6, 0.5)	(-14.1, 2.2)	(-8.6, 5.4)	
			Pr >  t			0.6572
	Week 40	n	51	46		
		LS Mean	-8.900	-5.954	-2.946	
		SEM	4.170	4.225	3.737	
		95% CI	(-17.1,-0.7)	(-14.3, 2.4)	(-10.3, 4.4)	
		Pr >  t			0.4309	
Week 48	n	50	37			
	LS Mean	-11.18	-5.621	-5.560		
	SEM	4.180	4.356	3.895		
	95% CI	(-19.4,-3.0)	(-14.2, 2.9)	(-13.2, 2.1)		
		Pr >  t			0.1539	
Week 56	n	43	33			
	LS Mean	-9.100	-6.453	-2.647		
	SEM	4.259	4.434	4.068		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-17.5,-0.7)	(-15.2, 2.3)	(-10.6, 5.3)
	Pr >  t			0.5154
	n	35	33	
	LS Mean	-7.699	-4.822	-2.877
	SEM	4.382	4.435	4.200
Week 72	95% CI	(-16.3, 0.9)	(-13.5, 3.9)	(-11.1, 5.4)
	Pr >  t			0.4935
	n	35	31	
	LS Mean	-8.942	-6.091	-2.850
	SEM	4.382	4.479	4.247
Week 84	95% CI	(-17.6,-0.3)	(-14.9, 2.7)	(-11.2, 5.5)
	Pr >  t			0.5023
	n	31	29	
	LS Mean	-12.39	-5.029	-7.363
	SEM	4.473	4.529	4.384
Week 96	95% CI	(-21.2,-3.6)	(-13.9, 3.9)	(-16.0, 1.2)
	Pr >  t			0.0934
	n	27	22	
	LS Mean	-10.08	-7.622	-2.453
	SEM	4.569	4.766	4.731
Week 108	95% CI	(-19.1,-1.1)	(-17.0, 1.7)	(-11.7, 6.8)
	Pr >  t			0.6043
	n	19	20	
	LS Mean	-10.60	-8.497	-2.104
	SEM	4.906	4.861	5.138
Week 120	95% CI	(-20.2,-1.0)	(-18.0, 1.0)	(-12.2, 8.0)
	Pr >  t			0.6823
	n	20	15	
	LS Mean	-8.888	-6.762	-2.126
	SEM	4.838	5.190	5.402
Week 132	95% CI	(-18.4, 0.6)	(-17.0, 3.4)	(-12.7, 8.5)
	Pr >  t			0.6939
	n	15	7	
	LS Mean	-15.38	-12.66	-2.726
	SEM	5.178	6.472	6.886
Week 144	95% CI	(-25.6,-5.2)	(-25.4, 0.0)	(-16.2,10.8)
	Pr >  t			0.6923
	n	10	5	
Week 144	LS Mean	-19.94	-3.114	-16.82
	SEM	5.753	7.292	8.078

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-31.2,-8.6)	(-17.4,11.2)	(-32.7,-1.0)
		Pr >  t			0.0375
	Week 156	n	6	3	
		LS Mean	-4.401	-12.81	8.414
		SEM	6.816	8.897	10.22
		95% CI	(-17.8, 9.0)	(-30.3, 4.6)	(-11.6,28.5)
		Pr >  t			0.4103
	Week 168	n	3	2	
		LS Mean	-4.931	0.672	-5.602
		SEM	8.890	10.57	13.02
		95% CI	(-22.4,12.5)	(-20.1,21.4)	(-31.1,19.9)
		Pr >  t			0.6670
	Week 180	n	1	1	
		LS Mean	-25.09	-26.87	1.786
		SEM	14.46	14.45	19.91
		95% CI	(-53.5, 3.3)	(-55.2, 1.5)	(-37.3,40.9)
		Pr >  t			0.9286
	Week 192	n	1	1	
		LS Mean	8.242	6.457	1.786
		SEM	14.46	14.45	19.91
		95% CI	(-20.1,36.6)	(-21.9,34.8)	(-37.3,40.9)
		Pr >  t			0.9286
1	Week 8	n	43	50	
		LS Mean	0.758	-1.157	1.915
		SEM	4.898	5.106	4.983
		95% CI	(-8.9,10.5)	(-11.3, 9.0)	(-7.9,11.8)
		Pr >  t			0.7013
	Week 16	n	35	35	
		LS Mean	1.231	-3.339	4.570
		SEM	5.129	5.309	5.490
		95% CI	(-8.9,11.4)	(-13.8, 7.2)	(-6.3,15.4)
		Pr >  t			0.4062
	Week 24	n	29	26	
		LS Mean	-1.393	1.185	-2.578
		SEM	5.337	5.686	5.951
		95% CI	(-11.9, 9.2)	(-10.0,12.4)	(-14.3, 9.1)
		Pr >  t			0.6652
	Week 32	n	23	21	
		LS Mean	3.495	-6.800	10.295
		SEM	5.644	5.985	6.397

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.6,14.6)	(-18.6, 5.0)	(-2.3,22.9)
		Pr >  t			0.1087
	Week 40	n	23	16	
		LS Mean	7.710	-11.07	18.781
		SEM	5.656	6.343	6.743
		95% CI	(-3.5,18.9)	(-23.6, 1.4)	( 5.5,32.0)
		Pr >  t			0.0057
	Week 48	n	18	14	
		LS Mean	7.387	-6.658	14.045
		SEM	5.947	6.549	7.191
		95% CI	(-4.3,19.1)	(-19.6, 6.2)	(-0.1,28.2)
		Pr >  t			0.0516
	Week 56	n	15	12	
		LS Mean	2.191	-7.880	10.071
		SEM	6.212	6.804	7.650
		95% CI	(-10.0,14.4)	(-21.3, 5.5)	(-5.0,25.1)
		Pr >  t			0.1888
	Week 64	n	11	9	
		LS Mean	0.438	-9.069	9.507
		SEM	6.717	7.365	8.553
		95% CI	(-12.8,13.7)	(-23.6, 5.4)	(-7.3,26.3)
		Pr >  t			0.2670
	Week 72	n	12	4	
		LS Mean	-0.367	2.069	-2.435
		SEM	6.578	9.664	10.51
		95% CI	(-13.3,12.6)	(-16.9,21.1)	(-23.1,18.2)
		Pr >  t			0.8168
	Week 84	n	8	4	
		LS Mean	2.835	-6.264	9.099
		SEM	7.425	9.664	11.04
		95% CI	(-11.8,17.4)	(-25.3,12.7)	(-12.6,30.8)
		Pr >  t			0.4103
	Week 96	n	8	2	
		LS Mean	7.004	1.379	5.625
		SEM	7.425	12.73	13.81
		95% CI	(-7.6,21.6)	(-23.7,26.4)	(-21.5,32.8)
		Pr >  t			0.6839
	Week 108	n	6	1	
		LS Mean	0.323	-10.97	11.291
		SEM	8.160	17.29	18.40

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.7,16.4)	(-45.0,23.0)	(-24.9,47.5)
		Pr >  t			0.5399
	Week 120	n	8	1	
		LS Mean	-2.033	5.702	-7.736
		SEM	7.446	17.29	18.10
		95% CI	(-16.7,12.6)	(-28.3,39.7)	(-43.3,27.9)
		Pr >  t			0.6693
	Week 132	n	5	1	
		LS Mean	4.134	5.702	-1.568
		SEM	8.695	17.29	18.64
		95% CI	(-13.0,21.2)	(-28.3,39.7)	(-38.2,35.1)
		Pr >  t			0.9330
	Week 144	n	5		
		LS Mean	4.134		
		SEM	8.695		
		95% CI	(-13.0,21.2)		
		Pr >  t			
	Week 156	n	4		
		LS Mean	-6.312		
		SEM	9.432		
		95% CI	(-24.9,12.2)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-7.093		
		SEM	17.01		
		95% CI	(-40.5,26.4)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	0.222	-1.030	1.252		
			SEM	7.846	9.016	9.083		
			95% CI	(-15.7,16.1)	(-19.3,17.2)	(-17.1,19.6)		
					Pr >  t			0.8910
		Week 16	n	17	10			
			LS Mean	1.704	-3.092	4.795		
			SEM	8.130	9.794	9.872		
			95% CI	(-14.7,18.1)	(-22.8,16.6)	(-15.0,24.6)		
					Pr >  t			0.6291
		Week 24	n	9	5			
			LS Mean	5.188	-21.54	26.728		
			SEM	8.739	10.90	11.56		
			95% CI	(-12.3,22.7)	(-43.3, 0.2)	( 3.7,49.7)		
					Pr >  t			0.0232
		Week 32	n	8	4			
			LS Mean	8.926	-13.48	22.402		
			SEM	8.889	11.40	12.15		
			95% CI	( -8.9,26.7)	(-36.2, 9.2)	( -1.7,46.5)		
					Pr >  t			0.0684
		Week 40	n	5	4			
			LS Mean	8.627	-9.311	17.938		
			SEM	9.629	11.40	12.77		
			95% CI	(-10.6,27.8)	(-32.0,13.4)	( -7.4,43.3)		
			Pr >  t			0.1632		
Week 48	n	5	3					
	LS Mean	1.959	-16.45	18.410				
	SEM	9.629	12.09	13.39				
	95% CI	(-17.2,21.2)	(-40.5, 7.6)	( -8.1,45.0)				
			Pr >  t			0.1722		
Week 56	n	4	3					
	LS Mean	0.559	-5.341	5.900				
	SEM	10.08	12.09	13.75				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-19.5,20.6)	(-29.4,18.7)	(-21.3,33.1)
		Pr >  t			0.6686
		n	4	3	
		LS Mean	8.891	-5.341	14.232
		SEM	10.08	12.09	13.75
Week 72		95% CI	(-11.2,28.9)	(-29.4,18.7)	(-13.0,41.5)
		Pr >  t			0.3028
		n	4	3	
		LS Mean	0.559	-5.341	5.900
		SEM	10.08	12.09	13.75
Week 84		95% CI	(-19.5,20.6)	(-29.4,18.7)	(-21.3,33.1)
		Pr >  t			0.6686
		n	2	3	
		LS Mean	-6.545	-5.341	-1.204
		SEM	12.21	12.09	15.29
Week 96		95% CI	(-30.7,17.7)	(-29.4,18.7)	(-31.5,29.1)
		Pr >  t			0.9374
		n	1	3	
		LS Mean	3.888	-5.341	9.229
		SEM	15.40	12.09	18.09
Week 108		95% CI	(-26.6,34.4)	(-29.4,18.7)	(-26.6,45.1)
		Pr >  t			0.6110
		n		2	
		LS Mean		-12.48	
		SEM		13.28	
Week 120		95% CI		(-38.8,13.9)	
		Pr >  t			
		n	1	1	
		LS Mean	3.888	6.721	-2.833
		SEM	15.40	16.30	21.14
Week 132		95% CI	(-26.6,34.4)	(-25.6,39.0)	(-44.8,39.1)
		Pr >  t			0.8936
		n		1	
		LS Mean		-43.28	
		SEM		16.30	
Week 144		95% CI		(-75.6, -11)	
		Pr >  t			
		n	1		
		LS Mean	3.888		
		SEM	15.40		



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-26.6,34.4)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-8.314	-6.794	-1.521
		SEM	3.606	3.598	3.023
		95% CI	(-15.4,-1.2)		(-7.5, 4.4)
		Pr >  t			0.6153
	Week 16	n	83	81	
		LS Mean	-6.628	-9.225	2.597
		SEM	3.695	3.762	3.278
		95% CI	(-13.9, 0.6)		(-3.8, 9.0)
		Pr >  t			0.4285
	Week 24	n	75	62	
		LS Mean	-8.692	-5.771	-2.921
		SEM	3.762	3.932	3.503
		95% CI	(-16.1,-1.3)		(-9.8, 4.0)
		Pr >  t			0.4047
	Week 32	n	59	56	
		LS Mean	-7.424	-8.846	1.422
		SEM	3.943	3.991	3.713
		95% CI	(-15.2, 0.3)		(-5.9, 8.7)
		Pr >  t			0.7018
	Week 40	n	52	48	
		LS Mean	-9.191	-10.17	0.983
		SEM	4.019	4.105	3.897
		95% CI	(-17.1,-1.3)		(-6.7, 8.6)
		Pr >  t			0.8010
	Week 48	n	47	37	
		LS Mean	-9.534	-8.113	-1.422
		SEM	4.084	4.296	4.161
		95% CI	(-17.6,-1.5)		(-9.6, 6.7)
		Pr >  t			0.7327
	Week 56	n	41	31	
		LS Mean	-8.476	-11.07	2.592
		SEM	4.179	4.448	4.412
		95% CI	(-16.7,-0.3)		(-6.1,11.3)
		Pr >  t			0.5570
	Week 64	n	32	28	
		LS Mean	-7.890	-8.195	0.305
		SEM	4.378	4.546	4.695

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72		95% CI	(-16.5, 0.7)	(-17.1, 0.7)	(-8.9, 9.5)
		Pr >  t			0.9482
		n	29	22	
		LS Mean	-8.186	-6.533	-1.653
		SEM	4.472	4.804	5.029
Week 84		95% CI	(-17.0, 0.6)	(-16.0, 2.9)	(-11.5, 8.2)
		Pr >  t			0.7425
		n	26	21	
		LS Mean	-9.522	-7.219	-2.303
		SEM	4.576	4.859	5.174
Week 96		95% CI	(-18.5,-0.5)	(-16.8, 2.3)	(-12.5, 7.9)
		Pr >  t			0.6564
		n	23	14	
		LS Mean	-6.414	-9.806	3.392
		SEM	4.710	5.426	5.817
Week 108		95% CI	(-15.7, 2.8)	(-20.5, 0.8)	(-8.0,14.8)
		Pr >  t			0.5599
		n	18	13	
		LS Mean	-11.02	-10.50	-0.526
		SEM	5.014	5.548	6.175
Week 120		95% CI	(-20.9,-1.2)	(-21.4, 0.4)	(-12.6,11.6)
		Pr >  t			0.9321
		n	19	10	
		LS Mean	-13.09	-10.42	-2.669
		SEM	4.947	6.032	6.562
Week 132		95% CI	(-22.8,-3.4)	(-22.3, 1.4)	(-15.5,10.2)
		Pr >  t			0.6843
		n	13	4	
		LS Mean	-16.12	-4.523	-11.60
		SEM	5.501	8.513	9.217
Week 144		95% CI	(-26.9,-5.3)	(-21.2,12.2)	(-29.7, 6.5)
		Pr >  t			0.2084
		n	8	1	
		LS Mean	-16.24	5.339	-21.58
		SEM	6.469	15.90	16.64
Week 156		95% CI	(-28.9,-3.6)	(-25.9,36.5)	(-54.2,11.1)
		Pr >  t			0.1949
		n	5	1	
		LS Mean	-0.956	-27.99	27.036
		SEM	7.738	15.90	17.17

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-16.1,14.2)	(-59.2, 3.2)	(-6.7,60.7)
		Pr >  t			0.1157
		n	3	1	
	Week 180	LS Mean	-4.415	5.339	-9.753
		SEM	9.575	15.90	18.08
		95% CI	(-23.2,14.4)	(-25.9,36.5)	(-45.2,25.7)
	Week 180	Pr >  t			0.5896
		n	1	1	
		LS Mean	-24.51	-27.99	3.479
	Week 192	SEM	15.83	15.90	22.04
		95% CI	(-55.6, 6.6)	(-59.2, 3.2)	(-39.8,46.7)
		Pr >  t			0.8746
	Week 192	n	1	1	
		LS Mean	8.818	5.339	3.479
		SEM	15.83	15.90	22.04
	Week 8	95% CI	(-22.2,39.9)	(-25.9,36.5)	(-39.8,46.7)
		Pr >  t			0.8746
		n	17	16	
	Week 8	LS Mean	3.760	1.170	2.590
		SEM	3.747	3.855	5.284
		95% CI	(-3.7,11.2)	(-6.5, 8.8)	(-7.9,13.1)
	Week 16	Pr >  t			0.6250
		n	18	14	
		LS Mean	2.161	6.021	-3.859
	Week 16	SEM	3.668	4.053	5.408
		95% CI	(-5.1, 9.4)	(-2.0,14.1)	(-14.6, 6.9)
		Pr >  t			0.4770
	Week 24	n	16	13	
LS Mean		2.872	7.436	-4.564	
SEM		3.856	4.162	5.610	
Week 24	95% CI	(-4.8,10.5)	(-0.8,15.7)	(-15.7, 6.5)	
	Pr >  t			0.4176	
	n	15	13		
Week 32	LS Mean	0.870	6.218	-5.348	
	SEM	3.924	4.171	5.673	
	95% CI	(-6.9, 8.6)	(-2.0,14.5)	(-16.6, 5.9)	
Week 32	Pr >  t			0.3478	
	n	14	10		
	LS Mean	9.564	5.329	4.235	
Week 40	SEM	4.043	4.573	6.054	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	( 1.6,17.6)	( -3.7,14.4)	( -7.7,16.2)
	Pr >  t			0.4854
	n	14	11	
	LS Mean	1.231	6.010	-4.778
	SEM	4.043	4.430	5.944
Week 56	95% CI	( -6.8, 9.2)	( -2.8,14.8)	( -16.5, 7.0)
	Pr >  t			0.4229
	n	11	11	
	LS Mean	2.716	7.525	-4.809
	SEM	4.381	4.430	6.184
Week 64	95% CI	( -5.9,11.4)	( -1.2,16.3)	( -17.0, 7.4)
	Pr >  t			0.4381
	n	8	11	
	LS Mean	2.248	4.495	-2.247
	SEM	4.902	4.430	6.569
Week 72	95% CI	( -7.4,11.9)	( -4.3,13.3)	( -15.2,10.7)
	Pr >  t			0.7327
	n	11	10	
	LS Mean	2.717	3.292	-0.575
	SEM	4.381	4.580	6.294
Week 84	95% CI	( -5.9,11.4)	( -5.8,12.3)	( -13.0,11.9)
	Pr >  t			0.9273
	n	9	9	
	LS Mean	-5.179	4.602	-9.781
	SEM	4.696	4.752	6.645
Week 96	95% CI	( -14.4, 4.1)	( -4.8,14.0)	( -22.9, 3.3)
	Pr >  t			0.1429
	n	8	7	
	LS Mean	-4.088	4.107	-8.195
	SEM	4.908	5.206	7.122
Week 108	95% CI	( -13.8, 5.6)	( -6.2,14.4)	( -22.2, 5.9)
	Pr >  t			0.2513
	n	7	6	
	LS Mean	1.461	2.750	-1.290
	SEM	5.161	5.529	7.534
Week 120	95% CI	( -8.7,11.6)	( -8.1,13.6)	( -16.1,13.6)
	Pr >  t			0.8642
	n	6	5	
	LS Mean	9.575	6.979	2.596
	SEM	5.485	5.952	8.054

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-1.2,20.4)	(-4.7,18.7)	(-13.3,18.5)
	Pr >  t			0.7475
	n	5	3	
	LS Mean	3.371	0.018	3.353
	SEM	5.898	7.352	9.397
Week 144	95% CI	(-8.2,15.0)	(-14.5,14.5)	(-15.1,21.9)
	Pr >  t			0.7215
	n	5	4	
	LS Mean	-6.629	5.533	-12.16
	SEM	5.898	6.512	8.754
Week 156	95% CI	(-18.2, 5.0)	(-7.3,18.4)	(-29.4, 5.1)
	Pr >  t			0.1659
	n	4	2	
	LS Mean	-10.08	5.384	-15.47
	SEM	6.464	8.796	10.90
Week 168	95% CI	(-22.8, 2.6)	(-11.9,22.7)	(-36.9, 6.0)
	Pr >  t			0.1569
	n	1	1	
	LS Mean	-8.250	5.919	-14.17
	SEM	12.11	12.14	17.14
	95% CI	(-32.1,15.6)	(-18.0,29.8)	(-47.9,19.6)
	Pr >  t			0.4091

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	-9.168	-13.06	3.891		
			SEM	9.429	9.696	3.481		
					95% CI	(-27.8, 9.5)	(-32.2, 6.1)	(-3.0,10.7)
					Pr >  t			0.2649
				Week 16	n	69	55	
					LS Mean	-10.33	-14.97	4.648
					SEM	9.438	9.756	3.695
					95% CI	(-29.0, 8.3)	(-34.3, 4.3)	(-2.6,11.9)
					Pr >  t			0.2095
				Week 24	n	54	46	
					LS Mean	-11.73	-14.72	2.988
					SEM	9.469	9.799	3.936
					95% CI	(-30.5, 7.0)	(-34.1, 4.7)	(-4.8,10.7)
					Pr >  t			0.4482
				Week 32	n	49	41	
					LS Mean	-10.43	-13.94	3.513
					SEM	9.550	9.826	4.064
					95% CI	(-29.3, 8.5)	(-33.4, 5.5)	(-4.5,11.5)
					Pr >  t			0.3879
				Week 40	n	40	33	
					LS Mean	-5.972	-13.63	7.656
					SEM	9.604	9.884	4.329
					95% CI	(-25.0,13.0)	(-33.2, 5.9)	(-0.9,16.2)
					Pr >  t			0.0776
				Week 48	n	38	28	
					LS Mean	-11.22	-11.16	-0.059
					SEM	9.617	9.941	4.487
					95% CI	(-30.2, 7.8)	(-30.8, 8.5)	(-8.9, 8.8)
					Pr >  t			0.9895
				Week 56	n	32	28	
					LS Mean	-8.973	-13.78	4.803
					SEM	9.670	9.942	4.598

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-28.1,10.1)	(-33.4, 5.9)	(-4.2,13.8)
	Pr >  t			0.2967
	n	23	26	
	LS Mean	-11.13	-11.94	0.813
	SEM	9.790	9.968	4.908
Week 72	95% CI	(-30.5, 8.2)	(-31.6, 7.8)	(-8.8,10.4)
	Pr >  t			0.8685
	n	27	25	
	LS Mean	-8.934	-14.21	5.275
	SEM	9.727	9.980	4.811
Week 84	95% CI	(-28.2,10.3)	(-33.9, 5.5)	(-4.2,14.7)
	Pr >  t			0.2733
	n	23	22	
	LS Mean	-14.34	-13.71	-0.623
	SEM	9.790	10.03	5.045
Week 96	95% CI	(-33.7, 5.0)	(-33.5, 6.1)	(-10.5, 9.3)
	Pr >  t			0.9017
	n	20	16	
	LS Mean	-12.62	-12.47	-0.159
	SEM	9.855	10.20	5.479
Week 108	95% CI	(-32.1, 6.8)	(-32.6, 7.7)	(-10.9,10.6)
	Pr >  t			0.9769
	n	20	14	
	LS Mean	-11.56	-17.62	6.059
	SEM	9.855	10.28	5.636
Week 120	95% CI	(-31.0, 7.9)	(-37.9, 2.7)	(-5.0,17.1)
	Pr >  t			0.2827
	n	17	11	
	LS Mean	-10.56	-12.15	1.592
	SEM	9.940	10.46	6.096
Week 132	95% CI	(-30.2, 9.1)	(-32.8, 8.5)	(-10.4,13.6)
	Pr >  t			0.7941
	n	13	6	
	LS Mean	-9.190	-18.05	8.858
	SEM	10.11	11.12	7.406
Week 144	95% CI	(-29.2,10.8)	(-40.0, 3.9)	(-5.7,23.4)
	Pr >  t			0.2320
	n	10	5	
	LS Mean	-19.96	-10.25	-9.706
	SEM	10.32	11.40	8.098

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-40.3, 0.4)	(-32.7, 12.2)	(-25.6, 6.2)
		Pr >  t			0.2310
	Week 156	n	7	3	
		LS Mean	-14.26	-19.89	5.625
		SEM	10.71	12.46	9.934
		95% CI	(-35.4, 6.8)	(-44.4, 4.6)	(-13.9, 25.1)
		Pr >  t			0.5714
	Week 168	n	3	2	
		LS Mean	-3.990	-6.375	2.385
		SEM	12.27	13.66	12.88
		95% CI	(-28.1, 20.1)	(-33.2, 20.5)	(-22.9, 27.7)
		Pr >  t			0.8531
	Week 180	n		1	
		LS Mean		-33.77	
		SEM		16.73	
		95% CI		(-66.6, -0.9)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.444	
		SEM		16.73	
		95% CI		(-33.3, 32.4)	
		Pr >  t			
Second Line	Week 8	n	66	67	
		LS Mean	-8.946	-1.913	-7.034
		SEM	3.450	3.459	3.757
		95% CI	(-15.8, -2.1)	(-8.7, 4.9)	(-14.4, 0.4)
		Pr >  t			0.0623
	Week 16	n	54	52	
		LS Mean	-4.745	-4.373	-0.372
		SEM	3.635	3.727	4.097
		95% CI	(-11.9, 2.4)	(-11.7, 3.0)	(-8.4, 7.7)
		Pr >  t			0.9277
	Week 24	n	49	35	
		LS Mean	-6.470	-0.823	-5.647
		SEM	3.732	4.104	4.501
		95% CI	(-13.8, 0.9)	(-8.9, 7.3)	(-14.5, 3.2)
		Pr >  t			0.2103
	Week 32	n	36	32	
		LS Mean	-4.524	-5.434	0.910
		SEM	4.025	4.209	4.808



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.4, 3.4)	(-13.7, 2.8)	(-8.5,10.4)
		Pr >  t			0.8500
	Week 40	n	33	29	
		LS Mean	-7.634	-7.829	0.195
		SEM	4.107	4.337	4.972
		95% CI	(-15.7, 0.4)	(-16.4, 0.7)	(-9.6,10.0)
		Pr >  t			0.9687
	Week 48	n	29	23	
		LS Mean	-6.794	-7.998	1.203
		SEM	4.238	4.601	5.311
		95% CI	(-15.1, 1.5)	(-17.0, 1.0)	(-9.2,11.6)
		Pr >  t			0.8208
	Week 56	n	25	17	
		LS Mean	-10.73	-7.250	-3.484
		SEM	4.397	5.013	5.801
		95% CI	(-19.4,-2.1)	(-17.1, 2.6)	(-14.9, 7.9)
		Pr >  t			0.5483
	Week 64	n	22	16	
		LS Mean	-6.228	-7.012	0.784
		SEM	4.549	5.108	5.998
		95% CI	(-15.2, 2.7)	(-17.0, 3.0)	(-11.0,12.6)
		Pr >  t			0.8960
	Week 72	n	20	10	
		LS Mean	-11.55	-0.085	-11.47
		SEM	4.673	5.967	6.832
		95% CI	(-20.7,-2.4)	(-11.8,11.6)	(-24.9, 1.9)
		Pr >  t			0.0937
	Week 84	n	16	11	
		LS Mean	-8.672	-1.882	-6.790
		SEM	5.013	5.772	6.891
		95% CI	(-18.5, 1.2)	(-13.2, 9.5)	(-20.3, 6.7)
		Pr >  t			0.3248
	Week 96	n	15	8	
		LS Mean	-4.051	-9.201	5.150
		SEM	5.107	6.465	7.552
		95% CI	(-14.1, 6.0)	(-21.9, 3.5)	(-9.7,20.0)
		Pr >  t			0.4955
	Week 108	n	6	7	
		LS Mean	-11.09	-3.670	-7.422
		SEM	7.128	6.798	9.276

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-25.1, 2.9)	(-17.0, 9.7)	(-25.6,10.8)
		Pr >  t			0.4239
	Week 120	n	11	5	
		LS Mean	-10.55	-7.000	-3.551
		SEM	5.676	7.767	9.040
		95% CI	(-21.7, 0.6)	(-22.2, 8.3)	(-21.3,14.2)
		Pr >  t			0.6946
	Week 132	n	7	2	
		LS Mean	-22.35	-8.626	-13.72
		SEM	6.706	11.57	12.96
		95% CI	(-35.5,-9.2)	(-31.4,14.1)	(-39.2,11.7)
		Pr >  t			0.2900
	Week 144	n	5		
		LS Mean	-8.647		
		SEM	7.660		
		95% CI	(-23.7, 6.4)		
		Pr >  t			
	Week 156	n	3		
		LS Mean	-1.560		
		SEM	9.569		
		95% CI	(-20.4,17.2)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-24.77		
		SEM	15.94		
		95% CI	(-56.1, 6.5)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-24.77		
		SEM	15.94		
		95% CI	(-56.1, 6.5)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	8.562		
		SEM	15.94		
		95% CI	(-22.8,39.9)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-12.62	-17.61	4.991
		SEM	10.18	10.60	4.259
		95% CI	(-32.8, 7.6)	(-38.7, 3.4)	(-3.4,13.4)
		Pr >  t			0.2429
	Week 16	n	51	41	
		LS Mean	-13.63	-21.73	8.100
		SEM	10.19	10.69	4.582
		95% CI	(-33.9, 6.6)	(-43.0,-0.5)	(-0.9,17.1)
		Pr >  t			0.0785
	Week 24	n	38	33	
		LS Mean	-15.91	-22.14	6.230
		SEM	10.25	10.76	4.947
		95% CI	(-36.2, 4.4)	(-43.5,-0.8)	(-3.5,16.0)
		Pr >  t			0.2091
	Week 32	n	34	28	
		LS Mean	-13.25	-20.60	7.351
		SEM	10.38	10.81	5.156
		95% CI	(-33.8, 7.3)	(-42.1, 0.8)	(-2.8,17.5)
		Pr >  t			0.1550
	Week 40	n	26	23	
		LS Mean	-10.97	-19.72	8.754
		SEM	10.49	10.89	5.534
		95% CI	(-31.8, 9.8)	(-41.3, 1.9)	(-2.1,19.6)
		Pr >  t			0.1145
	Week 48	n	24	17	
		LS Mean	-14.58	-16.20	1.626
		SEM	10.52	11.05	5.914
95% CI		(-35.4, 6.3)	(-38.1, 5.7)	(-10.0,13.3)	
	Pr >  t			0.7834	
Week 56	n	21	17		
	LS Mean	-11.90	-21.53	9.634	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	10.59	11.06	6.032
		95% CI	(-32.9, 9.1)	(-43.4, 0.4)	(-2.2, 21.5)
		Pr >  t			0.1109
	Week 64	n	15	15	
		LS Mean	-15.02	-16.28	1.269
		SEM	10.79	11.13	6.515
		95% CI	(-36.4, 6.3)	(-38.3, 5.8)	(-11.5, 14.1)
		Pr >  t			0.8456
	Week 72	n	16	15	
		LS Mean	-11.63	-19.33	7.695
		SEM	10.74	11.13	6.445
		95% CI	(-32.9, 9.6)	(-41.4, 2.7)	(-5.0, 20.4)
		Pr >  t			0.2330
	Week 84	n	14	13	
		LS Mean	-15.63	-19.38	3.748
		SEM	10.83	11.23	6.766
		95% CI	(-37.1, 5.8)	(-41.6, 2.9)	(-9.5, 17.0)
		Pr >  t			0.5798
	Week 96	n	12	9	
		LS Mean	-13.47	-16.69	3.223
		SEM	10.96	11.56	7.482
		95% CI	(-35.2, 8.2)	(-39.6, 6.2)	(-11.5, 17.9)
		Pr >  t			0.6668
	Week 108	n	13	8	
		LS Mean	-15.15	-24.80	9.649
		SEM	10.89	11.69	7.596
		95% CI	(-36.7, 6.4)	(-47.9, -1.7)	(-5.3, 24.6)
		Pr >  t			0.2045
	Week 120	n	11	6	
		LS Mean	-18.16	-18.38	0.215
		SEM	11.03	12.07	8.357
		95% CI	(-40.0, 3.7)	(-42.2, 5.5)	(-16.2, 16.6)
		Pr >  t			0.9795
	Week 132	n	8	3	
		LS Mean	-12.62	-23.55	10.927
		SEM	11.36	13.49	10.65
		95% CI	(-35.1, 9.8)	(-50.1, 3.0)	(-10.0, 31.8)
		Pr >  t			0.3052
	Week 144	n	5	1	
		LS Mean	-24.25	-6.103	-18.15

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	12.05	18.08	16.56
		95% CI	(-48.0,-0.5)	(-41.6,29.4)	(-50.7,14.4)
		Pr >  t			0.2736
	Week 168	n	3	1	
		LS Mean	-6.276	-39.43	33.157
		SEM	13.20	18.08	17.42
	Week 180	95% CI	(-32.3,19.7)	(-75.0,-3.9)	(-1.1,67.4)
		Pr >  t			0.0575
		n	2	1	
	Week 192	LS Mean	1.536	-6.103	7.639
		SEM	14.49	18.08	18.41
		95% CI	(-27.0,30.0)	(-41.6,29.4)	(-28.5,43.8)
	Week 8	Pr >  t			0.6784
		n		1	
		LS Mean		-39.43	
	Week 16	SEM		18.08	
		95% CI		(-75.0,-3.9)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-6.103	
		SEM		18.08	
	Week 32	95% CI		(-41.6,29.4)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	3.760	1.170	2.590	
	SEM	3.747	3.855	5.284	
	95% CI	(-3.7,11.2)	(-6.5, 8.8)	(-7.9,13.1)	
Week 16	Pr >  t			0.6250	
	n	18	14		
	LS Mean	2.161	6.021	-3.859	
Week 24	SEM	3.668	4.053	5.408	
	95% CI	(-5.1, 9.4)	(-2.0,14.1)	(-14.6, 6.9)	
	Pr >  t			0.4770	
Week 32	n	16	13		
	LS Mean	2.872	7.436	-4.564	
	SEM	3.856	4.162	5.610	
Week 8	95% CI	(-4.8,10.5)	(-0.8,15.7)	(-15.7, 6.5)	
	Pr >  t			0.4176	
	n	15	13		
Week 16	LS Mean	0.870	6.218	-5.348	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	SEM	3.924	4.171	5.673	
	95% CI	(-6.9, 8.6)	(-2.0, 14.5)	(-16.6, 5.9)	
	Pr >  t			0.3478	
Week 48	n	14	10		
	LS Mean	9.564	5.329	4.235	
	SEM	4.043	4.573	6.054	
Week 56	95% CI	(1.6, 17.6)	(-3.7, 14.4)	(-7.7, 16.2)	
	Pr >  t			0.4854	
	n	14	11		
Week 64	LS Mean	1.231	6.010	-4.778	
	SEM	4.043	4.430	5.944	
	95% CI	(-6.8, 9.2)	(-2.8, 14.8)	(-16.5, 7.0)	
Week 72	Pr >  t			0.4229	
	n	11	11		
	LS Mean	2.716	7.525	-4.809	
Week 84	SEM	4.381	4.430	6.184	
	95% CI	(-5.9, 11.4)	(-1.2, 16.3)	(-17.0, 7.4)	
	Pr >  t			0.4381	
Week 96	n	8	11		
	LS Mean	2.248	4.495	-2.247	
	SEM	4.902	4.430	6.569	
Week 108	95% CI	(-7.4, 11.9)	(-4.3, 13.3)	(-15.2, 10.7)	
	Pr >  t			0.7327	
	n	11	10		
Week 40	LS Mean	2.717	3.292	-0.575	
	SEM	4.381	4.580	6.294	
	95% CI	(-5.9, 11.4)	(-5.8, 12.3)	(-13.0, 11.9)	
Week 48	Pr >  t			0.9273	
	n	9	9		
	LS Mean	-5.179	4.602	-9.781	
Week 56	SEM	4.696	4.752	6.645	
	95% CI	(-14.4, 4.1)	(-4.8, 14.0)	(-22.9, 3.3)	
	Pr >  t			0.1429	
Week 64	n	8	7		
	LS Mean	-4.088	4.107	-8.195	
	SEM	4.908	5.206	7.122	
Week 72	95% CI	(-13.8, 5.6)	(-6.2, 14.4)	(-22.2, 5.9)	
	Pr >  t			0.2513	
	n	7	6		
Week 84	LS Mean	1.461	2.750	-1.290	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.161	5.529	7.534
		95% CI	(-8.7,11.6)	(-8.1,13.6)	(-16.1,13.6)
		Pr >  t			0.8642
	Week 120	n	6	5	
		LS Mean	9.575	6.979	2.596
		SEM	5.485	5.952	8.054
		95% CI	(-1.2,20.4)	(-4.7,18.7)	(-13.3,18.5)
		Pr >  t			0.7475
	Week 132	n	5	3	
		LS Mean	3.371	0.018	3.353
		SEM	5.898	7.352	9.397
		95% CI	(-8.2,15.0)	(-14.5,14.5)	(-15.1,21.9)
		Pr >  t			0.7215
	Week 144	n	5	4	
		LS Mean	-6.629	5.533	-12.16
		SEM	5.898	6.512	8.754
		95% CI	(-18.2, 5.0)	(-7.3,18.4)	(-29.4, 5.1)
		Pr >  t			0.1659
	Week 156	n	4	2	
		LS Mean	-10.08	5.384	-15.47
		SEM	6.464	8.796	10.90
		95% CI	(-22.8, 2.6)	(-11.9,22.7)	(-36.9, 6.0)
		Pr >  t			0.1569
	Week 168	n	1	1	
		LS Mean	-8.250	5.919	-14.17
		SEM	12.11	12.14	17.14
		95% CI	(-32.1,15.6)	(-18.0,29.8)	(-47.9,19.6)
		Pr >  t			0.4091
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-10.80	-6.198	-4.602
		SEM	7.520	6.858	8.212
		95% CI	(-26.0, 4.4)	(-20.1, 7.7)	(-21.2,12.0)
		Pr >  t			0.5781
	Week 16	n	15	17	
		LS Mean	-9.398	-10.98	1.583
		SEM	7.747	7.072	8.441
		95% CI	(-25.0, 6.2)	(-25.2, 3.3)	(-15.4,18.6)
		Pr >  t			0.8520
	Week 24	n	14	11	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	-9.364	-10.77	1.405
	SEM	7.811	7.464	8.879
	95% CI	(-25.1, 6.4)	(-25.7, 4.2)	(-16.4,19.2)
	Pr >  t			0.8749
	n	12	9	
Week 40	LS Mean	-7.968	-7.677	-0.291
	SEM	7.992	7.742	9.221
	95% CI	(-24.0, 8.1)	(-23.2, 7.8)	(-18.7,18.1)
	Pr >  t			0.9750
	n	11	7	
Week 48	LS Mean	-7.949	-11.53	3.586
	SEM	8.100	8.179	9.626
	95% CI	(-24.2, 8.3)	(-27.8, 4.8)	(-15.6,22.8)
	Pr >  t			0.7106
	n	8	6	
Week 56	LS Mean	-8.060	-12.05	3.989
	SEM	8.452	8.439	10.14
	95% CI	(-25.0, 8.9)	(-28.8, 4.7)	(-16.2,24.1)
	Pr >  t			0.6951
	n	7	5	
Week 64	LS Mean	-10.14	-10.59	0.446
	SEM	8.631	8.747	10.56
	95% CI	(-27.4, 7.1)	(-28.0, 6.8)	(-20.5,21.4)
	Pr >  t			0.9664
	n	5	3	
Week 72	LS Mean	-7.054	-4.179	-2.874
	SEM	9.157	9.945	11.96
	95% CI	(-25.3,11.2)	(-23.9,15.5)	(-26.5,20.8)
	Pr >  t			0.8104
	n	5	2	
Week 84	LS Mean	-9.296	-2.847	-6.449
	SEM	9.192	11.25	13.09
	95% CI	(-27.6, 9.0)	(-25.1,19.4)	(-32.3,19.4)
	Pr >  t			0.6230
	n	4	2	
Week 96	LS Mean	-5.163	-2.847	-2.316
	SEM	9.579	11.25	13.37
	95% CI	(-24.2,13.9)	(-25.1,19.4)	(-28.7,24.1)
	Pr >  t			0.8627
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	1.631	-2.847	4.478
		SEM	9.590	11.25	13.38
		95% CI	(-17.4,20.7)	(-25.1,19.4)	(-21.9,30.9)
		Pr >  t			0.7383
	Week 108	n	1	2	
		LS Mean	-5.714	9.409	-15.12
		SEM	14.50	11.20	17.21
		95% CI	(-34.3,22.9)	(-12.7,31.5)	(-49.1,18.9)
		Pr >  t			0.3808
	Week 120	n	5	1	
		LS Mean	-9.296	1.032	-10.33
		SEM	9.192	14.32	15.81
		95% CI	(-27.6, 9.0)	(-27.2,29.3)	(-41.5,20.9)
		Pr >  t			0.5145
	Week 132	n	3	1	
		LS Mean	-12.86	1.032	-13.89
		SEM	10.26	14.32	16.46
		95% CI	(-33.2, 7.5)	(-27.2,29.3)	(-46.4,18.6)
		Pr >  t			0.3999
	Week 144	n	3		
		LS Mean	-12.86		
		SEM	10.26		
		95% CI	(-33.2, 7.5)		
		Pr >  t			
	Week 156	n	3		
		LS Mean	-1.750		
		SEM	10.26		
		95% CI	(-22.1,18.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-25.03		
		SEM	14.49		
		95% CI	(-53.6, 3.6)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-25.03		
		SEM	14.49		
		95% CI	(-53.6, 3.6)		
		Pr >  t			
	Week 192	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	8.296		
		SEM	14.49		
		95% CI	(-20.3,36.9)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	-10.10	0.607	-10.71
		SEM	4.530	4.535	4.973
		95% CI	(-19.1,-1.1)	(-8.4, 9.6)	(-20.5,-0.9)
		Pr >  t			0.0328
	Week 16	n	30	29	
		LS Mean	-4.404	0.459	-4.863
		SEM	4.719	4.987	5.525
		95% CI	(-13.7, 4.9)	(-9.4,10.3)	(-15.8, 6.0)
		Pr >  t			0.3798
	Week 24	n	26	20	
		LS Mean	-6.841	2.969	-9.810
		SEM	4.936	5.572	6.148
		95% CI	(-16.6, 2.9)	(-8.0,14.0)	(-21.9, 2.3)
		Pr >  t			0.1119
	Week 32	n	18	20	
		LS Mean	-5.486	-3.697	-1.788
		SEM	5.469	5.572	6.572
		95% CI	(-16.3, 5.3)	(-14.7, 7.3)	(-14.7,11.1)
		Pr >  t			0.7857
	Week 40	n	18	19	
		LS Mean	-3.468	-7.483	4.015
		SEM	5.468	5.647	6.632
		95% CI	(-14.2, 7.3)	(-18.6, 3.6)	(-9.0,17.1)
		Pr >  t			0.5454
	Week 48	n	16	14	
		LS Mean	-1.621	-6.638	5.016
		SEM	5.645	6.114	7.181
		95% CI	(-12.7, 9.5)	(-18.7, 5.4)	(-9.1,19.1)
		Pr >  t			0.4853
	Week 56	n	14	10	
		LS Mean	-7.881	-9.114	1.232
		SEM	5.863	6.762	7.915
		95% CI	(-19.4, 3.7)	(-22.4, 4.2)	(-14.3,16.8)
		Pr >  t			0.8764

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n		13	11	
	LS Mean		-3.529	-8.314	4.785
	SEM		5.995	6.568	7.852
	95% CI		(-15.3, 8.3)	(-21.2, 4.6)	(-10.7,20.2)
	Pr >  t				0.5427
Week 72	n		10	6	
	LS Mean		-11.17	-1.118	-10.05
	SEM		6.499	8.052	9.480
	95% CI		(-24.0, 1.6)	(-17.0,14.7)	(-28.7, 8.6)
	Pr >  t				0.2896
Week 84	n		8	7	
	LS Mean		-10.04	-1.113	-8.928
	SEM		7.085	7.621	9.496
	95% CI		(-24.0, 3.9)	(-16.1,13.9)	(-27.6, 9.7)
	Pr >  t				0.3478
Week 96	n		6	5	
	LS Mean		-7.725	-14.47	6.750
	SEM		7.836	8.607	10.87
	95% CI		(-23.1, 7.7)	(-31.4, 2.5)	(-14.6,28.1)
	Pr >  t				0.5349
Week 108	n		2	4	
	LS Mean		-11.97	-4.326	-7.640
	SEM		12.43	9.395	14.99
	95% CI		(-36.4,12.5)	(-22.8,14.1)	(-37.1,21.8)
	Pr >  t				0.6106
Week 120	n		4	4	
	LS Mean		-3.880	-8.493	4.613
	SEM		9.185	9.395	12.47
	95% CI		(-21.9,14.2)	(-27.0,10.0)	(-19.9,29.1)
	Pr >  t				0.7117
Week 132	n		3	1	
	LS Mean		-15.30	-17.68	2.379
	SEM		10.41	17.22	19.66
	95% CI		(-35.8, 5.2)	(-51.6,16.2)	(-36.3,41.1)
	Pr >  t				0.9038
Week 144	n		2		
	LS Mean		-0.522		
	SEM		12.36		
	95% CI		(-24.8,23.8)		
	Pr >  t				

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-7.358	-5.747	-1.611		
			SEM	4.203	4.205	3.357		
			95% CI	(-15.6, 0.9)	(-14.0, 2.5)	(-8.2, 5.0)		
					Pr >  t			0.6316
		Week 16	n	79	68			
			LS Mean	-3.711	-6.811	3.099		
			SEM	4.245	4.403	3.620		
			95% CI	(-12.1, 4.7)	(-15.5, 1.9)	(-4.0, 10.2)		
					Pr >  t			0.3924
		Week 24	n	64	55			
			LS Mean	-6.813	-3.516	-3.297		
			SEM	4.359	4.556	3.882		
			95% CI	(-15.4, 1.8)	(-12.5, 5.5)	(-10.9, 4.3)		
					Pr >  t			0.3962
		Week 32	n	49	53			
			LS Mean	-5.077	-6.468	1.391		
			SEM	4.539	4.580	4.074		
			95% CI	(-14.0, 3.9)	(-15.5, 2.5)	(-6.6, 9.4)		
					Pr >  t			0.7329
		Week 40	n	44	45			
			LS Mean	-2.915	-8.077	5.161		
			SEM	4.607	4.675	4.256		
			95% CI	(-12.0, 6.1)	(-17.3, 1.1)	(-3.2, 13.5)		
					Pr >  t			0.2257
		Week 48	n	41	36			
			LS Mean	-6.828	-6.511	-0.317		
			SEM	4.651	4.825	4.466		
95% CI	(-16.0, 2.3)		(-16.0, 3.0)	(-9.1, 8.5)				
			Pr >  t			0.9435		
Week 56	n	33	32					
	LS Mean	-7.380	-9.246	1.866				
	SEM	4.804	4.915	4.724				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-16.8, 2.1)	(-18.9, 0.4)	(-7.4, 11.1)
	Pr >  t			0.6929
	n	27	31	
	LS Mean	-5.864	-7.719	1.855
	SEM	4.968	4.942	4.921
Week 72	95% CI	(-15.6, 3.9)	(-17.4, 2.0)	(-7.8, 11.5)
	Pr >  t			0.7063
	n	26	26	
	LS Mean	-7.093	-5.800	-1.294
	SEM	5.002	5.095	5.108
Week 84	95% CI	(-16.9, 2.7)	(-15.8, 4.2)	(-11.3, 8.7)
	Pr >  t			0.8001
	n	22	23	
	LS Mean	-12.30	-5.691	-6.610
	SEM	5.184	5.211	5.385
Week 96	95% CI	(-22.5, -2.1)	(-15.9, 4.5)	(-17.2, 4.0)
	Pr >  t			0.2199
	n	18	18	
	LS Mean	-10.65	-8.906	-1.740
	SEM	5.413	5.484	5.860
Week 108	95% CI	(-21.3, -0.0)	(-19.7, 1.9)	(-13.2, 9.8)
	Pr >  t			0.7665
	n	14	14	
	LS Mean	-9.935	-9.072	-0.864
	SEM	5.756	5.822	6.478
Week 120	95% CI	(-21.2, 1.4)	(-20.5, 2.4)	(-13.6, 11.8)
	Pr >  t			0.8940
	n	12	12	
	LS Mean	-3.846	-8.974	5.127
	SEM	5.992	6.061	6.897
Week 132	95% CI	(-15.6, 7.9)	(-20.9, 2.9)	(-8.4, 18.7)
	Pr >  t			0.4574
	n	9	5	
	LS Mean	-6.905	-14.99	8.083
	SEM	6.513	8.006	9.025
Week 144	95% CI	(-19.7, 5.9)	(-30.7, 0.7)	(-9.6, 25.8)
	Pr >  t			0.3707
	n	7	4	
	LS Mean	-5.806	-6.055	0.249
	SEM	7.062	8.716	10.04

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.7, 8.1)	(-23.2,11.0)	(-19.5,20.0)
		Pr >  t			0.9802
	Week 156	n	4	2	
		LS Mean	-13.06	-6.236	-6.826
		SEM	8.652	11.59	13.57
		95% CI	(-30.0, 3.9)	(-29.0,16.5)	(-33.5,19.8)
		Pr >  t			0.6150
	Week 168	n	2	1	
		LS Mean	2.417	-5.729	8.147
		SEM	11.53	15.85	18.95
		95% CI	(-20.2,25.0)	(-36.8,25.4)	(-29.0,45.3)
		Pr >  t			0.6674
Yes	Week 8	n	53	48	
		LS Mean	-2.561	-2.040	-0.522
		SEM	3.867	4.029	3.813
		95% CI	(-10.2, 5.1)	(-10.0, 5.9)	(-8.0, 7.0)
		Pr >  t			0.8913
	Week 16	n	45	39	
		LS Mean	-5.781	-6.474	0.693
		SEM	4.035	4.203	4.066
		95% CI	(-13.8, 2.2)	(-14.8, 1.8)	(-7.3, 8.7)
		Pr >  t			0.8648
	Week 24	n	41	26	
		LS Mean	-3.553	-8.327	4.774
		SEM	4.089	4.499	4.458
		95% CI	(-11.6, 4.5)	(-17.2, 0.5)	(-4.0,13.5)
		Pr >  t			0.2850
	Week 32	n	37	20	
		LS Mean	-3.064	-6.795	3.731
		SEM	4.177	4.777	4.771
		95% CI	(-11.3, 5.2)	(-16.2, 2.6)	(-5.7,13.1)
		Pr >  t			0.4347
	Week 40	n	31	17	
		LS Mean	-5.229	-6.113	0.884
		SEM	4.296	4.990	5.055
		95% CI	(-13.7, 3.2)	(-15.9, 3.7)	(-9.1,10.8)
		Pr >  t			0.8613
	Week 48	n	28	15	
		LS Mean	-4.235	-5.444	1.209
		SEM	4.369	5.137	5.264



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.8, 4.4)	(-15.6, 4.7)	(-9.1,11.6)
		Pr >  t			0.8185
	Week 56	n	26	13	
		LS Mean	-3.385	-1.744	-1.641
		SEM	4.426	5.320	5.493
		95% CI	(-12.1, 5.3)	(-12.2, 8.7)	(-12.4, 9.2)
		Pr >  t			0.7653
	Week 64	n	20	11	
		LS Mean	-3.968	-0.631	-3.337
		SEM	4.651	5.557	5.902
		95% CI	(-13.1, 5.2)	(-11.6,10.3)	(-14.9, 8.3)
		Pr >  t			0.5720
	Week 72	n	22	9	
		LS Mean	-5.025	-3.472	-1.553
		SEM	4.568	5.873	6.137
		95% CI	(-14.0, 4.0)	(-15.0, 8.1)	(-13.6,10.5)
		Pr >  t			0.8004
	Week 84	n	18	10	
		LS Mean	-2.751	-3.832	1.081
		SEM	4.768	5.704	6.120
		95% CI	(-12.1, 6.6)	(-15.0, 7.4)	(-10.9,13.1)
		Pr >  t			0.8599
	Week 96	n	17	6	
		LS Mean	0.463	-0.631	1.095
		SEM	4.816	6.662	7.066
		95% CI	(-9.0, 9.9)	(-13.7,12.5)	(-12.8,15.0)
		Pr >  t			0.8769
	Week 108	n	12	7	
		LS Mean	-3.678	-6.933	3.255
		SEM	5.259	6.335	7.071
		95% CI	(-14.0, 6.7)	(-19.4, 5.5)	(-10.6,17.1)
		Pr >  t			0.6454
	Week 120	n	16	4	
		LS Mean	-8.561	3.440	-12.00
		SEM	4.888	7.688	8.084
		95% CI	(-18.2, 1.1)	(-11.7,18.5)	(-27.9, 3.9)
		Pr >  t			0.1382
	Week 132	n	11	3	
		LS Mean	-11.89	-1.891	-10.00
		SEM	5.384	8.589	9.219

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.5,-1.3)	(-18.8,15.0)	(-28.1, 8.1)
		Pr >  t			0.2784
	Week 144	n	8	1	
		LS Mean	-17.49	9.602	-27.09
		SEM	5.889	13.82	14.43
		95% CI	(-29.1,-5.9)	(-17.5,36.7)	(-55.4, 1.2)
		Pr >  t			0.0609
	Week 156	n	6	1	
		LS Mean	-1.584	-23.73	22.144
		SEM	6.502	13.82	14.68
		95% CI	(-14.4,11.2)	(-50.9, 3.4)	(-6.7,51.0)
		Pr >  t			0.1319
	Week 168	n	2	1	
		LS Mean	-12.47	9.602	-22.08
		SEM	10.03	13.82	16.55
		95% CI	(-32.2, 7.2)	(-17.5,36.7)	(-54.6,10.4)
		Pr >  t			0.1827
	Week 180	n	1	1	
		LS Mean	-21.80	-23.73	1.933
		SEM	13.69	13.82	18.99
		95% CI	(-48.7, 5.1)	(-50.9, 3.4)	(-35.4,39.2)
		Pr >  t			0.9190
	Week 192	n	1	1	
		LS Mean	11.535	9.602	1.933
		SEM	13.69	13.82	18.99
		95% CI	(-15.4,38.4)	(-17.5,36.7)	(-35.4,39.2)
		Pr >  t			0.9190

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Estrogen Receptor Status (L)	Negative	Week 8	n	2				
			LS Mean	13.888				
			SEM	0.000				
			95% CI	( 13.9,13.9)				
				Week 16	Pr >  t			
		n	2					
		LS Mean	13.888					
		SEM	0.000					
				Week 24	95% CI	( 13.9,13.9)		
		n	1					
		LS Mean	13.887					
		SEM	0.000					
				Week 32	95% CI	( 13.9,13.9)		
		n	1					
		LS Mean	13.887					
		SEM	0.000					
				Week 40	95% CI	( 13.9,13.9)		
		n	1					
		LS Mean	13.888					
		SEM	0.000					
				Week 48	95% CI	( 13.9,13.9)		
		n	1					
		LS Mean	13.888					
		SEM	0.000					
				Week 56	95% CI	( 13.9,13.9)		
		n	1					
		LS Mean	13.888					
		SEM	0.000					

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI Pr >  t  n	( 13.9,13.9) 1	
	Week 72	LS Mean SEM	13.887 0.000	
		95% CI Pr >  t  n	( 13.9,13.9) 1	
	Week 84	LS Mean SEM	13.887 0.000	
		95% CI Pr >  t  n	( 13.9,13.9) 1	
	Week 96	LS Mean SEM	13.887 0.000	
		95% CI Pr >  t  n	( 13.9,13.9) 1	
Positive	Week 8	LS Mean SEM	-5.897 2.960	-1.359 2.583
		95% CI Pr >  t  n	(-11.7,-0.1) 140	(-6.4, 3.7) 0.5990
	Week 16	LS Mean SEM	-4.786 3.028	1.970 2.774
		95% CI Pr >  t  n	(-10.7, 1.2) 122	(-3.5, 7.4) 0.4779
	Week 24	LS Mean SEM	-5.871 3.094	-0.727 2.985
		95% CI Pr >  t  n	(-12.0, 0.2) 104	(-6.6, 5.1) 0.8076
	Week 32	LS Mean SEM	-4.504 3.201	2.216 3.132
		95% CI Pr >  t  n	(-10.8, 1.8) 85	(-3.9, 8.4) 0.4793
	Week 40	LS Mean SEM	-4.145 3.266	3.537 3.290

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-10.6, 2.3)	(-14.4,-0.9)	(-2.9,10.0)
	Pr >  t			0.2826
Week 48	n	68	51	
	LS Mean	-6.156	-6.361	0.205
	SEM	3.307	3.546	3.452
	95% CI	(-12.7, 0.3)	(-13.3, 0.6)	(-6.6, 7.0)
	Pr >  t			0.9526
Week 56	n	58	45	
	LS Mean	-6.037	-7.263	1.226
	SEM	3.391	3.630	3.621
	95% CI	(-12.7, 0.6)	(-14.4,-0.1)	(-5.9, 8.3)
	Pr >  t			0.7350
Week 64	n	47	42	
	LS Mean	-5.341	-6.023	0.682
	SEM	3.518	3.680	3.791
	95% CI	(-12.2, 1.6)	(-13.2, 1.2)	(-6.8, 8.1)
	Pr >  t			0.8572
Week 72	n	47	35	
	LS Mean	-6.545	-5.304	-1.240
	SEM	3.520	3.822	3.930
	95% CI	(-13.5, 0.4)	(-12.8, 2.2)	(-9.0, 6.5)
	Pr >  t			0.7523
Week 84	n	39	33	
	LS Mean	-8.493	-5.347	-3.146
	SEM	3.662	3.872	4.096
	95% CI	(-15.7,-1.3)	(-12.9, 2.3)	(-11.2, 4.9)
	Pr >  t			0.4426
Week 96	n	34	24	
	LS Mean	-5.706	-6.956	1.250
	SEM	3.768	4.182	4.484
	95% CI	(-13.1, 1.7)	(-15.2, 1.2)	(-7.5,10.0)
	Pr >  t			0.7805
Week 108	n	26	21	
	LS Mean	-7.542	-8.595	1.053
	SEM	4.027	4.335	4.836
	95% CI	(-15.4, 0.4)	(-17.1,-0.1)	(-8.4,10.5)
	Pr >  t			0.8277
Week 120	n	28	16	
	LS Mean	-7.135	-5.996	-1.139
	SEM	3.948	4.695	5.104

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.9, 0.6)	(-15.2, 3.2)	(-11.1, 8.9)
		Pr >  t			0.8234
	Week 132	n	20	8	
		LS Mean	-10.28	-10.58	0.309
		SEM	4.323	5.955	6.521
		95% CI	(-18.8,-1.8)	(-22.3, 1.1)	(-12.5,13.1)
		Pr >  t			0.9623
	Week 144	n	15	5	
		LS Mean	-12.66	-2.866	-9.799
		SEM	4.710	7.187	7.894
		95% CI	(-21.9,-3.4)	(-17.0,11.2)	(-25.3, 5.7)
		Pr >  t			0.2147
	Week 156	n	10	3	
		LS Mean	-6.838	-12.53	5.691
		SEM	5.424	8.951	9.896
		95% CI	(-17.5, 3.8)	(-30.1, 5.0)	(-13.7,25.1)
		Pr >  t			0.5653
	Week 168	n	4	2	
		LS Mean	-5.443	0.961	-6.404
		SEM	7.841	10.76	12.87
		95% CI	(-20.8, 9.9)	(-20.1,22.1)	(-31.7,18.8)
		Pr >  t			0.6189
	Week 180	n	1	1	
		LS Mean	-22.22	-26.53	4.314
		SEM	14.89	14.90	20.79
		95% CI	(-51.4, 7.0)	(-55.8, 2.7)	(-36.5,45.1)
		Pr >  t			0.8356
	Week 192	n	1	1	
		LS Mean	11.113	6.799	4.314
		SEM	14.89	14.90	20.79
		95% CI	(-18.1,40.3)	(-22.4,36.0)	(-36.5,45.1)
		Pr >  t			0.8356

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-5.693	-4.894	-0.799
			SEM	3.129	3.228	2.958
			95% CI	(-11.9, 0.5)	(-11.2, 1.5)	(-6.6, 5.0)
		Pr >  t			0.7873	
		Week 16	n	90	75	
			LS Mean	-4.021	-6.888	2.867
			SEM	3.199	3.369	3.164
			95% CI	(-10.3, 2.3)	(-13.5,-0.3)	(-3.4, 9.1)
		Pr >  t			0.3654	
		Week 24	n	79	62	
			LS Mean	-3.052	-4.973	1.921
			SEM	3.266	3.490	3.335
			95% CI	(-9.5, 3.4)	(-11.8, 1.9)	(-4.6, 8.5)
		Pr >  t			0.5648	
		Week 32	n	70	56	
			LS Mean	-3.062	-7.221	4.159
			SEM	3.350	3.559	3.452
			95% CI	(-9.7, 3.5)	(-14.2,-0.2)	(-2.6,10.9)
		Pr >  t			0.2287	
		Week 40	n	61	46	
			LS Mean	-4.325	-6.350	2.025
			SEM	3.419	3.689	3.641
			95% CI	(-11.0, 2.4)	(-13.6, 0.9)	(-5.1, 9.2)
		Pr >  t			0.5783	
		Week 48	n	56	38	
			LS Mean	-4.727	-2.400	-2.327
			SEM	3.464	3.821	3.817
95% CI	(-11.5, 2.1)		(-9.9, 5.1)	(-9.8, 5.2)		
Pr >  t			0.5422			
Week 56	n	49	33			
	LS Mean	-6.170	-6.084	-0.086		
	SEM	3.539	3.930	3.996		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-13.1, 0.8)	(-13.8, 1.6)	(-7.9, 7.8)
	Pr >  t			0.9829
	n	37	29	
	LS Mean	-4.641	-3.670	-0.971
	SEM	3.721	4.043	4.268
Week 72	95% CI	(-12.0, 2.7)	(-11.6, 4.3)	(-9.3, 7.4)
	Pr >  t			0.8201
	n	40	25	
	LS Mean	-5.824	-6.828	1.004
	SEM	3.668	4.180	4.353
Week 84	95% CI	(-13.0, 1.4)	(-15.0, 1.4)	(-7.5, 9.5)
	Pr >  t			0.8176
	n	32	23	
	LS Mean	-7.067	-6.564	-0.503
	SEM	3.846	4.266	4.575
Week 96	95% CI	(-14.6, 0.5)	(-14.9, 1.8)	(-9.5, 8.5)
	Pr >  t			0.9125
	n	29	17	
	LS Mean	-4.838	-5.403	0.565
	SEM	3.925	4.619	4.972
Week 108	95% CI	(-12.5, 2.9)	(-14.5, 3.7)	(-9.2, 10.3)
	Pr >  t			0.9095
	n	22	15	
	LS Mean	-6.794	-6.013	-0.782
	SEM	4.205	4.788	5.340
Week 120	95% CI	(-15.1, 1.5)	(-15.4, 3.4)	(-11.3, 9.7)
	Pr >  t			0.8836
	n	23	13	
	LS Mean	-8.003	-3.651	-4.352
	SEM	4.152	5.002	5.499
Week 132	95% CI	(-16.2, 0.2)	(-13.5, 6.2)	(-15.1, 6.4)
	Pr >  t			0.4288
	n	17	5	
	LS Mean	-10.73	-10.79	0.057
	SEM	4.509	7.033	7.596
Week 144	95% CI	(-19.6, -1.9)	(-24.6, 3.0)	(-14.8, 15.0)
	Pr >  t			0.9940
	n	14	3	
Week 144	LS Mean	-12.61	-0.672	-11.94
	SEM	4.769	8.725	9.320

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.0,-3.3)	(-17.8,16.4)	(-30.2, 6.3)
		Pr >  t			0.2004
	Week 156	n	9	2	
		LS Mean	-2.712	-15.45	12.736
		SEM	5.542	10.44	11.29
		95% CI	(-13.6, 8.2)	(-35.9, 5.0)	(-9.4,34.9)
		Pr >  t			0.2597
	Week 168	n	4	1	
		LS Mean	-4.657	7.950	-12.61
		SEM	7.626	14.42	15.93
		95% CI	(-19.6,10.3)	(-20.3,36.2)	(-43.9,18.7)
		Pr >  t			0.4290
	Week 180	n	1	1	
		LS Mean	-21.41	-25.38	3.974
		SEM	14.36	14.42	20.05
		95% CI	(-49.6, 6.8)	(-53.7, 2.9)	(-35.4,43.3)
		Pr >  t			0.8429
	Week 192	n	1	1	
		LS Mean	11.924	7.950	3.974
		SEM	14.36	14.42	20.05
		95% CI	(-16.3,40.1)	(-20.3,36.2)	(-35.4,43.3)
		Pr >  t			0.8429
>= 3	Week 8	n	37	45	
		LS Mean	-3.183	-1.145	-2.038
		SEM	9.183	9.101	5.226
		95% CI	(-21.4,15.0)	(-19.2,16.9)	(-12.4, 8.3)
		Pr >  t			0.6972
	Week 16	n	34	32	
		LS Mean	-3.737	-4.038	0.301
		SEM	9.406	9.457	5.642
		95% CI	(-22.3,14.9)	(-22.7,14.7)	(-10.8,11.4)
		Pr >  t			0.9576
	Week 24	n	26	19	
		LS Mean	-11.14	-3.442	-7.702
		SEM	9.562	9.814	6.476
		95% CI	(-30.1, 7.8)	(-22.8,16.0)	(-20.5, 5.1)
		Pr >  t			0.2356
	Week 32	n	16	17	
		LS Mean	-6.461	-2.939	-3.523
		SEM	9.940	9.923	7.170

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-26.1,13.2)	(-22.5,16.7)	(-17.6,10.6)
		Pr >  t			0.6236
		n	14	16	
		LS Mean	1.128	-9.306	10.434
		SEM	10.08	9.975	7.426
Week 48		95% CI	(-18.8,21.0)	(-29.0,10.4)	(-4.2,25.0)
		Pr >  t			0.1611
		n	13	13	
		LS Mean	-7.586	-15.71	8.122
		SEM	10.15	10.18	7.790
Week 56		95% CI	(-27.6,12.5)	(-35.8, 4.4)	(-7.2,23.4)
		Pr >  t			0.2979
		n	10	12	
		LS Mean	-0.055	-8.525	8.470
		SEM	10.47	10.27	8.296
Week 64		95% CI	(-20.7,20.6)	(-28.8,11.7)	(-7.8,24.8)
		Pr >  t			0.3080
		n	10	13	
		LS Mean	-3.866	-9.394	5.528
		SEM	10.47	10.19	8.196
Week 72		95% CI	(-24.5,16.8)	(-29.5,10.7)	(-10.6,21.6)
		Pr >  t			0.5005
		n	8	10	
		LS Mean	-4.941	0.287	-5.228
		SEM	10.78	10.49	8.950
Week 84		95% CI	(-26.2,16.3)	(-20.4,21.0)	(-22.8,12.4)
		Pr >  t			0.5595
		n	8	10	
		LS Mean	-9.361	-0.640	-8.721
		SEM	10.79	10.49	8.951
Week 96		95% CI	(-30.6,11.9)	(-21.3,20.0)	(-26.3, 8.9)
		Pr >  t			0.3305
		n	6	7	
		LS Mean	-4.708	-8.671	3.963
		SEM	11.29	11.02	10.13
Week 108		95% CI	(-27.0,17.5)	(-30.4,13.1)	(-16.0,23.9)
		Pr >  t			0.6959
		n	4	6	
	LS Mean	-6.120	-12.99	6.874	
	SEM	12.21	11.29	11.43	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-30.2,17.9)	(-15.6,29.4)
		Pr >  t		0.5480
	Week 120	n	5	3
		LS Mean	1.470	-12.77
		SEM	11.67	13.08
		95% CI	(-21.5,24.5)	(-38.5,13.0)
		Pr >  t		(-10.7,39.2)
	Week 132	n	3	3
		LS Mean	-2.118	-8.847
		SEM	13.06	13.08
		95% CI	(-27.8,23.6)	(-34.6,16.9)
		Pr >  t		(-20.8,34.3)
	Week 144	n	1	2
		LS Mean	-2.435	-4.654
		SEM	18.53	14.64
		95% CI	(-38.9,34.0)	(-33.4,24.1)
		Pr >  t		(-37.7,42.2)
	Week 156	n	1	1
		LS Mean	-35.77	-4.535
		SEM	18.53	18.56
		95% CI	(-72.2, 0.7)	(-41.0,32.0)
		Pr >  t		(-77.0,14.6)
	Week 168	n		1
		LS Mean		-4.535
		SEM		18.56
		95% CI		(-41.0,32.0)
		Pr >  t		0.1807

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	2.277	6.330	-4.053		
			SEM	8.775	9.057	3.783		
			95% CI	(-15.1,19.7)	(-11.6,24.3)	(-11.5, 3.4)		
					Pr >  t			0.2850
		Week 16	n	59	49			
			LS Mean	1.410	1.742	-0.332		
			SEM	8.802	9.121	4.022		
			95% CI	(-16.1,18.9)	(-16.4,19.8)	(-8.2, 7.6)		
					Pr >  t			0.9342
		Week 24	n	54	41			
			LS Mean	2.334	6.833	-4.499		
			SEM	8.817	9.180	4.205		
			95% CI	(-15.2,19.8)	(-11.4,25.0)	(-12.8, 3.8)		
					Pr >  t			0.2854
		Week 32	n	48	37			
			LS Mean	2.582	2.306	0.276		
			SEM	8.842	9.213	4.344		
			95% CI	(-15.0,20.1)	(-16.0,20.6)	(-8.3, 8.8)		
					Pr >  t			0.9493
		Week 40	n	43	33			
			LS Mean	1.980	4.420	-2.440		
			SEM	8.867	9.254	4.492		
			95% CI	(-15.6,19.6)	(-13.9,22.8)	(-11.3, 6.4)		
			Pr >  t			0.5874		
Week 48	n	41	28					
	LS Mean	-1.236	5.776	-7.011				
	SEM	8.881	9.318	4.654				
	95% CI	(-18.8,16.4)	(-12.7,24.2)	(-16.2, 2.1)				
			Pr >  t			0.1326		
Week 56	n	35	22					
	LS Mean	-2.585	5.768	-8.353				
	SEM	8.925	9.433	4.974				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.3,15.1)	(-12.9,24.5)	(-18.1, 1.4)
		Pr >  t			0.0937
	Week 64	n	26	23	
		LS Mean	0.403	7.831	-7.428
		SEM	9.030	9.412	5.141
		95% CI	(-17.5,18.3)	(-10.8,26.5)	(-17.5, 2.7)
		Pr >  t			0.1490
	Week 72	n	28	18	
		LS Mean	-4.422	3.850	-8.272
		SEM	9.001	9.548	5.332
		95% CI	(-22.3,13.4)	(-15.1,22.8)	(-18.7, 2.2)
		Pr >  t			0.1214
	Week 84	n	22	18	
		LS Mean	-3.002	6.410	-9.412
		SEM	9.144	9.548	5.520
		95% CI	(-21.1,15.1)	(-12.5,25.3)	(-20.3, 1.4)
		Pr >  t			0.0887
	Week 96	n	21	13	
		LS Mean	-0.915	6.653	-7.568
		SEM	9.127	9.781	5.955
		95% CI	(-19.0,17.2)	(-12.7,26.0)	(-19.3, 4.1)
		Pr >  t			0.2042
	Week 108	n	17	12	
		LS Mean	-1.622	1.159	-2.781
		SEM	9.297	9.850	6.254
		95% CI	(-20.0,16.8)	(-18.3,20.6)	(-15.1, 9.5)
		Pr >  t			0.6567
	Week 120	n	18	11	
		LS Mean	-0.698	7.038	-7.736
		SEM	9.209	9.930	6.329
		95% CI	(-18.9,17.5)	(-12.6,26.7)	(-20.2, 4.7)
		Pr >  t			0.2220
	Week 132	n	13	5	
		LS Mean	-3.601	-0.386	-3.215
		SEM	9.492	11.00	8.179
		95% CI	(-22.4,15.2)	(-22.1,21.3)	(-19.3,12.8)
		Pr >  t			0.6944
	Week 144	n	12	3	
		LS Mean	-3.222	9.729	-12.95
		SEM	9.492	12.19	9.792

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.0,15.5)	(-14.3,33.7)	(-32.2, 6.3)
		Pr >  t			0.1863
	Week 156	n	7	2	
		LS Mean	4.706	-5.034	9.740
		SEM	10.18	13.51	11.92
		95% CI	(-15.4,24.8)	(-31.6,21.5)	(-13.7,33.1)
		Pr >  t			0.4140
	Week 168	n	3	1	
		LS Mean	0.628	18.349	-17.72
		SEM	11.93	16.88	16.83
		95% CI	(-22.9,24.1)	(-14.8,51.5)	(-50.8,15.3)
		Pr >  t			0.2927
	Week 180	n	1	1	
		LS Mean	-15.63	-14.98	-0.644
		SEM	16.70	16.88	20.49
		95% CI	(-48.4,17.2)	(-48.1,18.2)	(-40.9,39.6)
		Pr >  t			0.9749
	Week 192	n	1	1	
		LS Mean	17.705	18.349	-0.644
		SEM	16.70	16.88	20.49
		95% CI	(-15.1,50.5)	(-14.8,51.5)	(-40.9,39.6)
		Pr >  t			0.9749
Yes	Week 8	n	73	80	
		LS Mean	-9.970	-11.24	1.267
		SEM	4.700	4.746	3.539
		95% CI	(-19.2,-0.7)	(-20.6,-1.9)	(-5.7, 8.2)
		Pr >  t			0.7206
	Week 16	n	65	58	
		LS Mean	-7.185	-11.45	4.264
		SEM	4.819	4.945	3.818
		95% CI	(-16.7, 2.3)	(-21.2,-1.7)	(-3.2,11.8)
		Pr >  t			0.2649
	Week 24	n	51	40	
		LS Mean	-10.17	-13.31	3.147
		SEM	4.920	5.197	4.236
		95% CI	(-19.9,-0.5)	(-23.6,-3.1)	(-5.2,11.5)
		Pr >  t			0.4580
	Week 32	n	38	36	
		LS Mean	-7.626	-11.93	4.305
		SEM	5.146	5.274	4.523

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.8, 2.5)	(-22.3,-1.5)	( -4.6,13.2)
		Pr >  t			0.3416
	Week 40	n	32	29	
		LS Mean	-5.724	-16.28	10.561
		SEM	5.276	5.432	4.838
		95% CI	(-16.1, 4.7)	(-27.0,-5.6)	( 1.1,20.1)
		Pr >  t			0.0295
	Week 48	n	28	23	
		LS Mean	-5.976	-15.19	9.214
		SEM	5.374	5.634	5.160
		95% CI	(-16.6, 4.6)	(-26.3,-4.1)	( -0.9,19.3)
		Pr >  t			0.0746
	Week 56	n	24	23	
		LS Mean	-3.743	-16.52	12.780
		SEM	5.509	5.633	5.295
		95% CI	(-14.6, 7.1)	(-27.6,-5.4)	( 2.4,23.2)
		Pr >  t			0.0161
	Week 64	n	21	19	
		LS Mean	-6.600	-16.84	10.243
		SEM	5.637	5.819	5.620
		95% CI	(-17.7, 4.5)	(-28.3,-5.4)	( -0.8,21.3)
		Pr >  t			0.0688
	Week 72	n	20	17	
		LS Mean	-2.646	-10.74	8.096
		SEM	5.690	5.940	5.796
		95% CI	(-13.8, 8.5)	(-22.4, 0.9)	( -3.3,19.5)
		Pr >  t			0.1629
	Week 84	n	18	15	
		LS Mean	-9.225	-13.66	4.432
		SEM	5.787	6.092	6.049
		95% CI	(-20.6, 2.2)	(-25.6,-1.7)	( -7.4,16.3)
		Pr >  t			0.4640
	Week 96	n	14	11	
		LS Mean	-5.525	-17.45	11.928
		SEM	6.098	6.530	6.760
		95% CI	(-17.5, 6.5)	(-30.3,-4.6)	( -1.3,25.2)
		Pr >  t			0.0781
	Week 108	n	9	9	
		LS Mean	-9.074	-14.24	5.168
		SEM	6.784	6.866	7.689



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.4, 4.3)	(-27.7,-0.8)	( -9.9,20.3)
		Pr >  t			0.5017
	Week 120	n	10	5	
		LS Mean	-9.600	-17.74	8.138
		SEM	6.624	8.188	8.767
		95% CI	(-22.6, 3.4)	(-33.8,-1.7)	( -9.1,25.3)
		Pr >  t			0.3536
	Week 132	n	7	3	
		LS Mean	-13.18	-16.44	3.267
		SEM	7.285	9.811	10.75
		95% CI	(-27.5, 1.1)	(-35.7, 2.8)	(-17.8,24.4)
		Pr >  t			0.7612
	Week 144	n	3	2	
		LS Mean	-27.98	-12.25	-15.73
		SEM	9.747	11.54	13.94
		95% CI	(-47.1,-8.8)	(-34.9,10.4)	(-43.1,11.6)
		Pr >  t			0.2597
	Week 156	n	3	1	
		LS Mean	-21.40	-12.31	-9.091
		SEM	9.759	15.61	17.46
		95% CI	(-40.6,-2.2)	(-43.0,18.3)	(-43.4,25.2)
		Pr >  t			0.6028
	Week 168	n	1	1	
		LS Mean	-6.599	-12.31	5.709
		SEM	15.60	15.61	21.29
		95% CI	(-37.2,24.0)	(-43.0,18.3)	(-36.1,47.5)
		Pr >  t			0.7886

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-2.623	-6.535	3.912
			SEM	9.136	10.29	8.354
			95% CI	(-21.1,15.9)	(-27.4,14.3)	(-12.9,20.7)
			Pr >  t			0.6417
		Week 16	n	14	17	
			LS Mean	0.268	-12.80	13.073
			SEM	9.214	10.42	8.728
			95% CI	(-18.4,18.9)	(-33.9, 8.3)	( -4.4,30.6)
			Pr >  t			0.1399
		Week 24	n	14	11	
			LS Mean	-9.257	-9.078	-0.178
			SEM	9.214	10.76	9.119
			95% CI	(-27.9, 9.4)	(-30.8,12.6)	(-18.4,18.0)
			Pr >  t			0.9845
		Week 32	n	10	10	
			LS Mean	-5.524	-9.971	4.447
			SEM	9.726	10.86	9.497
			95% CI	(-25.1,14.0)	(-31.9,11.9)	(-14.5,23.4)
			Pr >  t			0.6410
		Week 40	n	8	10	
			LS Mean	-0.014	-12.77	12.761
			SEM	9.967	10.86	9.728
			95% CI	(-20.0,20.0)	(-34.7, 9.1)	( -6.6,32.1)
			Pr >  t			0.1933
		Week 48	n	7	11	
			LS Mean	-3.394	-24.73	21.337
			SEM	10.11	10.78	9.828
95% CI	(-23.6,16.8)		(-46.5,-3.0)	( 1.8,40.9)		
	Pr >  t			0.0328		
Week 56	n	6	9			
	LS Mean	-5.727	-13.48	7.751		
	SEM	10.30	10.96	10.23		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-26.3,14.9)	(-35.5, 8.6)	(-12.6,28.1)
		Pr >  t			0.4507
	Week 64	n	5	8	
		LS Mean	-3.526	-13.85	10.319
		SEM	10.57	11.07	10.62
		95% CI	(-24.6,17.6)	(-36.1, 8.4)	(-10.7,31.4)
		Pr >  t			0.3336
	Week 72	n	7	7	
		LS Mean	-8.016	-10.61	2.592
		SEM	10.09	11.21	10.31
		95% CI	(-28.2,12.2)	(-33.1,11.9)	(-17.9,23.0)
		Pr >  t			0.8020
	Week 84	n	7	7	
		LS Mean	-5.635	-12.99	7.354
		SEM	10.09	11.21	10.31
		95% CI	(-25.8,14.6)	(-35.5, 9.5)	(-13.1,27.8)
		Pr >  t			0.4773
	Week 96	n	5	6	
		LS Mean	-6.939	-10.55	3.608
		SEM	10.57	11.40	10.97
		95% CI	(-28.0,14.2)	(-33.4,12.3)	(-18.1,25.3)
		Pr >  t			0.7428
	Week 108	n	4	6	
		LS Mean	-10.12	-16.10	5.981
		SEM	10.97	11.40	11.36
		95% CI	(-32.0,11.7)	(-39.0, 6.8)	(-16.5,28.5)
		Pr >  t			0.5995
	Week 120	n	4	4	
		LS Mean	-18.81	-16.17	-2.641
		SEM	10.98	12.03	11.99
		95% CI	(-40.7, 3.0)	(-40.2, 7.8)	(-26.3,21.1)
		Pr >  t			0.8260
	Week 132	n	3	1	
		LS Mean	-13.95	-49.06	35.102
		SEM	11.60	16.47	16.86
		95% CI	(-37.0, 9.1)	(-81.6, -17)	( 1.9,68.3)
		Pr >  t			0.0386
	Week 144	n	1	1	
		LS Mean	-62.60	-13.10	-49.50
		SEM	15.73	16.51	19.97

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-93.6, -32)	(-45.7,19.5)	(-88.9, -10)
		Pr >  t			0.0140
		n	35	37	
		LS Mean	1.019	2.559	-1.540
	Week 16	SEM	10.89	11.37	4.953
		95% CI	(-20.5,22.5)	(-19.9,25.0)	(-11.3, 8.2)
		Pr >  t			0.7563
		n	34	30	
	Week 24	LS Mean	1.805	3.674	-1.869
		SEM	11.24	11.48	5.172
		95% CI	(-20.4,24.0)	(-19.0,26.4)	(-12.1, 8.3)
		Pr >  t			0.7183
	Week 32	n	32	23	
		LS Mean	2.125	2.669	-0.543
		SEM	11.27	11.62	5.549
		95% CI	(-20.1,24.4)	(-20.3,25.6)	(-11.5,10.4)
	Week 40	Pr >  t			0.9221
		n	21	22	
		LS Mean	0.292	-1.057	1.349
		SEM	11.48	11.65	6.043
	Week 48	95% CI	(-22.4,22.9)	(-24.1,21.9)	(-10.5,13.2)
		Pr >  t			0.8235
		n	20	20	
		LS Mean	-1.441	-5.154	3.713
	Week 56	SEM	11.52	11.71	6.214
		95% CI	(-24.2,21.3)	(-28.3,18.0)	(-8.5,15.9)
		Pr >  t			0.5507
		n	19	12	
Week 64	LS Mean	2.384	1.506	0.877	
	SEM	11.53	12.12	6.987	
	95% CI	(-20.4,25.1)	(-22.4,25.4)	(-12.9,14.6)	
	Pr >  t			0.9002	
Week 80	n	16	8		
	LS Mean	1.606	-0.556	2.162	
	SEM	11.65	12.59	7.961	
	95% CI	(-21.4,24.6)	(-25.4,24.3)	(-13.5,17.8)	
Week 88	Pr >  t			0.7861	
	n	12	11		
	LS Mean	1.799	-3.717	5.516	
		SEM	11.89	12.20	7.725

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72	95% CI	(-21.7,25.3)	(-27.8,20.3)	(-9.7,20.7)
	Pr >  t			0.4756
	n	13	7	
	LS Mean	3.343	-5.406	8.748
	SEM	11.84	12.78	8.521
Week 84	95% CI	(-20.0,26.7)	(-30.6,19.8)	(-8.0,25.5)
	Pr >  t			0.3052
	n	12	6	
	LS Mean	-3.096	-4.067	0.971
	SEM	11.88	13.04	8.985
Week 96	95% CI	(-26.5,20.3)	(-29.8,21.6)	(-16.7,18.6)
	Pr >  t			0.9140
	n	7	6	
	LS Mean	-5.351	-4.146	-1.205
	SEM	12.55	13.04	9.850
Week 108	95% CI	(-30.1,19.4)	(-29.8,21.5)	(-20.6,18.2)
	Pr >  t			0.9027
	n	5	3	
	LS Mean	1.402	-1.133	2.535
	SEM	13.15	14.66	12.57
Week 120	95% CI	(-24.5,27.3)	(-30.0,27.7)	(-22.2,27.3)
	Pr >  t			0.8403
	n	8	3	
	LS Mean	-9.966	4.423	-14.39
	SEM	12.41	14.66	11.76
Week 132	95% CI	(-34.4,14.5)	(-24.4,33.3)	(-37.5, 8.7)
	Pr >  t			0.2218
	n	2	1	
	LS Mean	-30.44	6.201	-36.64
	SEM	15.91	19.85	20.42
Week 144	95% CI	(-61.7, 0.9)	(-32.8,45.2)	(-76.8, 3.5)
	Pr >  t			0.0737
	n	2		
	LS Mean	4.792		
	SEM	15.93		
Week 156	95% CI	(-26.5,36.1)		
	Pr >  t			
	n	2		
	LS Mean	4.792		
	SEM	15.93		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-26.5,36.1)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	-5.753	-4.100	-1.653
		SEM	3.653	3.773	3.527
		95% CI	(-13.0, 1.5)		(-8.6, 5.3)
		Pr >  t			0.6398
	Week 16	n	70	52	
		LS Mean	-4.624	-5.581	0.958
		SEM	3.738	3.952	3.743
		95% CI	(-12.0, 2.7)		(-6.4, 8.3)
		Pr >  t			0.7982
	Week 24	n	54	40	
		LS Mean	-5.239	-3.691	-1.548
		SEM	3.873	4.153	4.059
		95% CI	(-12.9, 2.4)		(-9.5, 6.4)
		Pr >  t			0.7031
	Week 32	n	50	36	
		LS Mean	-2.730	-4.303	1.572
		SEM	3.929	4.226	4.174
		95% CI	(-10.5, 5.0)		(-6.6, 9.8)
		Pr >  t			0.7066
	Week 40	n	42	28	
		LS Mean	-1.293	-3.092	1.799
		SEM	4.028	4.437	4.463
		95% CI	(-9.2, 6.6)		(-7.0,10.6)
		Pr >  t			0.6870
	Week 48	n	38	24	
		LS Mean	-7.131	0.942	-8.073
		SEM	4.090	4.572	4.654
		95% CI	(-15.2, 0.9)		(-17.2, 1.1)
		Pr >  t			0.0834
	Week 56	n	33	24	
		LS Mean	-5.756	-4.247	-1.509
		SEM	4.185	4.575	4.745
		95% CI	(-14.0, 2.5)		(-10.8, 7.8)
		Pr >  t			0.7506
	Week 64	n	27	19	
		LS Mean	-5.338	0.553	-5.892
		SEM	4.337	4.812	5.104

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.9, 3.2)	(-8.9,10.0)	(-15.9, 4.1)
		Pr >  t			0.2488
	Week 72	n	26	17	
		LS Mean	-7.003	0.575	-7.578
		SEM	4.369	4.936	5.247
		95% CI	(-15.6, 1.6)	(-9.1,10.3)	(-17.9, 2.7)
		Pr >  t			0.1491
	Week 84	n	18	16	
		LS Mean	-6.902	-0.230	-6.672
		SEM	4.750	5.009	5.620
		95% CI	(-16.2, 2.4)	(-10.1, 9.6)	(-17.7, 4.4)
		Pr >  t			0.2355
	Week 96	n	20	10	
		LS Mean	-2.688	-2.879	0.191
		SEM	4.630	5.689	6.150
		95% CI	(-11.8, 6.4)	(-14.1, 8.3)	(-11.9,12.3)
		Pr >  t			0.9753
	Week 108	n	14	10	
		LS Mean	-6.397	-4.946	-1.450
		SEM	5.069	5.689	6.480
		95% CI	(-16.4, 3.6)	(-16.1, 6.2)	(-14.2,11.3)
		Pr >  t			0.8230
	Week 120	n	14	7	
		LS Mean	2.382	3.232	-0.849
		SEM	5.053	6.373	7.086
		95% CI	(-7.5,12.3)	(-9.3,15.7)	(-14.8,13.1)
		Pr >  t			0.9046
	Week 132	n	12	5	
		LS Mean	-2.776	-0.337	-2.439
		SEM	5.285	7.181	7.964
		95% CI	(-13.2, 7.6)	(-14.4,13.8)	(-18.1,13.2)
		Pr >  t			0.7594
	Week 144	n	11	4	
		LS Mean	-9.938	2.148	-12.09
		SEM	5.404	7.817	8.626
		95% CI	(-20.6, 0.7)	(-13.2,17.5)	(-29.0, 4.8)
		Pr >  t			0.1616
	Week 156	n	8	3	
		LS Mean	-6.148	-8.217	2.068
		SEM	5.986	8.771	9.834

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168		95% CI	(-17.9, 5.6)	(-25.4, 9.0)	(-17.2,21.4)
		Pr >  t			0.8335
		n	4	2	
		LS Mean	-3.528	5.213	-8.741
		SEM	7.719	10.42	12.33
Week 180		95% CI	(-18.7,11.6)	(-15.2,25.7)	(-33.0,15.5)
		Pr >  t			0.4787
		n	1	1	
		LS Mean	-20.28	-22.22	1.937
		SEM	14.21	14.25	19.72
Week 192		95% CI	(-48.2, 7.6)	(-50.2, 5.7)	(-36.8,40.6)
		Pr >  t			0.9218
		n	1	1	
		LS Mean	13.047	11.110	1.937
		SEM	14.21	14.25	19.72
	95% CI	(-14.8,40.9)	(-16.9,39.1)	(-36.8,40.6)	
	Pr >  t			0.9218	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-38: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Emotionale Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73			
			LS Mean	-0.411	-0.626	0.215		
			SEM	3.171	3.194	2.867		
			95% CI	(-6.7, 5.8)	(-6.9, 5.7)	(-5.4, 5.9)		
					Pr >  t			0.9403
		Week 16	n	67	56			
			LS Mean	-0.853	-4.016	3.163		
			SEM	3.221	3.372	3.086		
			95% CI	(-7.2, 5.5)	(-10.7, 2.6)	(-2.9, 9.2)		
					Pr >  t			0.3059
		Week 24	n	61	46			
			LS Mean	-4.938	1.123	-6.062		
			SEM	3.279	3.474	3.251		
			95% CI	(-11.4, 1.5)	(-5.7, 8.0)	(-12.5, 0.3)		
					Pr >  t			0.0630
		Week 32	n	52	41			
			LS Mean	-0.132	-2.286	2.154		
			SEM	3.385	3.557	3.401		
			95% CI	(-6.8, 6.5)	(-9.3, 4.7)	(-4.5, 8.8)		
					Pr >  t			0.5268
		Week 40	n	45	36			
			LS Mean	-2.034	-1.981	-0.053		
			SEM	3.459	3.654	3.557		
			95% CI	(-8.8, 4.8)	(-9.2, 5.2)	(-7.0, 6.9)		
			Pr >  t			0.9881		
Week 48	n	42	30					
	LS Mean	-6.424	-0.703	-5.722				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	3.500	3.778	3.724
	95% CI	(-13.3, 0.5)	(-8.1, 6.7)	(-13.0, 1.6)
	Pr >  t			0.1249
Week 56	n	35	24	
	LS Mean	-3.685	-0.200	-3.485
	SEM	3.607	3.956	4.005
	95% CI	(-10.8, 3.4)	(-8.0, 7.6)	(-11.3, 4.4)
	Pr >  t			0.3845
Week 64	n	25	25	
	LS Mean	-4.928	-2.226	-2.703
	SEM	3.847	3.923	4.196
	95% CI	(-12.5, 2.6)	(-9.9, 5.5)	(-10.9, 5.5)
	Pr >  t			0.5196
Week 72	n	27	20	
	LS Mean	-8.100	-3.893	-4.207
	SEM	3.787	4.122	4.328
	95% CI	(-15.5,-0.7)	(-12.0, 4.2)	(-12.7, 4.3)
	Pr >  t			0.3313
Week 84	n	23	19	
	LS Mean	-5.136	-2.946	-2.190
	SEM	3.930	4.173	4.492
	95% CI	(-12.9, 2.6)	(-11.1, 5.3)	(-11.0, 6.6)
	Pr >  t			0.6260
Week 96	n	20	13	
	LS Mean	-5.096	-4.412	-0.685
	SEM	4.059	4.608	5.002
	95% CI	(-13.1, 2.9)	(-13.5, 4.6)	(-10.5, 9.1)
	Pr >  t			0.8912
Week 108	n	17	13	
	LS Mean	-0.140	-6.249	6.109
	SEM	4.227	4.609	5.139
	95% CI	(-8.4, 8.2)	(-15.3, 2.8)	(-4.0,16.2)
	Pr >  t			0.2349
Week 120	n	17	12	
	LS Mean	-5.607	-3.441	-2.166
	SEM	4.225	4.717	5.235
	95% CI	(-13.9, 2.7)	(-12.7, 5.8)	(-12.4, 8.1)
	Pr >  t			0.6791
Week 132	n	13	6	
	LS Mean	-7.714	-1.708	-6.006

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 144	SEM	4.546	5.927	6.566
		95% CI	(-16.6, 1.2)	(-13.3, 9.9)	(-18.9, 6.9)
		Pr >  t			0.3606
		n	11	4	
		LS Mean	-6.211	-0.074	-6.137
		SEM	4.778	6.934	7.629
	Week 156	95% CI	(-15.6, 3.2)	(-13.7,13.5)	(-21.1, 8.8)
		Pr >  t			0.4214
		n	7	2	
		LS Mean	1.114	0.579	0.535
		SEM	5.552	9.297	10.23
		95% CI	(-9.8,12.0)	(-17.7,18.8)	(-19.5,20.6)
	Week 168	Pr >  t			0.9583
		n	3	1	
		LS Mean	-8.819	1.187	-10.01
		SEM	7.745	12.78	14.51
		95% CI	(-24.0, 6.4)	(-23.9,26.3)	(-38.5,18.5)
		Pr >  t			0.4907
	Week 180	n	1	1	
		LS Mean	-14.08	1.187	-15.27
		SEM	12.75	12.78	17.69
		95% CI	(-39.1,10.9)	(-23.9,26.3)	(-50.0,19.5)
		Pr >  t			0.3883
		n	1	1	
Week 192	LS Mean	-5.745	1.187	-6.932	
	SEM	12.75	12.78	17.69	
	95% CI	(-30.8,19.3)	(-23.9,26.3)	(-41.7,27.8)	
	Pr >  t			0.6953	
	n	65	67		
	LS Mean	-1.374	-0.117	-1.256	
Week 8	SEM	3.608	3.722	3.064	
	95% CI	(-8.5, 5.7)	(-7.5, 7.2)	(-7.3, 4.8)	
	Pr >  t			0.6821	
	n	57	51		
	LS Mean	-1.466	-2.502	1.036	
	SEM	3.730	3.864	3.280	
Week 16	95% CI	(-8.8, 5.9)	(-10.1, 5.1)	(-5.4, 7.5)	
	Pr >  t			0.7523	
	n	44	35		
	LS Mean	-2.758	-1.844	-0.914	
	SEM				
	95% CI				
Week 24	Pr >  t				
	n				
	LS Mean				
	SEM				
	95% CI				
	Pr >  t				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	SEM	3.837	4.101	3.645
	95% CI	(-10.3, 4.8)	(-9.9, 6.2)	(-8.1, 6.3)
	Pr >  t			0.8021
	n	34	32	
	LS Mean	1.933	-5.170	7.104
Week 40	SEM	3.990	4.159	3.855
	95% CI	(-5.9, 9.8)	(-13.4, 3.0)	(-0.5, 14.7)
	Pr >  t			0.0661
	n	30	26	
	LS Mean	0.836	-4.208	5.044
Week 48	SEM	4.068	4.293	4.080
	95% CI	(-7.2, 8.8)	(-12.7, 4.2)	(-3.0, 13.1)
	Pr >  t			0.2171
	n	27	21	
	LS Mean	-2.285	-4.722	2.436
Week 56	SEM	4.129	4.456	4.312
	95% CI	(-10.4, 5.8)	(-13.5, 4.0)	(-6.0, 10.9)
	Pr >  t			0.5723
	n	24	21	
	LS Mean	4.109	-2.292	6.401
Week 64	SEM	4.213	4.456	4.392
	95% CI	(-4.2, 12.4)	(-11.1, 6.5)	(-2.2, 15.0)
	Pr >  t			0.1456
	n	22	17	
	LS Mean	2.649	-6.344	8.994
Week 72	SEM	4.276	4.639	4.640
	95% CI	(-5.8, 11.1)	(-15.5, 2.8)	(-0.1, 18.1)
	Pr >  t			0.0531
	n	21	15	
	LS Mean	6.107	-3.667	9.774
Week 84	SEM	4.314	4.759	4.797
	95% CI	(-2.4, 14.6)	(-13.0, 5.7)	(0.4, 19.2)
	Pr >  t			0.0420
	n	17	14	
	LS Mean	2.953	-6.004	8.957
Week 96	SEM	4.505	4.829	5.026
	95% CI	(-5.9, 11.8)	(-15.5, 3.5)	(-0.9, 18.8)
	Pr >  t			0.0752
	n	15	11	
	LS Mean	4.789	-5.102	9.892

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.614	5.112	5.405
		95% CI	(-4.3,13.9)	(-15.1, 4.9)	(-0.7,20.5)
		Pr >  t			0.0677
	Week 108	n	9	8	
		LS Mean	6.344	2.034	4.310
		SEM	5.259	5.570	6.352
		95% CI	(-4.0,16.7)	(-8.9,13.0)	(-8.2,16.8)
		Pr >  t			0.4977
	Week 120	n	11	4	
		LS Mean	4.113	6.301	-2.188
		SEM	4.978	6.988	7.445
		95% CI	(-5.7,13.9)	(-7.4,20.0)	(-16.8,12.4)
		Pr >  t			0.7690
	Week 132	n	7	2	
		LS Mean	4.684	-0.699	5.383
		SEM	5.667	9.144	9.869
		95% CI	(-6.4,15.8)	(-18.7,17.3)	(-14.0,24.8)
		Pr >  t			0.5857
	Week 144	n	4	1	
		LS Mean	-2.244	8.754	-11.00
		SEM	6.823	12.40	13.51
		95% CI	(-15.6,11.2)	(-15.6,33.1)	(-37.5,15.5)
		Pr >  t			0.4161
	Week 156	n	3	1	
		LS Mean	13.557	0.424	13.134
		SEM	7.666	12.40	13.94
		95% CI	(-1.5,28.6)	(-23.9,24.8)	(-14.2,40.5)
		Pr >  t			0.3464
	Week 168	n	1	1	
		LS Mean	3.946	0.424	3.523
		SEM	12.35	12.40	16.97
		95% CI	(-20.3,28.2)	(-23.9,24.8)	(-29.8,36.9)
		Pr >  t			0.8357

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Presence of Lung Metastases (L)	No	Week 8	n	98	84	
			LS Mean	-2.078	-0.195	-1.883
			SEM	2.654	2.820	2.636
			95% CI	(-7.3, 3.1)	(-5.7, 5.4)	(-7.1, 3.3)
		Pr >  t			0.4755	
		Week 16	n	86	68	
			LS Mean	-2.280	-4.576	2.295
			SEM	2.718	2.934	2.811
			95% CI	(-7.6, 3.1)	(-10.3, 1.2)	(-3.2, 7.8)
		Pr >  t			0.4147	
		Week 24	n	73	48	
			LS Mean	-6.600	-0.382	-6.218
			SEM	2.796	3.154	3.102
			95% CI	(-12.1,-1.1)	(-6.6, 5.8)	(-12.3,-0.1)
		Pr >  t			0.0455	
		Week 32	n	60	43	
			LS Mean	-0.660	-4.324	3.664
			SEM	2.924	3.239	3.265
			95% CI	(-6.4, 5.1)	(-10.7, 2.0)	(-2.7,10.1)
		Pr >  t			0.2621	
		Week 40	n	50	38	
			LS Mean	-3.633	-1.106	-2.527
			SEM	3.024	3.335	3.439
			95% CI	(-9.6, 2.3)	(-7.7, 5.4)	(-9.3, 4.2)
		Pr >  t			0.4627	
		Week 48	n	48	31	
			LS Mean	-7.354	-1.436	-5.918
			SEM	3.050	3.489	3.613
95% CI	(-13.3,-1.4)		(-8.3, 5.4)	(-13.0, 1.2)		
Pr >  t			0.1018			
Week 56	n	41	25			
	LS Mean	-3.513	-1.336	-2.177		
	SEM	3.147	3.680	3.879		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.7, 2.7)	(-8.6, 5.9)	(-9.8, 5.4)
	Pr >  t			0.5747
	n	30	24	
	LS Mean	-4.156	-1.671	-2.485
	SEM	3.374	3.720	4.107
Week 72	95% CI	(-10.8, 2.5)	(-9.0, 5.6)	(-10.5, 5.6)
	Pr >  t			0.5453
	n	32	19	
	LS Mean	-6.618	-3.168	-3.450
	SEM	3.324	3.964	4.288
Week 84	95% CI	(-13.1,-0.1)	(-11.0, 4.6)	(-11.9, 5.0)
	Pr >  t			0.4212
	n	26	19	
	LS Mean	-5.452	-3.589	-1.863
	SEM	3.514	3.964	4.427
Week 96	95% CI	(-12.4, 1.4)	(-11.4, 4.2)	(-10.5, 6.8)
	Pr >  t			0.6739
	n	23	14	
	LS Mean	-3.534	-5.284	1.750
	SEM	3.624	4.344	4.858
Week 108	95% CI	(-10.7, 3.6)	(-13.8, 3.2)	(-7.8,11.3)
	Pr >  t			0.7188
	n	19	13	
	LS Mean	0.584	-5.589	6.173
	SEM	3.838	4.448	5.103
Week 120	95% CI	(-6.9, 8.1)	(-14.3, 3.1)	(-3.8,16.2)
	Pr >  t			0.2267
	n	19	11	
	LS Mean	-4.425	-4.132	-0.293
	SEM	3.827	4.704	5.327
Week 132	95% CI	(-11.9, 3.1)	(-13.4, 5.1)	(-10.7,10.2)
	Pr >  t			0.9562
	n	15	5	
	LS Mean	-6.352	2.545	-8.897
	SEM	4.127	6.332	6.976
Week 144	95% CI	(-14.5, 1.7)	(-9.9,15.0)	(-22.6, 4.8)
	Pr >  t			0.2025
	n	12	3	
Week 144	LS Mean	-5.621	2.001	-7.622
	SEM	4.437	7.884	8.573



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.3, 3.1)	(-13.5,17.5)	(-24.4, 9.2)
		Pr >  t			0.3742
	Week 156	n	7	2	
		LS Mean	1.013	0.674	0.339
		SEM	5.437	9.454	10.51
		95% CI	(-9.7,11.7)	(-17.9,19.2)	(-20.3,21.0)
		Pr >  t			0.9743
	Week 168	n	3	1	
		LS Mean	-8.871	1.276	-10.15
		SEM	7.788	13.09	14.95
		95% CI	(-24.2, 6.4)	(-24.4,27.0)	(-39.5,19.2)
		Pr >  t			0.4975
	Week 180	n	1	1	
		LS Mean	-14.19	1.276	-15.47
		SEM	13.04	13.09	18.24
		95% CI	(-39.8,11.4)	(-24.4,27.0)	(-51.3,20.3)
		Pr >  t			0.3967
	Week 192	n	1	1	
		LS Mean	-5.853	1.276	-7.129
		SEM	13.04	13.09	18.24
		95% CI	(-31.4,19.7)	(-24.4,27.0)	(-42.9,28.7)
		Pr >  t			0.6960
Yes	Week 8	n	44	56	
		LS Mean	4.317	1.999	2.318
		SEM	5.478	5.248	3.427
		95% CI	(-6.5,15.1)	(-8.4,12.4)	(-4.4, 9.1)
		Pr >  t			0.4997
	Week 16	n	38	39	
		LS Mean	4.032	1.604	2.428
		SEM	5.614	5.504	3.708
		95% CI	(-7.0,15.1)	(-9.3,12.5)	(-4.9, 9.7)
		Pr >  t			0.5134
	Week 24	n	32	33	
		LS Mean	4.486	2.964	1.522
		SEM	5.685	5.561	3.902
		95% CI	(-6.7,15.7)	(-8.0,13.9)	(-6.2, 9.2)
		Pr >  t			0.6968
	Week 32	n	26	30	
		LS Mean	6.447	0.348	6.100
		SEM	5.774	5.605	4.090

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-4.9,17.8)	(-10.7,11.4)	(-2.0,14.2)
	Pr >  t			0.1370
	n	25	24	
	LS Mean	7.625	-3.052	10.677
	SEM	5.795	5.706	4.254
Week 48	95% CI	(-3.8,19.1)	(-14.3, 8.2)	( 2.3,19.0)
	Pr >  t			0.0126
	n	21	20	
	LS Mean	3.902	-1.184	5.086
	SEM	5.875	5.803	4.490
Week 56	95% CI	(-7.7,15.5)	(-12.6,10.3)	( -3.7,13.9)
	Pr >  t			0.2582
	n	18	20	
	LS Mean	9.078	1.814	7.264
	SEM	5.962	5.802	4.602
Week 64	95% CI	(-2.7,20.8)	( -9.6,13.2)	( -1.8,16.3)
	Pr >  t			0.1153
	n	17	18	
	LS Mean	6.556	-4.246	10.802
	SEM	5.996	5.864	4.725
Week 72	95% CI	(-5.3,18.4)	(-15.8, 7.3)	( 1.5,20.1)
	Pr >  t			0.0228
	n	16	16	
	LS Mean	10.389	-1.940	12.329
	SEM	6.036	5.937	4.867
Week 84	95% CI	(-1.5,22.3)	(-13.6, 9.8)	( 2.8,21.9)
	Pr >  t			0.0117
	n	14	14	
	LS Mean	8.525	-2.480	11.005
	SEM	6.124	6.029	5.086
Week 96	95% CI	(-3.5,20.6)	(-14.4, 9.4)	( 1.0,21.0)
	Pr >  t			0.0310
	n	12	10	
	LS Mean	7.350	-1.233	8.583
	SEM	6.245	6.315	5.558
Week 108	95% CI	(-5.0,19.7)	(-13.7,11.2)	( -2.3,19.5)
	Pr >  t			0.1231
	n	7	8	
	LS Mean	8.806	3.432	5.374
	SEM	6.799	6.556	6.421

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-4.6,22.2)	(-9.5,16.3)	(-7.2,18.0)
		Pr >  t			0.4029
	Week 120	n	9	5	
		LS Mean	6.959	8.097	-1.138
		SEM	6.523	7.223	6.833
		95% CI	(-5.9,19.8)	(-6.1,22.3)	(-14.6,12.3)
		Pr >  t			0.8678
	Week 132	n	5	3	
		LS Mean	7.670	-6.022	13.693
		SEM	7.290	8.255	8.561
		95% CI	(-6.7,22.0)	(-22.2,10.2)	(-3.1,30.5)
		Pr >  t			0.1103
	Week 144	n	3	2	
		LS Mean	-0.618	3.131	-3.749
		SEM	8.312	9.396	10.46
		95% CI	(-17.0,15.7)	(-15.3,21.6)	(-24.3,16.8)
		Pr >  t			0.7201
	Week 156	n	3	1	
		LS Mean	18.009	2.348	15.661
		SEM	8.320	12.18	13.02
		95% CI	( 1.7,34.4)	(-21.6,26.3)	(-9.9,41.2)
		Pr >  t			0.2296
	Week 168	n	1	1	
		LS Mean	8.273	2.348	5.924
		SEM	12.25	12.18	15.82
		95% CI	(-15.8,32.3)	(-21.6,26.3)	(-25.2,37.0)
		Pr >  t			0.7082

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	0.262	1.158	-0.895		
			SEM	2.681	2.685	2.341		
			95% CI	(-5.0, 5.5)	(-4.1, 6.4)	(-5.5, 3.7)		
					Pr >  t			0.7023
		Week 16	n	92	83			
			LS Mean	-0.762	-1.268	0.506		
			SEM	2.749	2.825	2.510		
			95% CI	(-6.2, 4.6)	(-6.8, 4.3)	(-4.4, 5.4)		
					Pr >  t			0.8402
		Week 24	n	77	59			
			LS Mean	-3.617	-0.038	-3.579		
			SEM	2.807	2.984	2.746		
			95% CI	(-9.1, 1.9)	(-5.9, 5.8)	(-9.0, 1.8)		
					Pr >  t			0.1930
		Week 32	n	57	53			
			LS Mean	2.133	-3.270	5.403		
			SEM	2.960	3.036	2.932		
			95% CI	(-3.7, 8.0)	(-9.2, 2.7)	(-0.4, 11.2)		
					Pr >  t			0.0658
		Week 40	n	50	44			
			LS Mean	1.256	-2.964	4.221		
			SEM	3.024	3.144	3.098		
			95% CI	(-4.7, 7.2)	(-9.1, 3.2)	(-1.9, 10.3)		
					Pr >  t			0.1735
		Week 48	n	47	37			
			LS Mean	-3.308	-3.345	0.037		
			SEM	3.054	3.247	3.233		
95% CI	(-9.3, 2.7)		(-9.7, 3.0)	(-6.3, 6.4)				
			Pr >  t			0.9908		
Week 56	n	40	32					
	LS Mean	1.246	-0.536	1.782				
	SEM	3.142	3.343	3.410				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-4.9, 7.4)	(-7.1, 6.0)	(-4.9, 8.5)
	Pr >  t			0.6015
	n	32	27	
Week 72	LS Mean	0.795	-3.973	4.769
	SEM	3.282	3.469	3.660
	95% CI	(-5.7, 7.2)	(-10.8, 2.8)	(-2.4,12.0)
Week 84	Pr >  t			0.1929
	n	31	23	
	LS Mean	3.214	-2.196	5.410
Week 96	SEM	3.306	3.601	3.806
	95% CI	(-3.3, 9.7)	(-9.3, 4.9)	(-2.1,12.9)
	Pr >  t			0.1555
Week 108	n	27	21	
	LS Mean	1.248	-3.213	4.461
	SEM	3.410	3.682	3.967
Week 120	95% CI	(-5.4, 7.9)	(-10.4, 4.0)	(-3.3,12.2)
	Pr >  t			0.2611
	n	23	16	
Week 132	LS Mean	-0.500	-5.458	4.957
	SEM	3.535	3.958	4.333
	95% CI	(-7.4, 6.4)	(-13.2, 2.3)	(-3.5,13.5)
Week 144	Pr >  t			0.2528
	n	15	14	
	LS Mean	2.723	-0.080	2.803
Week 120	SEM	3.974	4.115	4.827
	95% CI	(-5.1,10.5)	(-8.2, 8.0)	(-6.7,12.3)
	Pr >  t			0.5615
Week 132	n	18	8	
	LS Mean	1.376	2.401	-1.025
	SEM	3.772	4.948	5.416
Week 144	95% CI	(-6.0, 8.8)	(-7.3,12.1)	(-11.7, 9.6)
	Pr >  t			0.8499
	n	12	4	
Week 120	LS Mean	3.131	-8.793	11.924
	SEM	4.257	6.463	7.104
	95% CI	(-5.2,11.5)	(-21.5, 3.9)	(-2.0,25.9)
Week 132	Pr >  t			0.0936
	n	8	3	
	LS Mean	-7.087	2.788	-9.875
Week 144	SEM	4.875	7.313	8.245

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.7, 2.5)	(-11.6,17.1)	(-26.1, 6.3)
		Pr >  t			0.2313
	Week 156	n	5	1	
		LS Mean	7.901	0.545	7.355
		SEM	5.857	12.07	13.06
		95% CI	(-3.6,19.4)	(-23.1,24.2)	(-18.3,33.0)
		Pr >  t			0.5735
	Week 168	n	2	1	
		LS Mean	-3.997	0.545	-4.543
		SEM	8.721	12.07	14.57
		95% CI	(-21.1,13.1)	(-23.1,24.2)	(-33.1,24.1)
		Pr >  t			0.7553
	Week 180	n	1		
		LS Mean	-9.849		
		SEM	12.03		
		95% CI	(-33.5,13.8)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-1.509		
		SEM	12.03		
		95% CI	(-25.1,22.1)		
		Pr >  t			
Yes	Week 8	n	38	30	
		LS Mean	-4.383	-5.807	1.424
		SEM	5.085	5.466	4.557
		95% CI	(-14.5, 5.7)	(-16.7, 5.1)	(-7.6,10.4)
		Pr >  t			0.7551
	Week 16	n	32	24	
		LS Mean	-2.698	-10.53	7.828
		SEM	5.171	5.620	4.901
		95% CI	(-13.0, 7.6)	(-21.7, 0.6)	(-1.8,17.5)
		Pr >  t			0.1120
	Week 24	n	28	22	
		LS Mean	-5.828	-1.465	-4.363
		SEM	5.321	5.686	5.083
		95% CI	(-16.4, 4.7)	(-12.7, 9.8)	(-14.4, 5.7)
		Pr >  t			0.3917
	Week 32	n	29	20	
		LS Mean	-3.326	-5.261	1.936
		SEM	5.302	5.833	5.154

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-13.8, 7.2)	(-16.8, 6.3)	(-8.2,12.1)
	Pr >  t			0.7076
	n	25	18	
	LS Mean	-6.320	-4.159	-2.162
	SEM	5.395	5.918	5.348
Week 48	95% CI	(-17.0, 4.4)	(-15.9, 7.6)	(-12.7, 8.4)
	Pr >  t			0.6864
	n	22	14	
	LS Mean	-8.627	-1.030	-7.597
	SEM	5.486	6.153	5.704
Week 56	95% CI	(-19.5, 2.2)	(-13.2,11.1)	(-18.8, 3.6)
	Pr >  t			0.1841
	n	19	13	
	LS Mean	-5.006	-3.872	-1.134
	SEM	5.596	6.237	5.906
Week 64	95% CI	(-16.1, 6.1)	(-16.2, 8.5)	(-12.8,10.5)
	Pr >  t			0.8479
	n	15	15	
	LS Mean	-7.613	-5.502	-2.111
	SEM	5.801	6.091	5.960
Week 72	95% CI	(-19.1, 3.9)	(-17.6, 6.5)	(-13.8, 9.6)
	Pr >  t			0.7234
	n	17	12	
	LS Mean	-12.69	-8.491	-4.197
	SEM	5.687	6.326	6.089
Week 84	95% CI	(-23.9,-1.4)	(-21.0, 4.0)	(-16.2, 7.8)
	Pr >  t			0.4912
	n	13	12	
	LS Mean	-8.805	-7.717	-1.088
	SEM	5.989	6.328	6.343
Week 96	95% CI	(-20.6, 3.0)	(-20.2, 4.8)	(-13.6,11.4)
	Pr >  t			0.8639
	n	12	8	
	LS Mean	-2.883	-4.730	1.847
	SEM	6.080	6.874	6.966
Week 108	95% CI	(-14.9, 9.1)	(-18.3, 8.8)	(-11.9,15.5)
	Pr >  t			0.7911
	n	11	7	
	LS Mean	0.046	-10.97	11.020
	SEM	6.189	7.094	7.274

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.2,12.3)	(-25.0, 3.0)	(-3.3,25.3)
		Pr >  t			0.1305
	Week 120	n	10	8	
		LS Mean	-8.565	-6.989	-1.576
		SEM	6.309	6.874	7.165
		95% CI	(-21.0, 3.9)	(-20.5, 6.6)	(-15.7,12.5)
		Pr >  t			0.8260
	Week 132	n	8	4	
		LS Mean	-14.25	3.286	-17.53
		SEM	6.639	8.282	8.774
		95% CI	(-27.3,-1.2)	(-13.0,19.6)	(-34.8,-0.3)
		Pr >  t			0.0463
	Week 144	n	7	2	
		LS Mean	-3.729	-2.166	-1.563
		SEM	6.864	10.54	11.07
		95% CI	(-17.3, 9.8)	(-22.9,18.5)	(-23.3,20.2)
		Pr >  t			0.8877
	Week 156	n	5	2	
		LS Mean	0.222	-2.166	2.388
		SEM	7.538	10.54	11.50
		95% CI	(-14.6,15.1)	(-22.9,18.5)	(-20.2,25.0)
		Pr >  t			0.8355
	Week 168	n	2	1	
		LS Mean	-8.183	-1.487	-6.696
		SEM	10.36	13.99	16.35
		95% CI	(-28.5,12.2)	(-29.0,26.0)	(-38.8,25.4)
		Pr >  t			0.6823
	Week 180	n		1	
		LS Mean		-1.487	
		SEM		13.99	
		95% CI		(-29.0,26.0)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-1.487	
		SEM		13.99	
		95% CI		(-29.0,26.0)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis



-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-0.929	-0.716	-0.214		
			SEM	2.413	2.474	2.163		
			95% CI	(-5.7, 3.8)	(-5.6, 4.2)	(-4.5, 4.0)		
					Pr >  t			0.9213
		Week 16	n	119	97			
			LS Mean	-1.607	-3.550	1.943		
			SEM	2.472	2.599	2.332		
			95% CI	(-6.5, 3.3)	(-8.7, 1.6)	(-2.6, 6.5)		
					Pr >  t			0.4050
		Week 24	n	100	75			
			LS Mean	-4.466	-0.317	-4.150		
			SEM	2.531	2.712	2.508		
			95% CI	(-9.4, 0.5)	(-5.6, 5.0)	(-9.1, 0.8)		
					Pr >  t			0.0984
		Week 32	n	82	69			
			LS Mean	0.412	-3.631	4.043		
			SEM	2.621	2.757	2.621		
			95% CI	(-4.7, 5.6)	(-9.0, 1.8)	(-1.1, 9.2)		
					Pr >  t			0.1233
		Week 40	n	73	58			
			LS Mean	-1.259	-2.750	1.491		
			SEM	2.667	2.842	2.750		
			95% CI	(-6.5, 4.0)	(-8.3, 2.8)	(-3.9, 6.9)		
					Pr >  t			0.5879
		Week 48	n	66	48			
			LS Mean	-5.708	-2.249	-3.459		
			SEM	2.707	2.940	2.890		
95% CI	(-11.0,-0.4)		(-8.0, 3.5)	(-9.1, 2.2)				
			Pr >  t			0.2317		
Week 56	n	56	43					
	LS Mean	-0.908	-0.593	-0.315				
	SEM	2.781	3.004	3.025				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.4, 4.6)	(-6.5, 5.3)	(-6.3, 5.6)
		Pr >  t			0.9171
	Week 64	n	45	41	
		LS Mean	-1.608	-3.790	2.182
		SEM	2.894	3.033	3.160
		95% CI	(-7.3, 4.1)	(-9.7, 2.2)	(-4.0, 8.4)
		Pr >  t			0.4900
	Week 72	n	46	34	
		LS Mean	-2.114	-3.656	1.542
		SEM	2.883	3.154	3.267
		95% CI	(-7.8, 3.5)	(-9.8, 2.5)	(-4.9, 8.0)
		Pr >  t			0.6370
	Week 84	n	37	32	
		LS Mean	-2.364	-4.388	2.024
		SEM	3.022	3.197	3.423
		95% CI	(-8.3, 3.6)	(-10.7, 1.9)	(-4.7, 8.7)
		Pr >  t			0.5543
	Week 96	n	33	23	
		LS Mean	-0.970	-5.294	4.324
		SEM	3.097	3.468	3.743
		95% CI	(-7.0, 5.1)	(-12.1, 1.5)	(-3.0, 11.7)
		Pr >  t			0.2481
	Week 108	n	24	20	
		LS Mean	3.252	-2.100	5.353
		SEM	3.359	3.604	4.078
		95% CI	(-3.3, 9.8)	(-9.2, 5.0)	(-2.6, 13.4)
		Pr >  t			0.1895
	Week 120	n	25	16	
		LS Mean	0.588	-1.111	1.699
		SEM	3.319	3.850	4.270
		95% CI	(-5.9, 7.1)	(-8.7, 6.4)	(-6.7, 10.1)
		Pr >  t			0.6907
	Week 132	n	19	8	
		LS Mean	-4.223	-1.547	-2.676
		SEM	3.586	4.882	5.390
		95% CI	(-11.3, 2.8)	(-11.1, 8.0)	(-13.2, 7.9)
		Pr >  t			0.6196
	Week 144	n	14	5	
		LS Mean	-2.319	1.574	-3.893
		SEM	3.938	5.891	6.529

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.0, 5.4)	(-10.0,13.1)	(-16.7, 8.9)
		Pr >  t			0.5512
	Week 156	n	10	3	
		LS Mean	5.410	0.408	5.002
		SEM	4.437	7.335	8.115
		95% CI	( -3.3,14.1)	(-14.0,14.8)	(-10.9,20.9)
		Pr >  t			0.5377
	Week 168	n	4	2	
		LS Mean	-4.736	0.683	-5.418
		SEM	6.420	8.817	10.55
		95% CI	(-17.3, 7.9)	(-16.6,18.0)	(-26.1,15.3)
		Pr >  t			0.6077
	Week 180	n	1	1	
		LS Mean	-11.49	1.002	-12.49
		SEM	12.20	12.21	17.04
		95% CI	(-35.4,12.4)	(-23.0,25.0)	(-45.9,20.9)
		Pr >  t			0.4636
	Week 192	n	1	1	
		LS Mean	-3.150	1.002	-4.151
		SEM	12.20	12.21	17.04
		95% CI	(-27.1,20.8)	(-23.0,25.0)	(-37.6,29.3)
		Pr >  t			0.8075
Yes	Week 8	n	5	9	
		LS Mean	14.143	16.953	-2.810
		SEM	7.000	5.132	8.707
		95% CI	( 0.1,28.2)	( 6.6,27.3)	(-20.3,14.7)
		Pr >  t			0.7483
	Week 16	n	5	9	
		LS Mean	22.477	11.119	11.358
		SEM	7.000	5.127	8.709
		95% CI	( 8.4,36.6)	( 0.8,21.4)	( -6.2,28.9)
		Pr >  t			0.1985
	Week 24	n	5	5	
		LS Mean	17.477	17.334	0.143
		SEM	7.000	6.909	9.905
		95% CI	( 3.4,31.6)	( 3.5,31.2)	(-19.8,20.1)
		Pr >  t			0.9885
	Week 32	n	4	3	
		LS Mean	20.603	8.230	12.373
		SEM	7.783	9.003	12.00

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 5.0,36.2)	(-11.7,36.5)
		Pr >  t		0.3074
	Week 40	n	2	3
		LS Mean	24.678	17.838
		SEM	10.93	9.055
		95% CI	( 2.7,46.6)	(-0.3,36.0)
		Pr >  t		0.6312
	Week 48	n	3	2
		LS Mean	32.455	13.130
		SEM	8.954	11.20
		95% CI	( 14.5,50.4)	(-9.3,35.6)
		Pr >  t		0.1797
	Week 56	n	3	1
		LS Mean	24.125	-6.084
		SEM	8.954	15.77
		95% CI	( 6.1,42.1)	(-37.7,25.6)
		Pr >  t		0.1043
	Week 64	n	2	
		LS Mean	16.348	
		SEM	10.93	
		95% CI	( -5.6,38.3)	
		Pr >  t		
	Week 72	n	2	
		LS Mean	16.277	
		SEM	10.93	
		95% CI	( -5.7,38.2)	
		Pr >  t		
	Week 84	n	3	
		LS Mean	24.125	
		SEM	8.954	
		95% CI	( 6.1,42.1)	
		Pr >  t		
	Week 96	n	2	
		LS Mean	20.513	
		SEM	10.93	
		95% CI	( -1.4,42.5)	
		Pr >  t		
	Week 108	n	2	
		LS Mean	10.584	
		SEM	11.01	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-11.5,32.7)
		Pr >  t		
	Week 120	n	3	
		LS Mean	-0.879	
		SEM	8.954	
		95% CI		(-18.9,17.1)
		Pr >  t		
	Week 132	n	1	
		LS Mean	39.820	
		SEM	15.50	
		95% CI		( 8.7,71.0)
		Pr >  t		
	Week 144	n	1	
		LS Mean	-10.18	
		SEM	15.50	
		95% CI		(-41.3,21.0)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	1.537	2.394	-0.857		
			SEM	3.050	3.182	3.034		
			95% CI	(-4.5, 7.6)	(-3.9, 8.7)	(-6.8, 5.1)		
					Pr >  t			0.7778
		Week 16	n	70	52			
			LS Mean	1.259	-1.866	3.125		
			SEM	3.118	3.418	3.272		
			95% CI	(-4.9, 7.4)	(-8.6, 4.9)	(-3.3, 9.6)		
					Pr >  t			0.3402
		Week 24	n	61	37			
			LS Mean	-3.267	1.029	-4.296		
			SEM	3.193	3.668	3.564		
			95% CI	(-9.6, 3.0)	(-6.2, 8.2)	(-11.3, 2.7)		
					Pr >  t			0.2288
		Week 32	n	48	33			
			LS Mean	3.474	-1.539	5.013		
			SEM	3.343	3.752	3.766		
			95% CI	(-3.1, 10.1)	(-8.9, 5.8)	(-2.4, 12.4)		
					Pr >  t			0.1838
		Week 40	n	42	31			
			LS Mean	1.430	0.428	1.002		
			SEM	3.421	3.801	3.886		
			95% CI	(-5.3, 8.2)	(-7.0, 7.9)	(-6.6, 8.6)		
					Pr >  t			0.7966
		Week 48	n	40	25			
			LS Mean	-2.254	1.508	-3.762		
			SEM	3.452	3.973	4.082		
95% CI	(-9.0, 4.5)		(-6.3, 9.3)	(-11.8, 4.3)				
			Pr >  t			0.3571		
Week 56	n	35	20					
	LS Mean	1.257	0.443	0.814				
		SEM	3.536	4.186	4.362			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.7, 8.2)	(-7.8, 8.7)	(-7.8, 9.4)
		Pr >  t			0.8520
	Week 64	n	29	18	
		LS Mean	0.761	2.364	-1.603
		SEM	3.668	4.299	4.578
		95% CI	(-6.5, 8.0)	(-6.1, 10.8)	(-10.6, 7.4)
		Pr >  t			0.7263
	Week 72	n	28	18	
		LS Mean	-2.967	2.741	-5.708
		SEM	3.696	4.296	4.599
		95% CI	(-10.2, 4.3)	(-5.7, 11.2)	(-14.7, 3.3)
		Pr >  t			0.2149
	Week 84	n	27	17	
		LS Mean	0.367	-0.663	1.030
		SEM	3.742	4.361	4.682
		95% CI	(-7.0, 7.7)	(-9.2, 7.9)	(-8.2, 10.2)
		Pr >  t			0.8260
	Week 96	n	23	14	
		LS Mean	-0.038	-0.761	0.723
		SEM	3.873	4.593	5.006
		95% CI	(-7.6, 7.6)	(-9.8, 8.3)	(-9.1, 10.5)
		Pr >  t			0.8852
	Week 108	n	19	12	
		LS Mean	5.217	-2.039	7.256
		SEM	4.074	4.802	5.343
		95% CI	(-2.8, 13.2)	(-11.5, 7.4)	(-3.2, 17.7)
		Pr >  t			0.1748
	Week 120	n	18	8	
		LS Mean	-2.365	-2.055	-0.310
		SEM	4.119	5.468	5.985
		95% CI	(-10.5, 5.7)	(-12.8, 8.7)	(-12.1, 11.4)
		Pr >  t			0.9586
	Week 132	n	11	4	
		LS Mean	1.806	5.209	-3.403
		SEM	4.775	7.085	7.867
		95% CI	(-7.6, 11.2)	(-8.7, 19.1)	(-18.8, 12.0)
		Pr >  t			0.6654
	Week 144	n	11	4	
		LS Mean	0.285	5.027	-4.741
		SEM	4.762	7.089	7.871



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.1, 9.6)	(-8.9, 18.9)	(-20.2, 10.7)
		Pr >  t			0.5471
	Week 156	n	5	2	
		LS Mean	6.950	3.828	3.123
		SEM	6.360	9.517	10.95
		95% CI	(-5.5, 19.4)	(-14.9, 22.5)	(-18.4, 24.6)
		Pr >  t			0.7756
	Week 168	n	1	2	
		LS Mean	-0.435	3.828	-4.263
		SEM	12.98	9.517	15.75
		95% CI	(-25.9, 25.0)	(-14.9, 22.5)	(-35.2, 26.7)
		Pr >  t			0.7867
	Week 180	n		1	
		LS Mean		3.928	
		SEM		13.07	
		95% CI		(-21.7, 29.6)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		3.928	
		SEM		13.07	
		95% CI		(-21.7, 29.6)	
		Pr >  t			
>= 65 Years	Week 8	n	63	71	
		LS Mean	-5.559	-5.000	-0.559
		SEM	3.967	3.980	2.846
		95% CI	(-13.4, 2.3)	(-12.9, 2.9)	(-6.2, 5.0)
		Pr >  t			0.8444
	Week 16	n	54	55	
		LS Mean	-5.849	-6.682	0.833
		SEM	4.071	4.040	3.049
		95% CI	(-13.9, 2.2)	(-14.7, 1.3)	(-5.2, 6.8)
		Pr >  t			0.7849
	Week 24	n	44	44	
		LS Mean	-6.470	-3.197	-3.273
		SEM	4.154	4.121	3.287
		95% CI	(-14.7, 1.7)	(-11.3, 4.9)	(-9.7, 3.2)
		Pr >  t			0.3201
	Week 32	n	38	40	
		LS Mean	-4.329	-7.287	2.957
		SEM	4.253	4.194	3.426

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.7, 4.1)	(-15.6, 1.0)	(-3.8, 9.7)
		Pr >  t			0.3885
	Week 40	n	33	31	
		LS Mean	-5.302	-8.037	2.736
		SEM	4.327	4.345	3.665
		95% CI	(-13.8, 3.2)	(-16.6, 0.5)	(-4.5, 9.9)
		Pr >  t			0.4557
	Week 48	n	29	26	
		LS Mean	-9.188	-8.127	-1.061
		SEM	4.395	4.451	3.868
		95% CI	(-17.8,-0.5)	(-16.9, 0.6)	(-8.7, 6.5)
		Pr >  t			0.7840
	Week 56	n	24	25	
		LS Mean	-3.958	-4.702	0.744
		SEM	4.510	4.475	4.027
		95% CI	(-12.8, 4.9)	(-13.5, 4.1)	(-7.2, 8.7)
		Pr >  t			0.8535
	Week 64	n	18	24	
		LS Mean	-6.165	-11.05	4.885
		SEM	4.720	4.503	4.295
		95% CI	(-15.5, 3.1)	(-19.9,-2.2)	(-3.6,13.3)
		Pr >  t			0.2559
	Week 72	n	20	17	
		LS Mean	-1.719	-12.26	10.544
		SEM	4.642	4.763	4.484
		95% CI	(-10.9, 7.4)	(-21.6,-2.9)	( 1.7,19.3)
		Pr >  t			0.0190
	Week 84	n	13	16	
		LS Mean	-6.037	-9.567	3.530
		SEM	5.018	4.814	4.928
		95% CI	(-15.9, 3.8)	(-19.0,-0.1)	(-6.1,13.2)
		Pr >  t			0.4741
	Week 96	n	12	10	
		LS Mean	-2.855	-10.65	7.800
		SEM	5.109	5.327	5.514
		95% CI	(-12.9, 7.2)	(-21.1,-0.2)	(-3.0,18.6)
		Pr >  t			0.1576
	Week 108	n	7	9	
		LS Mean	-3.816	-5.631	1.815
		SEM	5.845	5.468	6.324

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.3, 7.7)	(-16.4, 5.1)	(-10.6,14.2)
		Pr >  t			0.7742
	Week 120	n	10	8	
		LS Mean	-0.779	-2.167	1.388
		SEM	5.341	5.640	6.020
		95% CI	(-11.3, 9.7)	(-13.2, 8.9)	(-10.4,13.2)
		Pr >  t			0.8177
	Week 132	n	9	4	
		LS Mean	-10.50	-10.23	-0.268
		SEM	5.467	6.975	7.378
		95% CI	(-21.2, 0.2)	(-23.9, 3.5)	(-14.8,14.2)
		Pr >  t			0.9711
	Week 144	n	4	1	
		LS Mean	-15.52	-5.171	-10.35
		SEM	6.972	12.23	13.19
		95% CI	(-29.2,-1.8)	(-29.2,18.8)	(-36.3,15.6)
		Pr >  t			0.4331
	Week 156	n	5	1	
		LS Mean	1.829	-5.171	7.000
		SEM	6.476	12.23	12.94
		95% CI	(-10.9,14.5)	(-29.2,18.8)	(-18.4,32.4)
		Pr >  t			0.5887
	Week 168	n	3		
		LS Mean	-9.436		
		SEM	7.740		
		95% CI	(-24.6, 5.8)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-15.66		
		SEM	12.22		
		95% CI	(-39.7, 8.3)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-7.318		
		SEM	12.22		
		95% CI	(-31.3,16.7)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	-1.823	1.550	-3.373		
			SEM	4.845	4.534	4.097		
			95% CI	(-11.5, 7.8)	(-7.5,10.6)	(-11.5, 4.7)		
					Pr >  t			0.4122
		Week 16	n	30	30			
			LS Mean	-3.572	0.566	-4.138		
			SEM	4.876	4.722	4.281		
			95% CI	(-13.3, 6.1)	(-8.8,10.0)	(-12.6, 4.3)		
					Pr >  t			0.3356
		Week 24	n	21	26			
			LS Mean	-0.053	1.931	-1.984		
			SEM	5.100	4.794	4.640		
			95% CI	(-10.2,10.1)	(-7.6,11.5)	(-11.1, 7.2)		
					Pr >  t			0.6696
		Week 32	n	19	24			
			LS Mean	1.254	-4.763	6.017		
			SEM	5.160	4.845	4.770		
			95% CI	(-9.0,11.5)	(-14.4, 4.9)	(-3.4,15.4)		
					Pr >  t			0.2090
		Week 40	n	16	19			
			LS Mean	0.426	-4.800	5.226		
			SEM	5.287	5.048	5.082		
			95% CI	(-10.1,10.9)	(-14.8, 5.2)	(-4.8,15.2)		
					Pr >  t			0.3050
		Week 48	n	16	18			
			LS Mean	-4.781	-4.593	-0.188		
			SEM	5.287	5.088	5.120		
95% CI	(-15.3, 5.7)		(-14.7, 5.5)	(-10.3, 9.9)				
			Pr >  t			0.9707		
Week 56	n	12	14					
	LS Mean	-3.294	-3.789	0.495				
	SEM	5.537	5.294	5.590				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.3, 7.7)	(-14.3, 6.7)	(-10.5,11.5)
		Pr >  t			0.9295
	Week 64	n	12	11	
		LS Mean	-3.296	-9.990	6.694
		SEM	5.537	5.538	5.824
		95% CI	(-14.3, 7.7)	(-20.9, 1.0)	(-4.8,18.2)
		Pr >  t			0.2514
	Week 72	n	10	9	
		LS Mean	-1.399	-7.006	5.606
		SEM	5.722	5.770	6.207
		95% CI	(-12.7, 9.9)	(-18.4, 4.4)	(-6.6,17.8)
		Pr >  t			0.3671
	Week 84	n	8	8	
		LS Mean	-0.678	-9.881	9.203
		SEM	6.040	5.929	6.605
		95% CI	(-12.6,11.3)	(-21.6, 1.8)	(-3.8,22.2)
		Pr >  t			0.1645
	Week 96	n	6	6	
		LS Mean	-0.708	-4.505	3.797
		SEM	6.473	6.373	7.385
		95% CI	(-13.5,12.1)	(-17.1, 8.1)	(-10.7,18.3)
		Pr >  t			0.6075
	Week 108	n	4	5	
		LS Mean	0.519	-5.611	6.131
		SEM	7.251	6.705	8.340
		95% CI	(-13.8,14.8)	(-18.8, 7.6)	(-10.3,22.5)
		Pr >  t			0.4627
	Week 120	n	4	4	
		LS Mean	2.604	-7.953	10.557
		SEM	7.251	7.174	8.725
		95% CI	(-11.7,16.9)	(-22.1, 6.2)	(-6.6,27.7)
		Pr >  t			0.2270
	Week 132	n	3	2	
		LS Mean	-12.94	-7.334	-5.605
		SEM	7.944	9.102	10.86
		95% CI	(-28.6, 2.7)	(-25.2,10.6)	(-27.0,15.8)
		Pr >  t			0.6061
	Week 144	n	3	1	
		LS Mean	-15.72	-2.378	-13.34
		SEM	7.944	12.09	13.45

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-31.4,-0.1)	(-26.1,21.4)	(-39.8,13.1)
		Pr >  t			0.3220
	Week 156	n	2	1	
		LS Mean	4.720	-2.378	7.098
		SEM	9.165	12.09	14.21
		95% CI	(-13.3,22.7)	(-26.1,21.4)	(-20.8,35.0)
		Pr >  t			0.6177
	Week 168	n	1		
		LS Mean	-5.859		
		SEM	12.11		
		95% CI	(-29.7,18.0)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	-0.983	-0.510	-0.473
		SEM	7.554	7.382	4.804
		95% CI	(-16.1,14.1)	(-15.2,14.2)	(-10.1, 9.1)
		Pr >  t			0.9220
	Week 16	n	15	14	
		LS Mean	1.560	0.440	1.119
		SEM	7.593	6.999	4.989
		95% CI	(-13.6,16.7)	(-13.6,14.5)	(-8.8,11.1)
		Pr >  t			0.8232
	Week 24	n	12	11	
		LS Mean	-4.580	-1.203	-3.377
		SEM	7.707	7.517	5.354
		95% CI	(-20.0,10.8)	(-16.2,13.8)	(-14.0, 7.3)
		Pr >  t			0.5301
	Week 32	n	8	9	
		LS Mean	-5.581	-2.264	-3.317
		SEM	7.973	7.656	5.901
		95% CI	(-21.5,10.3)	(-17.5,13.0)	(-15.0, 8.4)
		Pr >  t			0.5754
	Week 40	n	6	7	
		LS Mean	-3.941	-2.681	-1.260
		SEM	8.222	7.824	6.439
		95% CI	(-20.3,12.4)	(-18.3,12.9)	(-14.0,11.5)
		Pr >  t			0.8452
	Week 48	n	4	6	
		LS Mean	-9.575	-1.920	-7.655
		SEM	8.659	7.959	7.151

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-26.8, 7.6)	(-17.8,13.9)	(-21.8, 6.5)
		Pr >  t			0.2864
	Week 56	n	4	6	
		LS Mean	0.527	-1.497	2.025
		SEM	8.658	7.977	7.166
		95% CI	(-16.7,17.7)	(-17.4,14.4)	(-12.2,16.2)
		Pr >  t			0.7780
	Week 64	n	4	4	
		LS Mean	2.962	2.894	0.068
		SEM	8.670	8.409	7.643
		95% CI	(-14.3,20.2)	(-13.8,19.6)	(-15.0,15.2)
		Pr >  t			0.9929
	Week 72	n	4	4	
		LS Mean	-5.370	-3.356	-2.014
		SEM	8.670	8.409	7.643
		95% CI	(-22.6,11.9)	(-20.1,13.3)	(-17.1,13.1)
		Pr >  t			0.7925
	Week 84	n	4	4	
		LS Mean	-1.243	-3.359	2.116
		SEM	8.659	8.409	7.649
		95% CI	(-18.5,16.0)	(-20.1,13.3)	(-13.0,17.2)
		Pr >  t			0.7825
	Week 96	n	3	2	
		LS Mean	1.764	-2.756	4.520
		SEM	9.074	9.589	9.318
		95% CI	(-16.2,19.8)	(-21.7,16.2)	(-13.9,22.9)
		Pr >  t			0.6283
	Week 108	n	3	3	
		LS Mean	-1.016	5.363	-6.379
		SEM	9.074	8.840	8.542
		95% CI	(-19.0,17.0)	(-12.2,22.9)	(-23.3,10.5)
		Pr >  t			0.4565
	Week 120	n	2	1	
		LS Mean	-1.614	2.468	-4.082
		SEM	9.830	11.58	11.96
		95% CI	(-21.1,17.9)	(-20.4,25.4)	(-27.7,19.6)
		Pr >  t			0.7335
	Week 132	n	2	1	
		LS Mean	-17.70	2.468	-20.16
		SEM	9.821	11.58	11.97



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-37.2, 1.8)	(-20.4,25.4)	(-43.8, 3.5)
		Pr >  t			0.0943
	Week 156	n	1		
		LS Mean	-2.243		
		SEM	11.80		
		95% CI	(-25.6,21.1)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-2.243		
		SEM	11.80		
		95% CI	(-25.6,21.1)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	-0.595	-1.644	1.049
		SEM	2.938	3.099	2.758
		95% CI	(-6.4, 5.2)	(-7.7, 4.5)	(-4.4, 6.5)
		Pr >  t			0.7039
	Week 16	n	79	61	
		LS Mean	-1.070	-6.127	5.058
		SEM	3.035	3.328	3.033
		95% CI	(-7.0, 4.9)	(-12.7, 0.4)	(-0.9,11.0)
		Pr >  t			0.0961
	Week 24	n	71	43	
		LS Mean	-5.287	-1.217	-4.070
		SEM	3.093	3.530	3.304
		95% CI	(-11.4, 0.8)	(-8.2, 5.7)	(-10.6, 2.4)
		Pr >  t			0.2185
	Week 32	n	59	39	
		LS Mean	1.202	-2.875	4.077
		SEM	3.215	3.614	3.456
		95% CI	(-5.1, 7.5)	(-10.0, 4.2)	(-2.7,10.9)
		Pr >  t			0.2385
	Week 40	n	52	35	
		LS Mean	-0.631	-1.830	1.199
		SEM	3.281	3.689	3.595
		95% CI	(-7.1, 5.8)	(-9.1, 5.4)	(-5.9, 8.3)
		Pr >  t			0.7389
	Week 48	n	48	26	
		LS Mean	-4.192	-1.354	-2.838
		SEM	3.324	3.922	3.871

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.7, 2.3)	(-9.1, 6.4)	(-10.4, 4.8)
		Pr >  t			0.4637
	Week 56	n	42	24	
		LS Mean	-0.641	-0.200	-0.441
		SEM	3.400	3.993	4.011
		95% CI	(-7.3, 6.0)	(-8.0, 7.6)	(-8.3, 7.4)
		Pr >  t			0.9125
	Week 64	n	30	26	
		LS Mean	-2.088	-2.826	0.738
		SEM	3.628	3.924	4.143
		95% CI	(-9.2, 5.0)	(-10.5, 4.9)	(-7.4, 8.9)
		Pr >  t			0.8587
	Week 72	n	34	21	
		LS Mean	-1.930	-3.383	1.453
		SEM	3.538	4.120	4.253
		95% CI	(-8.9, 5.0)	(-11.5, 4.7)	(-6.9, 9.8)
		Pr >  t			0.7327
	Week 84	n	28	20	
		LS Mean	-2.256	-2.711	0.455
		SEM	3.691	4.168	4.421
		95% CI	(-9.5, 5.0)	(-10.9, 5.5)	(-8.2, 9.1)
		Pr >  t			0.9180
	Week 96	n	26	15	
		LS Mean	-1.391	-2.448	1.057
		SEM	3.746	4.493	4.779
		95% CI	(-8.7, 6.0)	(-11.3, 6.4)	(-8.3, 10.4)
		Pr >  t			0.8250
	Week 108	n	19	12	
		LS Mean	3.131	-5.085	8.216
		SEM	4.060	4.797	5.295
		95% CI	(-4.8, 11.1)	(-14.5, 4.3)	(-2.2, 18.6)
		Pr >  t			0.1211
	Week 120	n	22	10	
		LS Mean	-2.566	1.169	-3.735
		SEM	3.902	5.080	5.445
		95% CI	(-10.2, 5.1)	(-8.8, 11.1)	(-14.4, 6.9)
		Pr >  t			0.4929
	Week 132	n	15	4	
		LS Mean	0.708	2.764	-2.056
		SEM	4.335	7.127	7.625

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.8, 9.2)	(-11.2,16.7)	(-17.0,12.9)
		Pr >  t			0.7875
	Week 144	n	12	4	
		LS Mean	-1.360	2.596	-3.956
		SEM	4.633	7.131	7.809
		95% CI	(-10.5, 7.7)	(-11.4,16.6)	(-19.3,11.4)
		Pr >  t			0.6125
	Week 156	n	7	2	
		LS Mean	6.446	1.335	5.111
		SEM	5.606	9.600	10.59
		95% CI	(-4.6,17.4)	(-17.5,20.2)	(-15.7,25.9)
		Pr >  t			0.6295
	Week 168	n	2	2	
		LS Mean	-6.768	1.335	-8.103
		SEM	9.501	9.600	13.08
		95% CI	(-25.4,11.9)	(-17.5,20.2)	(-33.8,17.6)
		Pr >  t			0.5356
	Week 180	n	1	1	
		LS Mean	-11.22	1.725	-12.94
		SEM	13.15	13.20	18.32
		95% CI	(-37.0,14.6)	(-24.2,27.6)	(-48.9,23.0)
		Pr >  t			0.4802
	Week 192	n	1	1	
		LS Mean	-2.877	1.725	-4.603
		SEM	13.15	13.20	18.32
		95% CI	(-28.7,22.9)	(-24.2,27.6)	(-40.6,31.4)
		Pr >  t			0.8017

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	1.340	3.709	-2.369	
		SEM	3.042	2.976	2.409	
		95% CI	(-4.6, 7.3)	(-2.1, 9.6)	(-7.1, 2.4)	
			Pr >  t			0.3260
	Week 16	n	88	71		
		LS Mean	1.795	-0.703	2.497	
		SEM	3.102	3.172	2.581	
		95% CI	(-4.3, 7.9)	(-6.9, 5.5)	(-2.6, 7.6)	
			Pr >  t			0.3337
	Week 24	n	75	54		
		LS Mean	-1.830	1.900	-3.729	
		SEM	3.153	3.290	2.801	
		95% CI	(-8.0, 4.4)	(-4.6, 8.4)	(-9.2, 1.8)	
			Pr >  t			0.1836
	Week 32	n	62	52		
		LS Mean	3.308	0.409	2.899	
		SEM	3.239	3.310	2.911	
		95% CI	(-3.1, 9.7)	(-6.1, 6.9)	(-2.8, 8.6)	
			Pr >  t			0.3196
	Week 40	n	51	46		
		LS Mean	1.593	2.221	-0.628	
		SEM	3.325	3.389	3.079	
		95% CI	(-4.9, 8.1)	(-4.4, 8.9)	(-6.7, 5.4)	
			Pr >  t			0.8384
	Week 48	n	50	37		
		LS Mean	-4.249	2.519	-6.768	
		SEM	3.334	3.513	3.224	
95% CI		(-10.8, 2.3)	(-4.4, 9.4)	(-13.1,-0.4)		
		Pr >  t			0.0361	
Week 56	n	43	33			
	LS Mean	2.615	3.265	-0.650		
	SEM	3.409	3.587	3.383		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.1, 9.3)	(-3.8, 10.3)	(-7.3, 6.0)
		Pr >  t			0.8476
	Week 64	n	35	33	
		LS Mean	0.890	-0.025	0.915
		SEM	3.526	3.587	3.503
		95% CI	(-6.0, 7.8)	(-7.1, 7.0)	(-6.0, 7.8)
		Pr >  t			0.7940
	Week 72	n	35	31	
		LS Mean	-0.147	0.036	-0.183
		SEM	3.526	3.629	3.546
		95% CI	(-7.1, 6.8)	(-7.1, 7.2)	(-7.1, 6.8)
		Pr >  t			0.9588
	Week 84	n	31	29	
		LS Mean	1.693	-0.493	2.186
		SEM	3.613	3.676	3.671
		95% CI	(-5.4, 8.8)	(-7.7, 6.7)	(-5.0, 9.4)
		Pr >  t			0.5517
	Week 96	n	27	22	
		LS Mean	3.198	-1.349	4.547
		SEM	3.702	3.898	3.987
		95% CI	(-4.1, 10.5)	(-9.0, 6.3)	(-3.3, 12.4)
		Pr >  t			0.2543
	Week 108	n	19	20	
		LS Mean	6.342	0.323	6.019
		SEM	4.018	3.986	4.354
		95% CI	(-1.5, 14.2)	(-7.5, 8.1)	(-2.5, 14.6)
		Pr >  t			0.1671
	Week 120	n	20	15	
		LS Mean	3.026	2.393	0.633
		SEM	3.954	4.291	4.592
		95% CI	(-4.7, 10.8)	(-6.0, 10.8)	(-8.4, 9.6)
		Pr >  t			0.8903
	Week 132	n	15	7	
		LS Mean	-0.886	1.740	-2.626
		SEM	4.271	5.462	5.917
		95% CI	(-9.3, 7.5)	(-9.0, 12.5)	(-14.2, 9.0)
		Pr >  t			0.6572
	Week 144	n	10	5	
		LS Mean	-3.980	5.385	-9.365
		SEM	4.799	6.200	6.973

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.4, 5.4)	(-6.8,17.5)	(-23.0, 4.3)
		Pr >  t			0.1795
	Week 156	n	6	3	
		LS Mean	4.736	4.203	0.533
		SEM	5.766	7.634	8.858
		95% CI	(-6.6,16.0)	(-10.8,19.2)	(-16.8,17.9)
		Pr >  t			0.9521
	Week 168	n	3	2	
		LS Mean	-2.356	4.474	-6.830
		SEM	7.624	9.119	11.32
		95% CI	(-17.3,12.6)	(-13.4,22.4)	(-29.0,15.4)
		Pr >  t			0.5465
	Week 180	n	1	1	
		LS Mean	-9.465	4.866	-14.33
		SEM	12.55	12.54	17.37
		95% CI	(-34.1,15.2)	(-19.7,29.5)	(-48.4,19.8)
		Pr >  t			0.4095
	Week 192	n	1	1	
		LS Mean	-1.125	4.866	-5.991
		SEM	12.55	12.54	17.37
		95% CI	(-25.7,23.5)	(-19.7,29.5)	(-40.1,28.1)
		Pr >  t			0.7302
1	Week 8	n	43	50	
		LS Mean	-1.854	-5.117	3.263
		SEM	4.129	4.324	4.192
		95% CI	(-10.0, 6.3)	(-13.7, 3.5)	(-5.0,11.6)
		Pr >  t			0.4378
	Week 16	n	35	35	
		LS Mean	-3.803	-4.940	1.138
		SEM	4.288	4.448	4.529
		95% CI	(-12.3, 4.7)	(-13.7, 3.9)	(-7.8,10.1)
		Pr >  t			0.8020
	Week 24	n	29	26	
		LS Mean	-4.746	-1.019	-3.727
		SEM	4.430	4.711	4.851
		95% CI	(-13.5, 4.0)	(-10.3, 8.3)	(-13.3, 5.8)
		Pr >  t			0.4432
	Week 32	n	23	21	
		LS Mean	-1.247	-8.340	7.093
		SEM	4.635	4.912	5.153

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-10.4, 7.9)	(-18.0, 1.4)	(-3.1,17.2)
	Pr >  t			0.1700
	n	23	16	
	LS Mean	-2.353	-11.39	9.035
	SEM	4.644	5.151	5.386
Week 48	95% CI	(-11.5, 6.8)	(-21.5,-1.2)	(-1.6,19.6)
	Pr >  t			0.0946
	n	18	14	
	LS Mean	-1.045	-9.956	8.912
	SEM	4.841	5.292	5.700
Week 56	95% CI	(-10.6, 8.5)	(-20.4, 0.5)	(-2.3,20.1)
	Pr >  t			0.1190
	n	15	12	
	LS Mean	-2.308	-7.379	5.071
	SEM	5.021	5.467	6.022
Week 64	95% CI	(-12.2, 7.6)	(-18.1, 3.4)	(-6.8,16.9)
	Pr >  t			0.4003
	n	11	9	
	LS Mean	-4.485	-9.048	4.563
	SEM	5.370	5.856	6.662
Week 72	95% CI	(-15.1, 6.1)	(-20.6, 2.5)	(-8.5,17.7)
	Pr >  t			0.4937
	n	12	4	
	LS Mean	-1.395	-9.029	7.634
	SEM	5.275	7.474	8.052
Week 84	95% CI	(-11.8, 9.0)	(-23.7, 5.7)	(-8.2,23.5)
	Pr >  t			0.3437
	n	8	4	
	LS Mean	-4.386	-9.032	4.646
	SEM	5.859	7.474	8.435
Week 96	95% CI	(-15.9, 7.1)	(-23.7, 5.7)	(-11.9,21.2)
	Pr >  t			0.5821
	n	8	2	
	LS Mean	-7.511	-4.862	-2.649
	SEM	5.859	9.682	10.44
Week 108	95% CI	(-19.0, 4.0)	(-23.9,14.2)	(-23.2,17.9)
	Pr >  t			0.7999
	n	6	1	
Week 108	LS Mean	-4.352	-3.276	-1.076
	SEM	6.374	13.01	13.81

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.9, 8.2)	(-28.2,26.1)
		Pr >  t		0.9379
	Week 120	n	8	1
		LS Mean	-8.808	-3.276
		SEM	5.876	13.01
		95% CI	(-20.4, 2.8)	(-28.9,22.3)
		Pr >  t		(-32.2,21.2)
	Week 132	n	5	1
		LS Mean	-3.475	-3.276
		SEM	6.753	13.01
		95% CI	(-16.8, 9.8)	(-28.9,22.3)
		Pr >  t		(-27.7,27.3)
	Week 144	n	5	
		LS Mean	-1.809	
		SEM	6.753	
		95% CI	(-15.1,11.5)	
		Pr >  t		0.9887
	Week 156	n	4	
		LS Mean	8.404	
		SEM	7.279	
		95% CI	(-5.9,22.7)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	-6.494	
		SEM	12.78	
		95% CI	(-31.6,18.6)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	-1.717	0.896	-2.613		
			SEM	6.093	7.282	7.298		
					95% CI	(-14.1,10.6)	(-13.9,15.7)	(-17.3,12.1)
					Pr >  t			0.7221
				Week 16	n	17	10	
					LS Mean	-5.800	-3.724	-2.076
					SEM	6.344	7.917	7.973
					95% CI	(-18.6, 7.0)	(-19.7,12.2)	(-18.1,13.9)
					Pr >  t			0.7956
				Week 24	n	9	5	
					LS Mean	-4.648	-4.265	-0.383
					SEM	6.884	8.843	9.393
					95% CI	(-18.4, 9.2)	(-21.9,13.4)	(-19.1,18.3)
					Pr >  t			0.9676
				Week 32	n	8	4	
					LS Mean	-0.626	0.124	-0.750
					SEM	7.022	9.240	9.891
					95% CI	(-14.7,13.4)	(-18.3,18.5)	(-20.4,18.9)
					Pr >  t			0.9397
				Week 40	n	5	4	
					LS Mean	-4.979	-8.208	3.229
					SEM	7.671	9.240	10.43
					95% CI	(-20.3,10.3)	(-26.6,10.2)	(-17.5,23.9)
			Pr >  t			0.7575		
		Week 48	n	5	3			
			LS Mean	-9.979	1.809	-11.79		
			SEM	7.671	9.825	10.95		
			95% CI	(-25.3, 5.3)	(-17.7,21.3)	(-33.5, 9.9)		
			Pr >  t			0.2840		
		Week 56	n	4	3			
			LS Mean	-9.919	1.806	-11.72		
			SEM	8.062	9.825	11.24		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	95% CI	(-25.9, 6.1)	(-17.7,21.3)	(-34.0,10.6)	
	Pr >  t			0.2993	
	n	4	3		
	LS Mean	-7.836	-0.971	-6.866	
	SEM	8.062	9.825	11.24	
Week 72	95% CI	(-23.9, 8.2)	(-20.5,18.6)	(-29.1,15.4)	
	Pr >  t			0.5427	
	n	4	3		
	LS Mean	-14.08	1.806	-15.89	
	SEM	8.062	9.825	11.24	
Week 84	95% CI	(-30.1, 1.9)	(-17.7,21.3)	(-38.2, 6.4)	
	Pr >  t			0.1604	
	n	2	3		
	LS Mean	-22.60	1.809	-24.41	
	SEM	9.891	9.825	12.54	
Week 96	95% CI	(-42.2,-3.0)	(-17.7,21.3)	(-49.3, 0.4)	
	Pr >  t			0.0541	
	n	1	3		
	LS Mean	-0.749	-12.08	11.332	
	SEM	12.58	9.825	14.88	
Week 108	95% CI	(-25.7,24.2)	(-31.6, 7.4)	(-18.2,40.8)	
	Pr >  t			0.4481	
	n		2		
	LS Mean		-8.996		
	SEM		10.83		
Week 120	95% CI		(-30.5,12.5)		
	Pr >  t				
	n	1	1		
	LS Mean	-0.749	-3.304	2.555	
	SEM	12.58	13.37	17.43	
Week 132	95% CI	(-25.7,24.2)	(-29.8,23.2)	(-32.0,37.1)	
	Pr >  t			0.8838	
	n		1		
	LS Mean		-11.64		
	SEM		13.37		
Week 144	95% CI		(-38.1,14.8)		
	Pr >  t				
	n	1			
	LS Mean	-0.749			
	SEM	12.58			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-25.7, 24.2)			
		Pr >  t				
Secondary resistant	Week 8	n	98	106		
		LS Mean	-1.678	-0.339	-1.339	
		SEM	2.840	2.849	2.415	
			95% CI	(-7.3, 3.9)	(-5.9, 5.3)	(-6.1, 3.4)
			Pr >  t			0.5796
	Week 16	n	83	81		
		LS Mean	-0.648	-3.215	2.567	
		SEM	2.917	2.980	2.618	
			95% CI	(-6.4, 5.1)	(-9.1, 2.6)	(-2.6, 7.7)
			Pr >  t			0.3273
	Week 24	n	75	62		
		LS Mean	-4.982	0.787	-5.769	
SEM		2.973	3.123	2.807		
		95% CI	(-10.8, 0.9)	(-5.4, 6.9)	(-11.3, -0.3)	
		Pr >  t			0.0403	
Week 32	n	59	56			
	LS Mean	-0.312	-2.830	2.518		
	SEM	3.128	3.174	2.983		
		95% CI	(-6.5, 5.8)	(-9.1, 3.4)	(-3.3, 8.4)	
		Pr >  t			0.3989	
Week 40	n	52	48			
	LS Mean	-1.819	-2.189	0.371		
	SEM	3.193	3.271	3.137		
		95% CI	(-8.1, 4.5)	(-8.6, 4.2)	(-5.8, 6.5)	
		Pr >  t			0.9059	
Week 48	n	47	37			
	LS Mean	-5.634	-2.570	-3.063		
	SEM	3.248	3.432	3.360		
		95% CI	(-12.0, 0.7)	(-9.3, 4.2)	(-9.7, 3.5)	
		Pr >  t			0.3621	
Week 56	n	41	31			
	LS Mean	1.002	-0.918	1.921		
	SEM	3.329	3.562	3.569		
		95% CI	(-5.5, 7.5)	(-7.9, 6.1)	(-5.1, 8.9)	
		Pr >  t			0.5906	
Week 64	n	32	28			
	LS Mean	-2.411	-5.737	3.327		
	SEM	3.498	3.645	3.806		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-9.3, 4.5)	(-12.9, 1.4)	(-4.1,10.8)	
	Pr >  t			0.3823	
	n	29	22		
	LS Mean	-1.824	-4.876	3.052	
	SEM	3.577	3.862	4.085	
Week 84	95% CI	(-8.8, 5.2)	(-12.5, 2.7)	(-5.0,11.1)	
	Pr >  t			0.4552	
	n	26	21		
	LS Mean	0.635	-3.763	4.398	
	SEM	3.666	3.909	4.206	
Week 96	95% CI	(-6.6, 7.8)	(-11.4, 3.9)	(-3.9,12.7)	
	Pr >  t			0.2959	
	n	23	14		
	LS Mean	2.143	-2.252	4.395	
	SEM	3.778	4.385	4.740	
Week 108	95% CI	(-5.3, 9.6)	(-10.9, 6.4)	(-4.9,13.7)	
	Pr >  t			0.3540	
	n	18	13		
	LS Mean	1.393	-3.588	4.981	
	SEM	4.035	4.487	5.038	
Week 120	95% CI	(-6.5, 9.3)	(-12.4, 5.2)	(-4.9,14.9)	
	Pr >  t			0.3231	
	n	19	10		
	LS Mean	-5.503	-2.270	-3.233	
	SEM	3.978	4.891	5.358	
Week 132	95% CI	(-13.3, 2.3)	(-11.9, 7.3)	(-13.7, 7.3)	
	Pr >  t			0.5464	
	n	13	4		
	LS Mean	-2.636	3.941	-6.578	
	SEM	4.444	6.956	7.556	
Week 144	95% CI	(-11.4, 6.1)	(-9.7,17.6)	(-21.4, 8.2)	
	Pr >  t			0.3842	
	n	8	1		
	LS Mean	-7.573	1.911	-9.484	
	SEM	5.253	13.06	13.68	
Week 156	95% CI	(-17.9, 2.7)	(-23.7,27.5)	(-36.3,17.4)	
	Pr >  t			0.4882	
	n	5	1		
	LS Mean	0.699	1.911	-1.212	
	SEM	6.309	13.06	14.12	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-11.7,13.1)	(-23.7,27.5)	(-28.9,26.5)
		Pr >  t			0.9316
		n	3	1	
	Week 180	LS Mean	-5.353	1.911	-7.264
		SEM	7.833	13.06	14.86
		95% CI	(-20.7,10.0)	(-23.7,27.5)	(-36.4,21.9)
	Week 180	Pr >  t			0.6251
		n	1	1	
		LS Mean	-12.37	1.911	-14.28
	Week 192	SEM	13.00	13.06	18.12
		95% CI	(-37.9,13.1)	(-23.7,27.5)	(-49.9,21.3)
		Pr >  t			0.4308
	Week 192	n	1	1	
		LS Mean	-4.033	1.911	-5.944
		SEM	13.00	13.06	18.12
	Week 8	95% CI	(-29.5,21.5)	(-23.7,27.5)	(-41.5,29.6)
		Pr >  t			0.7430
		n	17	16	
	Week 8	LS Mean	9.106	6.674	2.432
		SEM	4.074	4.163	5.724
		95% CI	( 1.0,17.2)	( -1.6,15.0)	( -9.0,13.8)
	Week 16	Pr >  t			0.6720
		n	18	14	
		LS Mean	6.124	6.876	-0.752
Week 16	SEM	4.006	4.351	5.836	
	95% CI	( -1.9,14.1)	( -1.8,15.5)	(-12.4,10.9)	
	Pr >  t			0.8978	
Week 24	n	16	13		
	LS Mean	4.171	7.889	-3.719	
	SEM	4.167	4.446	6.012	
Week 24	95% CI	( -4.1,12.5)	( -0.9,16.7)	(-15.7, 8.2)	
	Pr >  t			0.5378	
	n	15	13		
Week 32	LS Mean	10.668	2.071	8.597	
	SEM	4.226	4.456	6.064	
	95% CI	( 2.3,19.1)	( -6.8,10.9)	( -3.4,20.6)	
Week 32	Pr >  t			0.1596	
	n	14	10		
	LS Mean	9.562	5.816	3.747	
Week 40	SEM	4.326	4.804	6.393	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	95% CI	( 1.0,18.2)	( -3.7,15.3)	( -8.9,16.4)	
	Pr >  t			0.5590	
	n	14	11		
	LS Mean	4.802	6.681	-1.878	
	SEM	4.326	4.680	6.300	
Week 56	95% CI	( -3.8,13.4)	( -2.6,16.0)	(-14.4,10.6)	
	Pr >  t			0.7662	
	n	11	11		
	LS Mean	5.909	6.681	-0.772	
	SEM	4.617	4.680	6.507	
Week 64	95% CI	( -3.2,15.1)	( -2.6,16.0)	(-13.7,12.1)	
	Pr >  t			0.9058	
	n	8	11		
	LS Mean	7.939	8.954	-1.015	
	SEM	5.068	4.680	6.840	
Week 72	95% CI	( -2.1,18.0)	( -0.3,18.2)	(-14.5,12.5)	
	Pr >  t			0.8823	
	n	11	10		
	LS Mean	6.665	5.930	0.735	
	SEM	4.617	4.812	6.605	
Week 84	95% CI	( -2.5,15.8)	( -3.6,15.5)	(-12.3,13.8)	
	Pr >  t			0.9115	
	n	9	9		
	LS Mean	2.776	1.689	1.087	
	SEM	4.889	4.961	6.910	
Week 96	95% CI	( -6.9,12.4)	( -8.1,11.5)	(-12.6,14.8)	
	Pr >  t			0.8752	
	n	8	7		
	LS Mean	-1.992	2.964	-4.956	
	SEM	5.074	5.358	7.332	
Week 108	95% CI	(-12.0, 8.0)	( -7.6,13.5)	(-19.4, 9.5)	
	Pr >  t			0.5000	
	n	7	6		
	LS Mean	12.507	9.015	3.492	
	SEM	5.295	5.646	7.693	
Week 120	95% CI	( 2.1,23.0)	( -2.1,20.2)	(-11.7,18.7)	
	Pr >  t			0.6505	
	n	6	5		
	LS Mean	16.107	10.544	5.562	
	SEM	5.584	6.024	8.161	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	( 5.1,27.1)	( -1.3,22.4)	(-10.5,21.7)
	Pr >  t			0.4963
	n	5	3	
	LS Mean	2.140	3.403	-1.263
	SEM	5.954	7.292	9.369
Week 144	95% CI	( -9.6,13.9)	(-11.0,17.8)	(-19.7,17.2)
	Pr >  t			0.8929
	n	5	4	
	LS Mean	5.472	10.065	-4.593
	SEM	5.954	6.528	8.787
Week 156	95% CI	( -6.3,17.2)	( -2.8,22.9)	(-21.9,12.7)
	Pr >  t			0.6017
	n	4	2	
	LS Mean	19.405	8.460	10.945
	SEM	6.463	8.622	10.74
Week 168	95% CI	( 6.7,32.1)	( -8.5,25.4)	(-10.2,32.1)
	Pr >  t			0.3092
	n	1	1	
	LS Mean	3.660	8.815	-5.156
	SEM	11.70	11.74	16.55
	95% CI	(-19.4,26.7)	(-14.3,31.9)	(-37.7,27.4)
	Pr >  t			0.7557

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	-0.185	-0.312	0.127		
			SEM	7.396	7.606	2.830		
			95% CI	(-14.8,14.4)	(-15.3,14.7)	(-5.4, 5.7)		
					Pr >  t			0.9642
		Week 16	n	69	55			
			LS Mean	-0.991	-2.660	1.669		
			SEM	7.406	7.664	3.018		
			95% CI	(-15.6,13.6)	(-17.8,12.5)	(-4.3, 7.6)		
					Pr >  t			0.5806
		Week 24	n	54	46			
			LS Mean	-4.216	-0.975	-3.241		
			SEM	7.434	7.703	3.236		
			95% CI	(-18.9,10.5)	(-16.2,14.2)	(-9.6, 3.1)		
					Pr >  t			0.3171
		Week 32	n	49	41			
			LS Mean	0.418	-4.520	4.938		
			SEM	7.512	7.730	3.352		
			95% CI	(-14.4,15.3)	(-19.8,10.7)	(-1.7,11.5)		
					Pr >  t			0.1415
		Week 40	n	40	33			
			LS Mean	0.187	-0.120	0.308		
			SEM	7.562	7.789	3.594		
			95% CI	(-14.7,15.1)	(-15.5,15.3)	(-6.8, 7.4)		
			Pr >  t			0.9318		
Week 48	n	38	28					
	LS Mean	-5.060	-0.857	-4.204				
	SEM	7.574	7.842	3.737				
	95% CI	(-20.0, 9.9)	(-16.3,14.6)	(-11.5, 3.1)				
			Pr >  t			0.2611		
Week 56	n	32	28					
	LS Mean	-0.834	-1.051	0.217				
	SEM	7.624	7.843	3.838				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-15.9,14.2)	(-16.5,14.4)	(-7.3, 7.8)
	Pr >  t			0.9549
	n	23	26	
	LS Mean	-2.614	-0.162	-2.452
	SEM	7.740	7.869	4.118
Week 72	95% CI	(-17.9,12.7)	(-15.7,15.4)	(-10.5, 5.6)
	Pr >  t			0.5519
	n	27	25	
	LS Mean	-1.677	-1.481	-0.196
	SEM	7.680	7.882	4.030
Week 84	95% CI	(-16.8,13.5)	(-17.0,14.1)	(-8.1, 7.7)
	Pr >  t			0.9612
	n	23	22	
	LS Mean	-4.286	-2.962	-1.324
	SEM	7.740	7.933	4.241
Week 96	95% CI	(-19.6,11.0)	(-18.6,12.7)	(-9.7, 7.0)
	Pr >  t			0.7551
	n	20	16	
	LS Mean	-3.871	-4.464	0.593
	SEM	7.802	8.088	4.630
Week 108	95% CI	(-19.3,11.5)	(-20.4,11.5)	(-8.5, 9.7)
	Pr >  t			0.8982
	n	20	14	
	LS Mean	3.353	0.878	2.475
	SEM	7.802	8.168	4.770
Week 120	95% CI	(-12.0,18.7)	(-15.2,17.0)	(-6.9,11.8)
	Pr >  t			0.6040
	n	17	11	
	LS Mean	-1.185	-2.682	1.497
	SEM	7.883	8.337	5.181
Week 132	95% CI	(-16.7,14.4)	(-19.1,13.8)	(-8.7,11.7)
	Pr >  t			0.7726
	n	13	6	
	LS Mean	-2.597	-3.319	0.721
	SEM	8.047	8.962	6.343
Week 144	95% CI	(-18.5,13.3)	(-21.0,14.3)	(-11.7,13.2)
	Pr >  t			0.9095
	n	10	5	
	LS Mean	-2.622	2.393	-5.015
	SEM	8.248	9.227	6.953

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-18.9,13.6)	(-15.8,20.5)	(-18.7, 8.6)
		Pr >  t			0.4710
	Week 156	n	7	3	
		LS Mean	6.865	1.201	5.664
		SEM	8.611	10.20	8.567
		95% CI	(-10.1,23.8)	(-18.9,21.3)	(-11.1,22.5)
		Pr >  t			0.5087
	Week 168	n	3	2	
		LS Mean	-2.319	1.505	-3.824
		SEM	10.06	11.31	11.14
		95% CI	(-22.1,17.4)	(-20.7,23.7)	(-25.7,18.0)
		Pr >  t			0.7315
	Week 180	n		1	
		LS Mean		1.682	
		SEM		14.09	
		95% CI		(-26.0,29.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		1.682	
		SEM		14.09	
		95% CI		(-26.0,29.3)	
		Pr >  t			
Second Line	Week 8	n	66	67	
		LS Mean	-0.410	0.654	-1.065
		SEM	2.870	2.887	3.120
		95% CI	(-6.1, 5.3)	(-5.0, 6.3)	(-7.2, 5.1)
		Pr >  t			0.7332
	Week 16	n	54	52	
		LS Mean	-0.503	-2.886	2.382
		SEM	3.015	3.091	3.380
		95% CI	(-6.4, 5.4)	(-9.0, 3.2)	(-4.3, 9.0)
		Pr >  t			0.4816
	Week 24	n	49	35	
		LS Mean	-2.674	2.327	-5.001
		SEM	3.090	3.385	3.698
		95% CI	(-8.8, 3.4)	(-4.3, 9.0)	(-12.3, 2.3)
		Pr >  t			0.1771
	Week 32	n	36	32	
		LS Mean	2.331	-0.895	3.226
		SEM	3.317	3.467	3.939

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-4.2, 8.9)	(-7.7, 5.9)	(-4.5, 11.0)
	Pr >  t			0.4132
Week 40	n	33	29	
	LS Mean	-0.838	-4.798	3.960
	SEM	3.381	3.566	4.067
	95% CI	(-7.5, 5.8)	(-11.8, 2.2)	(-4.0, 12.0)
	Pr >  t			0.3308
Week 48	n	29	23	
	LS Mean	-3.241	-2.908	-0.332
	SEM	3.483	3.772	4.334
	95% CI	(-10.1, 3.6)	(-10.3, 4.5)	(-8.8, 8.2)
	Pr >  t			0.9389
Week 56	n	25	17	
	LS Mean	-0.008	0.291	-0.298
	SEM	3.605	4.094	4.716
	95% CI	(-7.1, 7.1)	(-7.8, 8.3)	(-9.6, 9.0)
	Pr >  t			0.9496
Week 64	n	22	16	
	LS Mean	0.619	-8.411	9.029
	SEM	3.724	4.167	4.871
	95% CI	(-6.7, 7.9)	(-16.6, -0.2)	(-0.5, 18.6)
	Pr >  t			0.0642
Week 72	n	20	10	
	LS Mean	-0.386	-7.199	6.813
	SEM	3.821	4.841	5.528
	95% CI	(-7.9, 7.1)	(-16.7, 2.3)	(-4.0, 17.7)
	Pr >  t			0.2182
Week 84	n	16	11	
	LS Mean	4.376	-4.979	9.355
	SEM	4.085	4.688	5.573
	95% CI	(-3.6, 12.4)	(-14.2, 4.2)	(-1.6, 20.3)
	Pr >  t			0.0937
Week 96	n	15	8	
	LS Mean	4.283	-3.355	7.638
	SEM	4.159	5.232	6.094
	95% CI	(-3.9, 12.5)	(-13.6, 6.9)	(-4.3, 19.6)
	Pr >  t			0.2105
Week 108	n	6	7	
	LS Mean	0.238	-9.374	9.612
	SEM	5.748	5.495	7.458

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-11.0,11.5)	(-20.2, 1.4)	( -5.0,24.3)
	Pr >  t			0.1979
Week 120	n	11	5	
	LS Mean	-1.505	4.142	-5.648
	SEM	4.606	6.258	7.271
	95% CI	(-10.6, 7.5)	( -8.1,16.4)	(-19.9, 8.6)
	Pr >  t			0.4376
Week 132	n	7	2	
	LS Mean	-2.869	6.295	-9.164
	SEM	5.415	9.277	10.38
	95% CI	(-13.5, 7.8)	(-11.9,24.5)	(-29.6,11.2)
	Pr >  t			0.3777
Week 144	n	5		
	LS Mean	-6.828		
	SEM	6.169		
	95% CI	(-18.9, 5.3)		
	Pr >  t			
Week 156	n	3		
	LS Mean	3.002		
	SEM	7.682		
	95% CI	(-12.1,18.1)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-11.15		
	SEM	12.75		
	95% CI	(-36.2,13.9)		
	Pr >  t			
Week 180	n	1		
	LS Mean	-11.15		
	SEM	12.75		
	95% CI	(-36.2,13.9)		
	Pr >  t			
Week 192	n	1		
	LS Mean	-2.807		
	SEM	12.75		
	95% CI	(-27.9,22.2)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-5.564	-1.374	-4.190		
			SEM	4.270	4.231	3.212		
			95% CI	(-14.0, 2.9)	(-9.7, 7.0)	(-10.5, 2.1)		
					Pr >  t			0.1932
		Week 16	n	60	51			
			LS Mean	-1.468	-8.937	7.469		
			SEM	4.346	4.423	3.403		
			95% CI	(-10.0, 7.1)	(-17.7,-0.2)	( 0.8,14.2)		
					Pr >  t			0.0289
		Week 24	n	51	42			
			LS Mean	-6.331	-3.343	-2.988		
			SEM	4.407	4.507	3.602		
			95% CI	(-15.0, 2.4)	(-12.2, 5.5)	(-10.1, 4.1)		
					Pr >  t			0.4074
		Week 32	n	46	36			
			LS Mean	-1.239	-7.551	6.312		
			SEM	4.479	4.621	3.763		
			95% CI	(-10.1, 7.6)	(-16.6, 1.5)	(-1.1,13.7)		
					Pr >  t			0.0942
		Week 40	n	40	33			
			LS Mean	-3.664	-5.098	1.435		
			SEM	4.546	4.669	3.904		
			95% CI	(-12.6, 5.3)	(-14.3, 4.1)	(-6.2, 9.1)		
			Pr >  t			0.7134		
Week 48	n	37	28					
	LS Mean	-4.018	-4.679	0.661				
	SEM	4.583	4.769	4.064				
	95% CI	(-13.0, 5.0)	(-14.1, 4.7)	(-7.3, 8.6)				
			Pr >  t			0.8708		
Week 56	n	33	23					
	LS Mean	-2.171	-1.438	-0.734				
	SEM	4.645	4.907	4.294				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	Pr >  t	95% CI	Pr >  t
Week 64	n	(-11.3, 7.0)		(-11.1, 8.2)	(-9.2, 7.7)
	LS Mean		26		0.8644
	SEM		4.788		4.572
	95% CI	(-9.8, 9.1)		(-16.3, 3.4)	(-2.9, 15.1)
	Pr >  t				0.1831
Week 72	n		28		
	LS Mean		-2.953		2.372
	SEM		4.742		4.677
	95% CI	(-12.3, 6.4)		(-15.5, 4.8)	(-6.8, 11.6)
	Pr >  t				0.6122
Week 84	n		23		
	LS Mean		-0.839		3.995
	SEM		4.871		4.813
	95% CI	(-10.4, 8.7)		(-15.0, 5.3)	(-5.5, 13.4)
	Pr >  t				0.4068
Week 96	n		23		
	LS Mean		0.485		10.446
	SEM		4.874		5.328
	95% CI	(-9.1, 10.1)		(-21.0, 1.1)	(-0.0, 20.9)
	Pr >  t				0.0503
Week 108	n		15		
	LS Mean		3.642		6.272
	SEM		5.247		5.473
	95% CI	(-6.7, 14.0)		(-13.3, 8.1)	(-4.5, 17.0)
	Pr >  t				0.2522
Week 120	n		16		
	LS Mean		1.787		4.911
	SEM		5.187		5.902
	95% CI	(-8.4, 12.0)		(-14.8, 8.5)	(-6.7, 16.5)
	Pr >  t				0.4056
Week 132	n		14		
	LS Mean		-4.275		-1.513
	SEM		5.319		7.106
	95% CI	(-14.7, 6.2)		(-16.6, 11.0)	(-15.5, 12.4)
	Pr >  t				0.8315
Week 144	n		8		
	LS Mean		2.319		3.414
	SEM		6.075		8.969

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-9.6,14.3)	(-17.6,15.4)	(-14.2,21.0)
		Pr >  t			0.7036
		n	7	2	
	Week 168	LS Mean	3.757	-1.522	5.279
		SEM	6.303	9.868	10.48
		95% CI	(-8.6,16.1)	(-20.9,17.8)	(-15.3,25.9)
	Week 180	Pr >  t			0.6147
		n	4	2	
		LS Mean	-5.144	-1.522	-3.622
	Week 192	SEM	7.537	9.868	11.27
		95% CI	(-19.9, 9.7)	(-20.9,17.8)	(-25.7,18.5)
		Pr >  t			0.7480
	Week 8	n	1	1	
		LS Mean	-11.98	-1.292	-10.69
		SEM	13.28	13.29	18.04
	Week 16	95% CI	(-38.0,14.1)	(-27.4,24.8)	(-46.1,24.7)
		Pr >  t			0.5537
		n	1	1	
	Week 24	LS Mean	-3.642	-1.292	-2.350
		SEM	13.28	13.29	18.04
		95% CI	(-29.7,22.4)	(-27.4,24.8)	(-37.8,33.1)
	Week 32	Pr >  t			0.8964
		n	18	17	
		LS Mean	1.598	1.994	-0.396
Week 8	SEM	3.275	3.399	4.707	
	95% CI	(-4.9, 8.1)	(-4.7, 8.7)	(-9.7, 8.9)	
	Pr >  t			0.9330	
Week 16	n	17	11		
	LS Mean	-3.493	-0.056	-3.437	
	SEM	3.368	4.184	5.367	
Week 24	95% CI	(-10.2, 3.2)	(-8.3, 8.2)	(-14.0, 7.2)	
	Pr >  t			0.5230	
	n	15	5		
Week 32	LS Mean	-4.324	2.588	-6.911	
	SEM	3.581	6.157	7.123	
	95% CI	(-11.4, 2.8)	(-9.6,14.7)	(-21.0, 7.2)	
Week 8	Pr >  t			0.3333	
	n	13	5		
	LS Mean	1.287	4.254	-2.966	
		SEM	3.840	6.157	7.266



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-6.3, 8.9)	(-7.9,16.4)	(-17.3,11.4)
	Pr >  t			0.6836
	n	11	5	
	LS Mean	2.936	0.922	2.015
	SEM	4.154	6.157	7.435
Week 48	95% CI	(-5.3,11.1)	(-11.2,13.1)	(-12.7,16.7)
	Pr >  t			0.7868
	n	11	2	
	LS Mean	-12.13	-0.184	-11.94
	SEM	4.161	9.509	10.38
Week 56	95% CI	(-20.3,-3.9)	(-19.0,18.6)	(-32.4, 8.5)
	Pr >  t			0.2516
	n	8	2	
	LS Mean	5.497	-4.354	9.850
	SEM	4.814	9.509	10.66
Week 64	95% CI	(-4.0,15.0)	(-23.1,14.4)	(-11.2,30.9)
	Pr >  t			0.3567
	n	7	3	
	LS Mean	-0.869	12.171	-13.04
	SEM	5.118	7.850	9.371
Week 72	95% CI	(-11.0, 9.2)	(-3.3,27.7)	(-31.5, 5.5)
	Pr >  t			0.1658
	n	7	3	
	LS Mean	6.809	12.171	-5.362
	SEM	5.130	7.850	9.376
Week 84	95% CI	(-3.3,16.9)	(-3.3,27.7)	(-23.9,13.1)
	Pr >  t			0.5682
	n	7	2	
	LS Mean	-3.906	3.981	-7.888
	SEM	5.130	9.509	10.81
Week 96	95% CI	(-14.0, 6.2)	(-14.8,22.7)	(-29.2,13.4)
	Pr >  t			0.4664
	n	6	3	
	LS Mean	-3.334	6.618	-9.952
	SEM	5.509	7.850	9.588
Week 108	95% CI	(-14.2, 7.5)	(-8.9,22.1)	(-28.9, 9.0)
	Pr >  t			0.3008
	n	7	2	
	LS Mean	3.236	-3.070	6.306
	SEM	5.130	9.500	10.79

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-6.9,13.4)	(-21.8,15.7)	(-15.0,27.6)
		Pr >  t			0.5597
		n	6	1	
	Week 132	LS Mean	-7.499	11.890	-19.39
		SEM	5.509	13.30	14.39
		95% CI	(-18.4, 3.4)	(-14.4,38.1)	(-47.8, 9.0)
	Week 144	Pr >  t			0.1797
		n	4		
		LS Mean	-5.308		
	Week 156	SEM	6.665		
		95% CI	(-18.5, 7.8)		
		Pr >  t			
	Week 8	n	5		
		LS Mean	-10.71		
		SEM	6.002		
Week 16	95% CI	(-22.6, 1.1)			
	Pr >  t				
	n	3			
Week 24	LS Mean	9.515			
	SEM	7.650			
	95% CI	(-5.6,24.6)			
Week 32	Pr >  t				
	n	59	57		
	LS Mean	4.043	0.693	3.350	
Week 16	SEM	3.177	3.333	3.291	
	95% CI	(-2.2,10.3)	(-5.9, 7.3)	(-3.1, 9.8)	
	Pr >  t			0.3102	
Week 24	n	47	44		
	LS Mean	-0.598	2.601	-3.199	
	SEM	3.292	3.478	3.542	
Week 32	95% CI	(-7.1, 5.9)	(-4.3, 9.5)	(-10.2, 3.8)	
	Pr >  t			0.3675	
	n	39	34		
Week 8	LS Mean	-2.100	3.767	-5.867	
	SEM	3.399	3.646	3.781	
	95% CI	(-8.8, 4.6)	(-3.4,11.0)	(-13.3, 1.6)	
Week 16	Pr >  t			0.1220	
	n	27	32		
	LS Mean	2.001	0.693	1.309	
Week 24	SEM	3.638	3.680	4.014	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.2, 9.2)	(-6.6, 9.2)
		Pr >  t		0.7446
	Week 40	n	24	24
		LS Mean	0.521	-0.185
		SEM	3.719	3.871
		95% CI	(-6.8, 7.9)	(-7.7, 9.1)
		Pr >  t		0.8683
	Week 48	n	21	21
		LS Mean	-3.666	0.134
		SEM	3.818	3.969
		95% CI	(-11.2, 3.9)	(-7.7, 8.0)
		Pr >  t		0.3917
	Week 56	n	18	20
		LS Mean	-1.813	-0.200
		SEM	3.940	4.008
		95% CI	(-9.6, 5.9)	(-8.1, 7.7)
		Pr >  t		0.7246
	Week 64	n	14	19
		LS Mean	-5.997	-2.733
		SEM	4.170	4.049
		95% CI	(-14.2, 2.2)	(-10.7, 5.2)
		Pr >  t		0.4982
	Week 72	n	13	15
		LS Mean	-6.554	-4.149
		SEM	4.249	4.256
		95% CI	(-14.9, 1.8)	(-12.5, 4.2)
		Pr >  t		0.6345
	Week 84	n	10	14
		LS Mean	-4.379	-4.487
		SEM	4.582	4.321
		95% CI	(-13.4, 4.6)	(-13.0, 4.0)
		Pr >  t		0.9839
	Week 96	n	6	10
		LS Mean	-7.527	-0.392
		SEM	5.363	4.698
		95% CI	(-18.1, 3.0)	(-9.6, 8.8)
		Pr >  t		0.2613
	Week 108	n	4	6
		LS Mean	-6.390	-4.261
		SEM	6.223	5.472
				7.610

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-18.6, 5.8)	(-15.0, 6.5)	(-17.1,12.8)
	Pr >  t			0.7798
	n	6	6	
	LS Mean	-7.617	0.182	-7.799
	SEM	5.363	5.474	6.938
Week 132	95% CI	(-18.2, 2.9)	(-10.6,10.9)	(-21.4, 5.8)
	Pr >  t			0.2615
	n	2	3	
	LS Mean	5.852	-1.524	7.376
	SEM	8.232	7.019	10.31
Week 144	95% CI	(-10.3,22.0)	(-15.3,12.3)	(-12.9,27.6)
	Pr >  t			0.4746
	n	2	2	
	LS Mean	-16.38	4.288	-20.67
	SEM	8.213	8.299	11.23
Week 156	95% CI	(-32.5,-0.3)	(-12.0,20.6)	(-42.7, 1.4)
	Pr >  t			0.0662
	n		1	
	LS Mean		1.666	
	SEM		11.24	
	95% CI		(-20.4,23.7)	
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-3.024	-2.142	-0.882
		SEM	7.238	7.546	3.234
		95% CI	(-17.4,11.3)	(-17.1,12.8)	(-7.3, 5.5)
		Pr >  t			0.7854
	Week 16	n	51	41	
		LS Mean	-3.086	-5.395	2.308
		SEM	7.258	7.631	3.504
		95% CI	(-17.5,11.3)	(-20.5, 9.7)	(-4.6, 9.2)
		Pr >  t			0.5107
	Week 24	n	38	33	
		LS Mean	-6.836	-3.415	-3.421
		SEM	7.306	7.695	3.833
		95% CI	(-21.3, 7.6)	(-18.7,11.8)	(-11.0, 4.1)
		Pr >  t			0.3729
	Week 32	n	34	28	
		LS Mean	-3.035	-5.954	2.919
		SEM	7.438	7.748	4.019
		95% CI	(-17.8,11.7)	(-21.3, 9.4)	(-5.0,10.8)
		Pr >  t			0.4681
	Week 40	n	26	23	
		LS Mean	-3.070	-1.281	-1.790
		SEM	7.544	7.831	4.364
		95% CI	(-18.0,11.9)	(-16.8,14.2)	(-10.4, 6.8)
		Pr >  t			0.6819
	Week 48	n	24	17	
		LS Mean	-8.668	-2.740	-5.928
		SEM	7.577	7.988	4.704
95% CI		(-23.7, 6.3)	(-18.5,13.1)	(-15.2, 3.3)	
	Pr >  t			0.2082	
Week 56	n	21	17		
	LS Mean	-2.623	-3.097	0.474	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	7.641	7.991	4.811
	95% CI	(-17.7,12.5)	(-18.9,12.7)	(-9.0, 9.9)
	Pr >  t			0.9216
Week 64	n	15	15	
	LS Mean	-6.324	-3.238	-3.085
	SEM	7.834	8.069	5.244
	95% CI	(-21.8, 9.2)	(-19.2,12.7)	(-13.4, 7.2)
	Pr >  t			0.5566
Week 72	n	16	15	
	LS Mean	-4.358	-3.327	-1.031
	SEM	7.794	8.070	5.181
	95% CI	(-19.8,11.0)	(-19.3,12.6)	(-11.2, 9.1)
	Pr >  t			0.8423
Week 84	n	14	13	
	LS Mean	-5.997	-2.858	-3.139
	SEM	7.882	8.167	5.465
	95% CI	(-21.6, 9.6)	(-19.0,13.3)	(-13.9, 7.6)
	Pr >  t			0.5659
Week 96	n	12	9	
	LS Mean	-2.110	-6.266	4.156
	SEM	8.002	8.492	6.096
	95% CI	(-17.9,13.7)	(-23.0,10.5)	(-7.8,16.1)
	Pr >  t			0.4956
Week 108	n	13	8	
	LS Mean	0.442	-1.511	1.953
	SEM	7.940	8.619	6.195
	95% CI	(-15.2,16.1)	(-18.5,15.5)	(-10.2,14.1)
	Pr >  t			0.7527
Week 120	n	11	6	
	LS Mean	-8.546	-9.353	0.806
	SEM	8.076	8.988	6.859
	95% CI	(-24.5, 7.4)	(-27.1, 8.4)	(-12.7,14.3)
	Pr >  t			0.9065
Week 132	n	8	3	
	LS Mean	-2.693	-4.527	1.834
	SEM	8.397	10.32	8.841
	95% CI	(-19.3,13.9)	(-24.8,15.8)	(-15.5,19.2)
	Pr >  t			0.8358
Week 144	n	5	1	
	LS Mean	-4.730	-0.138	-4.591

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	9.059	14.49	13.90
		95% CI	(-22.6,13.1)	(-28.6,28.3)	(-31.9,22.7)
		Pr >  t			0.7413
		n	3	1	
	Week 168	LS Mean	-1.111	-0.138	-0.973
		SEM	10.14	14.49	14.62
		95% CI	(-21.1,18.8)	(-28.6,28.3)	(-29.7,27.8)
		Pr >  t			0.9470
	Week 180	n	2	1	
		LS Mean	-3.880	-0.138	-3.742
		SEM	11.33	14.49	15.47
		95% CI	(-26.1,18.4)	(-28.6,28.3)	(-34.1,26.7)
	Week 192	Pr >  t			0.8090
		n		1	
		LS Mean		-0.138	
		SEM		14.49	
	Week 8	95% CI		(-28.6,28.3)	
		Pr >  t			
		n	17	16	
		LS Mean	9.106	6.674	2.432
	Week 16	SEM	4.074	4.163	5.724
		95% CI	( 1.0,17.2)	( -1.6,15.0)	( -9.0,13.8)
		Pr >  t			0.6720
		n	18	14	
Week 24	LS Mean	6.124	6.876	-0.752	
	SEM	4.006	4.351	5.836	
	95% CI	( -1.9,14.1)	( -1.8,15.5)	(-12.4,10.9)	
	Pr >  t			0.8978	
Week 32	n	16	13		
	LS Mean	4.171	7.889	-3.719	
	SEM	4.167	4.446	6.012	
	95% CI	( -4.1,12.5)	( -0.9,16.7)	(-15.7, 8.2)	
Week 32	Pr >  t			0.5378	
	n	15	13		
	LS Mean	10.668	2.071	8.597	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	4.226	4.456	6.064
	95% CI	( 2.3,19.1)	( -6.8,10.9)	( -3.4,20.6)
	Pr >  t			0.1596
Week 40	n	14	10	
	LS Mean	9.562	5.816	3.747
	SEM	4.326	4.804	6.393
	95% CI	( 1.0,18.2)	( -3.7,15.3)	( -8.9,16.4)
	Pr >  t			0.5590
Week 48	n	14	11	
	LS Mean	4.802	6.681	-1.878
	SEM	4.326	4.680	6.300
	95% CI	( -3.8,13.4)	( -2.6,16.0)	(-14.4,10.6)
	Pr >  t			0.7662
Week 56	n	11	11	
	LS Mean	5.909	6.681	-0.772
	SEM	4.617	4.680	6.507
	95% CI	( -3.2,15.1)	( -2.6,16.0)	(-13.7,12.1)
	Pr >  t			0.9058
Week 64	n	8	11	
	LS Mean	7.939	8.954	-1.015
	SEM	5.068	4.680	6.840
	95% CI	( -2.1,18.0)	( -0.3,18.2)	(-14.5,12.5)
	Pr >  t			0.8823
Week 72	n	11	10	
	LS Mean	6.665	5.930	0.735
	SEM	4.617	4.812	6.605
	95% CI	( -2.5,15.8)	( -3.6,15.5)	(-12.3,13.8)
	Pr >  t			0.9115
Week 84	n	9	9	
	LS Mean	2.776	1.689	1.087
	SEM	4.889	4.961	6.910
	95% CI	( -6.9,12.4)	( -8.1,11.5)	(-12.6,14.8)
	Pr >  t			0.8752
Week 96	n	8	7	
	LS Mean	-1.992	2.964	-4.956
	SEM	5.074	5.358	7.332
	95% CI	(-12.0, 8.0)	( -7.6,13.5)	(-19.4, 9.5)
	Pr >  t			0.5000
Week 108	n	7	6	
	LS Mean	12.507	9.015	3.492



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 120	SEM	5.295	5.646	7.693
		95% CI	( 2.1,23.0)	( -2.1,20.2)	(-11.7,18.7)
		Pr >  t			0.6505
	Week 132	n	6	5	
		LS Mean	16.107	10.544	5.562
		SEM	5.584	6.024	8.161
	Week 144	95% CI	( 5.1,27.1)	( -1.3,22.4)	(-10.5,21.7)
		Pr >  t			0.4963
		n	5	3	
	Week 156	LS Mean	2.140	3.403	-1.263
		SEM	5.954	7.292	9.369
		95% CI	( -9.6,13.9)	(-11.0,17.8)	(-19.7,17.2)
	Week 168	Pr >  t			0.8929
		n	5	4	
		LS Mean	5.472	10.065	-4.593
	Week 8	SEM	5.954	6.528	8.787
		95% CI	( -6.3,17.2)	( -2.8,22.9)	(-21.9,12.7)
		Pr >  t			0.6017
	Week 16	n	4	2	
		LS Mean	19.405	8.460	10.945
		SEM	6.463	8.622	10.74
	Week 24	95% CI	( 6.7,32.1)	( -8.5,25.4)	(-10.2,32.1)
		Pr >  t			0.3092
		n	1	1	
Week 8	LS Mean	3.660	8.815	-5.156	
	SEM	11.70	11.74	16.55	
	95% CI	(-19.4,26.7)	(-14.3,31.9)	(-37.7,27.4)	
Week 16	Pr >  t			0.7557	
	n	17	19		
	LS Mean	0.428	-0.031	0.459	
Week 24	SEM	4.830	4.464	5.328	
	95% CI	( -9.3,10.2)	( -9.0, 8.9)	(-10.2,11.1)	
	Pr >  t			0.9316	
Week 8	n	15	17		
	LS Mean	2.050	-5.399	7.449	
	SEM	5.077	4.657	5.560	
Week 16	95% CI	( -8.1,12.2)	(-14.7, 3.9)	( -3.7,18.6)	
	Pr >  t			0.1850	
	n	14	11		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	0.211	-2.740	2.951
		SEM	5.148	5.064	6.013
		95% CI	(-10.1,10.5)	(-12.8, 7.4)	(-9.0,14.9)
		Pr >  t			0.6249
	Week 32	n	12	9	
		LS Mean	10.453	-0.248	10.701
		SEM	5.360	5.343	6.370
		95% CI	(-0.3,21.2)	(-10.9,10.4)	(-1.9,23.3)
		Pr >  t			0.0962
	Week 40	n	11	7	
		LS Mean	4.158	-0.318	4.476
		SEM	5.475	5.783	6.771
		95% CI	(-6.8,15.1)	(-11.8,11.1)	(-8.9,17.9)
		Pr >  t			0.5099
	Week 48	n	8	6	
		LS Mean	2.294	0.088	2.206
		SEM	5.836	6.038	7.286
		95% CI	(-9.3,13.9)	(-11.9,12.0)	(-12.2,16.6)
		Pr >  t			0.7626
	Week 56	n	7	5	
		LS Mean	0.201	3.143	-2.941
		SEM	6.011	6.344	7.694
		95% CI	(-11.7,12.1)	(-9.4,15.7)	(-18.1,12.3)
		Pr >  t			0.7028
	Week 64	n	5	3	
		LS Mean	3.730	-6.436	10.166
		SEM	6.541	7.471	9.031
		95% CI	(-9.2,16.7)	(-21.2, 8.3)	(-7.7,28.0)
		Pr >  t			0.2619
	Week 72	n	5	2	
		LS Mean	8.072	1.381	6.691
		SEM	6.571	8.686	10.08
		95% CI	(-4.9,21.1)	(-15.8,18.5)	(-13.2,26.6)
		Pr >  t			0.5077
	Week 84	n	4	2	
		LS Mean	9.943	-2.784	12.727
		SEM	6.947	8.686	10.34
		95% CI	(-3.8,23.7)	(-19.9,14.4)	(-7.7,33.1)
		Pr >  t			0.2200
	Week 96	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 108	LS Mean	2.818	9.716	-6.898	
	SEM	6.967	8.686	10.35	
	95% CI	(-11.0,16.6)	(-7.4,26.9)	(-27.3,13.5)	
	Pr >  t			0.5059	
	n	1	2		
Week 120	LS Mean	8.779	3.900	4.880	
	SEM	11.51	8.680	13.79	
	95% CI	(-13.9,31.5)	(-13.2,21.0)	(-22.4,32.1)	
	Pr >  t			0.7240	
	n	5	1		
Week 132	LS Mean	-0.264	9.299	-9.563	
	SEM	6.571	11.46	12.54	
	95% CI	(-13.3,12.8)	(-13.3,31.9)	(-34.3,15.2)	
	Pr >  t			0.4468	
	n	3	1		
Week 144	LS Mean	-4.881	-7.361	2.480	
	SEM	7.620	11.46	13.13	
	95% CI	(-19.9,10.2)	(-30.0,15.3)	(-23.4,28.4)	
	Pr >  t			0.8504	
	n	3			
Week 156	LS Mean	0.673			
	SEM	7.620			
	95% CI	(-14.4,15.7)			
	Pr >  t				
	n	3			
Week 168	LS Mean	6.229			
	SEM	7.620			
	95% CI	(-8.8,21.3)			
	Pr >  t				
	n	1			
Week 180	LS Mean	-7.943			
	SEM	11.50			
	95% CI	(-30.6,14.8)			
	Pr >  t				
	n	1			
Week 192	LS Mean	-7.943			
	SEM	11.50			
	95% CI	(-30.6,14.8)			
	Pr >  t				
	n	1			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	0.397	
		SEM	11.50	
		95% CI	(-22.3,23.1)	
		Pr >  t		
Second Line (progression following metastatic treatment only)	Week 8	n	37	39
		LS Mean	6.410	1.999
		SEM	3.860	4.151
		95% CI	(-1.3,14.1)	(-6.2,10.2)
		Pr >  t		0.6310
	Week 16	n	30	29
		LS Mean	1.734	0.439
		SEM	3.968	4.496
		95% CI	(-6.1, 9.6)	(-8.4, 9.3)
		Pr >  t		0.9223
	Week 24	n	26	20
		LS Mean	2.759	-6.835
		SEM	4.112	4.917
		95% CI	(-5.4,10.9)	(-16.5, 2.9)
		Pr >  t		0.1661
	Week 32	n	18	20
		LS Mean	6.032	3.522
		SEM	4.461	5.206
		95% CI	(-2.8,14.8)	(-6.7,13.8)
		Pr >  t		0.4995
	Week 40	n	18	19
		LS Mean	3.512	4.962
		SEM	4.460	5.248
		95% CI	(-5.3,12.3)	(-10.4, 7.5)
		Pr >  t		0.3454
	Week 48	n	16	14
		LS Mean	-0.631	-1.104
		SEM	4.579	5.620
		95% CI	(-9.7, 8.4)	(-12.2,10.0)
		Pr >  t		0.8445
	Week 56	n	14	10
		LS Mean	5.397	1.334
		SEM	4.716	6.112
		95% CI	(-3.9,14.7)	(-10.7,13.4)
		Pr >  t		0.8273

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	0.204	-6.546	6.750
		SEM	4.801	5.157	6.068
		95% CI	(-9.3, 9.7)	(-16.7, 3.6)	(-5.2, 18.7)
		Pr >  t			0.2669
Week 72		n	10	6	
		LS Mean	-0.687	-4.270	3.584
		SEM	5.137	6.160	7.185
		95% CI	(-10.8, 9.4)	(-16.4, 7.8)	(-10.5, 17.7)
		Pr >  t			0.6183
Week 84		n	8	7	
		LS Mean	4.938	-3.094	8.033
		SEM	5.517	5.866	7.193
		95% CI	(-5.9, 15.8)	(-14.6, 8.4)	(-6.1, 22.2)
		Pr >  t			0.2649
Week 96		n	6	5	
		LS Mean	2.574	-7.251	9.825
		SEM	6.025	6.540	8.141
		95% CI	(-9.3, 14.4)	(-20.1, 5.6)	(-6.2, 25.8)
		Pr >  t			0.2283
Week 108		n	2	4	
		LS Mean	-7.439	-7.723	0.284
		SEM	9.212	7.081	11.04
		95% CI	(-25.6, 10.7)	(-21.6, 6.2)	(-21.4, 22.0)
		Pr >  t			0.9795
Week 120		n	4	4	
		LS Mean	1.211	6.860	-5.649
		SEM	6.951	7.081	9.259
		95% CI	(-12.5, 14.9)	(-7.1, 20.8)	(-23.9, 12.6)
		Pr >  t			0.5422
Week 132		n	3	1	
		LS Mean	1.414	27.295	-25.88
		SEM	7.796	12.60	14.37
		95% CI	(-13.9, 16.7)	( 2.5, 52.1)	(-54.1, 2.4)
		Pr >  t			0.0726
Week 144		n	2		
		LS Mean	-11.61		
		SEM	9.165		
		95% CI	(-29.6, 6.4)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	0.019	1.092	-1.073		
			SEM	3.338	3.331	2.681		
			95% CI	(-6.6, 6.6)	(-5.5, 7.7)	(-6.3, 4.2)		
					Pr >  t			0.6892
		Week 16	n	79	68			
			LS Mean	0.007	-0.301	0.308		
			SEM	3.368	3.490	2.881		
			95% CI	(-6.6, 6.6)	(-7.2, 6.6)	(-5.4, 6.0)		
					Pr >  t			0.9150
		Week 24	n	64	55			
			LS Mean	-3.088	3.610	-6.698		
			SEM	3.459	3.613	3.090		
			95% CI	(-9.9, 3.7)	(-3.5, 10.7)	(-12.8, -0.6)		
					Pr >  t			0.0307
		Week 32	n	49	53			
			LS Mean	3.078	-1.964	5.042		
			SEM	3.605	3.632	3.244		
			95% CI	(-4.0, 10.2)	(-9.1, 5.2)	(-1.3, 11.4)		
					Pr >  t			0.1206
		Week 40	n	44	45			
			LS Mean	1.622	-1.116	2.738		
			SEM	3.659	3.708	3.389		
			95% CI	(-5.6, 8.8)	(-8.4, 6.2)	(-3.9, 9.4)		
					Pr >  t			0.4194
		Week 48	n	41	36			
			LS Mean	-4.156	-0.698	-3.458		
			SEM	3.695	3.829	3.558		
95% CI	(-11.4, 3.1)		(-8.2, 6.8)	(-10.4, 3.5)				
			Pr >  t			0.3314		
Week 56	n	33	32					
	LS Mean	0.736	0.176	0.560				
	SEM	3.817	3.901	3.764				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-6.8, 8.2)	(-7.5, 7.8)	(-6.8, 7.9)
	Pr >  t			0.8818
	n	27	31	
	LS Mean	-2.136	-2.000	-0.136
	SEM	3.950	3.923	3.923
Week 72	95% CI	(-9.9, 5.6)	(-9.7, 5.7)	(-7.8, 7.6)
	Pr >  t			0.9723
	n	26	26	
	LS Mean	-1.687	-1.438	-0.249
	SEM	3.977	4.046	4.071
Week 84	95% CI	(-9.5, 6.1)	(-9.4, 6.5)	(-8.2, 7.7)
	Pr >  t			0.9513
	n	22	23	
	LS Mean	-1.177	-1.917	0.739
	SEM	4.122	4.139	4.292
Week 96	95% CI	(-9.3, 6.9)	(-10.0, 6.2)	(-7.7, 9.2)
	Pr >  t			0.8633
	n	18	18	
	LS Mean	-2.069	-4.845	2.776
	SEM	4.306	4.358	4.672
Week 108	95% CI	(-10.5, 6.4)	(-13.4, 3.7)	(-6.4, 11.9)
	Pr >  t			0.5525
	n	14	14	
	LS Mean	4.357	1.702	2.654
	SEM	4.581	4.629	5.166
Week 120	95% CI	(-4.6, 13.4)	(-7.4, 10.8)	(-7.5, 12.8)
	Pr >  t			0.6075
	n	12	12	
	LS Mean	0.406	-1.613	2.019
	SEM	4.770	4.821	5.501
Week 132	95% CI	(-9.0, 9.8)	(-11.1, 7.9)	(-8.8, 12.8)
	Pr >  t			0.7136
	n	9	5	
	LS Mean	-0.073	-3.359	3.286
	SEM	5.187	6.379	7.203
Week 144	95% CI	(-10.3, 10.1)	(-15.9, 9.2)	(-10.9, 17.4)
	Pr >  t			0.6484
	n	7	4	
	LS Mean	2.162	3.539	-1.377
	SEM	5.627	6.948	8.013



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.9,13.2)	(-10.1,17.2)	(-17.1,14.3)
		Pr >  t			0.8636
	Week 156	n	4	2	
		LS Mean	9.878	1.882	7.995
		SEM	6.899	9.246	10.83
		95% CI	(-3.7,23.4)	(-16.3,20.0)	(-13.3,29.3)
		Pr >  t			0.4607
	Week 168	n	2	1	
		LS Mean	-1.867	2.166	-4.032
		SEM	9.203	12.65	15.13
		95% CI	(-19.9,16.2)	(-22.7,27.0)	(-33.7,25.7)
		Pr >  t			0.7900
Yes	Week 8	n	53	48	
		LS Mean	0.559	-0.034	0.593
		SEM	3.368	3.516	3.319
		95% CI	(-6.1, 7.2)	(-7.0, 6.9)	(-5.9, 7.1)
		Pr >  t			0.8583
	Week 16	n	45	39	
		LS Mean	-0.282	-5.995	5.713
		SEM	3.518	3.666	3.561
		95% CI	(-7.2, 6.7)	(-13.2, 1.2)	(-1.3,12.7)
		Pr >  t			0.1098
	Week 24	n	41	26	
		LS Mean	-2.976	-4.412	1.436
		SEM	3.567	3.950	3.936
		95% CI	(-10.0, 4.1)	(-12.2, 3.4)	(-6.3, 9.2)
		Pr >  t			0.7154
	Week 32	n	37	20	
		LS Mean	-0.186	-2.425	2.240
		SEM	3.655	4.219	4.236
		95% CI	(-7.4, 7.0)	(-10.7, 5.9)	(-6.1,10.6)
		Pr >  t			0.5973
	Week 40	n	31	17	
		LS Mean	-2.173	-2.495	0.321
		SEM	3.770	4.423	4.507
		95% CI	(-9.6, 5.3)	(-11.2, 6.2)	(-8.5, 9.2)
		Pr >  t			0.9432
	Week 48	n	28	15	
		LS Mean	-2.971	-1.821	-1.151
		SEM	3.835	4.564	4.706

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.5, 4.6)	(-10.8, 7.2)	(-10.4, 8.1)
		Pr >  t			0.8069
	Week 56	n	26	13	
		LS Mean	0.243	0.536	-0.293
		SEM	3.891	4.743	4.924
		95% CI	(-7.4, 7.9)	(-8.8, 9.9)	(-10.0, 9.4)
		Pr >  t			0.9526
	Week 64	n	20	11	
		LS Mean	1.392	-3.653	5.045
		SEM	4.109	4.967	5.313
		95% CI	(-6.7, 9.5)	(-13.4, 6.1)	(-5.4, 15.5)
		Pr >  t			0.3428
	Week 72	n	22	9	
		LS Mean	-0.261	-4.903	4.642
		SEM	4.029	5.271	5.537
		95% CI	(-8.2, 7.7)	(-15.3, 5.5)	(-6.2, 15.5)
		Pr >  t			0.4021
	Week 84	n	18	10	
		LS Mean	-0.155	-5.053	4.898
		SEM	4.222	5.109	5.521
		95% CI	(-8.5, 8.2)	(-15.1, 5.0)	(-5.9, 15.7)
		Pr >  t			0.3754
	Week 96	n	17	6	
		LS Mean	2.401	1.834	0.568
		SEM	4.268	6.016	6.413
		95% CI	(-6.0, 10.8)	(-10.0, 13.7)	(-12.0, 13.2)
		Pr >  t			0.9295
	Week 108	n	12	7	
		LS Mean	2.401	-8.888	11.288
		SEM	4.693	5.714	6.419
		95% CI	(-6.8, 11.6)	(-20.1, 2.3)	(-1.3, 23.9)
		Pr >  t			0.0792
	Week 120	n	16	4	
		LS Mean	-1.569	6.361	-7.930
		SEM	4.338	6.992	7.371
		95% CI	(-10.1, 7.0)	(-7.4, 20.1)	(-22.4, 6.5)
		Pr >  t			0.2825
	Week 132	n	11	3	
		LS Mean	-3.672	4.848	-8.520
		SEM	4.813	7.837	8.433

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.1, 5.8)	(-10.5,20.2)	(-25.1, 8.0)
		Pr >  t			0.3128
	Week 144	n	8	1	
		LS Mean	-8.096	1.936	-10.03
		SEM	5.294	12.71	13.28
		95% CI	(-18.5, 2.3)	(-23.0,26.9)	(-36.1,16.1)
		Pr >  t			0.4502
	Week 156	n	6	1	
		LS Mean	3.940	1.936	2.004
		SEM	5.878	12.71	13.51
		95% CI	( -7.6,15.5)	(-23.0,26.9)	(-24.5,28.5)
		Pr >  t			0.8822
	Week 168	n	2	1	
		LS Mean	-5.432	1.936	-7.369
		SEM	9.191	12.71	15.25
		95% CI	(-23.5,12.6)	(-23.0,26.9)	(-37.3,22.6)
		Pr >  t			0.6291
	Week 180	n	1	1	
		LS Mean	-11.38	1.936	-13.32
		SEM	12.60	12.71	17.51
		95% CI	(-36.1,13.4)	(-23.0,26.9)	(-47.7,21.1)
		Pr >  t			0.4473
	Week 192	n	1	1	
		LS Mean	-3.042	1.936	-4.978
		SEM	12.60	12.71	17.51
		95% CI	(-27.8,21.7)	(-23.0,26.9)	(-39.4,29.4)
		Pr >  t			0.7763

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Estrogen Receptor Status (L)	Negative	LS Mean				
		SEM				
		95% CI	( , )			
		Pr >  t				
		Week 8	n	2		
		Week 16	n	2		
		Week 24	n	1		
		Week 32	n	1		
		Week 40	n	1		
		Week 48	n	1		
		Week 56	n	1		
		Week 72	n	1		
		Week 84	n	1		
	Week 96	n	1			
	Positive	Week 8	n	140	140	
			LS Mean	-0.804	-0.040	-0.764
			SEM	2.367	2.406	2.089
			95% CI	( -5.5, 3.8)	( -4.8, 4.7)	( -4.9, 3.3)
			Pr >  t			0.7146
		Week 16	n	122	107	
		LS Mean	-1.078	-2.996	1.918	
	SEM	2.425	2.521	2.247		
	95% CI	( -5.8, 3.7)	( -8.0, 2.0)	( -2.5, 6.3)		
	Pr >  t			0.3935		
Week 24	n	104	81			
	LS Mean	-4.012	0.259	-4.271		
	SEM	2.483	2.639	2.427		
	95% CI	( -8.9, 0.9)	( -4.9, 5.4)	( -9.0, 0.5)		
	Pr >  t			0.0788		
Week 32	n	85	73			
	LS Mean	0.774	-3.119	3.893		
	SEM	2.575	2.692	2.552		
	95% CI	( -4.3, 5.8)	( -8.4, 2.2)	( -1.1, 8.9)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.1276
Week 40	n	74	62	
	LS Mean	-0.865	-2.515	1.650
	SEM	2.631	2.773	2.687
	95% CI	(-6.0, 4.3)	(-8.0, 2.9)	(-3.6, 6.9)
	Pr >  t			0.5393
Week 48	n	68	51	
	LS Mean	-4.674	-1.987	-2.687
	SEM	2.666	2.874	2.826
	95% CI	(-9.9, 0.6)	(-7.6, 3.7)	(-8.2, 2.9)
	Pr >  t			0.3419
Week 56	n	58	45	
	LS Mean	-0.377	-0.716	0.339
	SEM	2.739	2.946	2.969
	95% CI	(-5.8, 5.0)	(-6.5, 5.1)	(-5.5, 6.2)
	Pr >  t			0.9091
Week 64	n	47	42	
	LS Mean	-1.534	-3.493	1.959
	SEM	2.849	2.989	3.114
	95% CI	(-7.1, 4.1)	(-9.4, 2.4)	(-4.2, 8.1)
	Pr >  t			0.5294
Week 72	n	47	35	
	LS Mean	-1.963	-3.355	1.391
	SEM	2.851	3.111	3.232
	95% CI	(-7.6, 3.6)	(-9.5, 2.8)	(-4.9, 7.7)
	Pr >  t			0.6669
Week 84	n	39	33	
	LS Mean	-1.686	-3.818	2.132
	SEM	2.973	3.153	3.373
	95% CI	(-7.5, 4.1)	(-10.0, 2.4)	(-4.5, 8.7)
	Pr >  t			0.5274
Week 96	n	34	24	
	LS Mean	-0.850	-4.260	3.410
	SEM	3.064	3.419	3.702
	95% CI	(-6.9, 5.2)	(-11.0, 2.4)	(-3.9, 10.7)
	Pr >  t			0.3571
Week 108	n	26	21	
	LS Mean	2.486	-2.753	5.238
	SEM	3.286	3.550	3.999
	95% CI	(-4.0, 8.9)	(-9.7, 4.2)	(-2.6, 13.1)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	Pr >  t			0.1904
	n	28	16	
	LS Mean	-1.609	-0.744	-0.865
	SEM	3.218	3.856	4.225
	95% CI	(-7.9, 4.7)	(-8.3, 6.8)	(-9.2, 7.4)
Week 132	Pr >  t			0.8377
	n	20	8	
	LS Mean	-2.968	-1.185	-1.782
	SEM	3.540	4.924	5.420
	95% CI	(-9.9, 4.0)	(-10.8, 8.5)	(-12.4, 8.8)
Week 144	Pr >  t			0.7423
	n	15	5	
	LS Mean	-4.224	1.984	-6.208
	SEM	3.869	5.963	6.572
	95% CI	(-11.8, 3.4)	(-9.7, 13.7)	(-19.1, 6.7)
Week 156	Pr >  t			0.3450
	n	10	3	
	LS Mean	5.482	0.825	4.657
	SEM	4.476	7.447	8.251
	95% CI	(-3.3, 14.3)	(-13.8, 15.4)	(-11.5, 20.8)
Week 168	Pr >  t			0.5726
	n	4	2	
	LS Mean	-4.642	1.104	-5.746
	SEM	6.514	8.965	10.74
	95% CI	(-17.4, 8.1)	(-16.5, 18.7)	(-26.8, 15.3)
Week 180	Pr >  t			0.5928
	n	1	1	
	LS Mean	-11.47	1.440	-12.91
	SEM	12.43	12.44	17.37
	95% CI	(-35.8, 12.9)	(-23.0, 25.8)	(-47.0, 21.2)
Week 192	Pr >  t			0.4574
	n	1	1	
	LS Mean	-3.131	1.440	-4.572
	SEM	12.43	12.44	17.37
	95% CI	(-27.5, 21.2)	(-23.0, 25.8)	(-38.6, 29.5)
	Pr >  t			0.7924

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35			
			LS Mean	-0.624	-1.815	1.190		
			SEM	3.659	3.986	3.869		
			95% CI	(-7.9, 6.6)	(-9.7, 6.1)	(-6.5, 8.8)		
					Pr >  t			0.7588
		Week 16	n	35	22			
			LS Mean	-5.019	0.090	-5.109		
			SEM	3.818	4.528	4.419		
			95% CI	(-12.6, 2.5)	(-8.9, 9.0)	(-13.8, 3.6)		
					Pr >  t			0.2490
		Week 24	n	28	16			
			LS Mean	-5.912	-2.850	-3.062		
			SEM	3.977	4.870	4.926		
			95% CI	(-13.8, 2.0)	(-12.5, 6.8)	(-12.8, 6.6)		
					Pr >  t			0.5348
		Week 32	n	22	16			
			LS Mean	-0.871	-6.897	6.026		
			SEM	4.243	4.884	5.097		
			95% CI	(-9.2, 7.5)	(-16.5, 2.7)	(-4.0, 16.1)		
					Pr >  t			0.2382
		Week 40	n	19	12			
			LS Mean	-1.600	-5.669	4.068		
			SEM	4.387	5.238	5.553		
			95% CI	(-10.3, 7.1)	(-16.0, 4.7)	(-6.9, 15.0)		
			Pr >  t			0.4643		
Week 48	n	16	10					
	LS Mean	-12.04	-4.572	-7.471				
	SEM	4.564	5.505	5.944				
	95% CI	(-21.0, -3.0)	(-15.4, 6.3)	(-19.2, 4.2)				
			Pr >  t			0.2097		
Week 56	n	14	7					
	LS Mean	-6.374	-1.493	-4.881				
	SEM	4.724	6.116	6.636				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-15.7, 2.9)	(-13.5,10.5)	(-17.9, 8.2)
	Pr >  t			0.4625
	n	8	7	
	LS Mean	-3.061	-12.70	9.635
	SEM	5.520	6.116	7.241
Week 72	95% CI	(-13.9, 7.8)	(-24.7,-0.7)	(-4.6,23.9)
	Pr >  t			0.1842
	n	12	6	
	LS Mean	-4.862	-8.491	3.629
	SEM	4.917	6.427	7.063
Week 84	95% CI	(-14.5, 4.8)	(-21.1, 4.2)	(-10.3,17.5)
	Pr >  t			0.6077
	n	8	5	
	LS Mean	-11.37	-10.26	-1.109
	SEM	5.563	6.832	7.859
Week 96	95% CI	(-22.3,-0.4)	(-23.7, 3.2)	(-16.6,14.3)
	Pr >  t			0.8878
	n	5	5	
	LS Mean	-14.24	-3.591	-10.65
	SEM	6.525	6.832	8.567
Week 108	95% CI	(-27.1,-1.4)	(-17.0, 9.8)	(-27.5, 6.2)
	Pr >  t			0.2147
	n	7	5	
	LS Mean	-3.888	-3.591	-0.297
	SEM	5.813	6.832	8.037
Week 120	95% CI	(-15.3, 7.5)	(-17.0, 9.8)	(-16.1,15.5)
	Pr >  t			0.9705
	n	5	3	
	LS Mean	-21.74	5.293	-27.03
	SEM	6.535	8.226	9.718
Week 132	95% CI	(-34.6,-8.9)	(-10.9,21.5)	(-46.1,-7.9)
	Pr >  t			0.0057
	n	2	2	
	LS Mean	-14.38	-6.370	-8.007
	SEM	9.423	9.617	12.86
Week 144	95% CI	(-32.9, 4.2)	(-25.3,12.5)	(-33.3,17.3)
	Pr >  t			0.5340
	n	2		
	LS Mean	-10.37		
	SEM	9.430		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-28.9, 8.2)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	-0.886		
		SEM	9.441		
		95% CI	(-19.5, 17.7)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-4.889		
		SEM	12.89		
		95% CI	(-30.2, 20.5)		
		Pr >  t			
Positive	Week 8	n	98	104	
		LS Mean	-0.944	0.177	-1.121
		SEM	3.089	3.063	2.494
		95% CI	(-7.0, 5.1)	(-5.9, 6.2)	(-6.0, 3.8)
		Pr >  t			0.6533
	Week 16	n	87	84	
		LS Mean	0.381	-4.236	4.617
		SEM	3.144	3.141	2.636
		95% CI	(-5.8, 6.6)	(-10.4, 1.9)	(-0.6, 9.8)
		Pr >  t			0.0805
	Week 24	n	76	65	
		LS Mean	-3.255	0.642	-3.897
		SEM	3.204	3.256	2.813
		95% CI	(-9.6, 3.0)	(-5.8, 7.0)	(-9.4, 1.6)
		Pr >  t			0.1665
	Week 32	n	62	57	
		LS Mean	2.237	-2.472	4.708
		SEM	3.291	3.323	2.966
		95% CI	(-4.2, 8.7)	(-9.0, 4.1)	(-1.1, 10.5)
		Pr >  t			0.1129
	Week 40	n	54	50	
		LS Mean	-0.007	-2.144	2.137
		SEM	3.349	3.393	3.097
		95% CI	(-6.6, 6.6)	(-8.8, 4.5)	(-3.9, 8.2)
		Pr >  t			0.4903
	Week 48	n	52	41	
		LS Mean	-1.839	-1.774	-0.065
		SEM	3.365	3.493	3.224

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-8.5, 4.8)	(-8.6, 5.1)	(-6.4, 6.3)
	Pr >  t			0.9840
	n	44	38	
	LS Mean	1.874	-0.844	2.718
	SEM	3.442	3.536	3.352
Week 64	95% CI	(-4.9, 8.6)	(-7.8, 6.1)	(-3.9, 9.3)
	Pr >  t			0.4176
	n	39	35	
	LS Mean	-0.481	-1.981	1.500
	SEM	3.505	3.586	3.469
Week 72	95% CI	(-7.4, 6.4)	(-9.0, 5.1)	(-5.3, 8.3)
	Pr >  t			0.6656
	n	36	29	
	LS Mean	-0.645	-2.650	2.005
	SEM	3.550	3.707	3.639
Week 84	95% CI	(-7.6, 6.3)	(-9.9, 4.6)	(-5.1, 9.1)
	Pr >  t			0.5818
	n	32	28	
	LS Mean	1.264	-2.937	4.201
	SEM	3.628	3.731	3.733
Week 96	95% CI	(-5.9, 8.4)	(-10.3, 4.4)	(-3.1, 11.5)
	Pr >  t			0.2607
	n	30	19	
	LS Mean	2.255	-4.978	7.233
	SEM	3.663	4.053	4.094
Week 108	95% CI	(-4.9, 9.5)	(-12.9, 3.0)	(-0.8, 15.3)
	Pr >  t			0.0775
	n	18	16	
	LS Mean	4.121	-3.181	7.302
	SEM	4.089	4.231	4.634
Week 120	95% CI	(-3.9, 12.2)	(-11.5, 5.1)	(-1.8, 16.4)
	Pr >  t			0.1154
	n	23	13	
	LS Mean	3.356	-2.574	5.930
	SEM	3.863	4.473	4.675
Week 132	95% CI	(-4.2, 10.9)	(-11.4, 6.2)	(-3.2, 15.1)
	Pr >  t			0.2048
	n	18	6	
Week 132	LS Mean	-0.516	-0.030	-0.486
	SEM	4.090	5.752	6.056

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-8.5, 7.5)	(-11.3,11.3)	(-12.4,11.4)
	Pr >  t			0.9360
Week 144	n	13	5	
	LS Mean	-2.233	2.009	-4.242
	SEM	4.441	6.162	6.683
	95% CI	(-10.9, 6.5)	(-10.1,14.1)	(-17.4, 8.9)
	Pr >  t			0.5257
Week 156	n	8	3	
	LS Mean	7.773	0.890	6.883
	SEM	5.175	7.565	8.418
	95% CI	(-2.4,17.9)	(-14.0,15.7)	(-9.6,23.4)
	Pr >  t			0.4137
Week 168	n	3	2	
	LS Mean	-4.482	1.178	-5.660
	SEM	7.538	9.019	11.18
	95% CI	(-19.3,10.3)	(-16.5,18.9)	(-27.6,16.3)
	Pr >  t			0.6128
Week 180	n	1	1	
	LS Mean	-9.758	1.398	-11.16
	SEM	12.38	12.38	17.13
	95% CI	(-34.0,14.5)	(-22.9,25.7)	(-44.8,22.5)
	Pr >  t			0.5150
Week 192	n	1	1	
	LS Mean	-1.418	1.398	-2.816
	SEM	12.38	12.38	17.13
	95% CI	(-25.7,22.9)	(-22.9,25.7)	(-36.4,30.8)
	Pr >  t			0.8694

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60	
		LS Mean	8.149	9.138	-0.989	
	SEM	6.737	6.962	3.052		
	95% CI	(-5.2,21.5)	(-4.7,22.9)	(-7.0, 5.0)		
	Pr >  t			0.7461		
	Week 16	n	59	49		
		LS Mean	9.082	4.162	4.921	
		SEM	6.763	7.018	3.255	
		95% CI	(-4.3,22.5)	(-9.8,18.1)	(-1.5,11.3)	
	Week 24	n	54	41		
		LS Mean	4.806	9.459	-4.653	
		SEM	6.778	7.072	3.416	
		95% CI	(-8.6,18.2)	(-4.6,23.5)	(-11.4, 2.1)	
	Week 32	n	48	37		
		LS Mean	9.751	7.025	2.726	
		SEM	6.801	7.104	3.540	
		95% CI	(-3.7,23.2)	(-7.1,21.1)	(-4.2, 9.7)	
	Week 40	n	43	33		
		LS Mean	6.805	8.190	-1.385	
		SEM	6.826	7.141	3.670	
		95% CI	(-6.7,20.3)	(-6.0,22.3)	(-8.6, 5.8)	
	Week 48	n	41	28		
		LS Mean	2.581	8.655	-6.075	
		SEM	6.837	7.201	3.815	
		95% CI	(-11.0,16.1)	(-5.6,22.9)	(-13.6, 1.4)	
	Week 56	n	35	22		
		LS Mean	5.810	9.225	-3.415	
		SEM	6.879	7.310	4.099	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.8,19.4)	(-5.2,23.7)	(-11.5, 4.6)
		Pr >  t			0.4052
	Week 64	n	26	23	
		LS Mean	4.380	7.017	-2.636
		SEM	6.979	7.289	4.248
		95% CI	(-9.4,18.2)	(-7.4,21.4)	(-11.0, 5.7)
		Pr >  t			0.5351
	Week 72	n	28	18	
		LS Mean	1.343	5.136	-3.793
		SEM	6.952	7.417	4.416
		95% CI	(-12.4,15.1)	(-9.5,19.8)	(-12.5, 4.9)
		Pr >  t			0.3907
	Week 84	n	22	18	
		LS Mean	4.166	6.095	-1.929
		SEM	7.086	7.418	4.582
		95% CI	(-9.9,18.2)	(-8.6,20.8)	(-10.9, 7.1)
		Pr >  t			0.6739
	Week 96	n	21	13	
		LS Mean	4.609	4.904	-0.294
		SEM	7.069	7.636	4.963
		95% CI	(-9.4,18.6)	(-10.2,20.0)	(-10.0, 9.4)
		Pr >  t			0.9528
	Week 108	n	17	12	
		LS Mean	9.324	2.407	6.917
		SEM	7.229	7.700	5.224
		95% CI	(-5.0,23.6)	(-12.8,17.6)	(-3.3,17.2)
		Pr >  t			0.1859
	Week 120	n	18	11	
		LS Mean	4.193	5.411	-1.218
		SEM	7.147	7.774	5.288
		95% CI	(-9.9,18.3)	(-9.9,20.8)	(-11.6, 9.2)
		Pr >  t			0.8179
	Week 132	n	13	5	
		LS Mean	1.764	12.106	-10.34
		SEM	7.412	8.767	6.900
		95% CI	(-12.9,16.4)	(-5.2,29.4)	(-23.9, 3.2)
		Pr >  t			0.1343
	Week 144	n	12	3	
		LS Mean	3.807	11.535	-7.728
		SEM	7.412	9.850	8.292

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.8,18.5)	(-7.8,30.9)	(-24.0, 8.5)
		Pr >  t			0.3516
	Week 156	n	7	2	
		LS Mean	10.598	10.214	0.384
		SEM	8.052	11.04	10.13
		95% CI	(-5.3,26.5)	(-11.5,31.9)	(-19.5,20.3)
		Pr >  t			0.9698
	Week 168	n	3	1	
		LS Mean	0.673	10.856	-10.18
		SEM	9.655	14.03	14.35
		95% CI	(-18.3,19.7)	(-16.7,38.4)	(-38.3,18.0)
		Pr >  t			0.4781
	Week 180	n	1	1	
		LS Mean	-4.583	10.856	-15.44
		SEM	13.90	14.03	17.48
		95% CI	(-31.9,22.7)	(-16.7,38.4)	(-49.8,18.9)
		Pr >  t			0.3775
	Week 192	n	1	1	
		LS Mean	3.757	10.856	-7.100
		SEM	13.90	14.03	17.48
		95% CI	(-23.5,31.0)	(-16.7,38.4)	(-41.4,27.2)
		Pr >  t			0.6848
Yes	Week 8	n	73	80	
		LS Mean	-0.977	-0.942	-0.035
		SEM	3.837	3.896	2.873
		95% CI	(-8.5, 6.6)	(-8.6, 6.7)	(-5.7, 5.6)
		Pr >  t			0.9903
	Week 16	n	65	58	
		LS Mean	-2.457	-2.018	-0.440
		SEM	3.939	4.048	3.096
		95% CI	(-10.2, 5.3)	(-10.0, 6.0)	(-6.5, 5.7)
		Pr >  t			0.8872
	Week 24	n	51	40	
		LS Mean	-4.005	-0.810	-3.195
		SEM	4.020	4.251	3.434
		95% CI	(-11.9, 3.9)	(-9.2, 7.6)	(-9.9, 3.6)
		Pr >  t			0.3528
	Week 32	n	38	36	
		LS Mean	0.483	-5.172	5.655
		SEM	4.201	4.313	3.666

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.8, 8.8)	(-13.7, 3.3)	(-1.5,12.9)
		Pr >  t			0.1236
	Week 40	n	32	29	
		LS Mean	0.806	-5.308	6.115
		SEM	4.305	4.440	3.921
		95% CI	(-7.7, 9.3)	(-14.0, 3.4)	(-1.6,13.8)
		Pr >  t			0.1195
	Week 48	n	28	23	
		LS Mean	-2.477	-4.770	2.293
		SEM	4.383	4.602	4.182
		95% CI	(-11.1, 6.1)	(-13.8, 4.3)	(-5.9,10.5)
		Pr >  t			0.5836
	Week 56	n	24	23	
		LS Mean	3.294	-2.557	5.851
		SEM	4.491	4.602	4.291
		95% CI	(-5.5,12.1)	(-11.6, 6.5)	(-2.6,14.3)
		Pr >  t			0.1732
	Week 64	n	21	19	
		LS Mean	2.288	-6.206	8.494
		SEM	4.594	4.751	4.554
		95% CI	(-6.7,11.3)	(-15.5, 3.1)	(-0.4,17.4)
		Pr >  t			0.0626
	Week 72	n	20	17	
		LS Mean	5.921	-3.802	9.724
		SEM	4.635	4.845	4.697
		95% CI	(-3.2,15.0)	(-13.3, 5.7)	( 0.5,18.9)
		Pr >  t			0.0388
	Week 84	n	18	15	
		LS Mean	2.221	-5.776	7.997
		SEM	4.715	4.968	4.901
		95% CI	(-7.0,11.5)	(-15.5, 4.0)	(-1.6,17.6)
		Pr >  t			0.1032
	Week 96	n	14	11	
		LS Mean	4.056	-5.403	9.460
		SEM	4.966	5.320	5.476
		95% CI	(-5.7,13.8)	(-15.9, 5.0)	(-1.3,20.2)
		Pr >  t			0.0845
	Week 108	n	9	9	
		LS Mean	5.694	1.544	4.150
		SEM	5.516	5.593	6.229



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.1,16.5)	(-9.4,12.5)	(-8.1,16.4)
		Pr >  t			0.5055
	Week 120	n	10	5	
		LS Mean	3.248	4.890	-1.642
		SEM	5.387	6.659	7.101
		95% CI	(-7.3,13.8)	(-8.2,18.0)	(-15.6,12.3)
		Pr >  t			0.8172
	Week 132	n	7	3	
		LS Mean	4.006	-9.228	13.234
		SEM	5.921	7.969	8.704
		95% CI	(-7.6,15.6)	(-24.9, 6.4)	(-3.9,30.3)
		Pr >  t			0.1289
	Week 144	n	3	2	
		LS Mean	-5.896	-0.037	-5.859
		SEM	7.909	9.364	11.29
		95% CI	(-21.4, 9.6)	(-18.4,18.3)	(-28.0,16.3)
		Pr >  t			0.6041
	Week 156	n	3	1	
		LS Mean	12.808	-0.840	13.648
		SEM	7.920	12.66	14.14
		95% CI	(-2.7,28.4)	(-25.7,24.0)	(-14.1,41.4)
		Pr >  t			0.3348
	Week 168	n	1	1	
		LS Mean	3.346	-0.840	4.186
		SEM	12.65	12.66	17.24
		95% CI	(-21.5,28.2)	(-25.7,24.0)	(-29.7,38.0)
		Pr >  t			0.8082

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-39: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Kognitive Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Stratum 3 - Lung and/or Liver metas (L)	Week 8	n	77	73	
		LS Mean	-2.958	-2.885	-0.073
		SEM	2.927	2.943	2.638
		95% CI	(-8.7, 2.8)	(-8.7, 2.9)	(-5.3, 5.1)
		Pr >  t			0.9779
	Week 16	n	67	56	
		LS Mean	-0.313	-5.350	5.037
		SEM	2.971	3.106	2.834
		95% CI	(-6.2, 5.5)	(-11.5, 0.8)	(-0.5, 10.6)
		Pr >  t			0.0763
	Week 24	n	61	46	
		LS Mean	-1.864	-4.319	2.455
		SEM	3.024	3.199	2.986
		95% CI	(-7.8, 4.1)	(-10.6, 2.0)	(-3.4, 8.3)
		Pr >  t			0.4115
	Week 32	n	52	41	
		LS Mean	-3.783	-2.123	-1.660
		SEM	3.120	3.274	3.122
		95% CI	(-9.9, 2.4)	(-8.6, 4.3)	(-7.8, 4.5)
		Pr >  t			0.5951
Week 40	n	45	36		
	LS Mean	0.688	-0.500	1.188	
	SEM	3.186	3.362	3.265	
	95% CI	(-5.6, 7.0)	(-7.1, 6.1)	(-5.2, 7.6)	
	Pr >  t			0.7161	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	n		42	30	
	LS Mean		-6.021	-3.789	-2.232
	SEM		3.222	3.474	3.414
	95% CI		(-12.4, 0.3)	(-10.6, 3.0)	(-8.9, 4.5)
	Pr >  t				0.5135
Week 56	n		35	24	
	LS Mean		-7.238	-3.140	-4.098
	SEM		3.319	3.636	3.670
	95% CI		(-13.8,-0.7)	(-10.3, 4.0)	(-11.3, 3.1)
	Pr >  t				0.2645
Week 64	n		25	25	
	LS Mean		-0.876	-1.689	0.813
	SEM		3.536	3.606	3.842
	95% CI		(-7.8, 6.1)	(-8.8, 5.4)	(-6.7, 8.4)
	Pr >  t				0.8324
Week 72	n		27	20	
	LS Mean		-7.772	-6.099	-1.673
	SEM		3.482	3.786	3.963
	95% CI		(-14.6,-0.9)	(-13.5, 1.3)	(-9.5, 6.1)
	Pr >  t				0.6731
Week 84	n		23	19	
	LS Mean		-3.686	-2.080	-1.606
	SEM		3.613	3.833	4.114
	95% CI		(-10.8, 3.4)	(-9.6, 5.5)	(-9.7, 6.5)
	Pr >  t				0.6963
Week 96	n		20	13	
	LS Mean		-1.867	-4.906	3.039
	SEM		3.730	4.228	4.578
	95% CI		(-9.2, 5.5)	(-13.2, 3.4)	(-5.9,12.0)
	Pr >  t				0.5070
Week 108	n		17	13	
	LS Mean		-2.790	-5.592	2.802
	SEM		3.882	4.229	4.704
	95% CI		(-10.4, 4.8)	(-13.9, 2.7)	(-6.4,12.0)
	Pr >  t				0.5515
Week 120	n		17	12	
	LS Mean		-1.507	-4.935	3.429
	SEM		3.880	4.327	4.791
	95% CI		(-9.1, 6.1)	(-13.4, 3.6)	(-6.0,12.8)
	Pr >  t				0.4744

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 132	n	13	6	
		LS Mean	-4.666	-10.99	6.328
		SEM	4.172	5.427	6.004
		95% CI	(-12.9, 3.5)	(-21.6,-0.3)	(-5.5,18.1)
	Week 144	Pr >  t			0.2921
		n	11	4	
		LS Mean	-7.596	-3.376	-4.219
		SEM	4.384	6.345	6.973
	Week 156	95% CI	(-16.2, 1.0)	(-15.8, 9.1)	(-17.9, 9.5)
		Pr >  t			0.5453
		n	7	2	
		LS Mean	-1.852	-3.964	2.112
	Week 168	SEM	5.086	8.498	9.341
		95% CI	(-11.8, 8.1)	(-20.6,12.7)	(-16.2,20.4)
		Pr >  t			0.8211
		n	3	1	
Week 180	LS Mean	-7.775	-1.429	-6.346	
	SEM	7.083	11.67	13.25	
	95% CI	(-21.7, 6.1)	(-24.3,21.5)	(-32.4,19.7)	
	Pr >  t			0.6322	
Week 192	n	1	1		
	LS Mean	-45.37	-1.429	-43.94	
	SEM	11.64	11.67	16.16	
	95% CI	(-68.2, -23)	(-24.3,21.5)	(-75.7, -12)	
Week 8	Pr >  t			0.0067	
	n	1	1		
	LS Mean	-62.04	-1.429	-60.61	
	SEM	11.64	11.67	16.16	
Week 16	95% CI	(-84.9, -39)	(-24.3,21.5)	(-92.3, -29)	
	Pr >  t			0.0002	
	n	65	67		
	LS Mean	-3.508	-1.825	-1.683	
Week 16	SEM	2.932	3.009	2.510	
	95% CI	(-9.3, 2.3)	(-7.8, 4.1)	(-6.6, 3.3)	
	Pr >  t			0.5031	
	n	57	51		
Week 16	LS Mean	-2.571	-4.518	1.947	
	SEM	3.036	3.139	2.701	
	95% CI	(-8.6, 3.4)	(-10.7, 1.7)	(-3.4, 7.3)	
	Pr >  t			0.4716	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	n	44	35	
	LS Mean	-6.052	-5.585	-0.467
	SEM	3.132	3.348	3.019
	95% CI	(-12.2, 0.1)	(-12.2, 1.0)	(-6.4, 5.5)
	Pr >  t			0.8772
Week 32	n	34	32	
	LS Mean	-1.925	-3.127	1.203
	SEM	3.268	3.401	3.203
	95% CI	(-8.4, 4.5)	(-9.8, 3.6)	(-5.1, 7.5)
	Pr >  t			0.7074
Week 40	n	30	26	
	LS Mean	-2.478	-3.830	1.352
	SEM	3.337	3.520	3.399
	95% CI	(-9.0, 4.1)	(-10.8, 3.1)	(-5.3, 8.0)
	Pr >  t			0.6909
Week 48	n	27	21	
	LS Mean	-1.175	-6.839	5.664
	SEM	3.392	3.663	3.600
	95% CI	(-7.9, 5.5)	(-14.0, 0.4)	(-1.4,12.7)
	Pr >  t			0.1162
Week 56	n	24	21	
	LS Mean	1.142	-7.196	8.337
	SEM	3.464	3.662	3.670
	95% CI	(-5.7, 8.0)	(-14.4, 0.0)	( 1.1,15.5)
	Pr >  t			0.0235
Week 64	n	22	17	
	LS Mean	-3.215	-8.252	5.037
	SEM	3.522	3.825	3.885
	95% CI	(-10.1, 3.7)	(-15.8,-0.7)	(-2.6,12.7)
	Pr >  t			0.1953
Week 72	n	21	15	
	LS Mean	-0.349	-5.792	5.442
	SEM	3.556	3.933	4.021
	95% CI	(-7.3, 6.6)	(-13.5, 1.9)	(-2.5,13.3)
	Pr >  t			0.1764
Week 84	n	17	14	
	LS Mean	-3.364	-6.945	3.581
	SEM	3.723	3.995	4.220
	95% CI	(-10.7, 4.0)	(-14.8, 0.9)	(-4.7,11.9)
	Pr >  t			0.3965

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	n		15	11	
	LS Mean		-1.608	-9.937	8.330
	SEM		3.818	4.243	4.548
	95% CI		(-9.1, 5.9)	(-18.3,-1.6)	(-0.6,17.3)
	Pr >  t				0.0675
Week 108	n		9	8	
	LS Mean		-3.977	-6.274	2.297
	SEM		4.385	4.641	5.365
	95% CI		(-12.6, 4.6)	(-15.4, 2.8)	(-8.2,12.8)
	Pr >  t				0.6687
Week 120	n		11	4	
	LS Mean		-5.328	-2.235	-3.093
	SEM		4.137	5.872	6.304
	95% CI		(-13.5, 2.8)	(-13.8, 9.3)	(-15.5, 9.3)
	Pr >  t				0.6239
Week 132	n		7	2	
	LS Mean		-2.057	-8.655	6.598
	SEM		4.740	7.732	8.383
	95% CI		(-11.4, 7.3)	(-23.8, 6.5)	(-9.9,23.1)
	Pr >  t				0.4316
Week 144	n		4	1	
	LS Mean		-20.87	-4.236	-16.64
	SEM		5.741	10.53	11.50
	95% CI		(-32.1,-9.6)	(-24.9,16.4)	(-39.2, 5.9)
	Pr >  t				0.1485
Week 156	n		3	1	
	LS Mean		-3.193	-20.91	17.714
	SEM		6.468	10.53	11.86
	95% CI		(-15.9, 9.5)	(-41.6,-0.2)	(-5.6,41.0)
	Pr >  t				0.1359
Week 168	n		1	1	
	LS Mean		-16.53	-4.236	-12.30
	SEM		10.49	10.53	14.45
	95% CI		(-37.1, 4.1)	(-24.9,16.4)	(-40.7,16.1)
	Pr >  t				0.3952

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction,

and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Presence of Lung Metastases (L)	No	Week 8	n	98	84		
			LS Mean	-4.452	-1.845	-2.606	
			SEM	2.268	2.396	2.275	
			95% CI	(-8.9, 0.0)	(-6.6, 2.9)	(-7.1, 1.9)	
					Pr >  t		0.2525
		Week 16	n	86	68		
			LS Mean	-1.539	-4.657	3.118	
			SEM	2.326	2.504	2.432	
			95% CI	(-6.1, 3.0)	(-9.6, 0.3)	(-1.7, 7.9)	
					Pr >  t		0.2004
		Week 24	n	73	48		
			LS Mean	-4.360	-4.167	-0.192	
			SEM	2.398	2.707	2.699	
			95% CI	(-9.1, 0.4)	(-9.5, 1.2)	(-5.5, 5.1)	
					Pr >  t		0.9432
		Week 32	n	60	43		
			LS Mean	-4.222	-1.330	-2.892	
			SEM	2.516	2.786	2.848	
			95% CI	(-9.2, 0.7)	(-6.8, 4.1)	(-8.5, 2.7)	
					Pr >  t		0.3103
		Week 40	n	50	38		
			LS Mean	0.341	-0.142	0.483	
			SEM	2.608	2.876	3.006	
			95% CI	(-4.8, 5.5)	(-5.8, 5.5)	(-5.4, 6.4)	
					Pr >  t		0.8724
		Week 48	n	48	31		
			LS Mean	-6.193	-2.527	-3.666	
			SEM	2.632	3.018	3.163	
95% CI	(-11.4, -1.0)		(-8.5, 3.4)	(-9.9, 2.5)			
			Pr >  t		0.2467		
Week 56	n	41	25				
	LS Mean	-6.386	-3.062	-3.325			
	SEM	2.722	3.194	3.405			



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-11.7,-1.0)	(-9.3, 3.2)	(-10.0, 3.4)
	Pr >  t			0.3291
	n	30	24	
	LS Mean	-1.815	-0.509	-1.305
	SEM	2.931	3.230	3.612
Week 72	95% CI	(-7.6, 3.9)	(-6.9, 5.8)	(-8.4, 5.8)
	Pr >  t			0.7179
	n	32	19	
	LS Mean	-7.605	-3.243	-4.362
	SEM	2.884	3.454	3.776
Week 84	95% CI	(-13.3,-1.9)	(-10.0, 3.5)	(-11.8, 3.0)
	Pr >  t			0.2482
	n	26	19	
	LS Mean	-4.491	-1.574	-2.917
	SEM	3.062	3.454	3.904
Week 96	95% CI	(-10.5, 1.5)	(-8.4, 5.2)	(-10.6, 4.7)
	Pr >  t			0.4551
	n	23	14	
	LS Mean	-1.735	-4.468	2.732
	SEM	3.162	3.803	4.294
Week 108	95% CI	(-7.9, 4.5)	(-11.9, 3.0)	(-5.7,11.2)
	Pr >  t			0.5247
	n	19	13	
	LS Mean	-2.640	-3.937	1.297
	SEM	3.357	3.898	4.517
Week 120	95% CI	(-9.2, 4.0)	(-11.6, 3.7)	(-7.6,10.2)
	Pr >  t			0.7740
	n	19	11	
	LS Mean	-2.384	-4.237	1.853
	SEM	3.347	4.132	4.719
Week 132	95% CI	(-9.0, 4.2)	(-12.3, 3.9)	(-7.4,11.1)
	Pr >  t			0.6946
	n	15	5	
	LS Mean	-5.280	-11.81	6.526
	SEM	3.623	5.609	6.208
Week 144	95% CI	(-12.4, 1.8)	(-22.8,-0.8)	(-5.7,18.7)
	Pr >  t			0.2934
	n	12	3	
Week 144	LS Mean	-10.03	-2.531	-7.500
	SEM	3.904	7.009	7.640

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Yes	Week 156	95% CI	(-17.7,-2.4)	(-16.3,11.2)	(-22.5, 7.5)
		Pr >  t			0.3265
		n	7	2	
		LS Mean	-2.600	-3.279	0.679
		SEM	4.811	8.421	9.380
	Week 168	95% CI	(-12.0, 6.8)	(-19.8,13.2)	(-17.7,19.1)
		Pr >  t			0.9423
		n	3	1	
		LS Mean	-8.550	-0.720	-7.830
		SEM	6.930	11.68	13.36
	Week 180	95% CI	(-22.1, 5.0)	(-23.6,22.2)	(-34.0,18.4)
		Pr >  t			0.5579
		n	1	1	
		LS Mean	-46.33	-0.720	-45.61
		SEM	11.64	11.68	16.31
Week 192	95% CI	(-69.2, -23)	(-23.6,22.2)	(-77.6, -14)	
	Pr >  t			0.0053	
	n	1	1		
	LS Mean	-63.00	-0.720	-62.28	
	SEM	11.64	11.68	16.31	
Yes	Week 8	95% CI	(-85.8, -40)	(-23.6,22.2)	(-94.3, -30)
		Pr >  t			0.0001
		n	44	56	
		LS Mean	-2.736	-5.256	2.521
		SEM	5.111	4.886	3.195
	Week 16	95% CI	(-12.8, 7.4)	(-14.9, 4.4)	( -3.8, 8.8)
		Pr >  t			0.4314
		n	38	39	
		LS Mean	-3.111	-7.601	4.491
		SEM	5.223	5.106	3.440
	Week 24	95% CI	(-13.4, 7.2)	(-17.7, 2.5)	( -2.3,11.3)
		Pr >  t			0.1933
		n	32	33	
		LS Mean	-4.344	-7.905	3.561
		SEM	5.282	5.157	3.604
Week 32	95% CI	(-14.8, 6.1)	(-18.1, 2.3)	( -3.5,10.7)	
	Pr >  t			0.3242	
	n	26	30		
	LS Mean	-2.865	-6.412	3.546	
	SEM	5.355	5.194	3.764	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-13.4, 7.7)	(-16.7, 3.8)	(-3.9,11.0)
	Pr >  t			0.3470
	n	25	24	
	LS Mean	-4.781	-6.723	1.942
	SEM	5.373	5.277	3.900
Week 48	95% CI	(-15.4, 5.8)	(-17.1, 3.7)	(-5.7, 9.6)
	Pr >  t			0.6190
	n	21	20	
	LS Mean	-1.843	-11.11	9.269
	SEM	5.440	5.358	4.099
Week 56	95% CI	(-12.6, 8.9)	(-21.7,-0.5)	( 1.2,17.3)
	Pr >  t			0.0244
	n	18	20	
	LS Mean	-0.386	-9.789	9.403
	SEM	5.511	5.357	4.193
Week 64	95% CI	(-11.3,10.5)	(-20.4, 0.8)	( 1.2,17.6)
	Pr >  t			0.0256
	n	17	18	
	LS Mean	-4.290	-11.94	7.647
	SEM	5.541	5.410	4.296
Week 72	95% CI	(-15.2, 6.6)	(-22.6,-1.3)	(-0.8,16.1)
	Pr >  t			0.0759
	n	16	16	
	LS Mean	-0.449	-11.87	11.422
	SEM	5.575	5.472	4.416
Week 84	95% CI	(-11.4,10.5)	(-22.7,-1.1)	( 2.7,20.1)
	Pr >  t			0.0101
	n	14	14	
	LS Mean	-3.957	-10.06	6.106
	SEM	5.648	5.549	4.601
Week 96	95% CI	(-15.1, 7.2)	(-21.0, 0.9)	(-2.9,15.2)
	Pr >  t			0.1853
	n	12	10	
	LS Mean	-4.084	-13.47	9.382
	SEM	5.749	5.788	5.003
Week 108	95% CI	(-15.4, 7.2)	(-24.9,-2.1)	(-0.4,19.2)
	Pr >  t			0.0614
	n	7	8	
Week 108	LS Mean	-7.454	-11.19	3.735
	SEM	6.214	5.990	5.742

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.7, 4.8)	(-23.0, 0.6)	(-7.5,15.0)
		Pr >  t			0.5157
	Week 120	n	9	5	
		LS Mean	-6.578	-6.502	-0.076
		SEM	5.982	6.552	6.098
		95% CI	(-18.4, 5.2)	(-19.4, 6.4)	(-12.1,11.9)
		Pr >  t			0.9901
	Week 132	n	5	3	
		LS Mean	-2.264	-11.02	8.754
		SEM	6.628	7.429	7.590
		95% CI	(-15.3,10.8)	(-25.6, 3.6)	(-6.2,23.7)
		Pr >  t			0.2493
	Week 144	n	3	2	
		LS Mean	-18.99	-8.290	-10.70
		SEM	7.495	8.407	9.239
		95% CI	(-33.7,-4.3)	(-24.8, 8.2)	(-28.9, 7.4)
		Pr >  t			0.2472
	Week 156	n	3	1	
		LS Mean	-4.070	-24.63	20.555
		SEM	7.501	10.81	11.47
		95% CI	(-18.8,10.7)	(-45.9,-3.4)	(-2.0,43.1)
		Pr >  t			0.0738
	Week 168	n	1	1	
		LS Mean	-17.67	-7.955	-9.710
		SEM	10.88	10.81	13.92
		95% CI	(-39.0, 3.7)	(-29.2,13.3)	(-37.1,17.6)
		Pr >  t			0.4857

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Bone Lesions Only (L)	No	Week 8	n	104	110		
			LS Mean	-2.440	-2.379	-0.061	
			SEM	2.347	2.334	2.044	
			95% CI	(-7.1, 2.2)	(-7.0, 2.2)	(-4.1, 4.0)	
					Pr >  t		0.9763
		Week 16	n	92	83		
			LS Mean	-0.880	-5.221	4.341	
			SEM	2.406	2.465	2.198	
			95% CI	(-5.6, 3.9)	(-10.1,-0.4)	( 0.0, 8.7)	
					Pr >  t		0.0488
		Week 24	n	77	59		
			LS Mean	-3.348	-4.794	1.446	
			SEM	2.457	2.606	2.406	
			95% CI	(-8.2, 1.5)	(-9.9, 0.3)	(-3.3, 6.2)	
					Pr >  t		0.5482
		Week 32	n	57	53		
			LS Mean	-1.383	-2.137	0.754	
			SEM	2.592	2.652	2.571	
			95% CI	(-6.5, 3.7)	(-7.3, 3.1)	(-4.3, 5.8)	
					Pr >  t		0.7694
		Week 40	n	50	44		
			LS Mean	-0.764	-2.187	1.423	
			SEM	2.649	2.748	2.718	
			95% CI	(-6.0, 4.4)	(-7.6, 3.2)	(-3.9, 6.8)	
					Pr >  t		0.6007
		Week 48	n	47	37		
			LS Mean	-2.346	-5.563	3.217	
			SEM	2.676	2.840	2.837	
95% CI	(-7.6, 2.9)		(-11.1, 0.0)	(-2.4, 8.8)			
			Pr >  t		0.2571		
Week 56	n	40	32				
	LS Mean	-0.713	-5.703	4.990			
	SEM	2.754	2.925	2.994			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-6.1, 4.7)	(-11.4, 0.0)	(-0.9, 10.9)
	Pr >  t			0.0959
	n	32	27	
	LS Mean	-1.096	-5.745	4.649
	SEM	2.879	3.036	3.214
Week 72	95% CI	(-6.8, 4.6)	(-11.7, 0.2)	(-1.7, 11.0)
	Pr >  t			0.1484
	n	31	23	
	LS Mean	-0.855	-5.113	4.258
	SEM	2.900	3.154	3.344
Week 84	95% CI	(-6.6, 4.8)	(-11.3, 1.1)	(-2.3, 10.8)
	Pr >  t			0.2031
	n	27	21	
	LS Mean	-1.082	-5.296	4.214
	SEM	2.993	3.226	3.487
Week 96	95% CI	(-7.0, 4.8)	(-11.6, 1.0)	(-2.6, 11.1)
	Pr >  t			0.2271
	n	23	16	
	LS Mean	0.306	-8.478	8.784
	SEM	3.103	3.471	3.810
Week 108	95% CI	(-5.8, 6.4)	(-15.3, -1.7)	( 1.3, 16.3)
	Pr >  t			0.0213
	n	15	14	
	LS Mean	-3.666	-5.961	2.294
	SEM	3.491	3.609	4.245
Week 120	95% CI	(-10.5, 3.2)	(-13.0, 1.1)	(-6.0, 10.6)
	Pr >  t			0.5890
	n	18	8	
	LS Mean	-3.982	-1.428	-2.554
	SEM	3.312	4.345	4.765
Week 132	95% CI	(-10.5, 2.5)	(-10.0, 7.1)	(-11.9, 6.8)
	Pr >  t			0.5921
	n	12	4	
	LS Mean	-0.393	-7.551	7.158
	SEM	3.741	5.683	6.254
Week 144	95% CI	(-7.7, 6.9)	(-18.7, 3.6)	(-5.1, 19.4)
	Pr >  t			0.2527
	n	8	3	
	LS Mean	-16.80	-3.337	-13.46
	SEM	4.286	6.434	7.259

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.2,-8.4)	(-16.0, 9.3)	(-27.7, 0.8)
		Pr >  t			0.0639
	Week 156	n	5	1	
		LS Mean	-4.605	-20.00	15.394
		SEM	5.153	10.63	11.50
		95% CI	(-14.7, 5.5)	(-40.9, 0.9)	(-7.2,38.0)
		Pr >  t			0.1812
	Week 168	n	2	1	
		LS Mean	-22.78	-3.329	-19.45
		SEM	7.678	10.63	12.84
		95% CI	(-37.8,-7.7)	(-24.2,17.5)	(-44.6, 5.7)
		Pr >  t			0.1301
	Week 180	n	1		
		LS Mean	-46.01		
		SEM	10.60		
		95% CI	(-66.8, -25)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-62.68		
		SEM	10.60		
		95% CI	(-83.5, -42)		
		Pr >  t			
Yes	Week 8	n	38	30	
		LS Mean	-4.475	-2.278	-2.197
		SEM	4.478	4.817	4.034
		95% CI	(-13.4, 4.4)	(-11.9, 7.3)	(-10.2, 5.8)
		Pr >  t			0.5867
	Week 16	n	32	24	
		LS Mean	-1.681	-3.692	2.011
		SEM	4.558	4.953	4.340
		95% CI	(-10.7, 7.4)	(-13.5, 6.1)	(-6.6,10.6)
		Pr >  t			0.6437
	Week 24	n	28	22	
		LS Mean	-3.609	-4.573	0.964
		SEM	4.694	5.019	4.508
		95% CI	(-12.9, 5.7)	(-14.5, 5.4)	(-7.9, 9.9)
		Pr >  t			0.8309
	Week 32	n	29	20	
		LS Mean	-6.188	-3.123	-3.064
		SEM	4.677	5.156	4.574

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-15.5, 3.1)	(-13.3, 7.1)	(-12.1, 6.0)
		Pr >  t			0.5036
		n	25	18	
		LS Mean	-0.170	-0.656	0.486
		SEM	4.763	5.235	4.756
Week 48		95% CI	(-9.6, 9.3)	(-11.0, 9.7)	(-8.9, 9.9)
		Pr >  t			0.9186
		n	22	14	
		LS Mean	-7.673	-3.172	-4.501
		SEM	4.847	5.454	5.082
Week 56		95% CI	(-17.3, 1.9)	(-14.0, 7.6)	(-14.5, 5.5)
		Pr >  t			0.3766
		n	19	13	
		LS Mean	-10.12	-2.700	-7.417
		SEM	4.950	5.531	5.269
Week 64		95% CI	(-19.9,-0.3)	(-13.6, 8.2)	(-17.8, 3.0)
		Pr >  t			0.1603
		n	15	15	
		LS Mean	-3.731	-1.426	-2.306
		SEM	5.141	5.395	5.319
Week 72		95% CI	(-13.9, 6.4)	(-12.1, 9.2)	(-12.8, 8.2)
		Pr >  t			0.6649
		n	17	12	
		LS Mean	-11.24	-7.116	-4.124
		SEM	5.036	5.614	5.439
Week 84		95% CI	(-21.2,-1.3)	(-18.2, 4.0)	(-14.8, 6.6)
		Pr >  t			0.4489
		n	13	12	
		LS Mean	-8.248	-1.666	-6.581
		SEM	5.316	5.615	5.675
Week 96		95% CI	(-18.7, 2.3)	(-12.8, 9.4)	(-17.7, 4.6)
		Pr >  t			0.2470
		n	12	8	
		LS Mean	-5.771	-4.151	-1.620
		SEM	5.401	6.124	6.252
Week 108		95% CI	(-16.4, 4.9)	(-16.2, 7.9)	(-13.9,10.7)
		Pr >  t			0.7957
		n	11	7	
	LS Mean	-3.015	-5.510	2.495	
	SEM	5.503	6.330	6.537	



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.9, 7.8)	(-18.0, 7.0)	(-10.4,15.3)
		Pr >  t			0.7029
	Week 120	n	10	8	
		LS Mean	-1.441	-7.138	5.697
		SEM	5.617	6.126	6.439
		95% CI	(-12.5, 9.6)	(-19.2, 4.9)	( -7.0,18.4)
		Pr >  t			0.3768
	Week 132	n	8	4	
		LS Mean	-9.521	-13.31	3.793
		SEM	5.920	7.429	7.915
		95% CI	(-21.2, 2.1)	(-27.9, 1.3)	(-11.8,19.3)
		Pr >  t			0.6320
	Week 144	n	7	2	
		LS Mean	-5.527	-4.240	-1.288
		SEM	6.130	9.504	10.02
		95% CI	(-17.6, 6.5)	(-22.9,14.4)	(-21.0,18.4)
		Pr >  t			0.8978
	Week 156	n	5	2	
		LS Mean	-0.941	-4.240	3.299
		SEM	6.753	9.504	10.41
		95% CI	(-14.2,12.3)	(-22.9,14.4)	(-17.2,23.8)
		Pr >  t			0.7514
	Week 168	n	2	1	
		LS Mean	1.500	-1.658	3.158
		SEM	9.344	12.66	14.83
		95% CI	(-16.9,19.9)	(-26.5,23.2)	(-26.0,32.3)
		Pr >  t			0.8315
	Week 180	n		1	
		LS Mean		-1.658	
		SEM		12.66	
		95% CI		(-26.5,23.2)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-1.658	
		SEM		12.66	
		95% CI		(-26.5,23.2)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	-3.364	-2.528	-0.835		
			SEM	1.348	1.351	1.909		
			95% CI	(-6.0,-0.7)	(-5.2, 0.1)	(-4.6, 2.9)		
					Pr >  t			0.6617
		Week 16	n	118	104			
			LS Mean	-1.677	-4.548	2.871		
			SEM	1.408	1.481	2.043		
			95% CI	(-4.4, 1.1)	(-7.5,-1.6)	(-1.1, 6.9)		
					Pr >  t			0.1604
		Week 24	n	100	79			
			LS Mean	-3.945	-4.599	0.654		
			SEM	1.489	1.629	2.206		
			95% CI	(-6.9,-1.0)	(-7.8,-1.4)	(-3.7, 5.0)		
					Pr >  t			0.7670
		Week 32	n	84	72			
			LS Mean	-3.072	-2.420	-0.652		
			SEM	1.576	1.684	2.305		
			95% CI	(-6.2, 0.0)	(-5.7, 0.9)	(-5.2, 3.9)		
					Pr >  t			0.7774
		Week 40	n	73	62			
			LS Mean	-1.011	-1.729	0.719		
			SEM	1.652	1.770	2.419		
			95% CI	(-4.3, 2.2)	(-5.2, 1.7)	(-4.0, 5.5)		
					Pr >  t			0.7665
		Week 48	n	67	51			
			LS Mean	-4.631	-4.851	0.220		
			SEM	1.700	1.893	2.542		
95% CI	(-8.0,-1.3)		(-8.6,-1.1)	(-4.8, 5.2)				
			Pr >  t			0.9312		
Week 56	n	57	45					
	LS Mean	-4.055	-4.762	0.707				
	SEM	1.795	1.979	2.671				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.6,-0.5)	(-8.6,-0.9)	(-4.5, 5.9)
	Pr >  t			0.7913
	n	45	42	
	LS Mean	-2.158	-4.186	2.028
	SEM	1.949	2.030	2.813
Week 72	95% CI	(-6.0, 1.7)	(-8.2,-0.2)	(-3.5, 7.5)
	Pr >  t			0.4711
	n	46	35	
	LS Mean	-4.433	-5.778	1.345
	SEM	1.936	2.170	2.907
Week 84	95% CI	(-8.2,-0.6)	(-10.0,-1.5)	(-4.4, 7.0)
	Pr >  t			0.6438
	n	40	33	
	LS Mean	-3.759	-3.983	0.224
	SEM	2.035	2.219	3.010
Week 96	95% CI	(-7.8, 0.2)	(-8.3, 0.4)	(-5.7, 6.1)
	Pr >  t			0.9407
	n	34	24	
	LS Mean	-2.129	-6.953	4.824
	SEM	2.164	2.512	3.315
Week 108	95% CI	(-6.4, 2.1)	(-11.9,-2.0)	(-1.7,11.3)
	Pr >  t			0.1458
	n	26	21	
	LS Mean	-3.307	-5.759	2.452
	SEM	2.404	2.653	3.579
Week 120	95% CI	(-8.0, 1.4)	(-11.0,-0.6)	(-4.6, 9.5)
	Pr >  t			0.4934
	n	27	16	
	LS Mean	-3.430	-4.441	1.011
	SEM	2.370	2.973	3.801
Week 132	95% CI	(-8.1, 1.2)	(-10.3, 1.4)	(-6.4, 8.5)
	Pr >  t			0.7902
	n	20	8	
	LS Mean	-3.922	-10.61	6.688
	SEM	2.676	4.037	4.842
Week 144	95% CI	(-9.2, 1.3)	(-18.5,-2.7)	(-2.8,16.2)
	Pr >  t			0.1675
	n	14	5	
	LS Mean	-9.985	-3.767	-6.218
	SEM	3.118	5.029	5.916

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-16.1,-3.9)	(-13.6, 6.1)	(-17.8, 5.4)
		Pr >  t			0.2933
	Week 156	n	10	3	
		LS Mean	-2.352	-9.616	7.265
		SEM	3.623	6.412	7.364
		95% CI	(-9.5, 4.8)	(-22.2, 3.0)	(-7.2,21.7)
		Pr >  t			0.3240
	Week 168	n	4	2	
		LS Mean	-10.22	-2.437	-7.779
		SEM	5.562	7.805	9.584
		95% CI	(-21.1, 0.7)	(-17.7,12.9)	(-26.6,11.0)
		Pr >  t			0.4171
	Week 180	n	1	1	
		LS Mean	-45.85	-2.336	-43.52
		SEM	10.95	10.95	15.49
		95% CI	(-67.3, -24)	(-23.8,19.2)	(-73.9, -13)
		Pr >  t			0.0050
	Week 192	n	1	1	
		LS Mean	-62.52	-2.336	-60.19
		SEM	10.95	10.95	15.49
		95% CI	(-84.0, -41)	(-23.8,19.2)	(-90.6, -30)
		Pr >  t			0.0001
Prior use	Week 8	n	8	6	
		LS Mean	-0.761	-5.238	4.476
		SEM	3.055	3.601	4.746
		95% CI	(-7.1, 5.6)	(-12.7, 2.2)	(-5.3,14.3)
		Pr >  t			0.3551
	Week 16	n	6	3	
		LS Mean	4.247	-25.12	29.368
		SEM	3.643	5.141	6.309
		95% CI	(-3.2,11.7)	(-35.7, -15)	(16.4,42.3)
		Pr >  t			<.0001
	Week 24	n	5	2	
		LS Mean	1.490	-22.75	24.242
		SEM	3.981	6.648	7.768
		95% CI	(-6.7, 9.7)	(-36.4,-9.1)	(8.3,40.2)
		Pr >  t			0.0042
	Week 32	n	2	1	
		LS Mean	-9.236	-9.344	0.108
		SEM	6.290	9.198	11.14

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-22.1, 3.7)	(-28.2, 9.5)	(-22.7,22.9)
	Pr >  t			0.9923
Week 40	n	2		
	LS Mean	7.434		
	SEM	6.290		
	95% CI	(-5.5,20.3)		
	Pr >  t			
Week 48	n	2		
	LS Mean	7.434		
	SEM	6.290		
	95% CI	(-5.5,20.3)		
	Pr >  t			
Week 56	n	2		
	LS Mean	-0.901		
	SEM	6.290		
	95% CI	(-13.8,12.0)		
	Pr >  t			
Week 64	n	2		
	LS Mean	-0.901		
	SEM	6.290		
	95% CI	(-13.8,12.0)		
	Pr >  t			
Week 72	n	2		
	LS Mean	-9.236		
	SEM	6.290		
	95% CI	(-22.1, 3.7)		
	Pr >  t			
Week 96	n	1		
	LS Mean	6.903		
	SEM	8.596		
	95% CI	(-10.8,24.6)		
	Pr >  t			
Week 120	n	1		
	LS Mean	6.903		
	SEM	8.596		
	95% CI	(-10.8,24.6)		
	Pr >  t			
Week 144	n	1		
	LS Mean	-26.43		
	SEM	8.596		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-44.1,-8.7)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-3.102	-2.701	-0.401		
			SEM	2.133	2.175	1.915		
			95% CI	(-7.3, 1.1)	(-7.0, 1.6)	(-4.2, 3.4)		
					Pr >  t			0.8343
		Week 16	n	119	97			
			LS Mean	-1.306	-4.835	3.529		
			SEM	2.186	2.294	2.071		
			95% CI	(-5.6, 3.0)	(-9.3,-0.3)	(-0.5, 7.6)		
					Pr >  t			0.0889
		Week 24	n	100	75			
			LS Mean	-3.922	-4.876	0.954		
			SEM	2.241	2.398	2.232		
			95% CI	(-8.3, 0.5)	(-9.6,-0.2)	(-3.4, 5.3)		
					Pr >  t			0.6693
		Week 32	n	82	69			
			LS Mean	-2.868	-2.612	-0.256		
			SEM	2.323	2.440	2.336		
			95% CI	(-7.4, 1.7)	(-7.4, 2.2)	(-4.8, 4.3)		
					Pr >  t			0.9128
		Week 40	n	73	58			
			LS Mean	-0.654	-1.735	1.081		
			SEM	2.366	2.519	2.454		
			95% CI	(-5.3, 4.0)	(-6.7, 3.2)	(-3.7, 5.9)		
					Pr >  t			0.6596
		Week 48	n	66	48			
			LS Mean	-4.589	-5.204	0.615		
			SEM	2.404	2.609	2.582		
95% CI	(-9.3, 0.1)		(-10.3,-0.1)	(-4.5, 5.7)				
			Pr >  t			0.8119		
Week 56	n	56	43					
	LS Mean	-4.332	-4.568	0.236				
		SEM	2.472	2.667	2.706			



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.2, 0.5)	(-9.8, 0.7)	(-5.1, 5.5)
		Pr >  t			0.9306
	Week 64	n	45	41	
		LS Mean	-2.066	-4.085	2.019
		SEM	2.575	2.694	2.828
		95% CI	(-7.1, 3.0)	(-9.4, 1.2)	(-3.5, 7.6)
		Pr >  t			0.4755
	Week 72	n	46	34	
		LS Mean	-4.881	-5.690	0.809
		SEM	2.565	2.807	2.926
		95% CI	(-9.9, 0.2)	(-11.2, -0.2)	(-4.9, 6.5)
		Pr >  t			0.7823
	Week 84	n	37	32	
		LS Mean	-4.255	-3.829	-0.426
		SEM	2.694	2.846	3.070
		95% CI	(-9.5, 1.0)	(-9.4, 1.8)	(-6.4, 5.6)
		Pr >  t			0.8896
	Week 96	n	33	23	
		LS Mean	-2.260	-6.849	4.590
		SEM	2.762	3.095	3.362
		95% CI	(-7.7, 3.2)	(-12.9, -0.8)	(-2.0, 11.2)
		Pr >  t			0.1723
	Week 108	n	24	20	
		LS Mean	-2.457	-4.732	2.275
		SEM	3.002	3.219	3.667
		95% CI	(-8.3, 3.4)	(-11.0, 1.6)	(-4.9, 9.5)
		Pr >  t			0.5350
	Week 120	n	25	16	
		LS Mean	-2.448	-4.398	1.950
		SEM	2.966	3.444	3.841
		95% CI	(-8.3, 3.4)	(-11.2, 2.4)	(-5.6, 9.5)
		Pr >  t			0.6117
	Week 132	n	19	8	
		LS Mean	-4.518	-10.56	6.045
		SEM	3.211	4.386	4.860
		95% CI	(-10.8, 1.8)	(-19.2, -2.0)	(-3.5, 15.6)
		Pr >  t			0.2137
	Week 144	n	14	5	
		LS Mean	-10.21	-3.736	-6.472
		SEM	3.532	5.306	5.894

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.1,-3.3)	(-14.1, 6.7)	(-18.0, 5.1)
		Pr >  t			0.2723
	Week 156	n	10	3	
		LS Mean	-2.274	-9.584	7.310
		SEM	3.987	6.618	7.332
		95% CI	(-10.1, 5.5)	(-22.6, 3.4)	( -7.1,21.7)
		Pr >  t			0.3189
	Week 168	n	4	2	
		LS Mean	-10.12	-2.407	-7.715
		SEM	5.790	7.962	9.539
		95% CI	(-21.5, 1.2)	(-18.0,13.2)	(-26.4,11.0)
		Pr >  t			0.4188
	Week 180	n	1	1	
		LS Mean	-45.76	-2.314	-43.45
		SEM	11.03	11.04	15.41
		95% CI	(-67.4, -24)	(-24.0,19.3)	(-73.7, -13)
		Pr >  t			0.0049
	Week 192	n	1	1	
		LS Mean	-62.43	-2.314	-60.12
		SEM	11.03	11.04	15.41
		95% CI	(-84.1, -41)	(-24.0,19.3)	(-90.4, -30)
		Pr >  t			0.0001
Yes	Week 8	n	5	9	
		LS Mean	4.989	4.007	0.982
		SEM	5.966	4.335	7.405
		95% CI	( -7.1,17.1)	( -4.7,12.7)	(-14.0,15.9)
		Pr >  t			0.8951
	Week 16	n	5	9	
		LS Mean	8.323	-0.823	9.146
		SEM	5.966	4.359	7.452
		95% CI	( -3.8,20.4)	( -9.6, 8.0)	( -5.9,24.2)
		Pr >  t			0.2270
	Week 24	n	5	5	
		LS Mean	11.657	-0.260	11.916
		SEM	5.966	5.890	8.432
		95% CI	( -0.4,23.7)	(-12.1,11.6)	( -5.1,28.9)
		Pr >  t			0.1648
	Week 32	n	4	3	
		LS Mean	1.550	1.697	-0.147
		SEM	6.607	7.678	10.20

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.8,14.9)	(-13.7,17.1)	(-20.6,20.3)
		Pr >  t			0.9886
	Week 40	n	2	3	
		LS Mean	7.443	-2.147	9.589
		SEM	9.153	7.607	11.85
		95% CI	(-10.9,25.8)	(-17.4,13.1)	(-14.2,33.4)
		Pr >  t			0.4221
	Week 48	n	3	2	
		LS Mean	14.411	-1.630	16.041
		SEM	7.580	9.331	11.88
		95% CI	(-0.8,29.7)	(-20.4,17.1)	(-7.8,39.9)
		Pr >  t			0.1830
	Week 56	n	3	1	
		LS Mean	14.411	-3.180	17.591
		SEM	7.580	13.14	15.26
		95% CI	(-0.8,29.7)	(-29.6,23.2)	(-13.1,48.2)
		Pr >  t			0.2545
	Week 64	n	2		
		LS Mean	7.443		
		SEM	9.153		
		95% CI	(-10.9,25.8)		
		Pr >  t			
	Week 72	n	2		
		LS Mean	12.328		
		SEM	9.129		
		95% CI	(-6.0,30.7)		
		Pr >  t			
	Week 84	n	3		
		LS Mean	14.411		
		SEM	7.580		
		95% CI	(-0.8,29.7)		
		Pr >  t			
	Week 96	n	2		
		LS Mean	15.778		
		SEM	9.153		
		95% CI	(-2.6,34.2)		
		Pr >  t			
	Week 108	n	2		
		LS Mean	-1.538		
		SEM	9.193		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI		(-20.0,16.9)
		Pr >  t		
	Week 120	n	3	
		LS Mean	3.297	
		SEM	7.580	
		95% CI		(-12.0,18.5)
		Pr >  t		
	Week 132	n	1	
		LS Mean	18.576	
		SEM	12.80	
		95% CI		( -7.2,44.3)
		Pr >  t		
	Week 144	n	1	
		LS Mean	-14.75	
		SEM	12.80	
		95% CI		(-40.5,11.0)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-3.219	-4.074	0.855		
			SEM	2.468	2.570	2.439		
			95% CI	(-8.1, 1.6)	(-9.1, 1.0)	(-3.9, 5.7)		
					Pr >  t			0.7261
		Week 16	n	70	52			
			LS Mean	-1.298	-4.682	3.384		
			SEM	2.519	2.758	2.629		
			95% CI	(-6.3, 3.7)	(-10.1, 0.8)	(-1.8, 8.6)		
					Pr >  t			0.1991
		Week 24	n	61	37			
			LS Mean	-3.987	-5.141	1.154		
			SEM	2.578	2.953	2.858		
			95% CI	(-9.1, 1.1)	(-11.0, 0.7)	(-4.5, 6.8)		
					Pr >  t			0.6867
		Week 32	n	48	33			
			LS Mean	-2.946	-0.599	-2.347		
			SEM	2.695	3.019	3.016		
			95% CI	(-8.3, 2.4)	(-6.5, 5.3)	(-8.3, 3.6)		
					Pr >  t			0.4369
		Week 40	n	42	31			
			LS Mean	0.023	-0.713	0.736		
			SEM	2.756	3.057	3.109		
			95% CI	(-5.4, 5.4)	(-6.7, 5.3)	(-5.4, 6.8)		
			Pr >  t			0.8129		
Week 48	n	40	25					
	LS Mean	-3.737	-2.881	-0.856				
	SEM	2.780	3.191	3.261				
	95% CI	(-9.2, 1.7)	(-9.2, 3.4)	(-7.3, 5.6)				
			Pr >  t			0.7931		
Week 56	n	35	20					
	LS Mean	-3.140	-5.045	1.905				
	SEM	2.846	3.357	3.481				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.7, 2.5)	(-11.6, 1.6)	(-4.9, 8.7)
		Pr >  t			0.5843
	Week 64	n	29	18	
		LS Mean	-3.045	-0.867	-2.178
		SEM	2.948	3.446	3.651
		95% CI	(-8.8, 2.8)	(-7.6, 5.9)	(-9.3, 5.0)
		Pr >  t			0.5511
	Week 72	n	28	18	
		LS Mean	-6.376	-6.470	0.094
		SEM	2.970	3.444	3.667
		95% CI	(-12.2,-0.5)	(-13.2, 0.3)	(-7.1, 7.3)
		Pr >  t			0.9796
	Week 84	n	27	17	
		LS Mean	-3.546	-3.814	0.268
		SEM	3.006	3.495	3.733
		95% CI	(-9.5, 2.4)	(-10.7, 3.1)	(-7.1, 7.6)
		Pr >  t			0.9427
	Week 96	n	23	14	
		LS Mean	-0.931	-8.147	7.216
		SEM	3.109	3.676	3.988
		95% CI	(-7.0, 5.2)	(-15.4,-0.9)	(-0.6,15.0)
		Pr >  t			0.0708
	Week 108	n	19	12	
		LS Mean	-0.041	-5.935	5.894
		SEM	3.264	3.839	4.252
		95% CI	(-6.5, 6.4)	(-13.5, 1.6)	(-2.5,14.2)
		Pr >  t			0.1660
	Week 120	n	18	8	
		LS Mean	-2.814	-7.939	5.125
		SEM	3.300	4.361	4.758
		95% CI	(-9.3, 3.7)	(-16.5, 0.6)	(-4.2,14.5)
		Pr >  t			0.2817
	Week 132	n	11	4	
		LS Mean	2.547	-5.101	7.648
		SEM	3.813	5.631	6.240
		95% CI	(-4.9,10.0)	(-16.2, 6.0)	(-4.6,19.9)
		Pr >  t			0.2207
	Week 144	n	11	4	
		LS Mean	-7.555	-2.519	-5.037
		SEM	3.803	5.636	6.244

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-15.0,-0.1)	(-13.6, 8.5)	(-17.3, 7.2)	
		Pr >  t			0.4201	
	Week 156	n	5	2		
		LS Mean	4.673	-10.30	14.972	
		SEM	5.058	7.549	8.675	
		95% CI	(-5.3,14.6)	(-25.1, 4.5)	(-2.1,32.0)	
		Pr >  t			0.0848	
	Week 168	n	1	2		
		LS Mean	8.716	-1.964	10.680	
		SEM	10.28	7.549	12.46	
		95% CI	(-11.5,28.9)	(-16.8,12.9)	(-13.8,35.1)	
		Pr >  t			0.3918	
	Week 180	n		1		
		LS Mean		-1.999		
		SEM		10.35		
		95% CI		(-22.3,18.3)		
		Pr >  t				
	Week 192	n		1		
		LS Mean		-1.999		
		SEM		10.35		
		95% CI		(-22.3,18.3)		
		Pr >  t				
	=> 65 Years	Week 8	n	63	71	
			LS Mean	-3.294	-0.914	-2.380
			SEM	3.974	3.960	2.854
			95% CI	(-11.1, 4.5)	(-8.7, 6.9)	(-8.0, 3.2)
			Pr >  t			0.4050
		Week 16	n	54	55	
			LS Mean	-1.487	-5.056	3.569
			SEM	4.077	4.029	3.065
			95% CI	(-9.5, 6.6)	(-13.0, 2.9)	(-2.5, 9.6)
			Pr >  t			0.2451
	Week 24	n	44	44		
		LS Mean	-3.226	-4.466	1.240	
		SEM	4.162	4.111	3.304	
		95% CI	(-11.4, 5.0)	(-12.6, 3.6)	(-5.3, 7.7)	
		Pr >  t			0.7076	
	Week 32	n	38	40		
		LS Mean	-3.386	-3.994	0.608	
		SEM	4.260	4.184	3.445	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 40	95% CI	(-11.8, 5.0)	(-12.2, 4.3)	(-6.2, 7.4)
	Pr >  t			0.8600
	n	33	31	
	LS Mean	-1.609	-2.900	1.291
	SEM	4.333	4.339	3.685
Week 48	95% CI	(-10.1, 6.9)	(-11.4, 5.6)	(-5.9, 8.5)
	Pr >  t			0.7262
	n	29	26	
	LS Mean	-4.769	-6.880	2.111
	SEM	4.402	4.446	3.889
Week 56	95% CI	(-13.4, 3.9)	(-15.6, 1.9)	(-5.5, 9.8)
	Pr >  t			0.5874
	n	24	25	
	LS Mean	-4.939	-4.726	-0.213
	SEM	4.519	4.470	4.049
Week 64	95% CI	(-13.8, 4.0)	(-13.5, 4.1)	(-8.2, 7.7)
	Pr >  t			0.9580
	n	18	24	
	LS Mean	-0.611	-6.918	6.306
	SEM	4.733	4.499	4.319
Week 72	95% CI	(-9.9, 8.7)	(-15.8, 1.9)	(-2.2, 14.8)
	Pr >  t			0.1448
	n	20	17	
	LS Mean	-2.183	-5.136	2.953
	SEM	4.653	4.765	4.510
Week 84	95% CI	(-11.3, 7.0)	(-14.5, 4.2)	(-5.9, 11.8)
	Pr >  t			0.5129
	n	13	16	
	LS Mean	-3.505	-4.187	0.681
	SEM	5.036	4.817	4.958
Week 96	95% CI	(-13.4, 6.4)	(-13.7, 5.3)	(-9.1, 10.4)
	Pr >  t			0.8907
	n	12	10	
	LS Mean	-3.610	-5.213	1.603
	SEM	5.127	5.338	5.549
Week 108	95% CI	(-13.7, 6.5)	(-15.7, 5.3)	(-9.3, 12.5)
	Pr >  t			0.7728
	n	7	9	
Week 108	LS Mean	-11.36	-5.559	-5.798
	SEM	5.870	5.480	6.365



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.9, 0.2)	(-16.3, 5.2)	(-18.3, 6.7)
		Pr >  t			0.3626
	Week 120	n	10	8	
		LS Mean	-3.395	-1.060	-2.335
		SEM	5.361	5.654	6.057
		95% CI	(-13.9, 7.1)	(-12.2,10.0)	(-14.2, 9.6)
		Pr >  t			0.7000
	Week 132	n	9	4	
		LS Mean	-11.87	-16.04	4.169
		SEM	5.488	7.003	7.427
		95% CI	(-22.7,-1.1)	(-29.8,-2.3)	(-10.4,18.8)
		Pr >  t			0.5748
	Week 144	n	4	1	
		LS Mean	-20.35	-7.672	-12.68
		SEM	7.004	12.30	13.28
		95% CI	(-34.1,-6.6)	(-31.8,16.5)	(-38.8,13.4)
		Pr >  t			0.3401
	Week 156	n	5	1	
		LS Mean	-9.961	-7.672	-2.290
		SEM	6.505	12.30	13.02
		95% CI	(-22.7, 2.8)	(-31.8,16.5)	(-27.9,23.3)
		Pr >  t			0.8605
	Week 168	n	3		
		LS Mean	-17.80		
		SEM	7.780		
		95% CI	(-33.1,-2.5)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-47.86		
		SEM	12.30		
		95% CI	(-72.0, -24)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-64.53		
		SEM	12.30		
		95% CI	(-88.7, -40)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-3.056	-3.839	0.783		
			SEM	2.129	2.166	1.972		
			95% CI	(-7.2, 1.1)	(-8.1, 0.4)	(-3.1, 4.7)		
					Pr >  t			0.6914
		Week 16	n	111	91			
			LS Mean	-1.435	-5.855	4.420		
			SEM	2.180	2.292	2.124		
			95% CI	(-5.7, 2.9)	(-10.4,-1.4)	( 0.2, 8.6)		
					Pr >  t			0.0378
		Week 24	n	96	70			
			LS Mean	-4.065	-5.987	1.922		
			SEM	2.231	2.405	2.285		
			95% CI	(-8.5, 0.3)	(-10.7,-1.3)	(-2.6, 6.4)		
					Pr >  t			0.4005
		Week 32	n	77	61			
			LS Mean	-2.379	-3.721	1.343		
			SEM	2.326	2.472	2.423		
			95% CI	(-6.9, 2.2)	(-8.6, 1.1)	(-3.4, 6.1)		
					Pr >  t			0.5797
		Week 40	n	69	52			
			LS Mean	-0.464	-2.607	2.143		
			SEM	2.368	2.555	2.541		
			95% CI	(-5.1, 4.2)	(-7.6, 2.4)	(-2.8, 7.1)		
					Pr >  t			0.3994
		Week 48	n	62	41			
			LS Mean	-4.117	-6.308	2.190		
			SEM	2.411	2.681	2.707		
95% CI	(-8.9, 0.6)		(-11.6,-1.0)	(-3.1, 7.5)				
			Pr >  t			0.4186		
Week 56	n	53	35					
	LS Mean	-3.737	-4.531	0.794				
	SEM	2.480	2.777	2.864				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.6, 1.1)	(-10.0, 0.9)	(-4.8, 6.4)
	Pr >  t			0.7817
	n	44	33	
	LS Mean	-1.870	-4.409	2.538
	SEM	2.571	2.817	2.982
Week 72	95% CI	(-6.9, 3.2)	(-9.9, 1.1)	(-3.3, 8.4)
	Pr >  t			0.3949
	n	45	28	
	LS Mean	-5.329	-6.655	1.326
	SEM	2.560	2.932	3.082
Week 84	95% CI	(-10.4,-0.3)	(-12.4,-0.9)	(-4.7, 7.4)
	Pr >  t			0.6671
	n	39	27	
	LS Mean	-3.627	-5.249	1.622
	SEM	2.647	2.960	3.174
Week 96	95% CI	(-8.8, 1.6)	(-11.1, 0.6)	(-4.6, 7.8)
	Pr >  t			0.6095
	n	34	19	
	LS Mean	-1.753	-8.006	6.253
	SEM	2.728	3.263	3.524
Week 108	95% CI	(-7.1, 3.6)	(-14.4,-1.6)	(-0.7,13.2)
	Pr >  t			0.0763
	n	26	17	
	LS Mean	-3.209	-7.231	4.022
	SEM	2.925	3.377	3.776
Week 120	95% CI	(-8.9, 2.5)	(-13.9,-0.6)	(-3.4,11.4)
	Pr >  t			0.2870
	n	27	11	
	LS Mean	-3.838	-5.946	2.107
	SEM	2.892	3.905	4.236
Week 132	95% CI	(-9.5, 1.8)	(-13.6, 1.7)	(-6.2,10.4)
	Pr >  t			0.6189
	n	20	6	
	LS Mean	-3.850	-8.942	5.092
	SEM	3.150	4.924	5.337
Week 144	95% CI	(-10.0, 2.3)	(-18.6, 0.7)	(-5.4,15.6)
	Pr >  t			0.3401
	n	15	4	
	LS Mean	-11.20	-3.743	-7.456
	SEM	3.443	5.849	6.357

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.0,-4.4)	(-15.2, 7.7)	(-19.9, 5.0)
		Pr >  t			0.2410
	Week 156	n	10	2	
		LS Mean	-2.302	-11.61	9.311
		SEM	3.981	7.984	8.596
		95% CI	(-10.1, 5.5)	(-27.3, 4.1)	( -7.6,26.2)
		Pr >  t			0.2790
	Week 168	n	4	2	
		LS Mean	-10.15	-3.277	-6.869
		SEM	5.792	7.984	9.571
		95% CI	(-21.5, 1.2)	(-18.9,12.4)	(-25.6,11.9)
		Pr >  t			0.4731
	Week 180	n	1	1	
		LS Mean	-45.75	-3.224	-42.52
		SEM	11.04	11.07	15.45
		95% CI	(-67.4, -24)	(-24.9,18.5)	(-72.8, -12)
		Pr >  t			0.0060
	Week 192	n	1	1	
		LS Mean	-62.42	-3.224	-59.19
		SEM	11.04	11.07	15.45
		95% CI	(-84.1, -41)	(-24.9,18.5)	(-89.5, -29)
		Pr >  t			0.0001
>= 75 Years	Week 8	n	17	19	
		LS Mean	-2.868	8.091	-10.96
		SEM	3.651	3.296	4.883
		95% CI	(-10.1, 4.4)	( -1.5,14.6)	(-20.7,-1.2)
		Pr >  t			0.0276
	Week 16	n	13	16	
		LS Mean	1.368	2.589	-1.221
		SEM	4.044	3.554	5.338
		95% CI	( -6.7, 9.4)	( -4.5, 9.6)	(-11.8, 9.4)
		Pr >  t			0.8195
	Week 24	n	9	11	
		LS Mean	2.341	4.484	-2.144
		SEM	4.617	4.107	6.141
		95% CI	( -6.8,11.5)	( -3.6,12.6)	(-14.3,10.0)
		Pr >  t			0.7276
	Week 32	n	9	12	
		LS Mean	-7.644	6.870	-14.51
		SEM	4.617	3.998	6.066

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-16.8, 1.5)	(-1.0,14.8)	(-26.5,-2.5)
	Pr >  t			0.0183
	n	6	10	
	LS Mean	-1.794	5.149	-6.944
	SEM	5.366	4.248	6.804
Week 48	95% CI	(-12.4, 8.8)	(-3.3,13.6)	(-20.4, 6.5)
	Pr >  t			0.3092
	n	7	10	
	LS Mean	-3.260	4.561	-7.821
	SEM	5.070	4.266	6.587
Week 56	95% CI	(-13.3, 6.8)	(-3.9,13.0)	(-20.8, 5.2)
	Pr >  t			0.2371
	n	6	10	
	LS Mean	-3.702	-1.642	-2.060
	SEM	5.358	4.269	6.809
Week 64	95% CI	(-14.3, 6.9)	(-10.1, 6.8)	(-15.5,11.4)
	Pr >  t			0.7627
	n	3	9	
	LS Mean	-2.986	0.387	-3.373
	SEM	7.058	4.435	8.304
Week 72	95% CI	(-16.9,10.9)	(-8.4, 9.2)	(-19.8,13.0)
	Pr >  t			0.6851
	n	3	7	
	LS Mean	8.120	1.059	7.062
	SEM	7.058	4.870	8.542
Week 84	95% CI	(-5.8,22.1)	(-8.6,10.7)	(-9.8,23.9)
	Pr >  t			0.4095
	n	1	6	
	LS Mean	-3.124	4.777	-7.901
	SEM	11.50	5.160	12.58
Week 96	95% CI	(-25.8,19.6)	(-5.4,15.0)	(-32.7,16.9)
	Pr >  t			0.5307
	n	1	5	
	LS Mean	-3.124	0.637	-3.760
	SEM	11.50	5.544	12.74
Week 108	95% CI	(-25.8,19.6)	(-10.3,11.6)	(-28.9,21.4)
	Pr >  t			0.7682
	n		4	
	LS Mean		3.590	
	SEM		6.071	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.4,15.6)	
		Pr >  t		
	Week 120	n	1	5
		LS Mean	21.283	3.969
		SEM	11.53	5.544
		95% CI	(-1.5,44.1)	(-7.0,14.9)
		Pr >  t		17.315
	Week 132	n		2
		LS Mean		-11.22
		SEM		8.157
		95% CI		(-27.3, 4.9)
		Pr >  t		0.1777
	Week 144	n		1
		LS Mean		-0.283
		SEM		11.24
		95% CI		(-22.5,21.9)
		Pr >  t		
	Week 156	n		1
		LS Mean		-0.283
		SEM		11.24
		95% CI		(-22.5,21.9)
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	-3.115	-2.245	-0.870		
			SEM	4.424	4.219	3.688		
			95% CI	(-11.9, 5.7)	(-10.6, 6.2)	(-8.2, 6.4)		
					Pr >  t			0.8138
		Week 16	n	30	30			
			LS Mean	-0.996	-6.795	5.799		
			SEM	4.451	4.383	3.849		
			95% CI	(-9.9, 7.9)	(-15.5, 1.9)	(-1.8, 13.4)		
					Pr >  t			0.1343
		Week 24	n	21	26			
			LS Mean	1.146	-2.966	4.113		
			SEM	4.626	4.438	4.131		
			95% CI	(-8.0, 10.3)	(-11.8, 5.8)	(-4.0, 12.3)		
					Pr >  t			0.3209
		Week 32	n	19	24			
			LS Mean	-1.223	-2.999	1.777		
			SEM	4.679	4.481	4.239		
			95% CI	(-10.5, 8.1)	(-11.9, 5.9)	(-6.6, 10.1)		
					Pr >  t			0.6756
		Week 40	n	16	19			
			LS Mean	-5.041	-2.108	-2.933		
			SEM	4.786	4.649	4.505		
			95% CI	(-14.5, 4.4)	(-11.3, 7.1)	(-11.8, 5.9)		
			Pr >  t			0.5157		
Week 48	n	16	18					
	LS Mean	-6.084	-7.715	1.631				
	SEM	4.786	4.681	4.539				
	95% CI	(-15.6, 3.4)	(-17.0, 1.6)	(-7.3, 10.6)				
			Pr >  t			0.7197		
Week 56	n	12	14					
	LS Mean	-4.553	-3.596	-0.957				
	SEM	4.995	4.853	4.944				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.4, 5.3)	(-13.2, 6.0)	(-10.7, 8.8)
		Pr >  t			0.8467
	Week 64	n	12	11	
		LS Mean	1.004	-8.015	9.019
		SEM	4.995	5.055	5.142
		95% CI	(-8.9,10.9)	(-18.0, 2.0)	(-1.1,19.1)
		Pr >  t			0.0805
	Week 72	n	10	9	
		LS Mean	-5.498	-8.440	2.942
		SEM	5.154	5.250	5.490
		95% CI	(-15.7, 4.7)	(-18.8, 1.9)	(-7.9,13.7)
		Pr >  t			0.5924
	Week 84	n	8	8	
		LS Mean	-0.662	-9.010	8.349
		SEM	5.424	5.385	5.837
		95% CI	(-11.4,10.1)	(-19.6, 1.6)	(-3.1,19.8)
		Pr >  t			0.1536
	Week 96	n	6	6	
		LS Mean	-1.107	-9.418	8.311
		SEM	5.788	5.758	6.505
		95% CI	(-12.5,10.3)	(-20.8, 1.9)	(-4.5,21.1)
		Pr >  t			0.2022
	Week 108	n	4	5	
		LS Mean	-7.051	-7.596	0.545
		SEM	6.451	6.039	7.330
		95% CI	(-19.8, 5.7)	(-19.5, 4.3)	(-13.9,15.0)
		Pr >  t			0.9408
	Week 120	n	4	4	
		LS Mean	-7.053	-8.693	1.640
		SEM	6.451	6.435	7.659
		95% CI	(-19.8, 5.7)	(-21.4, 4.0)	(-13.4,16.7)
		Pr >  t			0.8306
	Week 132	n	3	2	
		LS Mean	-3.361	-20.19	16.833
		SEM	7.045	8.077	9.513
		95% CI	(-17.2,10.5)	(-36.1,-4.3)	(-1.9,35.5)
		Pr >  t			0.0776
	Week 144	n	3	1	
		LS Mean	-20.03	-9.446	-10.58
		SEM	7.045	10.64	11.76

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-33.9,-6.2)	(-30.4,11.5)	(-33.7,12.6)
		Pr >  t			0.3690
	Week 156	n	2	1	
		LS Mean	-15.71	-9.446	-6.260
		SEM	8.095	10.64	12.42
		95% CI	(-31.6, 0.2)	(-30.4,11.5)	(-30.7,18.2)
		Pr >  t			0.6145
	Week 168	n	1		
		LS Mean	-2.403		
		SEM	10.64		
		95% CI	(-23.3,18.5)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	-8.132	-3.762	-4.370
		SEM	7.257	7.007	4.474
		95% CI	(-22.6, 6.4)	(-17.7,10.2)	(-13.3, 4.6)
		Pr >  t			0.3323
	Week 16	n	15	14	
		LS Mean	-5.322	-4.135	-1.187
		SEM	7.311	6.586	4.776
		95% CI	(-19.9, 9.3)	(-17.3, 9.0)	(-10.7, 8.3)
		Pr >  t			0.8044
	Week 24	n	12	11	
		LS Mean	-2.161	-8.720	6.560
		SEM	7.464	7.246	5.182
		95% CI	(-17.0,12.7)	(-23.1, 5.7)	(-3.7,16.9)
		Pr >  t			0.2089
	Week 32	n	8	9	
		LS Mean	-4.415	-5.433	1.019
		SEM	7.792	7.410	5.856
		95% CI	(-19.9,11.1)	(-20.2, 9.3)	(-10.6,12.6)
		Pr >  t			0.8622
	Week 40	n	6	7	
		LS Mean	0.952	-5.415	6.367
		SEM	8.099	7.634	6.487
		95% CI	(-15.1,17.0)	(-20.6, 9.7)	(-6.5,19.2)
		Pr >  t			0.3283
	Week 48	n	4	6	
		LS Mean	-1.532	-6.213	4.681
		SEM	8.622	7.799	7.299

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 56	95% CI	(-18.6,15.6)	(-21.7, 9.3)	(-9.7,19.1)	
	Pr >  t			0.5224	
	n	4	6		
	LS Mean	-9.465	-7.799	-1.666	
	SEM	8.626	7.810	7.320	
Week 64	95% CI	(-26.6, 7.6)	(-23.3, 7.7)	(-16.1,12.8)	
	Pr >  t			0.8203	
	n	4	4		
	LS Mean	-6.375	-5.693	-0.682	
	SEM	8.636	8.350	7.875	
Week 72	95% CI	(-23.5,10.8)	(-22.2,10.8)	(-16.2,14.9)	
	Pr >  t			0.9311	
	n	4	4		
	LS Mean	-2.208	-5.693	3.485	
	SEM	8.636	8.350	7.875	
Week 84	95% CI	(-19.3,14.9)	(-22.2,10.8)	(-12.1,19.1)	
	Pr >  t			0.6587	
	n	4	4		
	LS Mean	-5.697	-5.693	-0.004	
	SEM	8.622	8.350	7.876	
Week 96	95% CI	(-22.8,11.4)	(-22.2,10.8)	(-15.6,15.6)	
	Pr >  t			0.9996	
	n	3	2		
	LS Mean	-13.23	-2.399	-10.83	
	SEM	9.116	9.753	9.805	
Week 108	95% CI	(-31.3, 4.8)	(-21.7,16.9)	(-30.2, 8.6)	
	Pr >  t			0.2713	
	n	3	3		
	LS Mean	-24.34	-0.024	-24.31	
	SEM	9.116	8.845	8.912	
Week 120	95% CI	(-42.4,-6.3)	(-17.5,17.5)	(-41.9,-6.7)	
	Pr >  t			0.0072	
	n	2	1		
	LS Mean	-7.502	-0.216	-7.286	
	SEM	10.01	12.05	12.78	
Week 132	95% CI	(-27.3,12.3)	(-24.0,23.6)	(-32.6,18.0)	
	Pr >  t			0.5697	
	n	2	1		
	LS Mean	-40.70	-16.89	-23.81	
	SEM	10.00	12.05	12.79	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-60.5, -21)	(-40.7, 6.9)	(-49.1, 1.5)
		Pr >  t			0.0649
	Week 156	n	1		
		LS Mean	-6.702		
		SEM	12.29		
		95% CI	(-31.0, 17.6)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-23.37		
		SEM	12.29		
		95% CI	(-47.7, 0.9)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	-2.922	-3.162	0.240
		SEM	2.569	2.706	2.414
		95% CI	(-8.0, 2.1)	(-8.5, 2.2)	(-4.5, 5.0)
		Pr >  t			0.9209
	Week 16	n	79	61	
		LS Mean	-1.292	-4.991	3.699
		SEM	2.653	2.916	2.659
		95% CI	(-6.5, 3.9)	(-10.7, 0.7)	(-1.5, 8.9)
		Pr >  t			0.1649
	Week 24	n	71	43	
		LS Mean	-5.623	-5.859	0.236
		SEM	2.704	3.093	2.896
		95% CI	(-10.9, -0.3)	(-11.9, 0.2)	(-5.5, 5.9)
		Pr >  t			0.9351
	Week 32	n	59	39	
		LS Mean	-3.960	-2.277	-1.683
		SEM	2.812	3.166	3.029
		95% CI	(-9.5, 1.6)	(-8.5, 3.9)	(-7.6, 4.3)
		Pr >  t			0.5787
	Week 40	n	52	35	
		LS Mean	0.163	-2.115	2.278
		SEM	2.870	3.233	3.152
		95% CI	(-5.5, 5.8)	(-8.5, 4.2)	(-3.9, 8.5)
		Pr >  t			0.4701
	Week 48	n	48	26	
		LS Mean	-3.972	-3.544	-0.429
		SEM	2.908	3.438	3.394

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 56	95% CI	(-9.7, 1.7)	(-10.3, 3.2)	(-7.1, 6.2)
	Pr >  t			0.8996
	n	42	24	
	LS Mean	-3.812	-5.630	1.817
	SEM	2.974	3.501	3.517
Week 64	95% CI	(-9.7, 2.0)	(-12.5, 1.2)	(-5.1, 8.7)
	Pr >  t			0.6055
	n	30	26	
	LS Mean	-3.138	-3.659	0.521
	SEM	3.176	3.440	3.633
Week 72	95% CI	(-9.4, 3.1)	(-10.4, 3.1)	(-6.6, 7.7)
	Pr >  t			0.8861
	n	34	21	
	LS Mean	-4.969	-6.291	1.322
	SEM	3.096	3.612	3.730
Week 84	95% CI	(-11.1, 1.1)	(-13.4, 0.8)	(-6.0, 8.6)
	Pr >  t			0.7231
	n	28	20	
	LS Mean	-4.448	-3.185	-1.262
	SEM	3.231	3.654	3.877
Week 96	95% CI	(-10.8, 1.9)	(-10.4, 4.0)	(-8.9, 6.3)
	Pr >  t			0.7448
	n	26	15	
	LS Mean	-1.121	-6.182	5.062
	SEM	3.279	3.941	4.192
Week 108	95% CI	(-7.6, 5.3)	(-13.9, 1.6)	(-3.2, 13.3)
	Pr >  t			0.2275
	n	19	12	
	LS Mean	0.319	-7.162	7.481
	SEM	3.556	4.208	4.644
Week 120	95% CI	(-6.7, 7.3)	(-15.4, 1.1)	(-1.6, 16.6)
	Pr >  t			0.1075
	n	22	10	
	LS Mean	-2.121	-5.238	3.117
	SEM	3.417	4.456	4.777
Week 132	95% CI	(-8.8, 4.6)	(-14.0, 3.5)	(-6.3, 12.5)
	Pr >  t			0.5142
	n	15	4	
	LS Mean	0.424	-5.371	5.795
	SEM	3.798	6.252	6.689

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.0, 7.9)	(-17.6, 6.9)	(-7.3,18.9)
		Pr >  t			0.3865
	Week 144	n	12	4	
		LS Mean	-8.586	-2.768	-5.818
		SEM	4.059	6.257	6.852
		95% CI	(-16.6,-0.6)	(-15.0, 9.5)	(-19.3, 7.6)
		Pr >  t			0.3960
	Week 156	n	7	2	
		LS Mean	1.532	-10.57	12.104
		SEM	4.915	8.424	9.293
		95% CI	(-8.1,11.2)	(-27.1, 6.0)	(-6.1,30.3)
		Pr >  t			0.1931
	Week 168	n	2	2	
		LS Mean	-10.66	-2.236	-8.420
		SEM	8.335	8.424	11.48
		95% CI	(-27.0, 5.7)	(-18.8,14.3)	(-30.9,14.1)
		Pr >  t			0.4633
	Week 180	n	1	1	
		LS Mean	-45.15	-2.164	-42.99
		SEM	11.54	11.59	16.08
		95% CI	(-67.8, -23)	(-24.9,20.6)	(-74.6, -11)
		Pr >  t			0.0077
	Week 192	n	1	1	
		LS Mean	-61.82	-2.164	-59.66
		SEM	11.54	11.59	16.08
		95% CI	(-84.5, -39)	(-24.9,20.6)	(-91.2, -28)
		Pr >  t			0.0002

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	-1.576	-2.490	0.914		
			SEM	4.395	4.168	3.733		
			95% CI	(-10.3, 7.2)	(-10.8, 5.8)	(-6.5, 8.3)		
					Pr >  t			0.8071
		Week 16	n	28	29			
			LS Mean	0.137	-7.211	7.348		
			SEM	4.426	4.342	3.906		
			95% CI	(-8.7, 8.9)	(-15.8, 1.4)	(-0.4, 15.1)		
					Pr >  t			0.0622
		Week 24	n	21	25			
			LS Mean	2.180	-3.237	5.417		
			SEM	4.573	4.402	4.155		
			95% CI	(-6.9, 11.3)	(-12.0, 5.5)	(-2.8, 13.6)		
					Pr >  t			0.1942
		Week 32	n	19	23			
			LS Mean	-0.188	-3.285	3.097		
			SEM	4.626	4.450	4.265		
			95% CI	(-9.4, 9.0)	(-12.1, 5.5)	(-5.3, 11.5)		
					Pr >  t			0.4688
		Week 40	n	16	18			
			LS Mean	-4.007	-2.352	-1.655		
			SEM	4.733	4.633	4.545		
			95% CI	(-13.4, 5.4)	(-11.5, 6.8)	(-10.6, 7.3)		
					Pr >  t			0.7161
		Week 48	n	16	17			
			LS Mean	-5.050	-8.288	3.238		
			SEM	4.733	4.670	4.582		
95% CI	(-14.4, 4.3)		(-17.5, 1.0)	(-5.8, 12.3)				
			Pr >  t			0.4806		
Week 56	n	12	14					
	LS Mean	-3.513	-3.962	0.449				
	SEM	4.945	4.805	4.947				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.3, 6.3)	(-13.5, 5.5)	(-9.3,10.2)
		Pr >  t			0.9278
	Week 64	n	12	11	
		LS Mean	2.043	-8.393	10.436
		SEM	4.945	5.009	5.145
		95% CI	(-7.7,11.8)	(-18.3, 1.5)	( 0.3,20.6)
		Pr >  t			0.0435
	Week 72	n	10	8	
		LS Mean	-4.455	-9.393	4.938
		SEM	5.105	5.342	5.623
		95% CI	(-14.6, 5.6)	(-19.9, 1.1)	(-6.1,16.0)
		Pr >  t			0.3806
	Week 84	n	8	8	
		LS Mean	0.382	-9.392	9.774
		SEM	5.377	5.342	5.840
		95% CI	(-10.2,11.0)	(-19.9, 1.2)	(-1.7,21.3)
		Pr >  t			0.0952
	Week 96	n	6	6	
		LS Mean	-0.063	-9.802	9.740
		SEM	5.743	5.718	6.507
		95% CI	(-11.4,11.3)	(-21.1, 1.5)	(-3.1,22.5)
		Pr >  t			0.1353
	Week 108	n	4	5	
		LS Mean	-6.013	-7.984	1.971
		SEM	6.409	6.000	7.329
		95% CI	(-18.6, 6.6)	(-19.8, 3.8)	(-12.4,16.4)
		Pr >  t			0.7881
	Week 120	n	4	4	
		LS Mean	-6.015	-9.078	3.063
		SEM	6.409	6.397	7.658
		95% CI	(-18.6, 6.6)	(-21.7, 3.5)	(-12.0,18.1)
		Pr >  t			0.6894
	Week 132	n	3	2	
		LS Mean	-2.328	-20.58	18.256
		SEM	7.005	8.043	9.508
		95% CI	(-16.1,11.5)	(-36.4,-4.8)	(-0.4,37.0)
		Pr >  t			0.0556
	Week 144	n	3	1	
		LS Mean	-18.99	-9.806	-9.188
		SEM	7.005	10.61	11.75



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Europe	Week 156	95% CI	(-32.8,-5.2)	(-30.7,11.1)	(-32.3,13.9)
		Pr >  t			0.4349
		n	2	1	
	Week 168	LS Mean	-14.68	-9.806	-4.871
		SEM	8.059	10.61	12.41
		95% CI	(-30.5, 1.2)	(-30.7,11.1)	(-29.3,19.5)
	Week 8	Pr >  t			0.6949
		n	1		
		LS Mean	-1.336		
	Week 16	SEM	10.61		
		95% CI	(-22.2,19.5)		
		Pr >  t			
	Week 24	n	66	68	
		LS Mean	-8.485	-9.431	0.946
		SEM	5.335	5.331	2.878
	Week 32	95% CI	(-19.0, 2.1)	(-20.0, 1.1)	(-4.7, 6.6)
		Pr >  t			0.7425
		n	58	48	
	Week 40	LS Mean	-5.743	-11.27	5.528
		SEM	5.364	5.419	3.158
		95% CI	(-16.4, 4.9)	(-22.0,-0.6)	(-0.7,11.7)
	Week 48	Pr >  t			0.0810
		n	51	36	
		LS Mean	-12.27	-12.24	-0.025
Week 8	SEM	5.398	5.513	3.410	
	95% CI	(-22.9,-1.6)	(-23.1,-1.3)	(-6.7, 6.7)	
	Pr >  t			0.9940	
Week 16	n	43	30		
	LS Mean	-9.531	-7.192	-2.338	
	SEM	5.495	5.645	3.625	
Week 24	95% CI	(-20.4, 1.3)	(-18.3, 4.0)	(-9.5, 4.8)	
	Pr >  t			0.5192	
	n	37	25		
Week 32	LS Mean	-4.545	-6.395	1.850	
	SEM	5.547	5.735	3.840	
	95% CI	(-15.5, 6.4)	(-17.7, 4.9)	(-5.7, 9.4)	
Week 40	Pr >  t			0.6301	
	n	33	21		
	LS Mean	-11.50	-9.635	-1.865	
Week 48	SEM	5.591	5.834	4.046	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-22.5,-0.5)	(-21.1, 1.9)	(-9.8, 6.1)
	Pr >  t			0.6449
	n	29	20	
	LS Mean	-9.602	-11.36	1.753
	SEM	5.644	5.865	4.164
Week 64	95% CI	(-20.7, 1.5)	(-22.9, 0.2)	(-6.4, 9.9)
	Pr >  t			0.6739
	n	23	20	
	LS Mean	-7.806	-9.563	1.758
	SEM	5.755	5.866	4.316
Week 72	95% CI	(-19.2, 3.6)	(-21.1, 2.0)	(-6.7,10.2)
	Pr >  t			0.6839
	n	25	19	
	LS Mean	-8.472	-12.30	3.827
	SEM	5.715	5.897	4.303
Week 84	95% CI	(-19.8, 2.8)	(-23.9,-0.7)	(-4.6,12.3)
	Pr >  t			0.3742
	n	22	17	
	LS Mean	-11.21	-9.513	-1.700
	SEM	5.780	5.971	4.490
Week 96	95% CI	(-22.6, 0.2)	(-21.3, 2.3)	(-10.5, 7.1)
	Pr >  t			0.7050
	n	20	13	
	LS Mean	-8.241	-11.13	2.891
	SEM	5.836	6.182	4.834
Week 108	95% CI	(-19.8, 3.3)	(-23.3, 1.0)	(-6.6,12.4)
	Pr >  t			0.5499
	n	15	11	
	LS Mean	-9.662	-12.19	2.531
	SEM	6.035	6.340	5.264
Week 120	95% CI	(-21.6, 2.2)	(-24.7, 0.3)	(-7.8,12.9)
	Pr >  t			0.6307
	n	16	8	
	LS Mean	-4.594	-9.978	5.383
	SEM	5.990	6.707	5.651
Week 132	95% CI	(-16.4, 7.2)	(-23.2, 3.2)	(-5.7,16.5)
	Pr >  t			0.3411
	n	12	3	
	LS Mean	-8.375	-8.252	-0.122
	SEM	6.222	8.600	7.986

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-20.6, 3.9)	(-25.1, 8.6)	(-15.8,15.6)
		Pr >  t			0.9878
	Week 144	n	7	4	
		LS Mean	-11.37	-8.276	-3.095
		SEM	6.852	7.903	7.778
		95% CI	(-24.8, 2.1)	(-23.8, 7.3)	(-18.4,12.2)
		Pr >  t			0.6908
	Week 156	n	5	2	
		LS Mean	0.709	-16.04	16.747
		SEM	7.407	9.849	10.15
		95% CI	(-13.8,15.3)	(-35.4, 3.3)	( -3.2,36.7)
		Pr >  t			0.0993
	Week 168	n	2	2	
		LS Mean	-9.216	-7.704	-1.513
		SEM	9.815	9.849	12.02
		95% CI	(-28.5,10.1)	(-27.0,11.6)	(-25.1,22.1)
		Pr >  t			0.8999
	Week 180	n		1	
		LS Mean		-7.598	
		SEM		12.87	
		95% CI		(-32.9,17.7)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-7.598	
		SEM		12.87	
		95% CI		(-32.9,17.7)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	7.054	5.774	1.280
		SEM	3.649	3.629	5.236
		95% CI	( -0.3,14.4)	( -1.5,13.0)	( -9.2,11.8)
		Pr >  t			0.8078
	Week 16	n	13	12	
		LS Mean	4.453	5.562	-1.109
		SEM	3.721	3.750	5.364
		95% CI	( -3.0,11.9)	( -1.9,13.1)	(-11.9, 9.6)
		Pr >  t			0.8369
	Week 24	n	12	10	
		LS Mean	9.701	2.375	7.326
		SEM	3.813	3.972	5.567

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	( 2.1,17.3)	( -5.5,10.3)	( -3.8,18.5)
	Pr >  t			0.1931
Week 32	n	9	10	
	LS Mean	4.100	5.707	-1.606
	SEM	4.178	3.972	5.824
	95% CI	( -4.2,12.4)	( -2.2,13.6)	(-13.2,10.0)
	Pr >  t			0.7835
Week 40	n	7	10	
	LS Mean	3.207	5.707	-2.500
	SEM	4.525	3.972	6.075
	95% CI	( -5.8,12.2)	( -2.2,13.6)	(-14.6, 9.6)
	Pr >  t			0.6819
Week 48	n	7	7	
	LS Mean	0.825	3.027	-2.202
	SEM	4.525	4.453	6.388
	95% CI	( -8.2, 9.8)	( -5.8,11.9)	(-14.9,10.5)
	Pr >  t			0.7312
Week 56	n	6	7	
	LS Mean	2.787	-0.289	3.075
	SEM	4.772	4.458	6.583
	95% CI	( -6.7,12.3)	( -9.1, 8.6)	(-10.0,16.1)
	Pr >  t			0.6414
Week 64	n	4	7	
	LS Mean	-2.404	3.419	-5.823
	SEM	5.496	4.444	7.090
	95% CI	(-13.3, 8.5)	( -5.4,12.2)	(-19.9, 8.2)
	Pr >  t			0.4133
Week 72	n	4	4	
	LS Mean	-2.404	3.220	-5.623
	SEM	5.496	5.441	7.758
	95% CI	(-13.3, 8.5)	( -7.5,14.0)	(-21.0, 9.7)
	Pr >  t			0.4699
Week 84	n	4	5	
	LS Mean	1.889	5.796	-3.907
	SEM	5.503	5.003	7.472
	95% CI	( -9.0,12.8)	( -4.1,15.7)	(-18.7,10.9)
	Pr >  t			0.6020
Week 96	n	3	2	
	LS Mean	4.368	-0.973	5.341
	SEM	6.145	7.197	9.486

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
North America	Week 108	95% CI	(-7.8,16.5)	(-15.2,13.2)	(-13.4,24.1)
		Pr >  t			0.5743
		n	2	3	
	Week 120	LS Mean	15.721	4.818	10.903
		SEM	7.248	6.107	9.507
		95% CI	( 1.4,30.0)	(-7.3,16.9)	(-7.9,29.7)
	Week 120	Pr >  t			0.2533
		n	2	2	
		LS Mean	-3.863	0.547	-4.410
	Week 132	SEM	7.261	7.211	10.26
		95% CI	(-18.2,10.5)	(-13.7,14.8)	(-24.7,15.9)
		Pr >  t			0.6678
	Week 132	n	1	2	
		LS Mean	2.888	-7.788	10.676
		SEM	9.872	7.211	12.25
	Week 8	95% CI	(-16.6,22.4)	(-22.0, 6.5)	(-13.5,34.9)
		Pr >  t			0.3848
		n	16	19	
	Week 8	LS Mean	-0.530	6.221	-6.751
		SEM	4.228	4.194	5.105
		95% CI	(-9.0, 7.9)	(-2.2,14.6)	(-16.9, 3.4)
	Week 16	Pr >  t			0.1904
		n	12	14	
		LS Mean	0.940	0.312	0.628
Week 16	SEM	4.622	4.595	5.643	
	95% CI	(-8.3,10.2)	(-8.8, 9.5)	(-10.6,11.8)	
	Pr >  t			0.9117	
Week 24	n	12	8		
	LS Mean	2.223	-0.487	2.710	
	SEM	4.617	5.449	6.327	
Week 24	95% CI	(-7.0,11.4)	(-11.3,10.3)	(-9.8,15.3)	
	Pr >  t			0.6693	
	n	9	7		
Week 32	LS Mean	3.738	-3.586	7.324	
	SEM	5.025	5.653	6.777	
	95% CI	(-6.2,13.7)	(-14.8, 7.6)	(-6.1,20.7)	
Week 32	Pr >  t			0.2821	
	n	9	7		
	LS Mean	3.096	-3.585	6.682	
Week 40	SEM	5.029	5.653	6.807	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-6.9,13.1)	(-14.8, 7.6)	(-6.8,20.2)
	Pr >  t			0.3284
	n	8	5	
	LS Mean	7.704	1.021	6.683
	SEM	5.200	6.271	7.444
Week 56	95% CI	(-2.6,18.0)	(-11.4,13.4)	(-8.0,21.4)
	Pr >  t			0.3710
	n	7	3	
	LS Mean	-0.558	0.190	-0.748
	SEM	5.398	7.455	8.602
Week 64	95% CI	(-11.3,10.1)	(-14.6,14.9)	(-17.8,16.3)
	Pr >  t			0.9308
	n	5	3	
	LS Mean	-2.415	5.747	-8.162
	SEM	6.012	7.455	8.993
Week 72	95% CI	(-14.3, 9.5)	(-9.0,20.5)	(-25.9, 9.6)
	Pr >  t			0.3657
	n	5	3	
	LS Mean	-8.273	4.217	-12.49
	SEM	5.995	7.442	8.959
Week 84	95% CI	(-20.1, 3.6)	(-10.5,18.9)	(-30.2, 5.2)
	Pr >  t			0.1655
	n	2	2	
	LS Mean	5.836	5.583	0.254
	SEM	8.494	8.672	11.65
Week 96	95% CI	(-11.0,22.6)	(-11.6,22.7)	(-22.8,23.3)
	Pr >  t			0.9827
	n	3	2	
	LS Mean	0.966	-11.08	12.048
	SEM	7.170	8.672	10.77
Week 108	95% CI	(-13.2,15.1)	(-28.2, 6.1)	(-9.3,33.3)
	Pr >  t			0.2653
	n	1	2	
	LS Mean	-4.960	-2.752	-2.207
	SEM	11.39	8.672	13.90
Week 120	95% CI	(-27.5,17.6)	(-19.9,14.4)	(-29.7,25.3)
	Pr >  t			0.8741
	n	3	2	
	LS Mean	-10.15	5.583	-15.73
	SEM	7.170	8.672	10.77

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-24.3, 4.0)	(-11.6,22.7)	(-37.0, 5.6)
		Pr >  t			0.1465
	Week 132	n	1	1	
		LS Mean	-14.50	-6.587	-7.916
		SEM	11.37	11.52	15.85
		95% CI	(-37.0, 8.0)	(-29.4,16.2)	(-39.3,23.4)
		Pr >  t			0.6183
	Week 144	n	2		
		LS Mean	-29.41		
		SEM	8.402		
		95% CI	(-46.0, -13)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	-14.50		
		SEM	11.37		
		95% CI	(-37.0, 8.0)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-31.17		
		SEM	11.37		
		95% CI	(-53.7,-8.7)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	-47.83		
		SEM	11.37		
		95% CI	(-70.3, -25)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-64.50		
		SEM	11.37		
		95% CI	(-87.0, -42)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	-5.270	1.872	-7.142
		SEM	3.089	4.837	5.406
		95% CI	(-11.5, 0.9)	( -7.8,11.6)	(-18.0, 3.7)
		Pr >  t			0.1918
	Week 16	n	13	4	
		LS Mean	-3.332	7.081	-10.41
		SEM	3.357	5.595	6.014

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-10.1, 3.4)	(-4.1,18.3)	(-22.4, 1.6)
	Pr >  t			0.0884
	n	9	2	
	LS Mean	-7.359	0.418	-7.777
	SEM	3.848	7.441	7.904
Week 32	95% CI	(-15.0, 0.3)	(-14.4,15.2)	(-23.5, 8.0)
	Pr >  t			0.3283
	n	6	3	
	LS Mean	-5.425	1.997	-7.423
	SEM	4.578	6.288	7.200
Week 40	95% CI	(-14.5, 3.7)	(-10.5,14.5)	(-21.8, 6.9)
	Pr >  t			0.3061
	n	6	2	
	LS Mean	6.534	5.661	0.873
	SEM	4.647	7.441	8.245
Week 48	95% CI	(-2.7,15.8)	(-9.2,20.5)	(-15.5,17.3)
	Pr >  t			0.9159
	n	5	1	
	LS Mean	5.358	5.156	0.202
	SEM	4.968	10.16	10.95
Week 56	95% CI	(-4.5,15.2)	(-15.1,25.4)	(-21.6,22.0)
	Pr >  t			0.9853
	n	5	1	
	LS Mean	2.026	5.156	-3.130
	SEM	4.968	10.16	10.95
Week 64	95% CI	(-7.9,11.9)	(-15.1,25.4)	(-24.9,18.7)
	Pr >  t			0.7757
	n	3	1	
	LS Mean	5.391	5.156	0.235
	SEM	6.058	10.16	11.48
Week 72	95% CI	(-6.7,17.4)	(-15.1,25.4)	(-22.6,23.1)
	Pr >  t			0.9837
	n	4	1	
	LS Mean	4.391	5.156	-0.765
	SEM	5.432	10.16	11.17
Week 84	95% CI	(-6.4,15.2)	(-15.1,25.4)	(-23.0,21.5)
	Pr >  t			0.9456
	n	4	1	
	LS Mean	4.391	5.156	-0.765
	SEM	5.432	10.16	11.17



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-6.4,15.2)	(-15.1,25.4)	(-23.0,21.5)
	Pr >  t			0.9456
	n	3	1	
	LS Mean	5.391	5.156	0.235
	SEM	6.058	10.16	11.48
Week 108	95% CI	(-6.7,17.4)	(-15.1,25.4)	(-22.6,23.1)
	Pr >  t			0.9837
	n	4		
	LS Mean	4.391		
	SEM	5.432		
Week 120	95% CI	(-6.4,15.2)		
	Pr >  t			
	n	3		
	LS Mean	-0.165		
	SEM	6.058		
Week 132	95% CI	(-12.2,11.9)		
	Pr >  t			
	n	3		
	LS Mean	-0.165		
	SEM	6.058		
Week 144	95% CI	(-12.2,11.9)		
	Pr >  t			
	n	3		
	LS Mean	2.886		
	SEM	6.085		
Week 156	95% CI	(-9.2,15.0)		
	Pr >  t			
	n	2		
	LS Mean	0.834		
	SEM	7.163		
	95% CI	(-13.4,15.1)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	-2.314	0.041	-2.355		
			SEM	5.580	6.521	6.615		
					95% CI	(-13.6, 9.0)	(-13.2,13.3)	(-15.7,11.0)
					Pr >  t			0.7237
				Week 16	n	17	10	
					LS Mean	-3.029	-5.285	2.256
					SEM	5.821	7.140	7.245
					95% CI	(-14.8, 8.7)	(-19.6, 9.1)	(-12.3,16.8)
					Pr >  t			0.7567
				Week 24	n	9	5	
					LS Mean	-1.941	-14.26	12.322
					SEM	6.346	8.074	8.653
					95% CI	(-14.7,10.8)	(-30.4, 1.8)	( -4.9,29.5)
					Pr >  t			0.1580
				Week 32	n	8	4	
					LS Mean	-5.652	-3.629	-2.023
					SEM	6.478	8.485	9.157
					95% CI	(-18.6, 7.3)	(-20.5,13.3)	(-20.2,16.1)
					Pr >  t			0.8256
				Week 40	n	5	4	
					LS Mean	2.999	0.539	2.460
					SEM	7.111	8.485	9.673
					95% CI	(-11.2,17.2)	(-16.3,17.4)	(-16.7,21.6)
			Pr >  t			0.7998		
		Week 48	n	5	3			
			LS Mean	-0.335	-3.660	3.325		
			SEM	7.111	9.061	10.18		
			95% CI	(-14.5,13.8)	(-21.7,14.3)	(-16.9,23.5)		
			Pr >  t			0.7447		
		Week 56	n	4	3			
			LS Mean	-4.286	-14.77	10.487		
			SEM	7.487	9.061	10.47		

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-19.2,10.6)	(-32.8, 3.2)	(-10.3,31.2)
		Pr >  t			0.3188
		n	4	3	
		LS Mean	-0.119	-3.660	3.542
		SEM	7.487	9.061	10.47
Week 72		95% CI	(-15.0,14.8)	(-21.7,14.3)	(-17.2,24.3)
		Pr >  t			0.7358
		n	4	3	
		LS Mean	-4.286	-3.660	-0.626
		SEM	7.487	9.061	10.47
Week 84		95% CI	(-19.2,10.6)	(-21.7,14.3)	(-21.4,20.1)
		Pr >  t			0.9524
		n	2	3	
		LS Mean	2.764	-3.660	6.425
		SEM	9.248	9.061	11.73
Week 96		95% CI	(-15.6,21.1)	(-21.7,14.3)	(-16.8,29.7)
		Pr >  t			0.5848
		n	1	3	
		LS Mean	5.170	-20.33	25.497
		SEM	11.81	9.061	13.96
Week 108		95% CI	(-18.2,28.6)	(-38.3,-2.3)	(-2.2,53.2)
		Pr >  t			0.0707
		n		2	
		LS Mean		-20.55	
		SEM		10.03	
Week 120		95% CI		(-40.4,-0.7)	
		Pr >  t			
		n	1	1	
		LS Mean	5.170	3.971	1.199
		SEM	11.81	12.49	16.40
Week 132		95% CI	(-18.2,28.6)	(-20.8,28.7)	(-31.3,33.7)
		Pr >  t			0.9419
		n		1	
		LS Mean		-12.70	
		SEM		12.49	
Week 144		95% CI		(-37.4,12.0)	
		Pr >  t			
		n	1		
		LS Mean	-28.16		
		SEM	11.81		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-51.6,-4.7)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-2.562	-1.720	-0.842
		SEM	2.507	2.493	2.111
		95% CI	(-7.5, 2.4)	(-6.6, 3.2)	(-5.0, 3.3)
		Pr >  t			0.6901
	Week 16	n	83	81	
		LS Mean	-0.433	-3.684	3.251
		SEM	2.572	2.614	2.291
		95% CI	(-5.5, 4.6)	(-8.8, 1.5)	(-1.2, 7.8)
		Pr >  t			0.1565
	Week 24	n	75	62	
		LS Mean	-2.569	-2.360	-0.210
		SEM	2.622	2.737	2.454
		95% CI	(-7.7, 2.6)	(-7.7, 3.0)	(-5.0, 4.6)
		Pr >  t			0.9319
	Week 32	n	59	56	
		LS Mean	-4.092	-1.465	-2.627
		SEM	2.752	2.780	2.604
		95% CI	(-9.5, 1.3)	(-6.9, 4.0)	(-7.7, 2.5)
		Pr >  t			0.3135
	Week 40	n	52	48	
		LS Mean	-0.005	-2.156	2.151
		SEM	2.807	2.863	2.737
		95% CI	(-5.5, 5.5)	(-7.8, 3.5)	(-3.2, 7.5)
		Pr >  t			0.4322
	Week 48	n	47	37	
		LS Mean	-5.473	-3.682	-1.791
		SEM	2.854	3.001	2.926
		95% CI	(-11.1, 0.1)	(-9.6, 2.2)	(-7.5, 4.0)
		Pr >  t			0.5407
	Week 56	n	41	31	
		LS Mean	-4.615	-3.482	-1.132
		SEM	2.923	3.111	3.106
		95% CI	(-10.4, 1.1)	(-9.6, 2.6)	(-7.2, 5.0)
		Pr >  t			0.7156
	Week 64	n	32	28	
		LS Mean	-2.690	-3.823	1.133
		SEM	3.067	3.183	3.310

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-8.7, 3.3)	(-10.1, 2.4)	(-5.4, 7.6)	
	Pr >  t			0.7322	
	n	29	22		
	LS Mean	-6.275	-5.180	-1.095	
	SEM	3.134	3.369	3.549	
Week 84	95% CI	(-12.4,-0.1)	(-11.8, 1.4)	(-8.1, 5.9)	
	Pr >  t			0.7577	
	n	26	21		
	LS Mean	-2.897	-2.927	0.031	
	SEM	3.211	3.409	3.654	
Week 96	95% CI	(-9.2, 3.4)	(-9.6, 3.8)	(-7.1, 7.2)	
	Pr >  t			0.9933	
	n	23	14		
	LS Mean	-1.143	-3.057	1.914	
	SEM	3.306	3.817	4.114	
Week 108	95% CI	(-7.6, 5.3)	(-10.5, 4.4)	(-6.2,10.0)	
	Pr >  t			0.6418	
	n	18	13		
	LS Mean	-5.738	-3.116	-2.622	
	SEM	3.526	3.904	4.370	
Week 120	95% CI	(-12.7, 1.2)	(-10.8, 4.5)	(-11.2, 6.0)	
	Pr >  t			0.5487	
	n	19	10		
	LS Mean	-4.628	-4.076	-0.553	
	SEM	3.475	4.252	4.645	
Week 132	95% CI	(-11.5, 2.2)	(-12.4, 4.3)	(-9.7, 8.6)	
	Pr >  t			0.9053	
	n	13	4		
	LS Mean	-6.565	-9.486	2.921	
	SEM	3.876	6.028	6.542	
Week 144	95% CI	(-14.2, 1.0)	(-21.3, 2.3)	(-9.9,15.8)	
	Pr >  t			0.6553	
	n	8	1		
	LS Mean	-12.25	-0.417	-11.83	
	SEM	4.569	11.30	11.83	
Week 156	95% CI	(-21.2,-3.3)	(-22.6,21.7)	(-35.0,11.4)	
	Pr >  t			0.3175	
	n	5	1		
	LS Mean	-2.994	-0.417	-2.577	
	SEM	5.477	11.30	12.21	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-13.7, 7.8)	(-22.6,21.7)	(-26.5,21.4)
		Pr >  t			0.8329
		n	3	1	
	Week 180	LS Mean	-13.68	-0.417	-13.27
		SEM	6.789	11.30	12.85
		95% CI	(-27.0,-0.4)	(-22.6,21.7)	(-38.5,11.9)
	Week 180	Pr >  t			0.3021
		n	1	1	
		LS Mean	-46.51	-0.417	-46.09
	Week 192	SEM	11.25	11.30	15.67
		95% CI	(-68.6, -24)	(-22.6,21.7)	(-76.8, -15)
		Pr >  t			0.0033
	Week 192	n	1	1	
		LS Mean	-63.18	-0.417	-62.76
		SEM	11.25	11.30	15.67
	Week 8	95% CI	(-85.3, -41)	(-22.6,21.7)	(-93.5, -32)
		Pr >  t			<.0001
		n	17	16	
	Week 8	LS Mean	-0.638	-6.791	6.153
		SEM	3.927	3.987	5.464
		95% CI	( -8.5, 7.2)	(-14.7, 1.2)	( -4.7,17.0)
	Week 16	Pr >  t			0.2637
		n	18	14	
		LS Mean	0.035	-5.500	5.536
	Week 16	SEM	3.855	4.158	5.583
		95% CI	( -7.7, 7.7)	(-13.8, 2.8)	( -5.6,16.6)
		Pr >  t			0.3245
	Week 24	n	16	13	
LS Mean		-5.531	-8.246	2.715	
SEM		4.007	4.249	5.750	
Week 24	95% CI	(-13.5, 2.4)	(-16.7, 0.2)	( -8.7,14.1)	
	Pr >  t			0.6380	
	n	15	13		
Week 32	LS Mean	5.439	-3.333	8.772	
	SEM	4.063	4.260	5.801	
	95% CI	( -2.6,13.5)	(-11.8, 5.1)	( -2.8,20.3)	
Week 32	Pr >  t			0.1340	
	n	14	10		
	LS Mean	0.985	2.591	-1.606	
Week 40	SEM	4.166	4.595	6.122	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	95% CI	(-7.3, 9.3)	(-6.5, 11.7)	(-13.7, 10.5)	
	Pr >  t			0.7936	
	n	14	11		
	LS Mean	2.177	-7.087	9.264	
	SEM	4.166	4.475	6.032	
Week 56	95% CI	(-6.1, 10.5)	(-16.0, 1.8)	(-2.7, 21.2)	
	Pr >  t			0.1277	
	n	11	11		
	LS Mean	2.644	-4.057	6.702	
	SEM	4.442	4.475	6.231	
Week 64	95% CI	(-6.2, 11.5)	(-12.9, 4.8)	(-5.6, 19.0)	
	Pr >  t			0.2845	
	n	8	11		
	LS Mean	1.923	-4.057	5.980	
	SEM	4.868	4.475	6.548	
Week 72	95% CI	(-7.7, 11.5)	(-12.9, 4.8)	(-7.0, 18.9)	
	Pr >  t			0.3628	
	n	11	10		
	LS Mean	2.644	-6.936	9.580	
	SEM	4.442	4.601	6.323	
Week 84	95% CI	(-6.2, 11.5)	(-16.1, 2.2)	(-2.9, 22.1)	
	Pr >  t			0.1325	
	n	9	9		
	LS Mean	-3.603	-5.688	2.085	
	SEM	4.695	4.746	6.612	
Week 96	95% CI	(-12.9, 5.7)	(-15.1, 3.7)	(-11.0, 15.2)	
	Pr >  t			0.7530	
	n	8	7		
	LS Mean	-0.832	-8.462	7.630	
	SEM	4.870	5.128	7.015	
Week 108	95% CI	(-10.5, 8.8)	(-18.6, 1.7)	(-6.2, 21.5)	
	Pr >  t			0.2785	
	n	7	6		
	LS Mean	6.851	-5.384	12.236	
	SEM	5.087	5.406	7.367	
Week 120	95% CI	(-3.2, 16.9)	(-16.1, 5.3)	(-2.3, 26.8)	
	Pr >  t			0.0986	
	n	6	5		
	LS Mean	3.952	-5.587	9.539	
	SEM	5.360	5.770	7.814	



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132		95% CI	(-6.6,14.5)	(-17.0, 5.8)	(-5.9,25.0)
		Pr >  t			0.2237
		n	5	3	
		LS Mean	6.574	-11.21	17.780
		SEM	5.715	6.990	8.981
Week 144		95% CI	(-4.7,17.8)	(-25.0, 2.6)	( 0.1,35.5)
		Pr >  t			0.0489
		n	5	4	
		LS Mean	-3.426	-5.085	1.659
		SEM	5.715	6.254	8.420
Week 156		95% CI	(-14.7, 7.8)	(-17.4, 7.2)	(-14.9,18.3)
		Pr >  t			0.8440
		n	4	2	
		LS Mean	3.161	-14.35	17.509
		SEM	6.205	8.268	10.30
Week 168		95% CI	(-9.1,15.4)	(-30.6, 1.9)	(-2.8,37.8)
		Pr >  t			0.0903
		n	1	1	
		LS Mean	3.545	-3.590	7.135
		SEM	11.23	11.27	15.89
		95% CI	(-18.6,25.7)	(-25.8,18.6)	(-24.1,38.4)
		Pr >  t			0.6537

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73	
			LS Mean	-0.852	-2.450	1.598
		SEM	7.218	7.400	2.684	
		95% CI	(-15.1,13.4)	(-17.1,12.2)	(-3.7, 6.9)	
		Pr >  t			0.5522	
		Week 16	n	69	55	
			LS Mean	-0.195	-4.966	4.771
			SEM	7.225	7.454	2.851
			95% CI	(-14.5,14.1)	(-19.7, 9.8)	(-0.8,10.4)
			Pr >  t			0.0952
		Week 24	n	54	46	
			LS Mean	-3.845	-5.123	1.278
			SEM	7.248	7.487	3.040
			95% CI	(-18.2,10.5)	(-19.9, 9.7)	(-4.7, 7.3)
			Pr >  t			0.6744
		Week 32	n	49	41	
			LS Mean	0.376	-2.813	3.190
			SEM	7.312	7.510	3.140
			95% CI	(-14.1,14.8)	(-17.6,12.0)	(-3.0, 9.4)
			Pr >  t			0.3104
		Week 40	n	40	33	
			LS Mean	2.282	-1.112	3.394
			SEM	7.353	7.560	3.347
			95% CI	(-12.2,16.8)	(-16.0,13.8)	(-3.2,10.0)
			Pr >  t			0.3110
		Week 48	n	38	28	
			LS Mean	-0.829	-4.856	4.027
			SEM	7.363	7.604	3.470
95% CI	(-15.4,13.7)		(-19.9,10.2)	(-2.8,10.8)		
Pr >  t				0.2464		
Week 56	n	32	28			
	LS Mean	-0.494	-4.476	3.982		
	SEM	7.405	7.604	3.557		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-15.1,14.1)	(-19.5,10.5)	(-3.0,11.0)
	Pr >  t			0.2633
	n	23	26	
	LS Mean	-0.020	-2.764	2.744
	SEM	7.503	7.627	3.798
Week 72	95% CI	(-14.8,14.8)	(-17.8,12.3)	(-4.7,10.2)
	Pr >  t			0.4702
	n	27	25	
	LS Mean	-1.291	-4.609	3.319
	SEM	7.452	7.638	3.722
Week 84	95% CI	(-16.0,13.4)	(-19.7,10.5)	(-4.0,10.6)
	Pr >  t			0.3730
	n	23	22	
	LS Mean	-4.567	-4.697	0.130
	SEM	7.502	7.680	3.905
Week 96	95% CI	(-19.4,10.2)	(-19.9,10.5)	(-7.5, 7.8)
	Pr >  t			0.9735
	n	20	16	
	LS Mean	-0.483	-5.832	5.349
	SEM	7.553	7.808	4.242
Week 108	95% CI	(-15.4,14.4)	(-21.2, 9.6)	(-3.0,13.7)
	Pr >  t			0.2077
	n	20	14	
	LS Mean	1.172	-4.830	6.002
	SEM	7.553	7.874	4.364
Week 120	95% CI	(-13.7,16.1)	(-20.4,10.7)	(-2.6,14.6)
	Pr >  t			0.1694
	n	17	11	
	LS Mean	0.740	-3.462	4.202
	SEM	7.619	8.014	4.722
Week 132	95% CI	(-14.3,15.8)	(-19.3,12.3)	(-5.1,13.5)
	Pr >  t			0.3738
	n	13	6	
	LS Mean	2.909	-9.587	12.496
	SEM	7.755	8.533	5.741
Week 144	95% CI	(-12.4,18.2)	(-26.4, 7.2)	( 1.2,23.8)
	Pr >  t			0.0298
	n	10	5	
	LS Mean	-4.800	-3.398	-1.402
	SEM	7.921	8.757	6.278

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-20.4,10.8)	(-20.6,13.8)	(-13.7,10.9)
		Pr >  t			0.8234
	Week 156	n	7	3	
		LS Mean	2.648	-9.213	11.861
		SEM	8.222	9.580	7.704
		95% CI	(-13.5,18.8)	(-28.0, 9.6)	( -3.3,27.0)
		Pr >  t			0.1240
	Week 168	n	3	2	
		LS Mean	-0.409	-2.075	1.666
		SEM	9.441	10.52	9.989
		95% CI	(-19.0,18.2)	(-22.7,18.6)	(-17.9,21.3)
		Pr >  t			0.8676
	Week 180	n		1	
		LS Mean		-2.015	
		SEM		12.92	
		95% CI		(-27.4,23.3)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-2.015	
		SEM		12.92	
		95% CI		(-27.4,23.3)	
		Pr >  t			
Second Line	Week 8	n	66	67	
		LS Mean	-4.553	-1.177	-3.376
		SEM	2.254	2.259	2.492
		95% CI	( -9.0,-0.1)	( -5.6, 3.3)	( -8.3, 1.5)
		Pr >  t			0.1764
	Week 16	n	54	52	
		LS Mean	-1.329	-3.622	2.293
		SEM	2.389	2.454	2.732
		95% CI	( -6.0, 3.4)	( -8.5, 1.2)	( -3.1, 7.7)
		Pr >  t			0.4020
	Week 24	n	49	35	
		LS Mean	-2.006	-3.167	1.161
		SEM	2.463	2.736	3.031
		95% CI	( -6.9, 2.8)	( -8.5, 2.2)	( -4.8, 7.1)
		Pr >  t			0.7018
	Week 32	n	36	32	
		LS Mean	-5.741	-0.788	-4.953
		SEM	2.683	2.816	3.258

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-11.0,-0.5)	(-6.3, 4.7)	(-11.4, 1.4)
	Pr >  t			0.1291
Week 40	n	33	29	
	LS Mean	-2.923	-1.453	-1.470
	SEM	2.747	2.912	3.380
	95% CI	(-8.3, 2.5)	(-7.2, 4.3)	(-8.1, 5.2)
	Pr >  t			0.6639
Week 48	n	29	23	
	LS Mean	-7.342	-3.822	-3.520
	SEM	2.845	3.110	3.631
	95% CI	(-12.9,-1.7)	(-9.9, 2.3)	(-10.7, 3.6)
	Pr >  t			0.3327
Week 56	n	25	17	
	LS Mean	-7.662	-4.302	-3.359
	SEM	2.964	3.417	3.992
	95% CI	(-13.5,-1.8)	(-11.0, 2.4)	(-11.2, 4.5)
	Pr >  t			0.4003
Week 64	n	22	16	
	LS Mean	-3.323	-5.576	2.253
	SEM	3.078	3.488	4.137
	95% CI	(-9.4, 2.7)	(-12.4, 1.3)	(-5.9,10.4)
	Pr >  t			0.5862
Week 72	n	20	10	
	LS Mean	-7.690	-7.650	-0.040
	SEM	3.169	4.121	4.747
	95% CI	(-13.9,-1.5)	(-15.7, 0.4)	(-9.4, 9.3)
	Pr >  t			0.9932
Week 84	n	16	11	
	LS Mean	-0.301	-1.657	1.355
	SEM	3.426	3.978	4.791
	95% CI	(-7.0, 6.4)	(-9.5, 6.2)	(-8.1,10.8)
	Pr >  t			0.7774
Week 96	n	15	8	
	LS Mean	-1.920	-8.239	6.319
	SEM	3.494	4.486	5.272
	95% CI	(-8.8, 4.9)	(-17.0, 0.6)	(-4.0,16.7)
	Pr >  t			0.2311
Week 108	n	6	7	
	LS Mean	-10.91	-6.384	-4.522
	SEM	4.977	4.730	6.522

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-20.7,-1.1)	(-15.7, 2.9)	(-17.3, 8.3)
	Pr >  t			0.4884
Week 120	n	11	5	
	LS Mean	-6.886	-5.495	-1.391
	SEM	3.911	5.434	6.349
	95% CI	(-14.6, 0.8)	(-16.2, 5.2)	(-13.9,11.1)
	Pr >  t			0.8267
Week 132	n	7	2	
	LS Mean	-13.50	-12.08	-1.414
	SEM	4.670	8.179	9.172
	95% CI	(-22.7,-4.3)	(-28.1, 4.0)	(-19.4,16.6)
	Pr >  t			0.8775
Week 144	n	5		
	LS Mean	-20.82		
	SEM	5.361		
	95% CI	(-31.3, -10)		
	Pr >  t			
Week 156	n	3		
	LS Mean	-9.798		
	SEM	6.743		
	95% CI	(-23.0, 3.4)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-33.46		
	SEM	11.32		
	95% CI	(-55.7, -11)		
	Pr >  t			
Week 180	n	1		
	LS Mean	-50.12		
	SEM	11.32		
	95% CI	(-72.3, -28)		
	Pr >  t			
Week 192	n	1		
	LS Mean	-66.79		
	SEM	11.32		
	95% CI	(-89.0, -45)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-6.326	-4.554	-1.772		
			SEM	3.485	3.400	2.611		
			95% CI	(-13.2, 0.5)	(-11.3, 2.2)	(-6.9, 3.4)		
					Pr >  t			0.4978
		Week 16	n	60	51			
			LS Mean	-3.045	-8.869	5.823		
			SEM	3.551	3.575	2.781		
			95% CI	(-10.0, 4.0)	(-15.9, -1.8)	( 0.4, 11.3)		
					Pr >  t			0.0370
		Week 24	n	51	42			
			LS Mean	-6.151	-7.890	1.739		
			SEM	3.604	3.651	2.956		
			95% CI	(-13.3, 1.0)	(-15.1, -0.7)	(-4.1, 7.6)		
					Pr >  t			0.5568
		Week 32	n	46	36			
			LS Mean	-4.710	-6.249	1.539		
			SEM	3.668	3.753	3.096		
			95% CI	(-11.9, 2.5)	(-13.6, 1.1)	(-4.5, 7.6)		
					Pr >  t			0.6195
		Week 40	n	40	33			
			LS Mean	-2.626	-5.152	2.526		
			SEM	3.729	3.798	3.219		
			95% CI	(-10.0, 4.7)	(-12.6, 2.3)	(-3.8, 8.9)		
			Pr >  t			0.4330		
Week 48	n	37	28					
	LS Mean	-5.463	-9.455	3.991				
	SEM	3.762	3.887	3.361				
	95% CI	(-12.9, 1.9)	(-17.1, -1.8)	(-2.6, 10.6)				
			Pr >  t			0.2356		
Week 56	n	33	23					
	LS Mean	-6.118	-4.829	-1.290				
	SEM	3.817	4.008	3.561				



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-13.6, 1.4)	(-12.7, 3.1)	(-8.3, 5.7)
		Pr >  t			0.7173
		n	26	20	
		LS Mean	-4.894	-7.173	2.279
		SEM	3.942	4.107	3.803
Week 72		95% CI	(-12.7, 2.9)	(-15.2, 0.9)	(-5.2, 9.7)
		Pr >  t			0.5492
		n	28	17	
		LS Mean	-6.717	-8.047	1.329
		SEM	3.901	4.233	3.897
Week 84		95% CI	(-14.4, 1.0)	(-16.4, 0.3)	(-6.3, 9.0)
		Pr >  t			0.7331
		n	23	17	
		LS Mean	-4.937	-4.462	-0.475
		SEM	4.017	4.235	4.016
Week 96		95% CI	(-12.8, 3.0)	(-12.8, 3.9)	(-8.4, 7.4)
		Pr >  t			0.9058
		n	23	11	
		LS Mean	-1.994	-7.996	6.002
		SEM	4.018	4.662	4.465
Week 108		95% CI	(-9.9, 5.9)	(-17.2, 1.2)	(-2.8, 14.8)
		Pr >  t			0.1793
		n	15	13	
		LS Mean	-1.272	-6.447	5.176
		SEM	4.346	4.483	4.586
Week 120		95% CI	(-9.8, 7.3)	(-15.3, 2.4)	(-3.8, 14.2)
		Pr >  t			0.2594
		n	16	9	
		LS Mean	-7.419	-7.350	-0.069
		SEM	4.292	4.912	4.958
Week 132		95% CI	(-15.9, 1.0)	(-17.0, 2.3)	(-9.8, 9.7)
		Pr >  t			0.9888
		n	14	5	
		LS Mean	-11.37	-8.939	-2.431
		SEM	4.409	5.871	5.996
Week 144		95% CI	(-20.0, -2.7)	(-20.5, 2.6)	(-14.2, 9.3)
		Pr >  t			0.6852
		n	8	3	
		LS Mean	-8.000	-5.177	-2.823
		SEM	5.067	7.069	7.593

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-18.0, 2.0)	(-19.1, 8.7)	(-17.7,12.1)
		Pr >  t			0.7102
		n	7	2	
	Week 168	LS Mean	-6.393	-12.94	6.544
		SEM	5.266	8.323	8.890
		95% CI	(-16.7, 3.9)	(-29.3, 3.4)	(-10.9,24.0)
	Week 180	Pr >  t			0.4619
		n	4	2	
		LS Mean	-12.44	-4.602	-7.836
	Week 192	SEM	6.333	8.323	9.561
		95% CI	(-24.9,-0.0)	(-20.9,11.7)	(-26.6,10.9)
		Pr >  t			0.4127
	Week 8	n	1	1	
		LS Mean	-48.36	-4.644	-43.71
		SEM	11.26	11.26	15.35
	Week 16	95% CI	(-70.5, -26)	(-26.7,17.5)	(-73.8, -14)
		Pr >  t			0.0045
		n	1	1	
	Week 24	LS Mean	-65.03	-4.644	-60.38
		SEM	11.26	11.26	15.35
		95% CI	(-87.1, -43)	(-26.7,17.5)	(-90.5, -30)
	Week 32	Pr >  t			<.0001
		n	18	17	
		LS Mean	-2.981	-8.456	5.475
Week 8	SEM	3.359	3.561	4.919	
	95% CI	(-9.7, 3.7)	(-15.6,-1.4)	(-4.3,15.3)	
	Pr >  t			0.2690	
Week 16	n	17	11		
	LS Mean	-6.122	-9.241	3.120	
	SEM	3.443	4.248	5.488	
Week 24	95% CI	(-13.0, 0.7)	(-17.7,-0.8)	(-7.8,14.0)	
	Pr >  t			0.5711	
	n	15	5		
Week 32	LS Mean	-8.606	-11.01	2.409	
	SEM	3.612	5.983	7.012	
	95% CI	(-15.8,-1.4)	(-22.8, 0.8)	(-11.5,16.3)	
Week 8	Pr >  t			0.7317	
	n	13	5		
	LS Mean	-2.859	-1.012	-1.847	
		SEM	3.825	5.983	7.136

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	Pr >  t	95% CI	Pr >  t
Week 40	n	11	5		
	LS Mean	1.856	-4.346	6.202	
	SEM	4.077	5.983	7.286	
	95% CI	(-6.2, 9.9)	(-16.2, 7.5)	(-16.0, 12.3)	0.7961
	Pr >  t				
Week 48	n	11	2		
	LS Mean	-7.915	1.662	-9.577	
	SEM	4.079	8.692	9.634	
	95% CI	(-16.0, 0.2)	(-15.5, 18.8)	(-28.6, 9.4)	0.3960
	Pr >  t				
Week 56	n	8	2		
	LS Mean	-4.281	-23.34	19.057	
	SEM	4.596	8.692	9.868	
	95% CI	(-13.4, 4.8)	(-40.5, -6.2)	(-0.4, 38.5)	0.0551
	Pr >  t				
Week 64	n	7	3		
	LS Mean	-2.749	-6.134	3.385	
	SEM	4.832	7.344	8.823	
	95% CI	(-12.3, 6.8)	(-20.6, 8.4)	(-14.0, 20.8)	0.7017
	Pr >  t				
Week 72	n	7	3		
	LS Mean	-5.216	-11.69	6.475	
	SEM	4.848	7.344	8.836	
	95% CI	(-14.8, 4.4)	(-26.2, 2.8)	(-11.0, 23.9)	0.4647
	Pr >  t				
Week 84	n	7	2		
	LS Mean	-14.74	-15.01	0.269	
	SEM	4.848	8.692	9.986	
	95% CI	(-24.3, -5.2)	(-32.2, 2.1)	(-19.4, 20.0)	0.9785
	Pr >  t				
Week 96	n	6	3		
	LS Mean	-13.48	-11.69	-1.788	
	SEM	5.148	7.344	9.003	
	95% CI	(-23.6, -3.3)	(-26.2, 2.8)	(-19.6, 16.0)	0.8428
	Pr >  t				
Week 108	n	7	2		
	LS Mean	-9.976	-26.48	16.500	
	SEM	4.848	8.673	9.967	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-19.6,-0.4)	(-43.6,-9.4)	(-3.2,36.2)
		Pr >  t			0.0996
		n	6	1	
		LS Mean	-5.147	-5.056	-0.091
		SEM	5.148	11.84	12.93
	Week 132	95% CI	(-15.3, 5.0)	(-28.4,18.3)	(-25.6,25.4)
		Pr >  t			0.9944
		n	4		
		LS Mean	6.674		
		SEM	6.076		
	Week 144	95% CI	(-5.3,18.7)		
		Pr >  t			
		n	5		
		LS Mean	-15.79		
		SEM	5.539		
	Week 156	95% CI	(-26.7,-4.9)		
		Pr >  t			
		n	3		
		LS Mean	0.026		
		SEM	6.889		
	Week 8	95% CI	(-13.6,13.6)		
		Pr >  t			
		n	59	57	
		LS Mean	-0.580	-0.479	-0.101
SEM		2.878	3.014	3.015	
Week 16	95% CI	(-6.3, 5.1)	(-6.4, 5.5)	(-6.0, 5.8)	
	Pr >  t			0.9733	
	n	47	44		
	LS Mean	1.278	-1.471	2.749	
	SEM	2.997	3.169	3.270	
Week 24	95% CI	(-4.6, 7.2)	(-7.7, 4.8)	(-3.7, 9.2)	
	Pr >  t			0.4014	
	n	39	34		
	LS Mean	0.006	-2.181	2.187	
	SEM	3.113	3.346	3.523	
Week 32	95% CI	(-6.1, 6.1)	(-8.8, 4.4)	(-4.7, 9.1)	
	Pr >  t			0.5351	
	n	27	32		
	LS Mean	-3.015	-0.115	-2.900	
	SEM	3.368	3.383	3.767	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-9.6, 3.6)	(-6.8, 6.5)	(-10.3, 4.5)	
	Pr >  t				0.4419
	n	24	24		
	LS Mean	-1.074	0.555		-1.629
	SEM	3.453	3.587		4.016
Week 48	95% CI	(-7.9, 5.7)	(-6.5, 7.6)	(-9.5, 6.3)	
	Pr >  t				0.6852
	n	21	21		
	LS Mean	-2.806	-1.709		-1.097
	SEM	3.557	3.692		4.202
Week 56	95% CI	(-9.8, 4.2)	(-9.0, 5.6)	(-9.4, 7.2)	
	Pr >  t				0.7942
	n	18	20		
	LS Mean	-2.263	-4.566		2.302
	SEM	3.686	3.733		4.353
Week 64	95% CI	(-9.5, 5.0)	(-11.9, 2.8)	(-6.3, 10.9)	
	Pr >  t				0.5971
	n	14	19		
	LS Mean	0.913	-2.406		3.319
	SEM	3.932	3.777		4.602
Week 72	95% CI	(-6.8, 8.6)	(-9.8, 5.0)	(-5.7, 12.4)	
	Pr >  t				0.4711
	n	13	15		
	LS Mean	-3.374	-4.205		0.831
	SEM	4.013	3.996		4.852
Week 84	95% CI	(-11.3, 4.5)	(-12.1, 3.7)	(-8.7, 10.4)	
	Pr >  t				0.8641
	n	10	14		
	LS Mean	3.205	-3.841		7.046
	SEM	4.364	4.064		5.180
Week 96	95% CI	(-5.4, 11.8)	(-11.8, 4.2)	(-3.1, 17.2)	
	Pr >  t				0.1743
	n	6	10		
	LS Mean	2.247	-6.844		9.091
	SEM	5.170	4.460		6.173
Week 108	95% CI	(-7.9, 12.4)	(-15.6, 1.9)	(-3.0, 21.2)	
	Pr >  t				0.1414
	n	4	6		
	LS Mean	-7.898	-2.608		-5.289
	SEM	6.052	5.263		7.457

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-19.8, 4.0)	(-12.9, 7.7)	(-19.9, 9.4)
	Pr >  t			0.4784
	n	6	6	
	LS Mean	4.719	-2.703	7.423
	SEM	5.168	5.265	6.775
Week 132	95% CI	(-5.4, 14.9)	(-13.0, 7.6)	(-5.9, 20.7)
	Pr >  t			0.2737
	n	2	3	
	LS Mean	10.496	-15.87	26.364
	SEM	8.088	6.846	10.18
Week 144	95% CI	(-5.4, 26.4)	(-29.3, -2.4)	(6.4, 46.4)
	Pr >  t			0.0099
	n	2	2	
	LS Mean	-25.06	-3.252	-21.81
	SEM	8.067	8.143	11.10
Week 156	95% CI	(-40.9, -9.2)	(-19.2, 12.7)	(-43.6, 0.0)
	Pr >  t			0.0500
	n		1	
	LS Mean		-5.673	
	SEM		11.10	
	95% CI		(-27.5, 16.1)	
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-1.083	-1.566	0.483
		SEM	7.483	7.721	3.144
		95% CI	(-15.9,13.7)	(-16.9,13.7)	(-5.7, 6.7)
		Pr >  t			0.8781
	Week 16	n	51	41	
		LS Mean	-0.496	-5.303	4.806
		SEM	7.497	7.799	3.378
		95% CI	(-15.4,14.4)	(-20.8,10.2)	(-1.8,11.5)
		Pr >  t			0.1561
	Week 24	n	38	33	
		LS Mean	-3.294	-4.498	1.204
		SEM	7.536	7.851	3.644
		95% CI	(-18.2,11.6)	(-20.1,11.1)	(-6.0, 8.4)
		Pr >  t			0.7412
	Week 32	n	34	28	
		LS Mean	-2.159	-3.288	1.129
		SEM	7.628	7.894	3.799
		95% CI	(-17.3,12.9)	(-18.9,12.3)	(-6.3, 8.6)
		Pr >  t			0.7665
	Week 40	n	26	23	
		LS Mean	2.764	-3.380	6.144
		SEM	7.706	7.957	4.073
		95% CI	(-12.5,18.0)	(-19.1,12.4)	(-1.9,14.2)
		Pr >  t			0.1322
	Week 48	n	24	17	
		LS Mean	-2.794	-4.278	1.484
		SEM	7.731	8.074	4.345
95% CI		(-18.1,12.5)	(-20.3,11.7)	(-7.1,10.0)	
	Pr >  t			0.7329	
Week 56	n	21	17		
	LS Mean	-2.418	-5.647	3.229	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	7.778	8.074	4.431
	95% CI	(-17.8,13.0)	(-21.6,10.3)	(-5.5,11.9)
	Pr >  t			0.4665
Week 64	n	15	15	
	LS Mean	-1.277	-2.775	1.498
	SEM	7.923	8.133	4.779
	95% CI	(-16.9,14.4)	(-18.9,13.3)	(-7.9,10.9)
	Pr >  t			0.7541
Week 72	n	16	15	
	LS Mean	-4.085	-3.990	-0.094
	SEM	7.893	8.133	4.729
	95% CI	(-19.7,11.5)	(-20.1,12.1)	(-9.4, 9.2)
	Pr >  t			0.9841
Week 84	n	14	13	
	LS Mean	-5.320	-4.891	-0.429
	SEM	7.957	8.205	4.960
	95% CI	(-21.1,10.4)	(-21.1,11.3)	(-10.2, 9.3)
	Pr >  t			0.9311
Week 96	n	12	9	
	LS Mean	-0.368	-4.729	4.360
	SEM	8.045	8.444	5.477
	95% CI	(-16.3,15.5)	(-21.4,12.0)	(-6.4,15.1)
	Pr >  t			0.4263
Week 108	n	13	8	
	LS Mean	-2.187	-5.242	3.054
	SEM	7.999	8.538	5.559
	95% CI	(-18.0,13.6)	(-22.1,11.6)	(-7.9,14.0)
	Pr >  t			0.5829
Week 120	n	11	6	
	LS Mean	-1.315	-2.628	1.313
	SEM	8.099	8.815	6.109
	95% CI	(-17.3,14.7)	(-20.0,14.8)	(-10.7,13.3)
	Pr >  t			0.8299
Week 132	n	8	3	
	LS Mean	0.470	-9.179	9.649
	SEM	8.339	9.838	7.770
	95% CI	(-16.0,16.9)	(-28.6,10.2)	(-5.6,24.9)
	Pr >  t			0.2148
Week 144	n	5	1	
	LS Mean	-5.659	-1.413	-4.246



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	8.837	13.17	12.06
		95% CI	(-23.1,11.8)	(-27.3,24.5)	(-27.9,19.4)
		Pr >  t			0.7249
	Week 168	n	3	1	
		LS Mean	3.123	-1.413	4.536
		SEM	9.664	13.17	12.68
	Week 180	95% CI	(-15.9,22.1)	(-27.3,24.5)	(-20.4,29.4)
		Pr >  t			0.7206
		n	2	1	
	Week 192	LS Mean	-2.659	-1.413	-1.245
		SEM	10.60	13.17	13.40
		95% CI	(-23.5,18.2)	(-27.3,24.5)	(-27.6,25.1)
	Week 8	Pr >  t			0.9260
		n		1	
		LS Mean		-1.413	
	Week 16	SEM		13.17	
		95% CI		(-27.3,24.5)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-1.413	
		SEM		13.17	
	Week 32	95% CI		(-27.3,24.5)	
		Pr >  t			
		n	17	16	
Week 8	LS Mean	-0.638	-6.791	6.153	
	SEM	3.927	3.987	5.464	
	95% CI	(-8.5, 7.2)	(-14.7, 1.2)	(-4.7,17.0)	
Week 16	Pr >  t			0.2637	
	n	18	14		
	LS Mean	0.035	-5.500	5.536	
Week 24	SEM	3.855	4.158	5.583	
	95% CI	(-7.7, 7.7)	(-13.8, 2.8)	(-5.6,16.6)	
	Pr >  t			0.3245	
Week 32	n	16	13		
	LS Mean	-5.531	-8.246	2.715	
	SEM	4.007	4.249	5.750	
Week 8	95% CI	(-13.5, 2.4)	(-16.7, 0.2)	(-8.7,14.1)	
	Pr >  t			0.6380	
	n	15	13		
Week 16	LS Mean	5.439	-3.333	8.772	
	SEM				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.063	4.260	5.801
		95% CI	(-2.6,13.5)	(-11.8, 5.1)	(-2.8,20.3)
		Pr >  t			0.1340
	Week 40	n	14	10	
		LS Mean	0.985	2.591	-1.606
		SEM	4.166	4.595	6.122
		95% CI	(-7.3, 9.3)	(-6.5,11.7)	(-13.7,10.5)
		Pr >  t			0.7936
	Week 48	n	14	11	
		LS Mean	2.177	-7.087	9.264
		SEM	4.166	4.475	6.032
		95% CI	(-6.1,10.5)	(-16.0, 1.8)	(-2.7,21.2)
		Pr >  t			0.1277
	Week 56	n	11	11	
		LS Mean	2.644	-4.057	6.702
		SEM	4.442	4.475	6.231
		95% CI	(-6.2,11.5)	(-12.9, 4.8)	(-5.6,19.0)
		Pr >  t			0.2845
	Week 64	n	8	11	
		LS Mean	1.923	-4.057	5.980
		SEM	4.868	4.475	6.548
		95% CI	(-7.7,11.5)	(-12.9, 4.8)	(-7.0,18.9)
		Pr >  t			0.3628
	Week 72	n	11	10	
		LS Mean	2.644	-6.936	9.580
		SEM	4.442	4.601	6.323
		95% CI	(-6.2,11.5)	(-16.1, 2.2)	(-2.9,22.1)
		Pr >  t			0.1325
	Week 84	n	9	9	
		LS Mean	-3.603	-5.688	2.085
		SEM	4.695	4.746	6.612
		95% CI	(-12.9, 5.7)	(-15.1, 3.7)	(-11.0,15.2)
		Pr >  t			0.7530
	Week 96	n	8	7	
		LS Mean	-0.832	-8.462	7.630
		SEM	4.870	5.128	7.015
		95% CI	(-10.5, 8.8)	(-18.6, 1.7)	(-6.2,21.5)
		Pr >  t			0.2785
	Week 108	n	7	6	
		LS Mean	6.851	-5.384	12.236

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.087	5.406	7.367
		95% CI	(-3.2,16.9)	(-16.1, 5.3)	(-2.3,26.8)
		Pr >  t			0.0986
	Week 120	n	6	5	
		LS Mean	3.952	-5.587	9.539
		SEM	5.360	5.770	7.814
		95% CI	(-6.6,14.5)	(-17.0, 5.8)	(-5.9,25.0)
		Pr >  t			0.2237
	Week 132	n	5	3	
		LS Mean	6.574	-11.21	17.780
		SEM	5.715	6.990	8.981
		95% CI	(-4.7,17.8)	(-25.0, 2.6)	( 0.1,35.5)
		Pr >  t			0.0489
	Week 144	n	5	4	
		LS Mean	-3.426	-5.085	1.659
		SEM	5.715	6.254	8.420
		95% CI	(-14.7, 7.8)	(-17.4, 7.2)	(-14.9,18.3)
		Pr >  t			0.8440
	Week 156	n	4	2	
		LS Mean	3.161	-14.35	17.509
		SEM	6.205	8.268	10.30
		95% CI	(-9.1,15.4)	(-30.6, 1.9)	(-2.8,37.8)
		Pr >  t			0.0903
	Week 168	n	1	1	
		LS Mean	3.545	-3.590	7.135
		SEM	11.23	11.27	15.89
		95% CI	(-18.6,25.7)	(-25.8,18.6)	(-24.1,38.4)
		Pr >  t			0.6537
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-5.658	-0.059	-5.599
		SEM	4.913	4.508	5.408
		95% CI	(-15.6, 4.3)	(-9.2, 9.0)	(-16.5, 5.3)
		Pr >  t			0.3058
	Week 16	n	15	17	
		LS Mean	-2.551	-5.803	3.252
		SEM	5.092	4.668	5.594
		95% CI	(-12.8, 7.7)	(-15.2, 3.6)	(-8.0,14.5)
		Pr >  t			0.5635
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	-5.864	-9.128	3.264
	SEM	5.143	4.976	5.935
	95% CI	(-16.2, 4.5)	(-19.1, 0.8)	(-8.6,15.1)
	Pr >  t			0.5844
	n	12	9	
Week 40	LS Mean	-3.534	-5.170	1.637
	SEM	5.289	5.192	6.204
	95% CI	(-14.1, 7.1)	(-15.5, 5.2)	(-10.7,14.0)
	Pr >  t			0.7927
	n	11	7	
Week 48	LS Mean	0.432	-9.388	9.820
	SEM	5.374	5.531	6.515
	95% CI	(-10.3,11.2)	(-20.4, 1.6)	(-3.1,22.8)
	Pr >  t			0.1354
	n	8	6	
Week 56	LS Mean	-5.768	-4.455	-1.313
	SEM	5.648	5.731	6.910
	95% CI	(-17.0, 5.5)	(-15.8, 6.9)	(-15.0,12.4)
	Pr >  t			0.8496
	n	7	5	
Week 64	LS Mean	-10.82	-4.542	-6.276
	SEM	5.785	5.967	7.225
	95% CI	(-22.3, 0.7)	(-16.4, 7.3)	(-20.6, 8.0)
	Pr >  t			0.3868
	n	5	3	
Week 72	LS Mean	-0.746	-13.03	12.282
	SEM	6.192	6.873	8.285
	95% CI	(-13.0,11.6)	(-26.6, 0.6)	(-4.1,28.7)
	Pr >  t			0.1403
	n	5	2	
Week 84	LS Mean	-8.279	-10.18	1.897
	SEM	6.220	7.851	9.135
	95% CI	(-20.6, 4.1)	(-25.7, 5.3)	(-16.1,19.9)
	Pr >  t			0.8357
	n	4	2	
Week 96	LS Mean	-5.216	-10.18	4.960
	SEM	6.516	7.851	9.341
	95% CI	(-18.1, 7.7)	(-25.7, 5.3)	(-13.5,23.4)
	Pr >  t			0.5961
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	LS Mean	-4.097	-10.18	6.079
	SEM	6.524	7.851	9.348
	95% CI	(-17.0, 8.8)	(-25.7, 5.3)	(-12.4, 24.5)
	Pr >  t			0.5164
	n	1	2	
Week 120	LS Mean	-7.320	4.136	-11.46
	SEM	10.21	7.810	12.18
	95% CI	(-27.5, 12.8)	(-11.3, 19.6)	(-35.5, 12.6)
	Pr >  t			0.3484
	n	5	1	
Week 132	LS Mean	-14.95	3.335	-18.28
	SEM	6.220	10.12	11.15
	95% CI	(-27.3, -2.6)	(-16.6, 23.3)	(-40.3, 3.7)
	Pr >  t			0.1029
	n	3	1	
Week 144	LS Mean	-10.23	-13.32	3.090
	SEM	7.039	10.12	11.63
	95% CI	(-24.2, 3.7)	(-33.3, 6.7)	(-19.9, 26.0)
	Pr >  t			0.7908
	n	3		
Week 156	LS Mean	-15.79		
	SEM	7.039		
	95% CI	(-29.7, -1.9)		
	Pr >  t			
	n	3		
Week 168	LS Mean	-10.23		
	SEM	7.039		
	95% CI	(-24.2, 3.7)		
	Pr >  t			
	n	1		
Week 180	LS Mean	-33.40		
	SEM	10.20		
	95% CI	(-53.5, -13)		
	Pr >  t			
	n	1		
Week 192	LS Mean	-50.06		
	SEM	10.20		
	95% CI	(-70.2, -30)		
	Pr >  t			
	n	1		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	-66.73		
		SEM	10.20		
		95% CI	(-86.9, -47)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	-5.163	-2.453	-2.710
		SEM	3.012	2.994	3.330
		95% CI	(-11.1, 0.8)	(-8.4, 3.5)	(-9.3, 3.9)
		Pr >  t			0.4167
	Week 16	n	30	29	
		LS Mean	-0.360	-3.539	3.179
		SEM	3.136	3.311	3.690
		95% CI	(-6.6, 5.8)	(-10.1, 3.0)	(-4.1, 10.4)
		Pr >  t			0.3899
	Week 24	n	26	20	
		LS Mean	-0.473	-0.695	0.222
		SEM	3.295	3.716	4.127
		95% CI	(-7.0, 6.0)	(-8.0, 6.6)	(-7.9, 8.3)
		Pr >  t			0.9571
	Week 32	n	18	20	
		LS Mean	-6.735	0.970	-7.705
		SEM	3.671	3.716	4.426
		95% CI	(-14.0, 0.5)	(-6.4, 8.3)	(-16.4, 1.0)
		Pr >  t			0.0827
	Week 40	n	18	19	
		LS Mean	-3.423	0.544	-3.967
		SEM	3.673	3.769	4.471
		95% CI	(-10.7, 3.8)	(-6.9, 8.0)	(-12.8, 4.8)
		Pr >  t			0.3756
	Week 48	n	16	14	
		LS Mean	-6.888	-5.412	-1.476
		SEM	3.792	4.101	4.853
		95% CI	(-14.4, 0.6)	(-13.5, 2.7)	(-11.0, 8.1)
		Pr >  t			0.7612
	Week 56	n	14	10	
		LS Mean	-6.728	-3.473	-3.255
		SEM	3.944	4.555	5.366
		95% CI	(-14.5, 1.0)	(-12.4, 5.5)	(-13.8, 7.3)
		Pr >  t			0.5445

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		n	13	11	
		LS Mean	-1.065	-2.404	1.340
		SEM	4.037	4.419	5.321
		95% CI	(-9.0, 6.9)	(-11.1, 6.3)	(-9.1,11.8)
		Pr >  t			0.8014
Week 72		n	10	6	
		LS Mean	-6.965	-8.446	1.481
		SEM	4.389	5.458	6.456
		95% CI	(-15.6, 1.7)	(-19.2, 2.3)	(-11.2,14.2)
		Pr >  t			0.8187
Week 84		n	8	7	
		LS Mean	3.980	1.296	2.684
		SEM	4.806	5.156	6.469
		95% CI	(-5.5,13.4)	(-8.8,11.4)	(-10.0,15.4)
		Pr >  t			0.6784
Week 96		n	6	5	
		LS Mean	1.139	-7.750	8.888
		SEM	5.327	5.847	7.421
		95% CI	(-9.3,11.6)	(-19.2, 3.7)	(-5.7,23.5)
		Pr >  t			0.2318
Week 108		n	2	4	
		LS Mean	-32.49	-7.441	-25.05
		SEM	8.516	6.392	10.27
		95% CI	(-49.2, -16)	(-20.0, 5.1)	(-45.3,-4.8)
		Pr >  t			0.0153
Week 120		n	4	4	
		LS Mean	6.500	-7.441	13.941
		SEM	6.257	6.392	8.528
		95% CI	(-5.8,18.8)	(-20.0, 5.1)	(-2.8,30.7)
		Pr >  t			0.1030
Week 132		n	3	1	
		LS Mean	-16.91	-11.93	-4.987
		SEM	7.115	11.82	13.51
		95% CI	(-30.9,-2.9)	(-35.2,11.3)	(-31.6,21.6)
		Pr >  t			0.7122
Week 144		n	2		
		LS Mean	-28.80		
		SEM	8.464		
		95% CI	(-45.4, -12)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-1.437	-1.926	0.488		
			SEM	3.120	3.111	2.505		
			95% CI	(-7.6, 4.7)	(-8.1, 4.2)	(-4.4, 5.4)		
					Pr >  t			0.8455
		Week 16	n	79	68			
			LS Mean	0.497	-4.852	5.348		
			SEM	3.151	3.268	2.702		
			95% CI	(-5.7, 6.7)	(-11.3, 1.6)	(0.0, 10.7)		
					Pr >  t			0.0484
		Week 24	n	64	55			
			LS Mean	-1.968	-3.373	1.405		
			SEM	3.241	3.387	2.907		
			95% CI	(-8.3, 4.4)	(-10.0, 3.3)	(-4.3, 7.1)		
					Pr >  t			0.6291
		Week 32	n	49	53			
			LS Mean	0.276	-1.529	1.805		
			SEM	3.382	3.405	3.056		
			95% CI	(-6.4, 6.9)	(-8.2, 5.2)	(-4.2, 7.8)		
					Pr >  t			0.5549
		Week 40	n	44	45			
			LS Mean	1.312	-0.545	1.857		
			SEM	3.435	3.480	3.197		
			95% CI	(-5.4, 8.1)	(-7.4, 6.3)	(-4.4, 8.1)		
					Pr >  t			0.5616
		Week 48	n	41	36			
			LS Mean	-3.898	-4.065	0.167		
			SEM	3.469	3.597	3.360		
95% CI	(-10.7, 2.9)		(-11.1, 3.0)	(-6.4, 6.8)				
			Pr >  t			0.9603		
Week 56	n	33	32					
	LS Mean	-2.825	-3.339	0.514				
		SEM	3.589	3.668	3.560			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.9, 4.2)	(-10.5, 3.9)	(-6.5, 7.5)
		Pr >  t			0.8852
	Week 64	n	27	31	
		LS Mean	-0.147	-2.668	2.521
		SEM	3.718	3.689	3.714
		95% CI	(-7.5, 7.2)	(-9.9, 4.6)	(-4.8, 9.8)
		Pr >  t			0.4975
	Week 72	n	26	26	
		LS Mean	-3.441	-4.460	1.020
		SEM	3.743	3.809	3.857
		95% CI	(-10.8, 3.9)	(-11.9, 3.0)	(-6.6, 8.6)
		Pr >  t			0.7916
	Week 84	n	22	23	
		LS Mean	-3.811	-3.457	-0.354
		SEM	3.888	3.900	4.073
		95% CI	(-11.4, 3.8)	(-11.1, 4.2)	(-8.3, 7.6)
		Pr >  t			0.9308
	Week 96	n	18	18	
		LS Mean	-0.351	-6.305	5.955
		SEM	4.066	4.113	4.439
		95% CI	(-8.3, 7.6)	(-14.4, 1.8)	(-2.8, 14.7)
		Pr >  t			0.1801
	Week 108	n	14	14	
		LS Mean	-2.008	-4.854	2.846
		SEM	4.332	4.376	4.916
		95% CI	(-10.5, 6.5)	(-13.4, 3.7)	(-6.8, 12.5)
		Pr >  t			0.5628
	Week 120	n	12	12	
		LS Mean	2.620	-3.573	6.193
		SEM	4.514	4.562	5.238
		95% CI	(-6.2, 11.5)	(-12.5, 5.4)	(-4.1, 16.5)
		Pr >  t			0.2374
	Week 132	n	9	5	
		LS Mean	-2.181	-10.61	8.433
		SEM	4.920	6.067	6.876
		95% CI	(-11.8, 7.5)	(-22.5, 1.3)	(-5.1, 21.9)
		Pr >  t			0.2203
	Week 144	n	7	4	
		LS Mean	-3.475	-3.287	-0.188
		SEM	5.345	6.616	7.653

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.0, 7.0)	(-16.3, 9.7)	(-15.2,14.8)
		Pr >  t			0.9804
	Week 156	n	4	2	
		LS Mean	5.651	-12.58	18.231
		SEM	6.571	8.825	10.36
		95% CI	(-7.2,18.5)	(-29.9, 4.7)	(-2.1,38.6)
		Pr >  t			0.0788
	Week 168	n	2	1	
		LS Mean	5.800	-1.903	7.703
		SEM	8.785	12.09	14.48
		95% CI	(-11.4,23.0)	(-25.6,21.8)	(-20.7,36.1)
		Pr >  t			0.5949
Yes	Week 8	n	53	48	
		LS Mean	-3.924	-1.571	-2.353
		SEM	2.459	2.561	2.474
		95% CI	(-8.8, 0.9)	(-6.6, 3.5)	(-7.2, 2.5)
		Pr >  t			0.3426
	Week 16	n	45	39	
		LS Mean	-2.413	-3.237	0.824
		SEM	2.585	2.693	2.662
		95% CI	(-7.5, 2.7)	(-8.6, 2.1)	(-4.4, 6.1)
		Pr >  t			0.7572
	Week 24	n	41	26	
		LS Mean	-4.486	-5.620	1.133
		SEM	2.626	2.918	2.955
		95% CI	(-9.7, 0.7)	(-11.4, 0.1)	(-4.7, 6.9)
		Pr >  t			0.7016
	Week 32	n	37	20	
		LS Mean	-6.308	-2.088	-4.220
		SEM	2.695	3.131	3.190
		95% CI	(-11.6,-1.0)	(-8.3, 4.1)	(-10.5, 2.1)
		Pr >  t			0.1866
	Week 40	n	31	17	
		LS Mean	-2.094	-2.417	0.323
		SEM	2.786	3.294	3.402
		95% CI	(-7.6, 3.4)	(-8.9, 4.1)	(-6.4, 7.0)
		Pr >  t			0.9244
	Week 48	n	28	15	
		LS Mean	-2.892	-4.510	1.618
		SEM	2.843	3.406	3.557

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-8.5, 2.7)	(-11.2, 2.2)	(-5.4, 8.6)
	Pr >  t			0.6494
	n	26	13	
	LS Mean	-3.908	-5.897	1.989
	SEM	2.887	3.544	3.726
Week 64	95% CI	(-9.6, 1.8)	(-12.9, 1.1)	(-5.3, 9.3)
	Pr >  t			0.5938
	n	20	11	
	LS Mean	-3.154	-5.763	2.609
	SEM	3.060	3.724	4.030
Week 72	95% CI	(-9.2, 2.9)	(-13.1, 1.6)	(-5.3, 10.5)
	Pr >  t			0.5176
	n	22	9	
	LS Mean	-4.956	-6.912	1.956
	SEM	2.996	3.961	4.204
Week 84	95% CI	(-10.9, 0.9)	(-14.7, 0.9)	(-6.3, 10.2)
	Pr >  t			0.6419
	n	18	10	
	LS Mean	-1.928	-3.053	1.125
	SEM	3.151	3.834	4.192
Week 96	95% CI	(-8.1, 4.3)	(-10.6, 4.5)	(-7.1, 9.4)
	Pr >  t			0.7885
	n	17	6	
	LS Mean	-2.342	-5.973	3.632
	SEM	3.186	4.548	4.885
Week 108	95% CI	(-8.6, 3.9)	(-14.9, 3.0)	(-6.0, 13.2)
	Pr >  t			0.4575
	n	12	7	
	LS Mean	-3.148	-5.598	2.450
	SEM	3.523	4.307	4.889
Week 120	95% CI	(-10.1, 3.8)	(-14.1, 2.9)	(-7.2, 12.1)
	Pr >  t			0.6166
	n	16	4	
	LS Mean	-6.863	-3.978	-2.885
	SEM	3.241	5.305	5.627
Week 132	95% CI	(-13.2, -0.5)	(-14.4, 6.4)	(-13.9, 8.2)
	Pr >  t			0.6084
	n	11	3	
	LS Mean	-4.565	-8.994	4.429
	SEM	3.617	5.963	6.449

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 144	95% CI	(-11.7, 2.5)	(-20.7, 2.7)	(-8.2,17.1)
	Pr >  t			0.4925
	n	8	1	
	LS Mean	-17.08	-1.651	-15.43
	SEM	3.994	9.732	10.19
Week 156	95% CI	(-24.9,-9.2)	(-20.8,17.5)	(-35.4, 4.6)
	Pr >  t			0.1304
	n	6	1	
	LS Mean	-7.404	-1.651	-5.753
	SEM	4.450	9.732	10.37
Week 168	95% CI	(-16.1, 1.3)	(-20.8,17.5)	(-26.1,14.6)
	Pr >  t			0.5791
	n	2	1	
	LS Mean	-25.30	-1.651	-23.65
	SEM	7.022	9.732	11.70
Week 180	95% CI	(-39.1, -12)	(-20.8,17.5)	(-46.6,-0.7)
	Pr >  t			0.0438
	n	1	1	
	LS Mean	-48.61	-1.651	-46.96
	SEM	9.654	9.732	13.45
Week 192	95% CI	(-67.6, -30)	(-20.8,17.5)	(-73.4, -21)
	Pr >  t			0.0005
	n	1	1	
	LS Mean	-65.28	-1.651	-63.63
	SEM	9.654	9.732	13.45
	95% CI	(-84.2, -46)	(-20.8,17.5)	(-90.1, -37)
	Pr >  t			<.0001

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60	
		LS Mean	-5.563	-2.615	-2.948	
	SEM	5.907	6.092	2.728		
	95% CI	(-17.3, 6.2)	(-14.7, 9.5)	(-8.3, 2.4)		
	Pr >  t			0.2808		
	Week 16	n	59	49		
		LS Mean	-2.448	-5.934	3.486	
		SEM	5.931	6.150	2.918	
		95% CI	(-14.2, 9.3)	(-18.1, 6.3)	(-2.3, 9.2)	
	Week 24	Pr >  t			0.2330	
		n	54	41		
		LS Mean	-2.889	-5.029	2.139	
		SEM	5.946	6.202	3.072	
	Week 32	95% CI	(-14.7, 8.9)	(-17.3, 7.3)	(-3.9, 8.2)	
		Pr >  t			0.4867	
		n	48	37		
		LS Mean	-6.112	-2.531	-3.581	
	Week 40	SEM	5.969	6.232	3.191	
		95% CI	(-17.9, 5.7)	(-14.9, 9.8)	(-9.9, 2.7)	
		Pr >  t			0.2624	
		n	43	33		
	Week 48	LS Mean	-0.820	-1.322	0.501	
		SEM	5.992	6.269	3.315	
		95% CI	(-12.7, 11.1)	(-13.7, 11.1)	(-6.0, 7.0)	
		Pr >  t			0.8798	
	Week 56	n	41	28		
		LS Mean	-8.100	-3.753	-4.347	
		SEM	6.004	6.329	3.450	
95% CI		(-20.0, 3.8)	(-16.3, 8.8)	(-11.1, 2.4)		
Week 56	Pr >  t			0.2082		
	n	35	22			
	LS Mean	-8.978	-3.636	-5.343		
	SEM	6.045	6.434	3.718		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.0, 3.0)	(-16.4, 9.1)	(-12.6, 2.0)
		Pr >  t			0.1513
	Week 64	n	26	23	
		LS Mean	-3.281	-2.058	-1.224
		SEM	6.142	6.414	3.858
		95% CI	(-15.4, 8.9)	(-14.8, 10.6)	(-8.8, 6.4)
		Pr >  t			0.7513
	Week 72	n	28	18	
		LS Mean	-9.876	-5.057	-4.818
		SEM	6.114	6.538	4.017
		95% CI	(-22.0, 2.2)	(-18.0, 7.9)	(-12.7, 3.1)
		Pr >  t			0.2307
	Week 84	n	22	18	
		LS Mean	-5.755	-2.361	-3.394
		SEM	6.248	6.539	4.175
		95% CI	(-18.1, 6.6)	(-15.3, 10.6)	(-11.6, 4.8)
		Pr >  t			0.4165
	Week 96	n	21	13	
		LS Mean	-3.569	-5.330	1.762
		SEM	6.231	6.751	4.532
		95% CI	(-15.9, 8.8)	(-18.7, 8.0)	(-7.1, 10.7)
		Pr >  t			0.6975
	Week 108	n	17	12	
		LS Mean	-4.819	-6.168	1.349
		SEM	6.385	6.812	4.778
		95% CI	(-17.4, 7.8)	(-19.6, 7.3)	(-8.0, 10.7)
		Pr >  t			0.7778
	Week 120	n	18	11	
		LS Mean	-3.176	-5.463	2.287
		SEM	6.305	6.885	4.838
		95% CI	(-15.6, 9.3)	(-19.1, 8.1)	(-7.2, 11.8)
		Pr >  t			0.6366
	Week 132	n	13	5	
		LS Mean	-6.700	-12.96	6.257
		SEM	6.563	7.840	6.345
		95% CI	(-19.7, 6.3)	(-28.4, 2.5)	(-6.2, 18.7)
		Pr >  t			0.3243
	Week 144	n	12	3	
		LS Mean	-11.40	-3.795	-7.603
		SEM	6.563	8.877	7.641

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-24.4, 1.6)	(-21.2,13.7)	(-22.6, 7.4)
		Pr >  t			0.3200
	Week 156	n	7	2	
		LS Mean	-3.939	-4.510	0.571
		SEM	7.180	10.01	9.344
		95% CI	(-18.1,10.2)	(-24.2,15.1)	(-17.8,18.9)
		Pr >  t			0.9513
	Week 168	n	3	1	
		LS Mean	-9.856	-1.967	-7.890
		SEM	8.710	12.82	13.26
		95% CI	(-27.0, 7.3)	(-27.1,23.2)	(-33.9,18.1)
		Pr >  t			0.5520
	Week 180	n	1	1	
		LS Mean	-47.49	-1.967	-45.53
		SEM	12.70	12.82	16.17
		95% CI	(-72.4, -23)	(-27.1,23.2)	(-77.3, -14)
		Pr >  t			0.0050
	Week 192	n	1	1	
		LS Mean	-64.16	-1.967	-62.20
		SEM	12.70	12.82	16.17
		95% CI	(-89.1, -39)	(-27.1,23.2)	(-93.9, -30)
		Pr >  t			0.0001
Yes	Week 8	n	73	80	
		LS Mean	-3.346	-4.522	1.176
		SEM	3.328	3.355	2.492
		95% CI	( -9.9, 3.2)	(-11.1, 2.1)	( -3.7, 6.1)
		Pr >  t			0.6375
	Week 16	n	65	58	
		LS Mean	-2.645	-6.431	3.787
		SEM	3.407	3.491	2.681
		95% CI	( -9.4, 4.1)	(-13.3, 0.4)	( -1.5, 9.1)
		Pr >  t			0.1588
	Week 24	n	51	40	
		LS Mean	-7.022	-7.086	0.064
		SEM	3.474	3.658	2.961
		95% CI	(-13.9,-0.2)	(-14.3, 0.1)	( -5.8, 5.9)
		Pr >  t			0.9828
	Week 32	n	38	36	
		LS Mean	-2.168	-4.977	2.809
		SEM	3.623	3.710	3.153



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.3, 5.0)	(-12.3, 2.3)	(-3.4, 9.0)
		Pr >  t			0.3733
	Week 40	n	32	29	
		LS Mean	-3.355	-5.018	1.663
		SEM	3.710	3.815	3.364
		95% CI	(-10.7, 3.9)	(-12.5, 2.5)	(-4.9, 8.3)
		Pr >  t			0.6213
	Week 48	n	28	23	
		LS Mean	-1.593	-9.174	7.581
		SEM	3.774	3.949	3.581
		95% CI	(-9.0, 5.8)	(-16.9,-1.4)	( 0.5,14.6)
		Pr >  t			0.0346
	Week 56	n	24	23	
		LS Mean	0.427	-8.760	9.187
		SEM	3.864	3.949	3.671
		95% CI	(-7.2, 8.0)	(-16.5,-1.0)	( 2.0,16.4)
		Pr >  t			0.0126
	Week 64	n	21	19	
		LS Mean	-3.229	-9.643	6.414
		SEM	3.950	4.073	3.890
		95% CI	(-11.0, 4.5)	(-17.7,-1.6)	( -1.2,14.1)
		Pr >  t			0.0997
	Week 72	n	20	17	
		LS Mean	-0.152	-9.441	9.288
		SEM	3.985	4.154	4.009
		95% CI	(-8.0, 7.7)	(-17.6,-1.3)	( 1.4,17.2)
		Pr >  t			0.0208
	Week 84	n	18	15	
		LS Mean	-3.735	-8.772	5.037
		SEM	4.050	4.255	4.179
		95% CI	(-11.7, 4.2)	(-17.1,-0.4)	( -3.2,13.2)
		Pr >  t			0.2285
	Week 96	n	14	11	
		LS Mean	-2.530	-11.95	9.420
		SEM	4.257	4.548	4.660
		95% CI	(-10.9, 5.8)	(-20.9,-3.0)	( 0.3,18.6)
		Pr >  t			0.0436
	Week 108	n	9	9	
		LS Mean	-4.427	-8.080	3.653
		SEM	4.716	4.773	5.289

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.7, 4.8)	(-17.5, 1.3)	( -6.7,14.0)
		Pr >  t			0.4900
	Week 120	n	10	5	
		LS Mean	-6.703	-4.718	-1.985
		SEM	4.608	5.662	6.020
		95% CI	(-15.8, 2.3)	(-15.8, 6.4)	(-13.8, 9.8)
		Pr >  t			0.7417
	Week 132	n	7	3	
		LS Mean	-2.488	-9.255	6.767
		SEM	5.053	6.758	7.365
		95% CI	(-12.4, 7.4)	(-22.5, 4.0)	( -7.7,21.2)
		Pr >  t			0.3585
	Week 144	n	3	2	
		LS Mean	-18.53	-6.441	-12.09
		SEM	6.712	7.929	9.540
		95% CI	(-31.7,-5.4)	(-22.0, 9.1)	(-30.8, 6.6)
		Pr >  t			0.2054
	Week 156	n	3	1	
		LS Mean	-3.580	-22.87	19.293
		SEM	6.721	10.70	11.94
		95% CI	(-16.8, 9.6)	(-43.9,-1.9)	( -4.1,42.7)
		Pr >  t			0.1066
	Week 168	n	1	1	
		LS Mean	-17.10	-6.203	-10.90
		SEM	10.69	10.70	14.55
		95% CI	(-38.1, 3.9)	(-27.2,14.8)	(-39.5,17.7)
		Pr >  t			0.4541

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	1.474	-2.187	3.661
			SEM	6.396	6.998	5.829
			95% CI	(-11.5,14.4)	(-16.4,12.0)	(-8.1,15.4)
			Pr >  t			0.5331
		Week 16	n	14	17	
			LS Mean	-1.556	-3.296	1.740
			SEM	6.435	7.158	6.076
			95% CI	(-14.6,11.5)	(-17.8,11.2)	(-10.5,13.9)
			Pr >  t			0.7757
		Week 24	n	14	11	
			LS Mean	-6.318	-3.855	-2.463
			SEM	6.435	7.385	6.336
			95% CI	(-19.4, 6.7)	(-18.8,11.0)	(-15.1,10.2)
			Pr >  t			0.6988
		Week 32	n	10	10	
			LS Mean	-1.466	-1.395	-0.071
			SEM	6.765	7.451	6.590
			95% CI	(-15.1,12.2)	(-16.4,13.6)	(-13.2,13.1)
			Pr >  t			0.9914
		Week 40	n	8	10	
			LS Mean	0.240	-1.564	1.803
			SEM	6.919	7.452	6.743
			95% CI	(-13.7,14.1)	(-16.6,13.5)	(-11.6,15.2)
			Pr >  t			0.7899
		Week 48	n	7	11	
			LS Mean	1.944	-2.752	4.695
			SEM	7.024	7.401	6.806
95% CI	(-12.1,16.0)		(-17.7,12.2)	(-8.9,18.2)		
	Pr >  t			0.4923		
Week 56	n	6	9			
	LS Mean	1.146	-5.013	6.159		
	SEM	7.160	7.517	7.074		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.2,15.5)	(-20.2,10.1)	(-7.9,20.2)
		Pr >  t			0.3863
	Week 64	n	5	8	
		LS Mean	-5.678	-5.303	-0.375
		SEM	7.339	7.595	7.336
		95% CI	(-20.3, 9.0)	(-20.6,10.0)	(-14.9,14.2)
		Pr >  t			0.9594
	Week 72	n	7	7	
		LS Mean	-4.044	-3.842	-0.202
		SEM	7.023	7.694	7.128
		95% CI	(-18.1,10.0)	(-19.3,11.6)	(-14.4,14.0)
		Pr >  t			0.9775
	Week 84	n	7	7	
		LS Mean	-1.662	-3.842	2.180
		SEM	7.023	7.694	7.128
		95% CI	(-15.7,12.4)	(-19.3,11.6)	(-12.0,16.3)
		Pr >  t			0.7604
	Week 96	n	5	6	
		LS Mean	-0.334	-7.599	7.265
		SEM	7.339	7.819	7.569
		95% CI	(-15.0,14.3)	(-23.3, 8.1)	(-7.7,22.3)
		Pr >  t			0.3392
	Week 108	n	4	6	
		LS Mean	-1.393	-10.38	8.984
		SEM	7.607	7.819	7.830
		95% CI	(-16.6,13.8)	(-26.1, 5.3)	(-6.5,24.5)
		Pr >  t			0.2535
	Week 120	n	4	4	
		LS Mean	-2.899	0.090	-2.989
		SEM	7.611	8.239	8.256
		95% CI	(-18.1,12.3)	(-16.4,16.5)	(-19.3,13.3)
		Pr >  t			0.7179
	Week 132	n	3	1	
		LS Mean	1.046	-9.353	10.399
		SEM	8.025	11.22	11.52
		95% CI	(-14.9,17.0)	(-31.5,12.8)	(-12.3,33.1)
		Pr >  t			0.3679
	Week 144	n	1	1	
		LS Mean	-10.94	-2.494	-8.451
		SEM	10.78	11.26	13.61

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-32.2,10.3)	(-24.7,19.7)	(-35.3,18.4)
		Pr >  t			0.5353
	Week 16	n	35	37	
		LS Mean	-0.107	2.419	-2.525
	Week 24	SEM	8.111	8.522	3.688
		95% CI	(-16.1,15.9)	(-14.4,19.3)	(-9.8, 4.8)
	Week 32	Pr >  t			0.4945
		n	34	30	
	Week 40	LS Mean	2.875	-0.288	3.163
		SEM	8.345	8.572	3.843
	Week 48	95% CI	(-13.6,19.4)	(-17.2,16.6)	(-4.4,10.7)
		Pr >  t			0.4115
	Week 56	n	32	23	
		LS Mean	-0.969	0.901	-1.870
	Week 64	SEM	8.356	8.666	4.087
		95% CI	(-17.5,15.5)	(-16.2,18.0)	(-9.9, 6.2)
	Week 8	Pr >  t			0.6476
		n	21	22	
	Week 16	LS Mean	0.315	6.259	-5.943
		SEM	8.497	8.685	4.413
	Week 24	95% CI	(-16.5,17.1)	(-10.9,23.4)	(-14.6, 2.7)
		Pr >  t			0.1793
	Week 32	n	20	20	
		LS Mean	1.811	3.253	-1.441
	Week 40	SEM	8.518	8.723	4.527
		95% CI	(-15.0,18.6)	(-14.0,20.5)	(-10.4, 7.5)
	Week 48	Pr >  t			0.7504
		n	19	12	
Week 56	LS Mean	-3.314	0.614	-3.928	
	SEM	8.538	8.978	5.041	
Week 64	95% CI	(-20.2,13.5)	(-17.1,18.3)	(-13.8, 6.0)	
	Pr >  t			0.4365	
Week 8	n	16	8		
	LS Mean	-1.573	-2.767	1.194	
Week 16	SEM	8.617	9.287	5.689	
	95% CI	(-18.6,15.4)	(-21.1,15.5)	(-10.0,12.4)	
Week 24	Pr >  t			0.8339	
	n	12	11		
Week 32	LS Mean	3.518	1.289	2.229	
	SEM	8.776	9.040	5.531	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.8,20.8)	(-16.5,19.1)	(-8.6,13.1)
		Pr >  t			0.6871
	Week 72	n	13	7	
		LS Mean	-0.525	-8.504	7.979
		SEM	8.741	9.417	6.062
		95% CI	(-17.8,16.7)	(-27.1,10.1)	(-3.9,19.9)
		Pr >  t			0.1889
	Week 84	n	12	6	
		LS Mean	3.601	-0.656	4.257
		SEM	8.767	9.586	6.372
		95% CI	(-13.7,20.9)	(-19.5,18.2)	(-8.3,16.8)
		Pr >  t			0.5045
	Week 96	n	7	6	
		LS Mean	2.495	-4.911	7.406
		SEM	9.198	9.585	6.954
		95% CI	(-15.6,20.6)	(-23.8,14.0)	(-6.3,21.1)
		Pr >  t			0.2875
	Week 108	n	5	3	
		LS Mean	0.501	-1.412	1.914
		SEM	9.591	10.66	8.797
		95% CI	(-18.4,19.4)	(-22.4,19.6)	(-15.4,19.2)
		Pr >  t			0.8279
	Week 120	n	8	3	
		LS Mean	1.117	4.144	-3.027
		SEM	9.111	10.66	8.242
		95% CI	(-16.8,19.1)	(-16.8,25.1)	(-19.2,13.2)
		Pr >  t			0.7136
	Week 132	n	2	1	
		LS Mean	-3.414	-7.563	4.149
		SEM	11.41	14.11	14.16
		95% CI	(-25.9,19.0)	(-35.3,20.2)	(-23.7,32.0)
		Pr >  t			0.7697
	Week 144	n	2		
		LS Mean	0.854		
		SEM	11.43		
		95% CI	(-21.6,23.3)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	0.854		
		SEM	11.43		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.6,23.3)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	-3.640	-1.574	-2.066
		SEM	2.546	2.651	2.532
		95% CI	(-8.7, 1.4)	(-6.8, 3.7)	(-7.0, 2.9)
		Pr >  t			0.4150
	Week 16	n	70	52	
		LS Mean	-1.215	-5.239	4.025
		SEM	2.618	2.803	2.715
		95% CI	(-6.4, 3.9)	(-10.8, 0.3)	(-1.3, 9.4)
		Pr >  t			0.1391
	Week 24	n	54	40	
		LS Mean	-2.729	-4.992	2.263
		SEM	2.741	2.979	2.986
		95% CI	(-8.1, 2.7)	(-10.9, 0.9)	(-3.6, 8.1)
		Pr >  t			0.4488
	Week 32	n	50	36	
		LS Mean	-3.053	-5.057	2.004
		SEM	2.790	3.044	3.087
		95% CI	(-8.5, 2.4)	(-11.0, 0.9)	(-4.1, 8.1)
		Pr >  t			0.5164
	Week 40	n	42	28	
		LS Mean	0.225	-2.398	2.623
		SEM	2.880	3.229	3.336
		95% CI	(-5.4, 5.9)	(-8.7, 3.9)	(-3.9, 9.2)
		Pr >  t			0.4320
	Week 48	n	38	24	
		LS Mean	-4.771	-5.970	1.199
		SEM	2.935	3.348	3.498
		95% CI	(-10.5, 1.0)	(-12.5, 0.6)	(-5.7, 8.1)
		Pr >  t			0.7319
	Week 56	n	33	24	
		LS Mean	-3.587	-2.991	-0.595
		SEM	3.021	3.350	3.576
		95% CI	(-9.5, 2.4)	(-9.6, 3.6)	(-7.6, 6.4)
		Pr >  t			0.8678
	Week 64	n	27	19	
		LS Mean	-1.367	-4.749	3.382
		SEM	3.155	3.555	3.880

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.6, 4.8)	(-11.7, 2.2)	(-4.2,11.0)
		Pr >  t			0.3836
	Week 72	n	26	17	
		LS Mean	-4.370	-2.664	-1.706
		SEM	3.182	3.662	3.999
		95% CI	(-10.6, 1.9)	(-9.9, 4.5)	(-9.6, 6.1)
		Pr >  t			0.6697
	Week 84	n	18	16	
		LS Mean	-7.505	-4.193	-3.312
		SEM	3.520	3.726	4.314
		95% CI	(-14.4,-0.6)	(-11.5, 3.1)	(-11.8, 5.2)
		Pr >  t			0.4429
	Week 96	n	20	10	
		LS Mean	-2.067	-4.215	2.148
		SEM	3.412	4.307	4.754
		95% CI	(-8.8, 4.6)	(-12.7, 4.2)	(-7.2,11.5)
		Pr >  t			0.6515
	Week 108	n	14	10	
		LS Mean	1.235	-2.075	3.310
		SEM	3.792	4.308	5.028
		95% CI	(-6.2, 8.7)	(-10.5, 6.4)	(-6.6,13.2)
		Pr >  t			0.5105
	Week 120	n	14	7	
		LS Mean	-4.241	-5.034	0.793
		SEM	3.777	4.884	5.527
		95% CI	(-11.7, 3.2)	(-14.6, 4.6)	(-10.1,11.6)
		Pr >  t			0.8860
	Week 132	n	12	5	
		LS Mean	-1.901	-9.312	7.411
		SEM	3.978	5.558	6.249
		95% CI	(-9.7, 5.9)	(-20.2, 1.6)	(-4.9,19.7)
		Pr >  t			0.2360
	Week 144	n	11	4	
		LS Mean	-11.07	-3.642	-7.433
		SEM	4.078	6.085	6.790
		95% CI	(-19.1,-3.1)	(-15.6, 8.3)	(-20.8, 5.9)
		Pr >  t			0.2740
	Week 156	n	8	3	
		LS Mean	-1.775	-9.190	7.415
		SEM	4.572	6.871	7.775



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.8, 7.2)	(-22.7, 4.3)	(-7.8,22.7)
		Pr >  t			0.3405
	Week 168	n	4	2	
		LS Mean	-9.854	-1.970	-7.884
		SEM	6.014	8.219	9.800
		95% CI	(-21.7, 1.9)	(-18.1,14.2)	(-27.1,11.4)
		Pr >  t			0.4214
	Week 180	n	1	1	
		LS Mean	-45.77	-2.021	-43.75
		SEM	11.30	11.33	15.75
		95% CI	(-67.9, -24)	(-24.3,20.2)	(-74.7, -13)
		Pr >  t			0.0056
	Week 192	n	1	1	
		LS Mean	-62.44	-2.021	-60.42
		SEM	11.30	11.33	15.75
		95% CI	(-84.6, -40)	(-24.3,20.2)	(-91.4, -29)
		Pr >  t			0.0001

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 10.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	-3.640	-1.574	-2.066		
			SEM	2.546	2.651	2.532		
			95% CI	(-8.7, 1.4)	(-6.8, 3.7)	(-7.0, 2.9)		
					Pr >  t			0.4150
		Week 16	n	70	52			
			LS Mean	-1.215	-5.239	4.025		
			SEM	2.618	2.803	2.715		
			95% CI	(-6.4, 3.9)	(-10.8, 0.3)	(-1.3, 9.4)		
					Pr >  t			0.1391
		Week 24	n	54	40			
			LS Mean	-2.729	-4.992	2.263		
			SEM	2.741	2.979	2.986		
			95% CI	(-8.1, 2.7)	(-10.9, 0.9)	(-3.6, 8.1)		
					Pr >  t			0.4488
		Week 32	n	50	36			
			LS Mean	-3.053	-5.057	2.004		
			SEM	2.790	3.044	3.087		
			95% CI	(-8.5, 2.4)	(-11.0, 0.9)	(-4.1, 8.1)		
					Pr >  t			0.5164
		Week 40	n	42	28			
			LS Mean	0.225	-2.398	2.623		
			SEM	2.880	3.229	3.336		
			95% CI	(-5.4, 5.9)	(-8.7, 3.9)	(-3.9, 9.2)		
			Pr >  t			0.4320		
Week 48	n	38	24					
	LS Mean	-4.771	-5.970	1.199				
	SEM	2.935	3.348	3.498				
	95% CI	(-10.5, 1.0)	(-12.5, 0.6)	(-5.7, 8.1)				
			Pr >  t			0.7319		
Week 56	n	33	24					
	LS Mean	-3.587	-2.991	-0.595				
	SEM	3.021	3.350	3.576				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-9.5, 2.4)	(-9.6, 3.6)	(-7.6, 6.4)
		Pr >  t			0.8678
		n	27	19	
		LS Mean	-1.367	-4.749	3.382
		SEM	3.155	3.555	3.880
Week 72		95% CI	(-7.6, 4.8)	(-11.7, 2.2)	(-4.2, 11.0)
		Pr >  t			0.3836
		n	26	17	
		LS Mean	-4.370	-2.664	-1.706
		SEM	3.182	3.662	3.999
Week 84		95% CI	(-10.6, 1.9)	(-9.9, 4.5)	(-9.6, 6.1)
		Pr >  t			0.6697
		n	18	16	
		LS Mean	-7.505	-4.193	-3.312
		SEM	3.520	3.726	4.314
Week 96		95% CI	(-14.4, -0.6)	(-11.5, 3.1)	(-11.8, 5.2)
		Pr >  t			0.4429
		n	20	10	
		LS Mean	-2.067	-4.215	2.148
		SEM	3.412	4.307	4.754
Week 108		95% CI	(-8.8, 4.6)	(-12.7, 4.2)	(-7.2, 11.5)
		Pr >  t			0.6515
		n	14	10	
		LS Mean	1.235	-2.075	3.310
		SEM	3.792	4.308	5.028
Week 120		95% CI	(-6.2, 8.7)	(-10.5, 6.4)	(-6.6, 13.2)
		Pr >  t			0.5105
		n	14	7	
		LS Mean	-4.241	-5.034	0.793
		SEM	3.777	4.884	5.527
Week 132		95% CI	(-11.7, 3.2)	(-14.6, 4.6)	(-10.1, 11.6)
		Pr >  t			0.8860
		n	12	5	
		LS Mean	-1.901	-9.312	7.411
		SEM	3.978	5.558	6.249
Week 144		95% CI	(-9.7, 5.9)	(-20.2, 1.6)	(-4.9, 19.7)
		Pr >  t			0.2360
		n	11	4	
	LS Mean	-11.07	-3.642	-7.433	
	SEM	4.078	6.085	6.790	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	(-19.1,-3.1)	(-15.6, 8.3)	(-20.8, 5.9)
		Pr >  t			0.2740
		n	8	3	
		LS Mean	-1.775	-9.190	7.415
	Week 168	SEM	4.572	6.871	7.775
		95% CI	(-10.8, 7.2)	(-22.7, 4.3)	(-7.8,22.7)
		Pr >  t			0.3405
		n	4	2	
	Week 180	LS Mean	-9.854	-1.970	-7.884
		SEM	6.014	8.219	9.800
		95% CI	(-21.7, 1.9)	(-18.1,14.2)	(-27.1,11.4)
		Pr >  t			0.4214
Week 192	n	1	1		
	LS Mean	-45.77	-2.021	-43.75	
	SEM	11.30	11.33	15.75	
	95% CI	(-67.9, -24)	(-24.3,20.2)	(-74.7, -13)	
Week 8	Pr >  t			0.0056	
	n	1	1		
	LS Mean	-62.44	-2.021	-60.42	
	SEM	11.30	11.33	15.75	
Week 16	95% CI	(-84.6, -40)	(-24.3,20.2)	(-91.4, -29)	
	Pr >  t			0.0001	
	n	53	64		
	LS Mean	-0.582	-0.812	0.230	
Week 24	SEM	4.378	4.703	2.954	
	95% CI	(-9.2, 8.1)	(-10.1, 8.5)	(-5.6, 6.1)	
	Pr >  t			0.9380	
	n	48	48		
Week 32	LS Mean	0.615	-2.255	2.870	
	SEM	4.459	4.790	3.132	
	95% CI	(-8.2, 9.4)	(-11.7, 7.2)	(-3.3, 9.0)	
	Pr >  t			0.3604	
Week 32	n	46	36		
	LS Mean	-3.541	-1.678	-1.863	
	SEM	4.471	4.888	3.303	
	95% CI	(-12.4, 5.3)	(-11.3, 8.0)	(-8.4, 4.6)	
Week 32	Pr >  t			0.5731	
	n	31	33		
	LS Mean	-1.044	2.638	-3.682	
	SEM	4.677	4.924	3.546	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.3, 8.2)	(-7.1, 12.4)	(-10.7, 3.3)
		Pr >  t			0.2998
	Week 40	n	28	30	
		LS Mean	0.496	0.619	-0.123
		SEM	4.722	4.961	3.655
		95% CI	(-8.8, 9.8)	(-9.2, 10.4)	(-7.3, 7.1)
		Pr >  t			0.9733
	Week 48	n	26	23	
		LS Mean	-2.762	-1.328	-1.434
		SEM	4.755	5.081	3.859
		95% CI	(-12.1, 6.6)	(-11.4, 8.7)	(-9.0, 6.2)
		Pr >  t			0.7104
	Week 56	n	22	17	
		LS Mean	-1.698	-3.992	2.293
		SEM	4.836	5.255	4.181
		95% CI	(-11.2, 7.8)	(-14.4, 6.4)	(-5.9, 10.5)
		Pr >  t			0.5835
	Week 64	n	17	19	
		LS Mean	-0.025	-2.051	2.026
		SEM	4.988	5.187	4.274
		95% CI	(-9.9, 9.8)	(-12.3, 8.2)	(-6.4, 10.4)
		Pr >  t			0.6356
	Week 72	n	20	14	
		LS Mean	-2.334	-6.330	3.995
		SEM	4.894	5.391	4.412
		95% CI	(-12.0, 7.3)	(-17.0, 4.3)	(-4.7, 12.7)
		Pr >  t			0.3656
	Week 84	n	19	13	
		LS Mean	1.045	-2.435	3.480
		SEM	4.919	5.448	4.511
		95% CI	(-8.7, 10.7)	(-13.2, 8.3)	(-5.4, 12.3)
		Pr >  t			0.4408
	Week 96	n	12	12	
		LS Mean	0.878	-6.454	7.331
		SEM	5.252	5.514	4.947
		95% CI	(-9.5, 11.2)	(-17.3, 4.4)	(-2.4, 17.0)
		Pr >  t			0.1389
	Week 108	n	9	9	
		LS Mean	-0.709	-7.039	6.330
		SEM	5.534	5.787	5.531

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.6,10.2)	(-18.4, 4.4)	( -4.5,17.2)
		Pr >  t			0.2529
	Week 120	n	12	7	
		LS Mean	-0.786	1.771	-2.557
		SEM	5.263	6.084	5.581
		95% CI	(-11.1, 9.6)	(-10.2,13.7)	(-13.5, 8.4)
		Pr >  t			0.6470
	Week 132	n	5	2	
		LS Mean	-0.803	-9.042	8.239
		SEM	6.345	8.699	9.079
		95% CI	(-13.3,11.7)	(-26.1, 8.0)	( -9.6,26.1)
		Pr >  t			0.3646
	Week 144	n	3	1	
		LS Mean	-3.842	-0.507	-3.335
		SEM	7.408	11.43	12.33
		95% CI	(-18.4,10.7)	(-23.0,21.9)	(-27.6,20.9)
		Pr >  t			0.7869
	Week 156	n	2		
		LS Mean	-0.848		
		SEM	8.553		
		95% CI	(-17.6,15.9)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-40: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Soziale Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	-6.687	1.301	-7.988		
			SEM	2.937	2.935	2.584		
			95% CI	(-12.5,-0.9)	(-4.5, 7.1)	(-13.1,-2.9)		
					Pr >  t			0.0021
		Week 16	n	92	83			
			LS Mean	-2.587	0.461	-3.048		
			SEM	3.015	3.102	2.783		
			95% CI	(-8.5, 3.3)	(-5.6, 6.6)	(-8.5, 2.4)		
					Pr >  t			0.2739
		Week 24	n	77	59			
			LS Mean	-7.182	-0.464	-6.719		
			SEM	3.082	3.289	3.055		
			95% CI	(-13.2,-1.1)	(-6.9, 6.0)	(-12.7,-0.7)		
					Pr >  t			0.0282
		Week 32	n	57	53			
			LS Mean	-2.830	-2.142	-0.688		
			SEM	3.262	3.348	3.271		
			95% CI	(-9.2, 3.6)	(-8.7, 4.4)	(-7.1, 5.7)		
					Pr >  t			0.8335
		Week 40	n	50	44			
			LS Mean	-1.762	-1.247	-0.514		
			SEM	3.337	3.475	3.461		
			95% CI	(-8.3, 4.8)	(-8.1, 5.6)	(-7.3, 6.3)		
			Pr >  t			0.8819		
Week 48	n	47	37					
	LS Mean	-3.793	-2.278	-1.514				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	3.372	3.595	3.616
	95% CI	(-10.4, 2.8)	(-9.3, 4.8)	(-8.6, 5.6)
	Pr >  t			0.6755
Week 56	n	40	32	
	LS Mean	-4.646	-0.391	-4.255
	SEM	3.476	3.707	3.822
	95% CI	(-11.5, 2.2)	(-7.7, 6.9)	(-11.8, 3.2)
	Pr >  t			0.2659
Week 64	n	32	27	
	LS Mean	-3.849	-2.196	-1.652
	SEM	3.639	3.853	4.109
	95% CI	(-11.0, 3.3)	(-9.8, 5.4)	(-9.7, 6.4)
	Pr >  t			0.6876
Week 72	n	31	23	
	LS Mean	-0.859	2.975	-3.835
	SEM	3.667	4.006	4.276
	95% CI	(-8.1, 6.3)	(-4.9, 10.8)	(-12.2, 4.6)
	Pr >  t			0.3700
Week 84	n	27	21	
	LS Mean	-4.392	-1.836	-2.556
	SEM	3.789	4.100	4.462
	95% CI	(-11.8, 3.0)	(-9.9, 6.2)	(-11.3, 6.2)
	Pr >  t			0.5669
Week 96	n	23	16	
	LS Mean	-3.193	-2.876	-0.317
	SEM	3.934	4.421	4.883
	95% CI	(-10.9, 4.5)	(-11.6, 5.8)	(-9.9, 9.3)
	Pr >  t			0.9483
Week 108	n	15	14	
	LS Mean	-3.450	-0.929	-2.522
	SEM	4.443	4.603	5.449
	95% CI	(-12.2, 5.3)	(-10.0, 8.1)	(-13.2, 8.2)
	Pr >  t			0.6436
Week 120	n	18	8	
	LS Mean	0.450	4.844	-4.394
	SEM	4.209	5.562	6.122
	95% CI	(-7.8, 8.7)	(-6.1, 15.8)	(-16.4, 7.6)
	Pr >  t			0.4731
Week 132	n	12	4	
	LS Mean	-7.467	-10.70	3.230



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	4.770	7.301	8.051
		95% CI	(-16.8, 1.9)	(-25.0, 3.6)	(-12.6,19.0)
		Pr >  t			0.6884
	Week 144	n	8	3	
		LS Mean	-7.642	-0.184	-7.458
		SEM	5.482	8.273	9.353
		95% CI	(-18.4, 3.1)	(-16.4,16.0)	(-25.8,10.9)
		Pr >  t			0.4254
	Week 156	n	5	1	
		LS Mean	-13.47	-1.020	-12.45
		SEM	6.610	13.70	14.84
		95% CI	(-26.4,-0.5)	(-27.9,25.9)	(-41.6,16.7)
		Pr >  t			0.4018
	Week 168	n	2	1	
		LS Mean	-6.345	-1.020	-5.325
		SEM	9.884	13.70	16.56
		95% CI	(-25.7,13.0)	(-27.9,25.9)	(-37.8,27.2)
		Pr >  t			0.7479
	Week 180	n	1		
		LS Mean	7.909		
		SEM	13.66		
		95% CI	(-18.9,34.7)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-8.751		
		SEM	13.66		
		95% CI	(-35.6,18.1)		
		Pr >  t			
Yes	Week 8	n	38	30	
		LS Mean	-3.453	1.342	-4.796
		SEM	5.088	5.450	4.537
		95% CI	(-13.6, 6.7)	( -9.5,12.2)	(-13.8, 4.2)
		Pr >  t			0.2924
	Week 16	n	32	24	
		LS Mean	-6.538	-2.333	-4.205
		SEM	5.168	5.606	4.874
		95% CI	(-16.8, 3.7)	(-13.5, 8.8)	(-13.8, 5.4)
		Pr >  t			0.3896
	Week 24	n	28	22	
		LS Mean	-4.271	3.660	-7.931

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	5.315	5.672	5.054
	95% CI	(-14.8, 6.3)	(-7.6,14.9)	(-17.9, 2.0)
	Pr >  t			0.1184
Week 32	n	29	20	
	LS Mean	-5.467	-1.521	-3.946
	SEM	5.296	5.819	5.125
	95% CI	(-16.0, 5.1)	(-13.1,10.0)	(-14.1, 6.2)
	Pr >  t			0.4423
Week 40	n	25	18	
	LS Mean	-4.323	-3.911	-0.411
	SEM	5.389	5.905	5.324
	95% CI	(-15.0, 6.4)	(-15.6, 7.8)	(-10.9,10.1)
	Pr >  t			0.9385
Week 48	n	22	14	
	LS Mean	-4.987	-0.287	-4.701
	SEM	5.479	6.141	5.678
	95% CI	(-15.9, 5.9)	(-12.4,11.9)	(-15.9, 6.5)
	Pr >  t			0.4085
Week 56	n	19	13	
	LS Mean	-2.760	-2.212	-0.548
	SEM	5.589	6.226	5.881
	95% CI	(-13.8, 8.3)	(-14.5,10.1)	(-12.1,11.0)
	Pr >  t			0.9258
Week 64	n	15	15	
	LS Mean	-6.616	0.298	-6.913
	SEM	5.794	6.079	5.934
	95% CI	(-18.1, 4.9)	(-11.7,12.3)	(-18.6, 4.8)
	Pr >  t			0.2450
Week 72	n	17	12	
	LS Mean	-12.20	-3.583	-8.613
	SEM	5.681	6.314	6.066
	95% CI	(-23.5,-0.9)	(-16.1, 8.9)	(-20.6, 3.3)
	Pr >  t			0.1567
Week 84	n	13	12	
	LS Mean	-15.87	-3.296	-12.57
	SEM	5.982	6.316	6.319
	95% CI	(-27.7,-4.0)	(-15.8, 9.2)	(-25.0,-0.1)
	Pr >  t			0.0475
Week 96	n	12	8	
	LS Mean	-7.498	-10.88	3.380

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	6.074	6.864	6.948
		95% CI	(-19.5, 4.5)	(-24.4, 2.7)	(-10.3,17.0)
		Pr >  t			0.6269
	Week 108	n	11	7	
		LS Mean	-6.301	-4.163	-2.137
		SEM	6.183	7.086	7.259
		95% CI	(-18.5, 5.9)	(-18.1, 9.8)	(-16.4,12.1)
		Pr >  t			0.7686
	Week 120	n	10	8	
		LS Mean	-15.46	-5.782	-9.681
		SEM	6.305	6.866	7.153
		95% CI	(-27.9,-3.0)	(-19.3, 7.8)	(-23.7, 4.4)
		Pr >  t			0.1767
	Week 132	n	8	4	
		LS Mean	-15.21	-1.192	-14.02
		SEM	6.632	8.275	8.760
		95% CI	(-28.3,-2.1)	(-17.5,15.1)	(-31.2, 3.2)
		Pr >  t			0.1103
	Week 144	n	7	2	
		LS Mean	-10.78	-0.602	-10.18
		SEM	6.859	10.54	11.06
		95% CI	(-24.3, 2.7)	(-21.3,20.1)	(-31.9,11.5)
		Pr >  t			0.3577
	Week 156	n	5	2	
		LS Mean	-1.496	-8.937	7.440
		SEM	7.534	10.54	11.49
		95% CI	(-16.3,13.3)	(-29.6,11.8)	(-15.1,30.0)
		Pr >  t			0.5176
	Week 168	n	2	1	
		LS Mean	-9.622	1.213	-10.83
		SEM	10.35	13.99	16.34
		95% CI	(-30.0,10.7)	(-26.3,28.7)	(-43.0,21.3)
		Pr >  t			0.5077
	Week 180	n		1	
		LS Mean		1.213	
		SEM		13.99	
		95% CI		(-26.3,28.7)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		1.213	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM		13.99	
	95% CI		(-26.3,28.7)	
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	-10.20	5.133	-15.33		
			SEM	4.537	4.248	3.924		
			95% CI	(-19.2,-1.2)	(-3.3,13.6)	(-23.1,-7.6)		
					Pr >  t			0.0001
		Week 16	n	30	30			
			LS Mean	-9.569	4.324	-13.89		
			SEM	4.565	4.463	4.119		
			95% CI	(-18.6,-0.5)	(-4.5,13.2)	(-22.0,-5.8)		
					Pr >  t			0.0009
		Week 24	n	21	26			
			LS Mean	-6.330	3.406	-9.736		
			SEM	4.829	4.553	4.536		
			95% CI	(-15.9, 3.2)	(-5.6,12.4)	(-18.7,-0.8)		
					Pr >  t			0.0330
		Week 32	n	19	24			
			LS Mean	-6.930	2.906	-9.836		
			SEM	4.913	4.614	4.696		
			95% CI	(-16.7, 2.8)	(-6.2,12.0)	(-19.1,-0.6)		
					Pr >  t			0.0373
		Week 40	n	16	19			
			LS Mean	-4.832	-1.200	-3.631		
			SEM	5.065	4.864	5.064		
			95% CI	(-14.9, 5.2)	(-10.8, 8.4)	(-13.6, 6.3)		
					Pr >  t			0.4739
		Week 48	n	16	18			
			LS Mean	-7.957	1.366	-9.322		
			SEM	5.065	4.913	5.111		
95% CI	(-18.0, 2.1)		(-8.4,11.1)	(-19.4, 0.7)				
			Pr >  t			0.0693		
Week 56	n	12	14					
	LS Mean	-9.383	-1.017	-8.366				
	SEM	5.369	5.165	5.665				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.0, 1.2)	(-11.2, 9.2)	(-19.5, 2.8)
		Pr >  t			0.1407
	Week 64	n	12	11	
		LS Mean	-2.439	-1.983	-0.457
		SEM	5.369	5.460	5.935
		95% CI	(-13.0, 8.2)	(-12.8, 8.8)	(-12.1,11.2)
		Pr >  t			0.9387
	Week 72	n	10	9	
		LS Mean	-3.703	2.462	-6.165
		SEM	5.601	5.742	6.389
		95% CI	(-14.8, 7.4)	(-8.9,13.8)	(-18.7, 6.4)
		Pr >  t			0.3352
	Week 84	n	8	8	
		LS Mean	-7.387	-1.718	-5.670
		SEM	5.996	5.932	6.854
		95% CI	(-19.2, 4.4)	(-13.4,10.0)	(-19.1, 7.8)
		Pr >  t			0.4086
	Week 96	n	6	6	
		LS Mean	-9.345	-8.859	-0.486
		SEM	6.510	6.456	7.743
		95% CI	(-22.2, 3.5)	(-21.6, 3.9)	(-15.7,14.7)
		Pr >  t			0.9500
	Week 108	n	4	5	
		LS Mean	-3.692	-1.539	-2.153
		SEM	7.427	6.847	8.827
		95% CI	(-18.3,10.9)	(-15.0,11.9)	(-19.5,15.2)
		Pr >  t			0.8074
	Week 120	n	4	4	
		LS Mean	-3.692	-3.293	-0.399
		SEM	7.427	7.391	9.256
		95% CI	(-18.3,10.9)	(-17.8,11.2)	(-18.6,17.8)
		Pr >  t			0.9656
	Week 132	n	3	2	
		LS Mean	-8.555	-10.55	1.998
		SEM	8.234	9.603	11.65
		95% CI	(-24.7, 7.6)	(-29.4, 8.3)	(-20.9,24.9)
		Pr >  t			0.8640
	Week 144	n	3	1	
		LS Mean	-19.66	-0.345	-19.32
		SEM	8.234	12.96	14.54

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-35.9,-3.5)	(-25.8,25.1)	(-47.9, 9.3)
		Pr >  t			0.1848
	Week 156	n	2	1	
		LS Mean	-3.655	-0.345	-3.310
		SEM	9.638	12.96	15.38
		95% CI	(-22.6,15.3)	(-25.8,25.1)	(-33.6,26.9)
		Pr >  t			0.8297
	Week 168	n	1		
		LS Mean	-36.92		
		SEM	12.96		
		95% CI	(-62.4, -11)		
		Pr >  t			
Other	Week 8	n	16	17	
		LS Mean	-8.036	-2.587	-5.449
		SEM	10.54	10.28	6.768
		95% CI	(-29.3,13.2)	(-23.2,18.1)	(-19.1, 8.2)
		Pr >  t			0.4256
	Week 16	n	15	14	
		LS Mean	-4.176	-2.634	-1.542
		SEM	10.60	9.772	7.265
		95% CI	(-25.5,17.2)	(-22.4,17.1)	(-16.2,13.1)
		Pr >  t			0.8329
	Week 24	n	12	11	
		LS Mean	-4.044	-10.15	6.106
		SEM	10.79	10.59	7.799
		95% CI	(-25.7,17.6)	(-31.4,11.1)	(-9.5,21.7)
		Pr >  t			0.4368
	Week 32	n	8	9	
		LS Mean	-5.544	-8.827	3.282
		SEM	11.21	10.80	8.619
		95% CI	(-28.0,16.9)	(-30.4,12.8)	(-13.9,20.4)
		Pr >  t			0.7043
	Week 40	n	6	7	
		LS Mean	-5.980	-5.780	-0.200
		SEM	11.59	11.07	9.404
		95% CI	(-29.2,17.2)	(-27.9,16.3)	(-18.9,18.5)
		Pr >  t			0.9830
	Week 48	n	4	6	
		LS Mean	-2.751	2.616	-5.367
		SEM	12.28	11.28	10.48

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-27.2,21.7)	(-19.9,25.1)	(-26.1,15.4)
		Pr >  t			0.6095
	Week 56	n	4	6	
		LS Mean	-8.325	2.087	-10.41
		SEM	12.28	11.31	10.51
		95% CI	(-32.8,16.1)	(-20.5,24.6)	(-31.2,10.4)
		Pr >  t			0.3239
	Week 64	n	4	4	
		LS Mean	-3.085	0.827	-3.912
		SEM	12.30	11.97	11.21
		95% CI	(-27.6,21.4)	(-23.0,24.6)	(-26.1,18.3)
		Pr >  t			0.7277
	Week 72	n	4	4	
		LS Mean	-3.085	-3.338	0.253
		SEM	12.30	11.97	11.21
		95% CI	(-27.6,21.4)	(-27.1,20.5)	(-21.9,22.4)
		Pr >  t			0.9821
	Week 84	n	4	4	
		LS Mean	-2.751	-7.505	4.754
		SEM	12.28	11.97	11.21
		95% CI	(-27.2,21.7)	(-31.3,16.3)	(-17.4,26.9)
		Pr >  t			0.6723
	Week 96	n	3	2	
		LS Mean	-2.692	-2.562	-0.130
		SEM	12.92	13.77	13.71
		95% CI	(-28.4,23.0)	(-29.8,24.7)	(-27.2,27.0)
		Pr >  t			0.9924
	Week 108	n	3	3	
		LS Mean	-8.249	3.674	-11.92
		SEM	12.92	12.64	12.58
		95% CI	(-33.9,17.4)	(-21.4,28.8)	(-36.8,12.9)
		Pr >  t			0.3449
	Week 120	n	2	1	
		LS Mean	-3.025	-2.553	-0.472
		SEM	14.09	16.80	17.65
		95% CI	(-30.9,24.9)	(-35.8,30.6)	(-35.4,34.4)
		Pr >  t			0.9787
	Week 132	n	2	1	
		LS Mean	-20.60	-2.553	-18.04
		SEM	14.07	16.80	17.66



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-48.5, 7.3)	(-35.8,30.6)	(-53.0,16.9)
		Pr >  t			0.3088
	Week 156	n	1		
		LS Mean	-5.837		
		SEM	17.09		
		95% CI	(-39.6,28.0)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-5.837		
		SEM	17.09		
		95% CI	(-39.6,28.0)		
		Pr >  t			
White	Week 8	n	93	85	
		LS Mean	-5.386	-0.950	-4.436
		SEM	3.210	3.378	2.999
		95% CI	(-11.7, 0.9)	( -7.6, 5.7)	(-10.3, 1.5)
		Pr >  t			0.1400
	Week 16	n	79	61	
		LS Mean	-2.731	-3.686	0.955
		SEM	3.311	3.623	3.293
		95% CI	( -9.3, 3.8)	(-10.8, 3.4)	( -5.5, 7.4)
		Pr >  t			0.7720
	Week 24	n	71	43	
		LS Mean	-7.728	0.363	-8.091
		SEM	3.371	3.836	3.579
		95% CI	(-14.4,-1.1)	( -7.2, 7.9)	(-15.1,-1.1)
		Pr >  t			0.0242
	Week 32	n	59	39	
		LS Mean	-3.610	-4.419	0.810
		SEM	3.498	3.923	3.739
		95% CI	(-10.5, 3.3)	(-12.1, 3.3)	( -6.5, 8.2)
		Pr >  t			0.8287
	Week 40	n	52	35	
		LS Mean	-2.383	-3.281	0.898
		SEM	3.568	4.002	3.887
		95% CI	( -9.4, 4.6)	(-11.1, 4.6)	( -6.7, 8.5)
		Pr >  t			0.8173
	Week 48	n	48	26	
		LS Mean	-4.183	-6.282	2.099
		SEM	3.614	4.247	4.178

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.3, 2.9)	(-14.6, 2.1)	(-6.1,10.3)
		Pr >  t			0.6155
	Week 56	n	42	24	
		LS Mean	-3.999	-3.397	-0.602
		SEM	3.692	4.322	4.325
		95% CI	(-11.3, 3.3)	(-11.9, 5.1)	(-9.1, 7.9)
		Pr >  t			0.8894
	Week 64	n	30	26	
		LS Mean	-6.904	-3.710	-3.194
		SEM	3.932	4.249	4.465
		95% CI	(-14.6, 0.8)	(-12.1, 4.6)	(-12.0, 5.6)
		Pr >  t			0.4745
	Week 72	n	34	21	
		LS Mean	-6.581	-1.830	-4.751
		SEM	3.838	4.455	4.581
		95% CI	(-14.1, 1.0)	(-10.6, 6.9)	(-13.7, 4.2)
		Pr >  t			0.3000
	Week 84	n	28	20	
		LS Mean	-10.33	-4.491	-5.837
		SEM	3.997	4.505	4.758
		95% CI	(-18.2,-2.5)	(-13.3, 4.4)	(-15.2, 3.5)
		Pr >  t			0.2203
	Week 96	n	26	15	
		LS Mean	-4.785	-5.509	0.724
		SEM	4.055	4.849	5.137
		95% CI	(-12.8, 3.2)	(-15.0, 4.0)	(-9.4,10.8)
		Pr >  t			0.8879
	Week 108	n	19	12	
		LS Mean	-5.051	-5.634	0.583
		SEM	4.387	5.170	5.684
		95% CI	(-13.7, 3.6)	(-15.8, 4.5)	(-10.6,11.7)
		Pr >  t			0.9183
	Week 120	n	22	10	
		LS Mean	-6.512	-1.928	-4.584
		SEM	4.221	5.469	5.844
		95% CI	(-14.8, 1.8)	(-12.7, 8.8)	(-16.1, 6.9)
		Pr >  t			0.4330
	Week 132	n	15	4	
		LS Mean	-10.23	-2.281	-7.950
		SEM	4.676	7.638	8.158

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.4,-1.1)	(-17.3,12.7)	(-24.0, 8.1)
		Pr >  t			0.3300
	Week 144	n	12	4	
		LS Mean	-6.795	-2.057	-4.738
		SEM	4.991	7.642	8.355
		95% CI	(-16.6, 3.0)	(-17.1,12.9)	(-21.1,11.7)
		Pr >  t			0.5707
	Week 156	n	7	2	
		LS Mean	-9.074	-10.16	1.087
		SEM	6.021	10.27	11.32
		95% CI	(-20.9, 2.7)	(-30.3,10.0)	(-21.1,23.3)
		Pr >  t			0.9235
	Week 168	n	2	2	
		LS Mean	5.094	-1.826	6.920
		SEM	10.16	10.27	13.96
		95% CI	(-14.8,25.0)	(-22.0,18.3)	(-20.5,34.3)
		Pr >  t			0.6204
	Week 180	n	1	1	
		LS Mean	7.841	-0.342	8.183
		SEM	14.05	14.10	19.56
		95% CI	(-19.7,35.4)	(-28.0,27.3)	(-30.2,46.6)
		Pr >  t			0.6758
	Week 192	n	1	1	
		LS Mean	-8.819	-0.342	-8.477
		SEM	14.05	14.10	19.56
		95% CI	(-36.4,18.8)	(-28.0,27.3)	(-46.9,29.9)
		Pr >  t			0.6648

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	-7.499	5.136	-12.64		
			SEM	4.657	4.309	4.056		
			95% CI	(-16.8, 1.8)	(-3.4,13.7)	(-20.7,-4.6)		
					Pr >  t			0.0022
		Week 16	n	28	29			
			LS Mean	-10.44	4.296	-14.73		
			SEM	4.686	4.528	4.255		
			95% CI	(-19.8,-1.1)	(-4.7,13.3)	(-23.1,-6.3)		
					Pr >  t			0.0007
		Week 24	n	21	25			
			LS Mean	-5.757	3.320	-9.077		
			SEM	4.890	4.620	4.605		
			95% CI	(-15.5, 4.0)	(-5.8,12.5)	(-18.2, 0.0)		
					Pr >  t			0.0502
		Week 32	n	19	23			
			LS Mean	-6.383	2.804	-9.187		
			SEM	4.970	4.683	4.762		
			95% CI	(-16.2, 3.5)	(-6.5,12.1)	(-18.6, 0.2)		
					Pr >  t			0.0551
		Week 40	n	16	18			
			LS Mean	-4.307	-1.556	-2.751		
			SEM	5.114	4.941	5.130		
			95% CI	(-14.4, 5.8)	(-11.3, 8.2)	(-12.9, 7.4)		
					Pr >  t			0.5923
		Week 48	n	16	17			
			LS Mean	-7.432	1.139	-8.571		
			SEM	5.114	4.993	5.180		
95% CI	(-17.6, 2.7)		(-8.7,11.0)	(-18.8, 1.6)				
			Pr >  t			0.0993		
Week 56	n	12	14					
	LS Mean	-8.848	-1.170	-7.678				
	SEM	5.403	5.182	5.658				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-19.5, 1.8)	(-11.4, 9.1)	(-18.8, 3.5)
	Pr >  t			0.1759
	n	12	11	
	LS Mean	-1.904	-2.138	0.234
	SEM	5.403	5.464	5.918
Week 72	95% CI	(-12.6, 8.8)	(-12.9, 8.6)	(-11.4,11.9)
	Pr >  t			0.9685
	n	10	8	
	LS Mean	-3.137	2.314	-5.451
	SEM	5.624	5.916	6.518
Week 84	95% CI	(-14.2, 8.0)	(-9.3,14.0)	(-18.3, 7.4)
	Pr >  t			0.4036
	n	8	8	
	LS Mean	-6.853	-1.852	-5.001
	SEM	6.000	5.916	6.801
Week 96	95% CI	(-18.7, 5.0)	(-13.5, 9.8)	(-18.4, 8.4)
	Pr >  t			0.4626
	n	6	6	
	LS Mean	-8.843	-9.008	0.165
	SEM	6.492	6.420	7.659
Week 108	95% CI	(-21.6, 3.9)	(-21.7, 3.6)	(-14.9,15.2)
	Pr >  t			0.9828
	n	4	5	
	LS Mean	-3.190	-1.665	-1.525
	SEM	7.373	6.795	8.708
Week 120	95% CI	(-17.7,11.3)	(-15.0,11.7)	(-18.6,15.6)
	Pr >  t			0.8611
	n	4	4	
	LS Mean	-3.190	-3.431	0.240
	SEM	7.373	7.320	9.125
Week 132	95% CI	(-17.7,11.3)	(-17.8,11.0)	(-17.7,18.2)
	Pr >  t			0.9790
	n	3	2	
	LS Mean	-8.045	-10.62	2.580
	SEM	8.151	9.459	11.45
Week 144	95% CI	(-24.1, 8.0)	(-29.2, 8.0)	(-19.9,25.1)
	Pr >  t			0.8219
	n	3	1	
	LS Mean	-19.16	-0.465	-18.69
	SEM	8.151	12.72	14.26

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-35.2,-3.1)	(-25.5,24.5)	(-46.7, 9.4)
		Pr >  t			0.1909
	Week 156	n	2	1	
		LS Mean	-3.149	-0.465	-2.683
		SEM	9.508	12.72	15.08
		95% CI	(-21.8,15.5)	(-25.5,24.5)	(-32.3,27.0)
		Pr >  t			0.8588
	Week 168	n	1		
		LS Mean	-36.40		
		SEM	12.73		
		95% CI	(-61.4, -11)		
		Pr >  t			
	Week 8	n	66	68	
		LS Mean	-6.974	-2.438	-4.536
		SEM	6.905	6.907	3.669
		95% CI	(-20.6, 6.7)	(-16.1,11.2)	(-11.8, 2.7)
		Pr >  t			0.2177
	Week 16	n	58	48	
		LS Mean	-2.415	-3.381	0.966
		SEM	6.939	7.012	4.001
		95% CI	(-16.2,11.3)	(-17.3,10.5)	( -6.9, 8.8)
		Pr >  t			0.8094
	Week 24	n	51	36	
		LS Mean	-10.01	-0.287	-9.725
		SEM	6.980	7.121	4.301
		95% CI	(-23.8, 3.8)	(-14.4,13.8)	(-18.2,-1.3)
		Pr >  t			0.0244
	Week 32	n	43	30	
		LS Mean	-5.623	-3.999	-1.624
		SEM	7.092	7.274	4.558
		95% CI	(-19.7, 8.4)	(-18.4,10.4)	(-10.6, 7.3)
		Pr >  t			0.7219
	Week 40	n	37	25	
		LS Mean	-3.624	1.287	-4.911
		SEM	7.153	7.377	4.812
		95% CI	(-17.8,10.5)	(-13.3,15.9)	(-14.4, 4.5)
		Pr >  t			0.3079
	Week 48	n	33	21	
		LS Mean	-6.064	-5.124	-0.940
		SEM	7.204	7.491	5.058

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-20.3, 8.2)	(-19.9, 9.7)	(-10.9, 9.0)
	Pr >  t			0.8526
	n	29	20	
	LS Mean	-4.982	-3.710	-1.272
	SEM	7.265	7.527	5.201
Week 64	95% CI	(-19.3, 9.4)	(-18.6,11.2)	(-11.5, 8.9)
	Pr >  t			0.8069
	n	23	20	
	LS Mean	-8.685	-2.935	-5.751
	SEM	7.394	7.529	5.382
Week 72	95% CI	(-23.3, 5.9)	(-17.8,11.9)	(-16.3, 4.8)
	Pr >  t			0.2857
	n	25	19	
	LS Mean	-9.035	-1.331	-7.705
	SEM	7.347	7.565	5.366
Week 84	95% CI	(-23.6, 5.5)	(-16.3,13.6)	(-18.2, 2.8)
	Pr >  t			0.1516
	n	22	17	
	LS Mean	-13.40	-3.795	-9.609
	SEM	7.423	7.651	5.591
Week 96	95% CI	(-28.1, 1.3)	(-18.9,11.3)	(-20.6, 1.4)
	Pr >  t			0.0861
	n	20	13	
	LS Mean	-7.567	-5.491	-2.076
	SEM	7.488	7.897	6.004
Week 108	95% CI	(-22.4, 7.2)	(-21.1,10.1)	(-13.9, 9.7)
	Pr >  t			0.7296
	n	15	11	
	LS Mean	-8.016	-5.464	-2.553
	SEM	7.720	8.081	6.520
Week 120	95% CI	(-23.2, 7.2)	(-21.4,10.5)	(-15.4,10.2)
	Pr >  t			0.6955
	n	16	8	
	LS Mean	-9.155	-1.284	-7.872
	SEM	7.667	8.512	6.986
Week 132	95% CI	(-24.3, 6.0)	(-18.0,15.5)	(-21.6, 5.8)
	Pr >  t			0.2602
	n	12	3	
	LS Mean	-13.60	-1.720	-11.88
	SEM	7.938	10.76	9.815

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-29.3, 2.0)	(-22.8,19.4)	(-31.2, 7.4)
		Pr >  t			0.2263
	Week 144	n	7	4	
		LS Mean	-12.51	-1.609	-10.90
		SEM	8.678	9.926	9.562
		95% CI	(-29.6, 4.6)	(-21.1,17.9)	(-29.7, 7.9)
		Pr >  t			0.2545
	Week 156	n	5	2	
		LS Mean	-9.119	-9.799	0.680
		SEM	9.333	12.25	12.44
		95% CI	(-27.5, 9.2)	(-33.9,14.3)	(-23.7,25.1)
		Pr >  t			0.9564
	Week 168	n	2	2	
		LS Mean	5.452	-1.464	6.916
		SEM	12.21	12.25	14.72
		95% CI	(-18.5,29.4)	(-25.5,22.6)	(-22.0,35.8)
		Pr >  t			0.6386
	Week 180	n		1	
		LS Mean		-0.069	
		SEM		15.89	
		95% CI		(-31.3,31.1)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.069	
		SEM		15.89	
		95% CI		(-31.3,31.1)	
		Pr >  t			
Latin America	Week 8	n	14	13	
		LS Mean	0.429	6.762	-6.334
		SEM	5.292	5.286	7.521
		95% CI	(-10.3,11.1)	(-3.9,17.4)	(-21.5, 8.9)
		Pr >  t			0.4048
	Week 16	n	13	12	
		LS Mean	4.089	5.441	-1.352
		SEM	5.383	5.406	7.646
		95% CI	(-6.8,15.0)	(-5.5,16.3)	(-16.8,14.1)
		Pr >  t			0.8605
	Week 24	n	12	10	
		LS Mean	2.615	1.549	1.067
		SEM	5.469	5.647	7.883



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-8.4,13.6)	(-9.8,12.9)	(-14.8,16.9)
	Pr >  t			0.8930
	n	9	10	
	LS Mean	1.405	3.216	-1.810
	SEM	5.836	5.647	8.141
Week 40	95% CI	(-10.3,13.1)	(-8.1,14.6)	(-18.2,14.5)
	Pr >  t			0.8249
	n	7	10	
	LS Mean	-1.646	3.215	-4.861
	SEM	6.196	5.647	8.401
Week 48	95% CI	(-14.0,10.7)	(-8.1,14.6)	(-21.7,12.0)
	Pr >  t			0.5651
	n	7	7	
	LS Mean	0.735	8.834	-8.099
	SEM	6.196	6.129	8.715
Week 56	95% CI	(-11.6,13.1)	(-3.4,21.1)	(-25.5, 9.3)
	Pr >  t			0.3563
	n	6	7	
	LS Mean	0.499	13.150	-12.65
	SEM	6.456	6.129	8.912
Week 64	95% CI	(-12.4,13.4)	( 0.9,25.4)	(-30.4, 5.1)
	Pr >  t			0.1603
	n	4	7	
	LS Mean	4.085	6.532	-2.447
	SEM	7.235	6.125	9.483
Week 72	95% CI	(-10.3,18.4)	(-5.7,18.8)	(-21.3,16.4)
	Pr >  t			0.7970
	n	4	4	
	LS Mean	4.085	5.798	-1.712
	SEM	7.235	7.158	10.18
Week 84	95% CI	(-10.3,18.4)	(-8.4,20.0)	(-21.9,18.5)
	Pr >  t			0.8668
	n	4	5	
	LS Mean	2.792	-0.260	3.052
	SEM	7.223	6.700	9.863
Week 96	95% CI	(-11.5,17.1)	(-13.6,13.1)	(-16.5,22.6)
	Pr >  t			0.7578
	n	3	2	
	LS Mean	9.996	5.756	4.240
	SEM	7.933	9.078	12.07

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-5.7,25.7)	(-12.2,23.7)	(-19.6,28.1)
		Pr >  t			0.7259
		n	2	3	
	Week 120	LS Mean	4.960	12.400	-7.440
		SEM	9.156	7.868	12.07
		95% CI	(-13.1,23.1)	(-3.2,28.0)	(-31.3,16.4)
	Week 120	Pr >  t			0.5387
		n	2	2	
		LS Mean	11.541	6.124	5.417
	Week 132	SEM	9.147	9.081	12.88
		95% CI	(-6.5,29.6)	(-11.8,24.1)	(-20.1,30.9)
		Pr >  t			0.6748
	Week 132	n	1	2	
		LS Mean	3.560	6.124	-2.564
		SEM	12.08	9.081	15.11
	Week 8	95% CI	(-20.3,27.4)	(-11.8,24.1)	(-32.4,27.3)
		Pr >  t			0.8655
		n	16	19	
	Week 8	LS Mean	-4.567	0.169	-4.736
		SEM	4.063	3.948	5.097
		95% CI	(-12.6, 3.5)	(-7.7, 8.0)	(-14.8, 5.4)
	Week 16	Pr >  t			0.3549
		n	12	14	
		LS Mean	-10.52	-5.827	-4.697
Week 16	SEM	4.597	4.493	5.818	
	95% CI	(-19.6,-1.4)	(-14.7, 3.1)	(-16.2, 6.8)	
	Pr >  t			0.4211	
Week 24	n	12	8		
	LS Mean	-3.690	-3.876	0.186	
	SEM	4.600	5.756	6.787	
Week 24	95% CI	(-12.8, 5.4)	(-15.3, 7.5)	(-13.2,13.6)	
	Pr >  t			0.9782	
	n	9	7		
Week 32	LS Mean	-1.834	-11.65	9.815	
	SEM	5.245	6.070	7.425	
	95% CI	(-12.2, 8.6)	(-23.7, 0.4)	(-4.9,24.5)	
Week 32	Pr >  t			0.1885	
	n	9	7		
	LS Mean	-2.641	-18.79	16.152	
Week 40	SEM	5.259	6.070	7.458	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-13.1, 7.8)	(-30.8,-6.8)	( -1.4,30.9)
	Pr >  t			0.0321
	n	8	5	
	LS Mean	-4.870	-12.06	7.195
	SEM	5.522	6.956	8.373
Week 56	95% CI	(-15.8, 6.1)	(-25.8, 1.7)	( -9.4,23.8)
	Pr >  t			0.3917
	n	7	3	
	LS Mean	-3.578	-10.53	6.947
	SEM	5.824	8.651	10.01
Week 64	95% CI	(-15.1, 7.9)	(-27.6, 6.6)	(-12.8,26.7)
	Pr >  t			0.4888
	n	5	3	
	LS Mean	-8.841	-4.969	-3.872
	SEM	6.717	8.651	10.58
Week 72	95% CI	(-22.1, 4.4)	(-22.1,12.1)	(-24.8,17.1)
	Pr >  t			0.7150
	n	5	3	
	LS Mean	-5.972	-1.459	-4.513
	SEM	6.673	8.651	10.53
Week 84	95% CI	(-19.2, 7.2)	(-18.6,15.6)	(-25.3,16.3)
	Pr >  t			0.6688
	n	2	2	
	LS Mean	-7.024	-0.181	-6.843
	SEM	10.20	10.37	14.21
Week 96	95% CI	(-27.2,13.1)	(-20.7,20.3)	(-35.0,21.3)
	Pr >  t			0.6310
	n	3	2	
	LS Mean	-13.12	-16.85	3.722
	SEM	8.354	10.37	13.04
Week 108	95% CI	(-29.6, 3.4)	(-37.3, 3.7)	(-22.1,29.5)
	Pr >  t			0.7757
	n	1	2	
	LS Mean	-21.85	-8.516	-13.34
	SEM	14.11	10.37	17.25
Week 120	95% CI	(-49.8, 6.1)	(-29.0,12.0)	(-47.5,20.8)
	Pr >  t			0.4409
	n	3	2	
	LS Mean	-13.12	-0.181	-12.94
	SEM	8.354	10.37	13.04

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-29.6, 3.4)	(-20.7,20.3)	(-38.7,12.8)
		Pr >  t			0.3226
	Week 132	n	1	1	
		LS Mean	-12.88	-28.70	15.821
		SEM	14.11	14.25	19.84
		95% CI	(-40.8,15.0)	(-56.9,-0.5)	(-23.4,55.1)
		Pr >  t			0.4266
	Week 144	n	2		
		LS Mean	-8.760		
		SEM	10.07		
		95% CI	(-28.7,11.1)		
		Pr >  t			
	Week 156	n	1		
		LS Mean	-12.88		
		SEM	14.11		
		95% CI	(-40.8,15.0)		
		Pr >  t			
	Week 168	n	1		
		LS Mean	-12.88		
		SEM	14.11		
		95% CI	(-40.8,15.0)		
		Pr >  t			
	Week 180	n	1		
		LS Mean	3.781		
		SEM	14.11		
		95% CI	(-24.1,31.7)		
		Pr >  t			
	Week 192	n	1		
		LS Mean	-12.88		
		SEM	14.11		
		95% CI	(-40.8,15.0)		
		Pr >  t			
Other	Week 8	n	16	5	
		LS Mean	-8.176	6.090	-14.27
		SEM	5.989	8.937	9.771
		95% CI	(-20.4, 4.1)	(-12.1,24.3)	(-34.1, 5.6)
		Pr >  t			0.1532
	Week 16	n	13	4	
		LS Mean	1.456	7.228	-5.772
		SEM	6.237	10.10	10.67

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-11.2,14.1)	(-13.1,27.6)	(-27.3,15.8)
	Pr >  t			0.5915
	n	9	2	
	LS Mean	-5.358	1.250	-6.609
	SEM	6.893	12.68	13.41
Week 32	95% CI	(-19.2, 8.5)	(-24.1,26.6)	(-33.4,20.2)
	Pr >  t			0.6239
	n	6	3	
	LS Mean	0.315	-10.23	10.549
	SEM	7.862	11.06	12.44
Week 40	95% CI	(-15.4,16.0)	(-32.4,12.0)	(-14.4,35.5)
	Pr >  t			0.4001
	n	6	2	
	LS Mean	2.773	-12.16	14.932
	SEM	7.970	12.64	13.93
Week 48	95% CI	(-13.2,18.7)	(-37.4,13.1)	(-12.9,42.7)
	Pr >  t			0.2876
	n	5	1	
	LS Mean	8.395	0.137	8.258
	SEM	8.418	16.56	17.82
Week 56	95% CI	(-8.4,25.2)	(-32.8,33.1)	(-27.2,43.7)
	Pr >  t			0.6444
	n	5	1	
	LS Mean	5.061	0.137	4.924
	SEM	8.418	16.56	17.82
Week 64	95% CI	(-11.7,21.9)	(-32.8,33.1)	(-30.5,40.4)
	Pr >  t			0.7830
	n	3	1	
	LS Mean	0.923	0.137	0.785
	SEM	9.932	16.56	18.59
Week 72	95% CI	(-18.9,20.7)	(-32.8,33.1)	(-36.2,37.8)
	Pr >  t			0.9664
	n	4	1	
	LS Mean	3.489	0.137	3.352
	SEM	9.049	16.56	18.13
Week 84	95% CI	(-14.5,21.5)	(-32.8,33.1)	(-32.7,39.4)
	Pr >  t			0.8538
	n	4	1	
	LS Mean	3.489	0.137	3.352
	SEM	9.049	16.56	18.13

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-14.5,21.5)	(-32.8,33.1)	(-32.7,39.4)
	Pr >  t			0.8538
	n	3	1	
	LS Mean	12.033	0.137	11.895
	SEM	9.932	16.56	18.59
Week 108	95% CI	(-7.7,31.8)	(-32.8,33.1)	(-25.1,48.9)
	Pr >  t			0.5241
	n	4		
	LS Mean	7.654		
	SEM	9.049		
Week 120	95% CI	(-10.4,25.7)		
	Pr >  t			
	n	3		
	LS Mean	6.476		
	SEM	9.932		
Week 132	95% CI	(-13.3,26.3)		
	Pr >  t			
	n	3		
	LS Mean	-4.634		
	SEM	9.932		
Week 144	95% CI	(-24.4,15.1)		
	Pr >  t			
	n	3		
	LS Mean	10.383		
	SEM	9.959		
Week 156	95% CI	(-9.4,30.2)		
	Pr >  t			
	n	2		
	LS Mean	-3.223		
	SEM	11.49		
	95% CI	(-26.1,19.6)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	-9.056	0.372	-9.429	
		SEM	3.387	3.309	2.643	
		95% CI	(-15.7,-2.4)	(-6.1, 6.9)	(-14.6,-4.2)	
			Pr >  t			0.0004
	Week 16	n	88	71		
		LS Mean	-4.720	-2.632	-2.088	
		SEM	3.445	3.507	2.817	
		95% CI	(-11.5, 2.1)	(-9.5, 4.3)	(-7.6, 3.4)	
			Pr >  t			0.4589
	Week 24	n	75	54		
		LS Mean	-9.239	-0.492	-8.747	
		SEM	3.495	3.621	3.034	
		95% CI	(-16.1,-2.4)	(-7.6, 6.6)	(-14.7,-2.8)	
			Pr >  t			0.0041
	Week 32	n	62	52		
		LS Mean	-7.893	-2.861	-5.032	
		SEM	3.578	3.641	3.144	
		95% CI	(-14.9,-0.9)	(-10.0, 4.3)	(-11.2, 1.1)	
			Pr >  t			0.1100
	Week 40	n	51	46		
		LS Mean	-7.516	-1.265	-6.251	
		SEM	3.661	3.716	3.308	
		95% CI	(-14.7,-0.3)	(-8.6, 6.0)	(-12.7, 0.2)	
		Pr >  t			0.0593	
Week 48	n	50	37			
	LS Mean	-9.810	-3.851	-5.959		
	SEM	3.670	3.836	3.452		
	95% CI	(-17.0,-2.6)	(-11.4, 3.7)	(-12.7, 0.8)		
		Pr >  t			0.0847	
Week 56	n	43	33			
	LS Mean	-8.596	-1.506	-7.090		
	SEM	3.743	3.908	3.609		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-16.0,-1.2)	(-9.2, 6.2)	(-14.2,-0.0)
	Pr >  t			0.0498
	n	35	33	
	LS Mean	-9.396	-1.574	-7.822
	SEM	3.856	3.908	3.728
Week 72	95% CI	(-17.0,-1.8)	(-9.3, 6.1)	(-15.1,-0.5)
	Pr >  t			0.0362
	n	35	31	
	LS Mean	-8.629	-0.252	-8.377
	SEM	3.856	3.948	3.771
Week 84	95% CI	(-16.2,-1.0)	(-8.0, 7.5)	(-15.8,-1.0)
	Pr >  t			0.0266
	n	31	29	
	LS Mean	-9.957	-3.216	-6.741
	SEM	3.939	3.994	3.896
Week 96	95% CI	(-17.7,-2.2)	(-11.1, 4.6)	(-14.4, 0.9)
	Pr >  t			0.0839
	n	27	22	
	LS Mean	-9.845	-7.175	-2.670
	SEM	4.027	4.210	4.211
Week 108	95% CI	(-17.8,-1.9)	(-15.4, 1.1)	(-10.9, 5.6)
	Pr >  t			0.5261
	n	19	20	
	LS Mean	-9.187	-3.261	-5.926
	SEM	4.335	4.297	4.579
Week 120	95% CI	(-17.7,-0.7)	(-11.7, 5.2)	(-14.9, 3.1)
	Pr >  t			0.1959
	n	20	15	
	LS Mean	-7.017	-1.373	-5.643
	SEM	4.272	4.597	4.818
Week 132	95% CI	(-15.4, 1.4)	(-10.4, 7.7)	(-15.1, 3.8)
	Pr >  t			0.2417
	n	15	7	
	LS Mean	-12.82	-7.620	-5.199
	SEM	4.583	5.760	6.158
Week 144	95% CI	(-21.8,-3.8)	(-18.9, 3.7)	(-17.3, 6.9)
	Pr >  t			0.3987
	n	10	5	
Week 144	LS Mean	-11.61	-1.594	-10.01
	SEM	5.106	6.503	7.231

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
1	Week 156	95% CI	(-21.6,-1.6)	(-14.4,11.2)	(-24.2, 4.2)
		Pr >  t			0.1664
		n	6	3	
	Week 168	LS Mean	-5.670	-7.253	1.583
		SEM	6.070	7.953	9.155
		95% CI	(-17.6, 6.2)	(-22.9, 8.3)	(-16.4,19.5)
	Week 180	Pr >  t			0.8628
		n	3	2	
		LS Mean	-1.176	-1.245	0.069
	Week 192	SEM	7.944	9.460	11.68
		95% CI	(-16.8,14.4)	(-19.8,17.3)	(-22.8,23.0)
		Pr >  t			0.9953
Week 8	n	1	1		
	LS Mean	4.561	0.066	4.494	
	SEM	12.96	12.95	17.87	
Week 16	95% CI	(-20.9,30.0)	(-25.4,25.5)	(-30.6,39.6)	
	Pr >  t			0.8015	
	n	1	1		
Week 24	LS Mean	-12.10	0.066	-12.17	
	SEM	12.96	12.95	17.87	
	95% CI	(-37.5,13.3)	(-25.4,25.5)	(-47.2,22.9)	
Week 32	Pr >  t			0.4962	
	n	43	50		
	LS Mean	-2.124	3.462	-5.586	
Week 8	SEM	4.084	4.254	4.235	
	95% CI	(-10.2, 6.0)	(-5.0,11.9)	(-13.9, 2.8)	
	Pr >  t			0.1889	
Week 16	n	35	35		
	LS Mean	-5.206	4.109	-9.315	
	SEM	4.310	4.450	4.723	
Week 24	95% CI	(-13.7, 3.3)	(-4.7,12.9)	(-18.6,-0.0)	
	Pr >  t			0.0499	
	n	29	26		
Week 32	LS Mean	-3.826	3.003	-6.829	
	SEM	4.520	4.832	5.175	
	95% CI	(-12.8, 5.1)	(-6.5,12.5)	(-17.0, 3.4)	
Week 8	Pr >  t			0.1881	
	n	23	21		
	LS Mean	2.281	-0.531	2.813	
Week 16	SEM	4.833	5.134	5.614	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-7.2,11.8)	(-10.7, 9.6)	(-8.2,13.9)
	Pr >  t			0.6167
	n	23	16	
	LS Mean	4.638	-5.686	10.324
	SEM	4.846	5.490	5.949
Week 48	95% CI	(-4.9,14.2)	(-16.5, 5.1)	(-1.4,22.0)
	Pr >  t			0.0836
	n	18	14	
	LS Mean	5.835	2.537	3.297
	SEM	5.136	5.695	6.387
Week 56	95% CI	(-4.3,16.0)	(-8.7,13.7)	(-9.3,15.9)
	Pr >  t			0.6060
	n	15	12	
	LS Mean	3.249	-0.593	3.842
	SEM	5.401	5.947	6.835
Week 64	95% CI	(-7.4,13.9)	(-12.3,11.1)	(-9.6,17.3)
	Pr >  t			0.5744
	n	11	9	
	LS Mean	2.574	-2.506	5.081
	SEM	5.901	6.502	7.708
Week 72	95% CI	(-9.0,14.2)	(-15.3,10.3)	(-10.1,20.2)
	Pr >  t			0.5102
	n	12	4	
	LS Mean	-0.007	1.263	-1.271
	SEM	5.763	8.729	9.574
Week 84	95% CI	(-11.3,11.3)	(-15.9,18.4)	(-20.1,17.5)
	Pr >  t			0.8945
	n	8	4	
	LS Mean	-11.79	-2.904	-8.887
	SEM	6.601	8.729	10.08
Week 96	95% CI	(-24.8, 1.2)	(-20.1,14.3)	(-28.7,10.9)
	Pr >  t			0.3786
	n	8	2	
	LS Mean	4.876	1.047	3.828
	SEM	6.601	11.66	12.70
Week 108	95% CI	(-8.1,17.9)	(-21.9,24.0)	(-21.1,28.8)
	Pr >  t			0.7633
	n	6	1	
	SEM	7.316	15.97	17.03

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.1,16.7)	(-32.3,34.7)
		Pr >  t		0.9444
	Week 120	n	8	1
		LS Mean	-5.384	1.125
		SEM	6.617	15.97
		95% CI	(-18.4, 7.6)	(-30.3,32.5)
		Pr >  t		(-39.4,26.4)
	Week 132	n	5	1
		LS Mean	-9.342	1.125
		SEM	7.833	15.97
		95% CI	(-24.7, 6.1)	(-30.3,32.5)
		Pr >  t		(-44.4,23.5)
	Week 144	n	5	
		LS Mean	-6.010	
		SEM	7.833	
		95% CI	(-21.4, 9.4)	
		Pr >  t		0.5446
	Week 156	n	4	
		LS Mean	-10.10	
		SEM	8.543	
		95% CI	(-26.9, 6.7)	
		Pr >  t		
	Week 168	n	1	
		LS Mean	-31.44	
		SEM	15.72	
		95% CI	(-62.4,-0.5)	
		Pr >  t		

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	-19.02	-2.800	-16.22		
			SEM	5.822	6.899	7.176		
			95% CI	(-30.8,-7.2)	(-16.8,11.2)	(-30.6,-1.8)		
					Pr >  t			0.0283
		Week 16	n	17	10			
			LS Mean	-11.54	-9.498	-2.044		
			SEM	6.238	7.952	8.316		
			95% CI	(-24.1, 1.0)	(-25.4, 6.4)	(-18.6,14.6)		
					Pr >  t			0.8066
		Week 24	n	9	5			
			LS Mean	-5.255	-15.84	10.581		
			SEM	7.127	9.471	10.51		
			95% CI	(-19.5, 9.0)	(-34.7, 3.0)	(-10.3,31.4)		
					Pr >  t			0.3162
		Week 32	n	8	4			
			LS Mean	-5.115	-20.65	15.539		
			SEM	7.374	10.08	11.26		
			95% CI	(-19.8, 9.6)	(-40.7,-0.6)	( -6.8,37.9)		
					Pr >  t			0.1704
		Week 40	n	5	4			
			LS Mean	-5.586	-16.49	10.900		
			SEM	8.397	10.08	12.04		
			95% CI	(-22.3,11.1)	(-36.5, 3.5)	(-13.0,34.8)		
			Pr >  t			0.3673		
Week 48	n	5	3					
	LS Mean	-5.586	-10.36	4.777				
	SEM	8.397	11.00	12.82				
	95% CI	(-22.3,11.1)	(-32.2,11.4)	(-20.6,30.2)				
			Pr >  t			0.7100		
Week 56	n	4	3					
	LS Mean	-9.211	-10.36	1.152				
	SEM	9.004	11.00	13.26				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-27.1, 8.6)	(-32.2,11.4)	(-25.1,27.4)
		Pr >  t			0.9309
		n	4	3	
		LS Mean	-5.043	-4.806	-0.237
		SEM	9.004	11.00	13.26
Week 72		95% CI	(-22.9,12.8)	(-26.6,17.0)	(-26.5,26.0)
		Pr >  t			0.9858
		n	4	3	
		LS Mean	-9.211	-4.806	-4.404
		SEM	9.004	11.00	13.26
Week 84		95% CI	(-27.1, 8.6)	(-26.6,17.0)	(-30.7,21.9)
		Pr >  t			0.7403
		n	2	3	
		LS Mean	-22.39	-4.806	-17.58
		SEM	11.76	11.00	15.15
Week 96		95% CI	(-45.7, 0.9)	(-26.6,17.0)	(-47.6,12.4)
		Pr >  t			0.2483
		n	1	3	
		LS Mean	-8.132	-15.92	7.784
		SEM	15.58	11.00	18.47
Week 108		95% CI	(-39.0,22.8)	(-37.7, 5.9)	(-28.9,44.4)
		Pr >  t			0.6744
		n		2	
		LS Mean		-27.25	
		SEM		12.53	
Week 120		95% CI		(-52.1,-2.4)	
		Pr >  t			
		n	1	1	
		LS Mean	-8.132	2.304	-10.44
		SEM	15.58	16.24	22.00
Week 132		95% CI	(-39.0,22.8)	(-29.9,34.5)	(-54.1,33.3)
		Pr >  t			0.6364
		n		1	
		LS Mean		-31.03	
		SEM		16.24	
Week 144		95% CI		(-63.2, 1.2)	
		Pr >  t			
		n	1		
		LS Mean	-8.132		
		SEM	15.58		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-39.0,22.8)		
		Pr >  t			
Secondary resistant	Week 8	n	98	106	
		LS Mean	-4.691	3.240	-7.931
		SEM	3.090	3.095	2.602
		95% CI	(-10.8, 1.4) (-2.9, 9.3)		(-13.0,-2.8)
		Pr >  t			0.0025
	Week 16	n	83	81	
		LS Mean	-2.094	0.358	-2.453
		SEM	3.169	3.237	2.825
		95% CI	(-8.3, 4.1) (-6.0, 6.7)		(-8.0, 3.1)
		Pr >  t			0.3857
	Week 24	n	75	62	
		LS Mean	-7.196	2.461	-9.658
		SEM	3.227	3.388	3.025
		95% CI	(-13.5,-0.8) (-4.2, 9.1)		(-15.6,-3.7)
		Pr >  t			0.0015
	Week 32	n	59	56	
		LS Mean	-5.003	0.100	-5.104
		SEM	3.388	3.439	3.211
		95% CI	(-11.7, 1.7) (-6.7, 6.9)		(-11.4, 1.2)
		Pr >  t			0.1124
	Week 40	n	52	48	
		LS Mean	-3.111	-0.495	-2.616
		SEM	3.457	3.540	3.374
		95% CI	(-9.9, 3.7) (-7.5, 6.5)		(-9.2, 4.0)
		Pr >  t			0.4384
	Week 48	n	47	37	
		LS Mean	-6.437	-0.393	-6.044
		SEM	3.514	3.709	3.607
		95% CI	(-13.3, 0.5) (-7.7, 6.9)		(-13.1, 1.0)
		Pr >  t			0.0942
	Week 56	n	41	31	
		LS Mean	-4.508	0.826	-5.334
		SEM	3.600	3.846	3.829
		95% CI	(-11.6, 2.6) (-6.7, 8.4)		(-12.8, 2.2)
		Pr >  t			0.1639
	Week 64	n	32	28	
		LS Mean	-5.552	0.857	-6.408
		SEM	3.777	3.931	4.078

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72		95% CI	(-13.0, 1.9)	(-6.9, 8.6)	(-14.4, 1.6)
		Pr >  t			0.1164
		n	29	22	
		LS Mean	-5.521	1.228	-6.749
		SEM	3.860	4.159	4.373
Week 84		95% CI	(-13.1, 2.1)	(-6.9, 9.4)	(-15.3, 1.8)
		Pr >  t			0.1230
		n	26	21	
		LS Mean	-4.448	-3.520	-0.928
		SEM	3.952	4.208	4.501
Week 96		95% CI	(-12.2, 3.3)	(-11.8, 4.7)	(-9.8, 7.9)
		Pr >  t			0.8368
		n	23	14	
		LS Mean	-2.276	-5.090	2.814
		SEM	4.071	4.709	5.067
Week 108		95% CI	(-10.3, 5.7)	(-14.3, 4.2)	(-7.1, 12.8)
		Pr >  t			0.5788
		n	18	13	
		LS Mean	-7.041	0.317	-7.358
		SEM	4.341	4.819	5.383
Week 120		95% CI	(-15.6, 1.5)	(-9.1, 9.8)	(-17.9, 3.2)
		Pr >  t			0.1719
		n	19	10	
		LS Mean	-4.206	-1.278	-2.928
		SEM	4.282	5.244	5.721
Week 132		95% CI	(-12.6, 4.2)	(-11.6, 9.0)	(-14.2, 8.3)
		Pr >  t			0.6089
		n	13	4	
		LS Mean	-12.27	-4.309	-7.957
		SEM	4.771	7.429	8.055
Week 144		95% CI	(-21.6,-2.9)	(-18.9,10.3)	(-23.8, 7.8)
		Pr >  t			0.3234
		n	8	1	
		LS Mean	-6.356	2.490	-8.846
		SEM	5.626	13.91	14.56
Week 156		95% CI	(-17.4, 4.7)	(-24.8,29.8)	(-37.4,19.7)
		Pr >  t			0.5437
		n	5	1	
		LS Mean	-2.014	-14.18	12.166
		SEM	6.745	13.91	15.03



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-15.2,11.2)	(-41.5,13.1)	(-17.3,41.7)
		Pr >  t			0.4185
		n	3	1	
	Week 180	LS Mean	2.390	2.490	-0.100
		SEM	8.360	13.91	15.82
		95% CI	(-14.0,18.8)	(-24.8,29.8)	(-31.1,30.9)
	Week 180	Pr >  t			0.9950
		n	1	1	
		LS Mean	8.140	2.490	5.650
	Week 192	SEM	13.85	13.91	19.29
		95% CI	(-19.0,35.3)	(-24.8,29.8)	(-32.2,43.5)
		Pr >  t			0.7697
	Week 192	n	1	1	
		LS Mean	-8.520	2.490	-11.01
		SEM	13.85	13.91	19.29
	Week 8	95% CI	(-35.7,18.7)	(-24.8,29.8)	(-48.9,26.9)
		Pr >  t			0.5684
		n	17	16	
	Week 8	LS Mean	4.415	0.295	4.120
		SEM	4.522	4.661	6.350
		95% CI	(-4.7,13.5)	(-9.1,9.6)	(-8.6,16.8)
	Week 16	Pr >  t			0.5192
		n	18	14	
		LS Mean	0.137	6.964	-6.827
	Week 16	SEM	4.456	4.844	6.461
		95% CI	(-8.8,9.1)	(-2.7,16.7)	(-19.8,6.1)
		Pr >  t			0.2951
	Week 24	n	16	13	
LS Mean		-0.296	3.353	-3.650	
SEM		4.619	4.935	6.631	
Week 24	95% CI	(-9.5,9.0)	(-6.5,13.2)	(-16.9,9.6)	
	Pr >  t			0.5840	
	n	15	13		
Week 32	LS Mean	6.809	0.018	6.791	
	SEM	4.679	4.945	6.689	
	95% CI	(-2.6,16.2)	(-9.9,9.9)	(-6.6,20.2)	
Week 32	Pr >  t			0.3137	
	n	14	10		
	LS Mean	4.599	1.701	2.898	
Week 40	SEM	4.779	5.274	7.002	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48		95% CI	(-4.9,14.1)	(-8.8,12.2)	(-11.0,16.8)
		Pr >  t			0.6801
		n	14	11	
		LS Mean	4.599	0.326	4.273
		SEM	4.779	5.157	6.912
Week 56		95% CI	(-4.9,14.1)	(-9.9,10.6)	(-9.5,18.0)
		Pr >  t			0.5383
		n	11	11	
		LS Mean	2.734	0.326	2.408
		SEM	5.053	5.157	7.111
Week 64		95% CI	(-7.3,12.8)	(-9.9,10.6)	(-11.7,16.6)
		Pr >  t			0.7358
		n	8	11	
		LS Mean	0.244	-2.705	2.949
		SEM	5.489	5.157	7.434
Week 72		95% CI	(-10.6,11.1)	(-13.0, 7.6)	(-11.8,17.7)
		Pr >  t			0.6925
		n	11	10	
		LS Mean	1.218	3.508	-2.289
		SEM	5.053	5.279	7.203
Week 84		95% CI	(-8.8,11.3)	(-7.0,14.0)	(-16.6,12.0)
		Pr >  t			0.7514
		n	9	9	
		LS Mean	-10.63	3.124	-13.76
		SEM	5.315	5.422	7.498
Week 96		95% CI	(-21.2,-0.1)	(-7.7,13.9)	(-28.6, 1.1)
		Pr >  t			0.0696
		n	8	7	
		LS Mean	-8.144	-1.321	-6.824
		SEM	5.492	5.804	7.903
Week 108		95% CI	(-19.0, 2.7)	(-12.8,10.2)	(-22.5, 8.8)
		Pr >  t			0.3897
		n	7	6	
		LS Mean	4.932	3.567	1.365
		SEM	5.710	6.084	8.258
Week 120		95% CI	(-6.4,16.2)	(-8.5,15.6)	(-15.0,17.7)
		Pr >  t			0.8690
		n	6	5	
		LS Mean	-3.043	4.210	-7.254
		SEM	5.988	6.454	8.714

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132		95% CI	(-14.9, 8.8)	(-8.5,17.0)	(-24.5,10.0)
		Pr >  t			0.4065
		n	5	3	
		LS Mean	-4.864	1.983	-6.847
		SEM	6.348	7.699	9.904
Week 144		95% CI	(-17.4, 7.7)	(-13.2,17.2)	(-26.4,12.7)
		Pr >  t			0.4901
		n	5	4	
		LS Mean	-11.53	2.313	-13.84
		SEM	6.348	6.945	9.328
Week 156		95% CI	(-24.1, 1.0)	(-11.4,16.0)	(-32.3, 4.6)
		Pr >  t			0.1396
		n	4	2	
		LS Mean	-3.154	1.886	-5.040
		SEM	6.849	9.023	11.27
Week 168		95% CI	(-16.7,10.4)	(-15.9,19.7)	(-27.2,17.2)
		Pr >  t			0.6550
		n	1	1	
		LS Mean	-30.87	1.826	-32.70
		SEM	12.10	12.16	17.11
		95% CI	(-54.7,-7.1)	(-22.1,25.8)	(-66.4, 1.0)
		Pr >  t			0.0571

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	-4.101	-0.177	-3.923		
			SEM	9.004	9.273	3.333		
					95% CI	(-21.9,13.7)	(-18.5,18.2)	(-10.5, 2.6)
					Pr >  t			0.2404
				Week 16	n	69	55	
					LS Mean	-4.291	-1.995	-2.297
					SEM	9.012	9.336	3.532
					95% CI	(-22.1,13.5)	(-20.5,16.5)	(-9.3, 4.7)
					Pr >  t			0.5161
				Week 24	n	54	46	
					LS Mean	-5.952	-3.171	-2.781
					SEM	9.040	9.374	3.751
					95% CI	(-23.8,11.9)	(-21.7,15.4)	(-10.2, 4.6)
					Pr >  t			0.4590
				Week 32	n	49	41	
					LS Mean	-2.806	-6.129	3.324
					SEM	9.114	9.398	3.869
					95% CI	(-20.8,15.2)	(-24.7,12.5)	(-4.3,10.9)
					Pr >  t			0.3909
				Week 40	n	40	33	
					LS Mean	-2.458	-3.982	1.524
					SEM	9.163	9.454	4.110
					95% CI	(-20.6,15.7)	(-22.7,14.7)	(-6.6, 9.6)
					Pr >  t			0.7110
				Week 48	n	38	28	
					LS Mean	-5.848	-4.795	-1.053
					SEM	9.176	9.503	4.254
					95% CI	(-24.0,12.3)	(-23.6,14.0)	(-9.4, 7.3)
					Pr >  t			0.8045
				Week 56	n	32	28	
					LS Mean	-4.618	-3.770	-0.848
					SEM	9.223	9.504	4.358

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-22.9,13.6)	(-22.6,15.0)	(-9.4, 7.7)
	Pr >  t			0.8459
	n	23	26	
	LS Mean	-4.594	-3.542	-1.052
	SEM	9.335	9.528	4.643
Week 72	95% CI	(-23.0,13.9)	(-22.4,15.3)	(-10.2, 8.1)
	Pr >  t			0.8208
	n	27	25	
	LS Mean	-5.368	-1.634	-3.734
	SEM	9.277	9.539	4.552
Week 84	95% CI	(-23.7,13.0)	(-20.5,17.2)	(-12.7, 5.2)
	Pr >  t			0.4125
	n	23	22	
	LS Mean	-10.25	-1.919	-8.334
	SEM	9.334	9.588	4.769
Week 96	95% CI	(-28.7, 8.2)	(-20.9,17.0)	(-17.7, 1.0)
	Pr >  t			0.0810
	n	20	16	
	LS Mean	-7.421	-6.019	-1.402
	SEM	9.393	9.738	5.171
Week 108	95% CI	(-26.0,11.1)	(-25.3,13.2)	(-11.6, 8.7)
	Pr >  t			0.7864
	n	20	14	
	LS Mean	-4.563	-4.194	-0.369
	SEM	9.394	9.814	5.316
Week 120	95% CI	(-23.1,14.0)	(-23.6,15.2)	(-10.8,10.1)
	Pr >  t			0.9446
	n	17	11	
	LS Mean	-5.710	-3.818	-1.892
	SEM	9.471	9.977	5.743
Week 132	95% CI	(-24.4,13.0)	(-23.5,15.9)	(-13.2, 9.4)
	Pr >  t			0.7419
	n	13	6	
	LS Mean	-7.267	-6.227	-1.040
	SEM	9.628	10.58	6.959
Week 144	95% CI	(-26.3,11.7)	(-27.1,14.6)	(-14.7,12.6)
	Pr >  t			0.8812
	n	10	5	
	LS Mean	-11.12	-2.630	-8.489
	SEM	9.823	10.84	7.602

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-30.5, 8.3)	(-24.0,18.7)	(-23.4, 6.4)
		Pr >  t			0.2644
	Week 156	n	7	3	
		LS Mean	-4.318	-8.217	3.898
		SEM	10.18	11.81	9.311
		95% CI	(-24.4,15.7)	(-31.5,15.0)	(-14.4,22.2)
		Pr >  t			0.6756
	Week 168	n	3	2	
		LS Mean	-6.644	-2.199	-4.445
		SEM	11.61	12.92	12.05
		95% CI	(-29.5,16.2)	(-27.6,23.2)	(-28.1,19.2)
		Pr >  t			0.7124
	Week 180	n		1	
		LS Mean		-0.935	
		SEM		15.77	
		95% CI		(-31.9,30.0)	
		Pr >  t			
	Week 192	n		1	
		LS Mean		-0.935	
		SEM		15.77	
		95% CI		(-31.9,30.0)	
		Pr >  t			
Second Line	Week 8	n	66	67	
		LS Mean	-8.524	3.023	-11.55
		SEM	2.881	2.891	3.169
		95% CI	(-14.2,-2.8)	(-2.7, 8.7)	(-17.8,-5.3)
		Pr >  t			0.0003
	Week 16	n	54	52	
		LS Mean	-3.518	1.444	-4.962
		SEM	3.051	3.135	3.479
		95% CI	(-9.5, 2.5)	(-4.7, 7.6)	(-11.8, 1.9)
		Pr >  t			0.1547
	Week 24	n	49	35	
		LS Mean	-7.391	4.784	-12.17
		SEM	3.141	3.485	3.851
		95% CI	(-13.6,-1.2)	(-2.1,11.6)	(-19.7,-4.6)
		Pr >  t			0.0017
	Week 32	n	36	32	
		LS Mean	-5.880	2.355	-8.235
		SEM	3.416	3.584	4.134

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-12.6, 0.8)	(-4.7, 9.4)	(-16.4,-0.1)
	Pr >  t			0.0469
Week 40	n	33	29	
	LS Mean	-3.437	-0.288	-3.149
	SEM	3.494	3.704	4.286
	95% CI	(-10.3, 3.4)	(-7.6, 7.0)	(-11.6, 5.3)
	Pr >  t			0.4628
Week 48	n	29	23	
	LS Mean	-3.217	1.290	-4.507
	SEM	3.615	3.950	4.598
	95% CI	(-10.3, 3.9)	(-6.5, 9.1)	(-13.5, 4.5)
	Pr >  t			0.3274
Week 56	n	25	17	
	LS Mean	-5.883	1.949	-7.831
	SEM	3.763	4.332	5.049
	95% CI	(-13.3, 1.5)	(-6.6,10.5)	(-17.7, 2.1)
	Pr >  t			0.1214
Week 64	n	22	16	
	LS Mean	-5.530	0.435	-5.965
	SEM	3.905	4.419	5.230
	95% CI	(-13.2, 2.1)	(-8.2, 9.1)	(-16.2, 4.3)
	Pr >  t			0.2544
Week 72	n	20	10	
	LS Mean	-5.571	2.283	-7.854
	SEM	4.020	5.210	5.992
	95% CI	(-13.5, 2.3)	(-7.9,12.5)	(-19.6, 3.9)
	Pr >  t			0.1904
Week 84	n	16	11	
	LS Mean	-5.605	-6.393	0.788
	SEM	4.337	5.031	6.046
	95% CI	(-14.1, 2.9)	(-16.3, 3.5)	(-11.1,12.7)
	Pr >  t			0.8964
Week 96	n	15	8	
	LS Mean	-2.058	-7.802	5.744
	SEM	4.422	5.665	6.648
	95% CI	(-10.7, 6.6)	(-18.9, 3.3)	(-7.3,18.8)
	Pr >  t			0.3878
Week 108	n	6	7	
	LS Mean	-6.402	-0.291	-6.111
	SEM	6.274	5.969	8.211

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-18.7, 5.9)	(-12.0,11.4)	(-22.2,10.0)
	Pr >  t			0.4570
Week 120	n	11	5	
	LS Mean	-5.590	3.990	-9.579
	SEM	4.945	6.850	7.997
	95% CI	(-15.3, 4.1)	(-9.5,17.4)	(-25.3, 6.1)
	Pr >  t			0.2314
Week 132	n	7	2	
	LS Mean	-17.14	-9.612	-7.529
	SEM	5.890	10.29	11.53
	95% CI	(-28.7,-5.6)	(-29.8,10.6)	(-30.2,15.1)
	Pr >  t			0.5140
Week 144	n	5		
	LS Mean	-5.094		
	SEM	6.755		
	95% CI	(-18.4, 8.2)		
	Pr >  t			
Week 156	n	3		
	LS Mean	-14.39		
	SEM	8.485		
	95% CI	(-31.1, 2.3)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-10.75		
	SEM	14.22		
	95% CI	(-38.7,17.2)		
	Pr >  t			
Week 180	n	1		
	LS Mean	5.913		
	SEM	14.22		
	95% CI	(-22.0,33.8)		
	Pr >  t			
Week 192	n	1		
	LS Mean	-10.75		
	SEM	14.22		
	95% CI	(-38.7,17.2)		
	Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis



-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	-6.293	0.206	-6.500
		SEM	9.126	9.535	3.904
		95% CI	(-24.4,11.8)	(-18.7,19.1)	(-14.2, 1.2)
		Pr >  t			0.0978
	Week 16	n	51	41	
		LS Mean	-5.175	-4.428	-0.748
		SEM	9.142	9.635	4.203
		95% CI	(-23.3,13.0)	(-23.6,14.7)	(-9.0, 7.5)
		Pr >  t			0.8590
	Week 24	n	38	33	
		LS Mean	-7.249	-4.737	-2.512
		SEM	9.188	9.697	4.534
		95% CI	(-25.5,11.0)	(-24.0,14.5)	(-11.4, 6.4)
		Pr >  t			0.5800
	Week 32	n	34	28	
		LS Mean	-5.880	-7.664	1.783
		SEM	9.307	9.741	4.722
		95% CI	(-24.4,12.6)	(-27.0,11.7)	(-7.5,11.1)
		Pr >  t			0.7060
	Week 40	n	26	23	
		LS Mean	-4.492	-5.289	0.798
		SEM	9.409	9.818	5.066
		95% CI	(-23.2,14.2)	(-24.8,14.2)	(-9.2,10.8)
		Pr >  t			0.8750
	Week 48	n	24	17	
		LS Mean	-9.955	-5.898	-4.056
		SEM	9.442	9.960	5.405
95% CI		(-28.7, 8.8)	(-25.6,13.8)	(-14.7, 6.6)	
	Pr >  t			0.4534	
Week 56	n	21	17		
	LS Mean	-6.804	-4.176	-2.628	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	9.503	9.964	5.515
	95% CI	(-25.6,12.0)	(-23.9,15.6)	(-13.5, 8.2)
	Pr >  t			0.6339
Week 64	n	15	15	
	LS Mean	-5.451	-1.491	-3.961
	SEM	9.687	10.03	5.954
	95% CI	(-24.6,13.7)	(-21.4,18.4)	(-15.7, 7.7)
	Pr >  t			0.5062
Week 72	n	16	15	
	LS Mean	-7.017	-2.666	-4.351
	SEM	9.649	10.03	5.888
	95% CI	(-26.1,12.1)	(-22.5,17.2)	(-15.9, 7.2)
	Pr >  t			0.4603
Week 84	n	14	13	
	LS Mean	-7.601	-2.891	-4.710
	SEM	9.733	10.13	6.181
	95% CI	(-26.9,11.7)	(-23.0,17.2)	(-16.9, 7.4)
	Pr >  t			0.4464
Week 96	n	12	9	
	LS Mean	-4.343	-6.883	2.540
	SEM	9.846	10.43	6.836
	95% CI	(-23.8,15.1)	(-27.5,13.8)	(-10.9,16.0)
	Pr >  t			0.7103
Week 108	n	13	8	
	LS Mean	-7.819	-7.287	-0.532
	SEM	9.787	10.55	6.939
	95% CI	(-27.2,11.6)	(-28.2,13.6)	(-14.2,13.1)
	Pr >  t			0.9389
Week 120	n	11	6	
	LS Mean	-5.285	-7.466	2.181
	SEM	9.915	10.91	7.634
	95% CI	(-24.9,14.3)	(-29.0,14.1)	(-12.8,17.2)
	Pr >  t			0.7752
Week 132	n	8	3	
	LS Mean	-6.410	-10.50	4.091
	SEM	10.22	12.21	9.727
	95% CI	(-26.6,13.8)	(-34.6,13.6)	(-15.0,23.2)
	Pr >  t			0.6742
Week 144	n	5	1	
	LS Mean	-6.561	-2.602	-3.959

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	10.86	16.43	15.13
		95% CI	(-28.0,14.9)	(-34.9,29.7)	(-33.7,25.8)
		Pr >  t			0.7936
	Week 168	n	3	1	
		LS Mean	0.081	-19.27	19.352
		SEM	11.93	16.43	15.90
	Week 180	95% CI	(-23.4,23.6)	(-51.6,13.0)	(-11.9,50.6)
		Pr >  t			0.2242
		n	2	1	
	Week 192	LS Mean	7.473	-2.602	10.074
		SEM	13.11	16.43	16.81
		95% CI	(-18.3,33.3)	(-34.9,29.7)	(-23.0,43.1)
	Week 8	Pr >  t			0.5493
		n		1	
		LS Mean		-2.602	
	Week 16	SEM		16.43	
		95% CI		(-34.9,29.7)	
		Pr >  t			
	Week 24	n		1	
		LS Mean		-2.602	
		SEM		16.43	
	Week 32	95% CI		(-34.9,29.7)	
		Pr >  t			
		n	17	16	
	Week 8	LS Mean	4.415	0.295	4.120
		SEM	4.522	4.661	6.350
		95% CI	(-4.7,13.5)	(-9.1, 9.6)	(-8.6,16.8)
	Week 16	Pr >  t			0.5192
n		18	14		
LS Mean		0.137	6.964	-6.827	
Week 24	SEM	4.456	4.844	6.461	
	95% CI	(-8.8, 9.1)	(-2.7,16.7)	(-19.8, 6.1)	
	Pr >  t			0.2951	
Week 32	n	16	13		
	LS Mean	-0.296	3.353	-3.650	
	SEM	4.619	4.935	6.631	
Week 8	95% CI	(-9.5, 9.0)	(-6.5,13.2)	(-16.9, 9.6)	
	Pr >  t			0.5840	
	n	15	13		
Week 16	LS Mean	6.809	0.018	6.791	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.679	4.945	6.689
		95% CI	(-2.6,16.2)	(-9.9, 9.9)	(-6.6,20.2)
		Pr >  t			0.3137
	Week 40	n	14	10	
		LS Mean	4.599	1.701	2.898
		SEM	4.779	5.274	7.002
		95% CI	(-4.9,14.1)	(-8.8,12.2)	(-11.0,16.8)
		Pr >  t			0.6801
	Week 48	n	14	11	
		LS Mean	4.599	0.326	4.273
		SEM	4.779	5.157	6.912
		95% CI	(-4.9,14.1)	(-9.9,10.6)	(-9.5,18.0)
		Pr >  t			0.5383
	Week 56	n	11	11	
		LS Mean	2.734	0.326	2.408
		SEM	5.053	5.157	7.111
		95% CI	(-7.3,12.8)	(-9.9,10.6)	(-11.7,16.6)
		Pr >  t			0.7358
	Week 64	n	8	11	
		LS Mean	0.244	-2.705	2.949
		SEM	5.489	5.157	7.434
		95% CI	(-10.6,11.1)	(-13.0, 7.6)	(-11.8,17.7)
		Pr >  t			0.6925
	Week 72	n	11	10	
		LS Mean	1.218	3.508	-2.289
		SEM	5.053	5.279	7.203
		95% CI	(-8.8,11.3)	(-7.0,14.0)	(-16.6,12.0)
		Pr >  t			0.7514
	Week 84	n	9	9	
		LS Mean	-10.63	3.124	-13.76
		SEM	5.315	5.422	7.498
		95% CI	(-21.2,-0.1)	(-7.7,13.9)	(-28.6, 1.1)
		Pr >  t			0.0696
	Week 96	n	8	7	
		LS Mean	-8.144	-1.321	-6.824
		SEM	5.492	5.804	7.903
		95% CI	(-19.0, 2.7)	(-12.8,10.2)	(-22.5, 8.8)
		Pr >  t			0.3897
	Week 108	n	7	6	
		LS Mean	4.932	3.567	1.365

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	5.710	6.084	8.258
		95% CI	(-6.4,16.2)	(-8.5,15.6)	(-15.0,17.7)
		Pr >  t			0.8690
	Week 120	n	6	5	
		LS Mean	-3.043	4.210	-7.254
		SEM	5.988	6.454	8.714
		95% CI	(-14.9, 8.8)	(-8.5,17.0)	(-24.5,10.0)
		Pr >  t			0.4065
	Week 132	n	5	3	
		LS Mean	-4.864	1.983	-6.847
		SEM	6.348	7.699	9.904
		95% CI	(-17.4, 7.7)	(-13.2,17.2)	(-26.4,12.7)
		Pr >  t			0.4901
	Week 144	n	5	4	
		LS Mean	-11.53	2.313	-13.84
		SEM	6.348	6.945	9.328
		95% CI	(-24.1, 1.0)	(-11.4,16.0)	(-32.3, 4.6)
		Pr >  t			0.1396
	Week 156	n	4	2	
		LS Mean	-3.154	1.886	-5.040
		SEM	6.849	9.023	11.27
		95% CI	(-16.7,10.4)	(-15.9,19.7)	(-27.2,17.2)
		Pr >  t			0.6550
	Week 168	n	1	1	
		LS Mean	-30.87	1.826	-32.70
		SEM	12.10	12.16	17.11
		95% CI	(-54.7,-7.1)	(-22.1,25.8)	(-66.4, 1.0)
		Pr >  t			0.0571
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	-20.76	-0.590	-20.17
		SEM	5.123	4.709	5.822
		95% CI	(-31.0, -11)	(-10.0, 8.8)	(-31.7,-8.6)
		Pr >  t			0.0008
	Week 16	n	15	17	
		LS Mean	-7.635	-1.368	-6.267
		SEM	5.427	4.982	6.104
		95% CI	(-18.4, 3.2)	(-11.3, 8.6)	(-18.4, 5.9)
		Pr >  t			0.3074
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	-10.03	2.047	-12.08
	SEM	5.520	5.519	6.697
	95% CI	(-21.0, 1.0)	(-8.9,13.0)	(-25.4, 1.2)
	Pr >  t			0.0741
Week 32	n	12	9	
	LS Mean	-9.395	-2.595	-6.800
	SEM	5.791	5.909	7.167
	95% CI	(-20.9, 2.1)	(-14.3, 9.1)	(-21.0, 7.4)
	Pr >  t			0.3446
Week 40	n	11	7	
	LS Mean	-5.180	2.767	-7.947
	SEM	5.947	6.493	7.686
	95% CI	(-17.0, 6.6)	(-10.1,15.6)	(-23.1, 7.2)
	Pr >  t			0.3029
Week 48	n	8	6	
	LS Mean	0.406	3.157	-2.751
	SEM	6.443	6.826	8.355
	95% CI	(-12.4,13.2)	(-10.3,16.6)	(-19.3,13.8)
	Pr >  t			0.7424
Week 56	n	7	5	
	LS Mean	-8.275	10.099	-18.37
	SEM	6.685	7.228	8.886
	95% CI	(-21.5, 5.0)	(-4.2,24.4)	(-35.9,-0.8)
	Pr >  t			0.0403
Week 64	n	5	3	
	LS Mean	-1.066	1.792	-2.858
	SEM	7.383	8.710	10.59
	95% CI	(-15.7,13.5)	(-15.4,19.0)	(-23.8,18.0)
	Pr >  t			0.7875
Week 72	n	5	2	
	LS Mean	-2.148	10.047	-12.20
	SEM	7.409	10.25	11.91
	95% CI	(-16.8,12.5)	(-10.2,30.3)	(-35.7,11.3)
	Pr >  t			0.3074
Week 84	n	4	2	
	LS Mean	-11.49	-6.618	-4.875
	SEM	7.929	10.25	12.24
	95% CI	(-27.2, 4.2)	(-26.8,13.6)	(-29.0,19.3)
	Pr >  t			0.6910
Week 96	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	0.319	10.047	-9.728
	SEM	7.939	10.25	12.25
	95% CI	(-15.4,16.0)	(-10.2,30.3)	(-33.9,14.5)
	Pr >  t			0.4283
Week 108	n	1	2	
	LS Mean	7.611	20.923	-13.31
	SEM	13.72	10.18	16.56
	95% CI	(-19.5,34.7)	( 0.8,41.0)	(-46.0,19.4)
	Pr >  t			0.4228
Week 120	n	5	1	
	LS Mean	-2.148	17.096	-19.24
	SEM	7.409	13.71	15.00
	95% CI	(-16.8,12.5)	(-10.0,44.2)	(-48.9,10.4)
	Pr >  t			0.2013
Week 132	n	3	1	
	LS Mean	-2.941	-16.23	13.293
	SEM	8.791	13.71	15.73
	95% CI	(-20.3,14.4)	(-43.3,10.9)	(-17.8,44.4)
	Pr >  t			0.3994
Week 144	n	3		
	LS Mean	-2.941		
	SEM	8.791		
	95% CI	(-20.3,14.4)		
	Pr >  t			
Week 156	n	3		
	LS Mean	-14.05		
	SEM	8.791		
	95% CI	(-31.4, 3.3)		
	Pr >  t			
Week 168	n	1		
	LS Mean	-10.50		
	SEM	13.71		
	95% CI	(-37.6,16.6)		
	Pr >  t			
Week 180	n	1		
	LS Mean	6.156		
	SEM	13.71		
	95% CI	(-20.9,33.2)		
	Pr >  t			
Week 192	n	1		



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	-10.50		
		SEM	13.71		
		95% CI	(-37.6,16.6)		
		Pr >  t			
Second Line (progression following metastatic treatment only)	Week 8	n	37	39	
		LS Mean	-4.012	4.057	-8.069
		SEM	3.990	3.985	4.366
		95% CI	(-11.9, 3.9)	(-3.8,12.0)	(-16.7, 0.6)
		Pr >  t			0.0665
	Week 16	n	30	29	
		LS Mean	-2.747	3.946	-6.694
		SEM	4.152	4.375	4.843
		95% CI	(-11.0, 5.5)	(-4.7,12.6)	(-16.2, 2.9)
		Pr >  t			0.1685
	Week 24	n	26	20	
		LS Mean	-8.218	6.936	-15.15
		SEM	4.337	4.878	5.382
		95% CI	(-16.8, 0.4)	(-2.7,16.6)	(-25.8,-4.6)
		Pr >  t			0.0053
	Week 32	n	18	20	
		LS Mean	-5.140	6.104	-11.24
		SEM	4.794	4.878	5.748
		95% CI	(-14.6, 4.3)	(-3.5,15.7)	(-22.6, 0.1)
		Pr >  t			0.0515
	Week 40	n	18	19	
		LS Mean	-1.713	-0.863	-0.850
		SEM	4.793	4.942	5.801
		95% CI	(-11.2, 7.7)	(-10.6, 8.9)	(-12.3,10.6)
		Pr >  t			0.8836
	Week 48	n	16	14	
		LS Mean	-4.986	0.121	-5.107
		SEM	4.945	5.348	6.277
		95% CI	(-14.7, 4.8)	(-10.4,10.7)	(-17.5, 7.2)
		Pr >  t			0.4166
	Week 56	n	14	10	
		LS Mean	-5.146	0.289	-5.434
		SEM	5.134	5.908	6.912
		95% CI	(-15.3, 5.0)	(-11.3,11.9)	(-19.0, 8.2)
		Pr >  t			0.4323

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n		13	11	
	LS Mean		-5.886	-1.017	-4.869
	SEM		5.248	5.739	6.857
	95% CI		(-16.2, 4.5)	(-12.3,10.3)	(-18.4, 8.6)
	Pr >  t				0.4782
Week 72	n		10	6	
	LS Mean		-7.289	0.375	-7.664
	SEM		5.683	7.025	8.268
	95% CI		(-18.5, 3.9)	(-13.4,14.2)	(-23.9, 8.6)
	Pr >  t				0.3546
Week 84	n		8	7	
	LS Mean		-2.773	-5.677	2.904
	SEM		6.189	6.650	8.282
	95% CI		(-14.9, 9.4)	(-18.8, 7.4)	(-13.4,19.2)
	Pr >  t				0.7261
Week 96	n		6	5	
	LS Mean		-1.062	-16.55	15.486
	SEM		6.839	7.506	9.472
	95% CI		(-14.5,12.4)	(-31.3,-1.8)	(-3.1,34.1)
	Pr >  t				0.1029
Week 108	n		2	4	
	LS Mean		-6.232	-2.748	-3.484
	SEM		10.82	8.186	13.05
	95% CI		(-27.5,15.1)	(-18.8,13.3)	(-29.2,22.2)
	Pr >  t				0.7896
Week 120	n		4	4	
	LS Mean		-9.619	1.417	-11.04
	SEM		8.009	8.186	10.86
	95% CI		(-25.4, 6.1)	(-14.7,17.5)	(-32.4,10.3)
	Pr >  t				0.3104
Week 132	n		3	1	
	LS Mean		-22.52	1.662	-24.18
	SEM		9.068	14.98	17.11
	95% CI		(-40.4,-4.7)	(-27.8,31.1)	(-57.8, 9.5)
	Pr >  t				0.1585
Week 144	n		2		
	LS Mean		-8.056		
	SEM		10.77		
	95% CI		(-29.2,13.1)		
	Pr >  t				

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-3.278	1.885	-5.163		
			SEM	3.823	3.832	3.083		
			95% CI	(-10.8, 4.3)	(-5.7, 9.4)	(-11.2, 0.9)		
					Pr >  t			0.0949
		Week 16	n	79	68			
			LS Mean	-3.647	1.207	-4.854		
			SEM	3.864	4.028	3.339		
			95% CI	(-11.3, 4.0)	(-6.7, 9.1)	(-11.4, 1.7)		
					Pr >  t			0.1469
		Week 24	n	64	55			
			LS Mean	-7.412	1.738	-9.150		
			SEM	3.978	4.178	3.596		
			95% CI	(-15.2, 0.4)	(-6.5, 10.0)	(-16.2, -2.1)		
					Pr >  t			0.0113
		Week 32	n	49	53			
			LS Mean	-1.356	-0.787	-0.569		
			SEM	4.158	4.201	3.785		
			95% CI	(-9.5, 6.8)	(-9.1, 7.5)	(-8.0, 6.9)		
					Pr >  t			0.8805
		Week 40	n	44	45			
			LS Mean	-1.191	-1.207	0.017		
			SEM	4.226	4.295	3.963		
			95% CI	(-9.5, 7.1)	(-9.7, 7.2)	(-7.8, 7.8)		
					Pr >  t			0.9966
		Week 48	n	41	36			
			LS Mean	-4.851	-1.977	-2.873		
			SEM	4.271	4.443	4.169		
95% CI	(-13.3, 3.6)		(-10.7, 6.8)	(-11.1, 5.3)				
			Pr >  t			0.4910		
Week 56	n	33	32					
	LS Mean	-4.059	-1.260	-2.799				
		SEM	4.422	4.533	4.422			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.8, 4.6)	(-10.2, 7.7)	(-11.5, 5.9)
		Pr >  t			0.5270
	Week 64	n	27	31	
		LS Mean	-4.919	-1.620	-3.299
		SEM	4.585	4.560	4.615
		95% CI	(-13.9, 4.1)	(-10.6, 7.3)	(-12.4, 5.8)
		Pr >  t			0.4749
	Week 72	n	26	26	
		LS Mean	-6.755	0.993	-7.748
		SEM	4.619	4.710	4.797
		95% CI	(-15.8, 2.3)	(-8.3, 10.3)	(-17.2, 1.7)
		Pr >  t			0.1067
	Week 84	n	22	23	
		LS Mean	-9.726	-1.367	-8.359
		SEM	4.800	4.826	5.068
		95% CI	(-19.2, -0.3)	(-10.9, 8.1)	(-18.3, 1.6)
		Pr >  t			0.0994
	Week 96	n	18	18	
		LS Mean	-5.988	-7.888	1.901
		SEM	5.027	5.096	5.530
		95% CI	(-15.9, 3.9)	(-17.9, 2.1)	(-9.0, 12.8)
		Pr >  t			0.7312
	Week 108	n	14	14	
		LS Mean	-5.776	-2.695	-3.081
		SEM	5.366	5.429	6.130
		95% CI	(-16.3, 4.8)	(-13.4, 8.0)	(-15.1, 8.9)
		Pr >  t			0.6153
	Week 120	n	12	12	
		LS Mean	-9.863	-1.035	-8.827
		SEM	5.598	5.664	6.537
		95% CI	(-20.9, 1.1)	(-12.2, 10.1)	(-21.7, 4.0)
		Pr >  t			0.1772
	Week 132	n	9	5	
		LS Mean	-11.63	-4.672	-6.959
		SEM	6.109	7.563	8.594
		95% CI	(-23.6, 0.4)	(-19.5, 10.2)	(-23.8, 9.9)
		Pr >  t			0.4182
	Week 144	n	7	4	
		LS Mean	-7.752	-0.345	-7.407
		SEM	6.646	8.253	9.571

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.8, 5.3)	(-16.5,15.8)	(-26.2,11.4)
		Pr >  t			0.4392
	Week 156	n	4	2	
		LS Mean	-6.688	-0.807	-5.881
		SEM	8.192	11.03	12.97
		95% CI	(-22.8, 9.4)	(-22.5,20.8)	(-31.3,19.6)
		Pr >  t			0.6503
	Week 168	n	2	1	
		LS Mean	-7.781	-0.843	-6.938
		SEM	10.98	15.13	18.13
		95% CI	(-29.3,13.8)	(-30.5,28.9)	(-42.5,28.7)
		Pr >  t			0.7021
Yes	Week 8	n	53	48	
		LS Mean	-9.747	1.994	-11.74
		SEM	3.050	3.180	3.029
		95% CI	(-15.8,-3.7)	( -4.3, 8.3)	(-17.7,-5.8)
		Pr >  t			0.0001
	Week 16	n	45	39	
		LS Mean	-3.095	-1.102	-1.992
		SEM	3.187	3.321	3.231
		95% CI	( -9.4, 3.2)	( -7.7, 5.5)	( -8.4, 4.4)
		Pr >  t			0.5380
	Week 24	n	41	26	
		LS Mean	-4.569	0.436	-5.005
		SEM	3.230	3.563	3.550
		95% CI	(-10.9, 1.8)	( -6.6, 7.5)	(-12.0, 2.0)
		Pr >  t			0.1595
	Week 32	n	37	20	
		LS Mean	-6.936	-2.538	-4.398
		SEM	3.302	3.788	3.803
		95% CI	(-13.4,-0.4)	(-10.0, 4.9)	(-11.9, 3.1)
		Pr >  t			0.2483
	Week 40	n	31	17	
		LS Mean	-4.748	-1.571	-3.177
		SEM	3.398	3.962	4.031
		95% CI	(-11.4, 1.9)	( -9.4, 6.2)	(-11.1, 4.7)
		Pr >  t			0.4310
	Week 48	n	28	15	
		LS Mean	-3.065	1.032	-4.097
		SEM	3.459	4.082	4.202

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.9, 3.7)	(-7.0, 9.1)	(-12.4, 4.2)
		Pr >  t			0.3300
	Week 56	n	26	13	
		LS Mean	-4.016	2.278	-6.294
		SEM	3.505	4.231	4.388
		95% CI	(-10.9, 2.9)	(-6.0, 10.6)	(-14.9, 2.3)
		Pr >  t			0.1521
	Week 64	n	20	11	
		LS Mean	-4.671	2.285	-6.956
		SEM	3.689	4.423	4.717
		95% CI	(-11.9, 2.6)	(-6.4, 11.0)	(-16.2, 2.3)
		Pr >  t			0.1409
	Week 72	n	22	9	
		LS Mean	-2.807	2.432	-5.240
		SEM	3.621	4.679	4.907
		95% CI	(-9.9, 4.3)	(-6.8, 11.6)	(-14.9, 4.4)
		Pr >  t			0.2860
	Week 84	n	18	10	
		LS Mean	-6.493	-2.535	-3.957
		SEM	3.785	4.542	4.895
		95% CI	(-13.9, 1.0)	(-11.5, 6.4)	(-13.6, 5.7)
		Pr >  t			0.4192
	Week 96	n	17	6	
		LS Mean	-3.453	4.038	-7.491
		SEM	3.823	5.318	5.657
		95% CI	(-11.0, 4.1)	(-6.4, 14.5)	(-18.6, 3.6)
		Pr >  t			0.1859
	Week 108	n	12	7	
		LS Mean	-3.290	1.467	-4.757
		SEM	4.184	5.056	5.664
		95% CI	(-11.5, 4.9)	(-8.5, 11.4)	(-15.9, 6.4)
		Pr >  t			0.4013
	Week 120	n	16	4	
		LS Mean	-1.950	4.574	-6.524
		SEM	3.882	6.149	6.479
		95% CI	(-9.6, 5.7)	(-7.5, 16.7)	(-19.2, 6.2)
		Pr >  t			0.3144
	Week 132	n	11	3	
		LS Mean	-9.344	-5.356	-3.988
		SEM	4.286	6.877	7.395

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.8,-0.9)	(-18.9, 8.2)	(-18.5,10.5)
		Pr >  t			0.5899
	Week 144	n	8	1	
		LS Mean	-9.801	2.757	-12.56
		SEM	4.695	11.09	11.59
		95% CI	(-19.0,-0.6)	(-19.0,24.5)	(-35.3,10.2)
		Pr >  t			0.2790
	Week 156	n	6	1	
		LS Mean	-7.383	-13.91	6.530
		SEM	5.191	11.09	11.79
		95% CI	(-17.6, 2.8)	(-35.7, 7.9)	(-16.6,29.7)
		Pr >  t			0.5799
	Week 168	n	2	1	
		LS Mean	-7.169	2.757	-9.926
		SEM	8.043	11.09	13.29
		95% CI	(-23.0, 8.6)	(-19.0,24.5)	(-36.0,16.2)
		Pr >  t			0.4556
	Week 180	n	1	1	
		LS Mean	7.095	2.757	4.338
		SEM	10.99	11.09	15.26
		95% CI	(-14.5,28.7)	(-19.0,24.5)	(-25.6,34.3)
		Pr >  t			0.7763
	Week 192	n	1	1	
		LS Mean	-9.565	2.757	-12.32
		SEM	10.99	11.09	15.26
		95% CI	(-31.2,12.0)	(-19.0,24.5)	(-42.3,17.7)
		Pr >  t			0.4197

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-5.160	1.527	-6.686
			SEM	2.704	2.802	2.561
			95% CI	(-10.5, 0.2)	(-4.0, 7.0)	(-11.7, -1.6)
		Pr >  t			0.0094	
		Week 16	n	90	75	
			LS Mean	-3.305	1.086	-4.391
			SEM	2.763	2.922	2.741
			95% CI	(-8.7, 2.1)	(-4.7, 6.8)	(-9.8, 1.0)
		Pr >  t			0.1099	
		Week 24	n	79	62	
			LS Mean	-2.761	1.328	-4.089
			SEM	2.821	3.025	2.887
			95% CI	(-8.3, 2.8)	(-4.6, 7.3)	(-9.8, 1.6)
		Pr >  t			0.1573	
		Week 32	n	70	56	
			LS Mean	-2.792	-1.626	-1.167
			SEM	2.893	3.085	2.989
			95% CI	(-8.5, 2.9)	(-7.7, 4.4)	(-7.0, 4.7)
		Pr >  t			0.6964	
		Week 40	n	61	46	
			LS Mean	-2.047	-0.579	-1.468
			SEM	2.954	3.196	3.151
			95% CI	(-7.9, 3.8)	(-6.9, 5.7)	(-7.7, 4.7)
Pr >  t			0.6414			
Week 48	n	56	38			
	LS Mean	-2.722	1.138	-3.860		
	SEM	2.992	3.310	3.302		
	95% CI	(-8.6, 3.2)	(-5.4, 7.6)	(-10.3, 2.6)		
Pr >  t			0.2428			
Week 56	n	49	33			
	LS Mean	-2.987	1.121	-4.108		
	SEM	3.057	3.404	3.458		

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-9.0, 3.0)	(-5.6, 7.8)	(-10.9, 2.7)
		Pr >  t			0.2352
		n	37	29	
		LS Mean	-5.166	1.677	-6.843
		SEM	3.215	3.501	3.692
Week 72		95% CI	(-11.5, 1.2)	(-5.2, 8.6)	(-14.1, 0.4)
		Pr >  t			0.0641
		n	40	25	
		LS Mean	-4.965	0.530	-5.495
		SEM	3.169	3.619	3.765
Week 84		95% CI	(-11.2, 1.3)	(-6.6, 7.6)	(-12.9, 1.9)
		Pr >  t			0.1447
		n	32	23	
		LS Mean	-6.887	-0.340	-6.547
		SEM	3.323	3.693	3.957
Week 96		95% CI	(-13.4,-0.4)	(-7.6, 6.9)	(-14.3, 1.2)
		Pr >  t			0.0984
		n	29	17	
		LS Mean	-4.462	-5.824	1.362
		SEM	3.391	3.997	4.300
Week 108		95% CI	(-11.1, 2.2)	(-13.7, 2.0)	(-7.1, 9.8)
		Pr >  t			0.7515
		n	22	15	
		LS Mean	-2.784	0.681	-3.465
		SEM	3.634	4.145	4.619
Week 120		95% CI	(-9.9, 4.4)	(-7.5, 8.8)	(-12.5, 5.6)
		Pr >  t			0.4533
		n	23	13	
		LS Mean	-6.652	-0.277	-6.375
		SEM	3.588	4.329	4.755
Week 132		95% CI	(-13.7, 0.4)	(-8.8, 8.2)	(-15.7, 3.0)
		Pr >  t			0.1803
		n	17	5	
		LS Mean	-10.09	-3.311	-6.783
		SEM	3.896	6.084	6.570
Week 144		95% CI	(-17.7,-2.4)	(-15.2, 8.6)	(-19.7, 6.1)
		Pr >  t			0.3021
		n	14	3	
		LS Mean	-7.633	1.346	-8.979
		SEM	4.121	7.546	8.059

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.7, 0.5)	(-13.5,16.2)	(-24.8, 6.8)
		Pr >  t			0.2655
	Week 156	n	9	2	
		LS Mean	-3.580	-7.081	3.501
		SEM	4.790	9.027	9.766
		95% CI	(-13.0, 5.8)	(-24.8,10.6)	(-15.7,22.7)
		Pr >  t			0.7201
	Week 168	n	4	1	
		LS Mean	-6.467	2.782	-9.249
		SEM	6.592	12.47	13.78
		95% CI	(-19.4, 6.5)	(-21.7,27.2)	(-36.3,17.8)
		Pr >  t			0.5022
	Week 180	n	1	1	
		LS Mean	8.217	2.782	5.435
		SEM	12.42	12.47	17.34
		95% CI	(-16.1,32.6)	(-21.7,27.2)	(-28.6,39.5)
		Pr >  t			0.7540
	Week 192	n	1	1	
		LS Mean	-8.443	2.782	-11.22
		SEM	12.42	12.47	17.34
		95% CI	(-32.8,15.9)	(-21.7,27.2)	(-45.2,22.8)
		Pr >  t			0.5175
>= 3	Week 8	n	37	45	
		LS Mean	-11.36	-0.774	-10.58
		SEM	8.228	8.157	4.720
		95% CI	(-27.6, 4.9)	(-16.9,15.3)	(-19.9,-1.3)
		Pr >  t			0.0261
	Week 16	n	34	32	
		LS Mean	-8.432	-5.691	-2.741
		SEM	8.472	8.541	5.160
		95% CI	(-25.1, 8.3)	(-22.5,11.2)	(-12.9, 7.4)
		Pr >  t			0.5958
	Week 24	n	26	19	
		LS Mean	-21.15	-2.902	-18.25
		SEM	8.654	8.939	6.078
		95% CI	(-38.2,-4.1)	(-20.5,14.7)	(-30.2,-6.3)
		Pr >  t			0.0029
	Week 32	n	16	17	
		LS Mean	-10.68	-4.755	-5.922
		SEM	9.086	9.063	6.838

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-28.6, 7.2)	(-22.6,13.1)	(-19.4, 7.5)
	Pr >  t			0.3871
	n	14	16	
	LS Mean	-7.735	-8.049	0.314
	SEM	9.243	9.122	7.118
Week 48	95% CI	(-25.9,10.5)	(-26.0, 9.9)	(-13.7,14.3)
	Pr >  t			0.9649
	n	13	13	
	LS Mean	-12.86	-12.12	-0.735
	SEM	9.323	9.356	7.517
Week 56	95% CI	(-31.2, 5.5)	(-30.6, 6.3)	(-15.5,14.0)
	Pr >  t			0.9222
	n	10	12	
	LS Mean	-11.04	-8.594	-2.449
	SEM	9.694	9.462	8.069
Week 64	95% CI	(-30.1, 8.0)	(-27.2,10.0)	(-18.3,13.4)
	Pr >  t			0.7617
	n	10	13	
	LS Mean	-6.366	-10.44	4.078
	SEM	9.699	9.365	7.959
Week 72	95% CI	(-25.5,12.7)	(-28.9, 8.0)	(-11.6,19.7)
	Pr >  t			0.6087
	n	8	10	
	LS Mean	-6.720	-1.144	-5.576
	SEM	10.05	9.714	8.778
Week 84	95% CI	(-26.5,13.1)	(-20.3,18.0)	(-22.8,11.7)
	Pr >  t			0.5256
	n	8	10	
	LS Mean	-16.14	-9.524	-6.612
	SEM	10.06	9.707	8.778
Week 96	95% CI	(-35.9, 3.7)	(-28.6, 9.6)	(-23.9,10.6)
	Pr >  t			0.4518
	n	6	7	
	LS Mean	-7.827	-7.285	-0.542
	SEM	10.63	10.32	10.05
Week 108	95% CI	(-28.8,13.1)	(-27.6,13.0)	(-20.3,19.2)
	Pr >  t			0.9570
	n	4	6	
Week 108	LS Mean	-15.53	-11.01	-4.513
	SEM	11.66	10.63	11.43

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-38.5, 7.4)	(-31.9, 9.9)	(-27.0,18.0)
		Pr >  t			0.6933
	Week 120	n	5	3	
		LS Mean	-1.167	-0.473	-0.694
		SEM	11.05	12.61	12.77
		95% CI	(-22.9,20.6)	(-25.3,24.3)	(-25.8,24.4)
		Pr >  t			0.9567
	Week 132	n	3	3	
		LS Mean	-13.32	-12.93	-0.394
		SEM	12.61	12.62	14.14
		95% CI	(-38.1,11.5)	(-37.7,11.9)	(-28.2,27.4)
		Pr >  t			0.9778
	Week 144	n	1	2	
		LS Mean	-20.62	-6.255	-14.36
		SEM	18.51	14.32	20.73
		95% CI	(-57.0,15.8)	(-34.4,21.9)	(-55.1,26.4)
		Pr >  t			0.4888
	Week 156	n	1	1	
		LS Mean	-37.28	-6.421	-30.86
		SEM	18.51	18.53	23.82
		95% CI	(-73.7,-0.9)	(-42.9,30.0)	(-77.7,16.0)
		Pr >  t			0.1961
	Week 168	n		1	
		LS Mean		-6.421	
		SEM		18.53	
		95% CI		(-42.9,30.0)	
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
PIK3CA mutation	E542K	Week 8	n	16	24		
			LS Mean	-1.587	-0.146	-1.440	
			SEM	8.476	9.428	7.674	
			95% CI	(-18.7,15.6)	(-19.3,19.0)	(-16.9,14.0)	
					Pr >  t	0.8519	
		Week 16	n	14	17		
			LS Mean	4.871	-6.233	11.103	
			SEM	8.546	9.606	8.033	
			95% CI	(-12.4,22.1)	(-25.7,13.2)	(-5.0,27.2)	
					Pr >  t	0.1725	
		Week 24	n	14	11		
			LS Mean	-4.652	-1.616	-3.036	
			SEM	8.546	9.886	8.367	
			95% CI	(-21.9,12.6)	(-21.5,18.3)	(-19.8,13.7)	
					Pr >  t	0.7179	
		Week 32	n	10	10		
			LS Mean	-4.694	-9.110	4.416	
			SEM	8.980	9.974	8.695	
			95% CI	(-22.7,13.4)	(-29.2,11.0)	(-12.9,21.7)	
					Pr >  t	0.6131	
		Week 40	n	8	10		
			LS Mean	0.597	-9.259	9.856	
			SEM	9.184	9.973	8.897	
			95% CI	(-17.8,19.0)	(-29.3,10.8)	(-7.9,27.6)	
					Pr >  t	0.2713	
		Week 48	n	7	11		
			LS Mean	-0.959	-10.34	9.377	
			SEM	9.314	9.908	8.974	
95% CI	(-19.6,17.7)		(-30.3, 9.6)	(-8.5,27.2)			
			Pr >  t	0.2992			
Week 56	n	6	9				
	LS Mean	-0.135	-8.333	8.197			
	SEM	9.477	10.06	9.322			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.1,18.8)	(-28.6,11.9)	(-10.3,26.7)
		Pr >  t			0.3815
	Week 64	n	5	8	
		LS Mean	-0.215	-6.578	6.363
		SEM	9.711	10.15	9.661
		95% CI	(-19.6,19.2)	(-27.0,13.8)	(-12.8,25.5)
		Pr >  t			0.5116
	Week 72	n	7	7	
		LS Mean	-0.398	1.181	-1.580
		SEM	9.299	10.28	9.389
		95% CI	(-19.0,18.2)	(-19.5,21.8)	(-20.2,17.1)
		Pr >  t			0.8667
	Week 84	n	7	7	
		LS Mean	-5.160	-1.200	-3.960
		SEM	9.299	10.28	9.389
		95% CI	(-23.8,13.5)	(-21.8,19.4)	(-22.6,14.7)
		Pr >  t			0.6742
	Week 96	n	5	6	
		LS Mean	-3.767	-11.77	8.001
		SEM	9.707	10.44	9.963
		95% CI	(-23.2,15.6)	(-32.7, 9.2)	(-11.7,27.7)
		Pr >  t			0.4236
	Week 108	n	4	6	
		LS Mean	-3.575	-11.77	8.193
		SEM	10.06	10.44	10.30
		95% CI	(-23.6,16.5)	(-32.7, 9.2)	(-12.2,28.6)
		Pr >  t			0.4279
	Week 120	n	4	4	
		LS Mean	0.354	0.994	-0.640
		SEM	10.06	10.98	10.85
		95% CI	(-19.7,20.4)	(-20.9,22.9)	(-22.1,20.8)
		Pr >  t			0.9530
	Week 132	n	3	1	
		LS Mean	-10.73	-26.22	15.498
		SEM	10.60	14.83	15.11
		95% CI	(-31.8,10.3)	(-55.5, 3.1)	(-14.3,45.3)
		Pr >  t			0.3061
	Week 144	n	1	1	
		LS Mean	-28.30	-4.506	-23.79
		SEM	14.18	14.88	17.85

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
E545X	Week 8	95% CI	(-56.3,-0.3)	(-33.9,24.9)	(-59.0,11.4)	
		Pr >  t			0.1839	
		n	35	37		
		LS Mean	-3.371	5.190	-8.561	
			SEM	9.052	9.453	4.156
			95% CI	(-21.2,14.5)	(-13.5,23.8)	(-16.8,-0.4)
			Pr >  t			0.0407
		Week 16	n	34	30	
			LS Mean	-1.746	2.118	-3.863
			SEM	9.374	9.539	4.354
			95% CI	(-20.2,16.7)	(-16.7,20.9)	(-12.4, 4.7)
			Pr >  t			0.3759
		Week 24	n	32	23	
			LS Mean	-8.884	4.056	-12.94
			SEM	9.395	9.657	4.684
			95% CI	(-27.4, 9.6)	(-15.0,23.1)	(-22.2,-3.7)
			Pr >  t			0.0062
		Week 32	n	21	22	
			LS Mean	-2.816	5.514	-8.329
			SEM	9.573	9.680	5.109
			95% CI	(-21.7,16.1)	(-13.6,24.6)	(-18.4, 1.7)
			Pr >  t			0.1041
		Week 40	n	20	20	
			LS Mean	-1.238	0.558	-1.797
			SEM	9.609	9.733	5.259
			95% CI	(-20.2,17.7)	(-18.6,19.8)	(-12.1, 8.6)
			Pr >  t			0.7329
		Week 48	n	19	12	
	LS Mean		-4.295	0.075	-4.370	
	SEM		9.631	10.08	5.941	
	95% CI		(-23.3,14.7)	(-19.8,19.9)	(-16.1, 7.3)	
		Pr >  t			0.4625	
	Week 56	n	16	8		
		LS Mean	1.774	5.915	-4.141	
		SEM	9.742	10.51	6.785	
		95% CI	(-17.4,21.0)	(-14.8,26.6)	(-17.5, 9.2)	
		Pr >  t			0.5420	
	Week 64	n	12	11		
		LS Mean	-1.927	-0.316	-1.611	
		SEM	9.955	10.17	6.577	



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.5,17.7)	(-20.4,19.7)	(-14.5,11.3)
		Pr >  t			0.8066
	Week 72	n	13	7	
		LS Mean	-2.939	0.717	-3.656
		SEM	9.904	10.68	7.268
		95% CI	(-22.5,16.6)	(-20.3,21.7)	(-17.9,10.6)
		Pr >  t			0.6152
	Week 84	n	12	6	
		LS Mean	-3.839	-10.91	7.067
		SEM	9.951	10.91	7.667
		95% CI	(-23.4,15.8)	(-32.4,10.6)	(-8.0,22.1)
		Pr >  t			0.3572
	Week 96	n	7	6	
		LS Mean	-0.354	-6.072	5.719
		SEM	10.54	10.91	8.419
		95% CI	(-21.1,20.4)	(-27.5,15.4)	(-10.8,22.3)
		Pr >  t			0.4974
	Week 108	n	5	3	
		LS Mean	-5.069	6.264	-11.33
		SEM	11.08	12.34	10.77
		95% CI	(-26.9,16.7)	(-18.0,30.5)	(-32.5, 9.8)
		Pr >  t			0.2934
	Week 120	n	8	3	
		LS Mean	-6.066	6.264	-12.33
		SEM	10.40	12.34	10.06
		95% CI	(-26.6,14.4)	(-18.0,30.5)	(-32.1, 7.5)
		Pr >  t			0.2213
	Week 132	n	2	1	
		LS Mean	-21.47	-19.77	-1.696
		SEM	13.47	16.87	17.53
		95% CI	(-48.0, 5.0)	(-52.9,13.4)	(-36.2,32.8)
		Pr >  t			0.9230
	Week 144	n	2		
		LS Mean	2.189		
		SEM	13.51		
		95% CI	(-24.4,28.8)		
		Pr >  t			
	Week 156	n	2		
		LS Mean	2.189		
		SEM	13.51		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-24.4,28.8)		
		Pr >  t			
H1047X	Week 8	n	81	64	
		LS Mean	-7.973	2.642	-10.62
		SEM	3.150	3.303	3.162
		95% CI	(-14.2,-1.8)	(-3.9, 9.2)	(-16.8,-4.4)
		Pr >  t			0.0009
	Week 16	n	70	52	
		LS Mean	-6.481	2.950	-9.431
		SEM	3.243	3.492	3.396
		95% CI	(-12.9,-0.1)	(-3.9, 9.8)	(-16.1,-2.8)
		Pr >  t			0.0058
	Week 24	n	54	40	
		LS Mean	-5.998	0.921	-6.919
		SEM	3.395	3.714	3.735
		95% CI	(-12.7, 0.7)	(-6.4, 8.2)	(-14.3, 0.4)
		Pr >  t			0.0646
	Week 32	n	50	36	
		LS Mean	-4.730	-3.296	-1.434
		SEM	3.459	3.789	3.854
		95% CI	(-11.5, 2.1)	(-10.8, 4.2)	(-9.0, 6.1)
		Pr >  t			0.7100
	Week 40	n	42	28	
		LS Mean	-4.587	0.609	-5.195
		SEM	3.570	4.018	4.160
		95% CI	(-11.6, 2.4)	(-7.3, 8.5)	(-13.4, 3.0)
		Pr >  t			0.2122
	Week 48	n	38	24	
		LS Mean	-4.736	1.823	-6.559
		SEM	3.639	4.166	4.362
		95% CI	(-11.9, 2.4)	(-6.4,10.0)	(-15.1, 2.0)
		Pr >  t			0.1332
	Week 56	n	33	24	
		LS Mean	-6.774	0.337	-7.111
		SEM	3.745	4.170	4.460
		95% CI	(-14.1, 0.6)	(-7.9, 8.5)	(-15.9, 1.6)
		Pr >  t			0.1114
	Week 64	n	27	19	
		LS Mean	-6.543	0.777	-7.320
		SEM	3.913	4.424	4.836

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.2, 1.1)	(-7.9, 9.5)	(-16.8, 2.2)
		Pr >  t			0.1305
	Week 72	n	26	17	
		LS Mean	-7.339	1.602	-8.941
		SEM	3.948	4.554	4.982
		95% CI	(-15.1, 0.4)	(-7.3, 10.5)	(-18.7, 0.8)
		Pr >  t			0.0731
	Week 84	n	18	16	
		LS Mean	-13.05	-0.703	-12.34
		SEM	4.367	4.634	5.374
		95% CI	(-21.6, -4.5)	(-9.8, 8.4)	(-22.9, -1.8)
		Pr >  t			0.0219
	Week 96	n	20	10	
		LS Mean	-7.520	-0.343	-7.177
		SEM	4.233	5.357	5.920
		95% CI	(-15.8, 0.8)	(-10.9, 10.2)	(-18.8, 4.4)
		Pr >  t			0.2257
	Week 108	n	14	10	
		LS Mean	-4.659	3.012	-7.671
		SEM	4.707	5.360	6.263
		95% CI	(-13.9, 4.6)	(-7.5, 13.5)	(-20.0, 4.6)
		Pr >  t			0.2210
	Week 120	n	14	7	
		LS Mean	-5.968	1.731	-7.700
		SEM	4.689	6.074	6.881
		95% CI	(-15.2, 3.2)	(-10.2, 13.7)	(-21.2, 5.8)
		Pr >  t			0.2635
	Week 132	n	12	5	
		LS Mean	-5.908	1.719	-7.628
		SEM	4.939	6.913	7.779
		95% CI	(-15.6, 3.8)	(-11.8, 15.3)	(-22.9, 7.6)
		Pr >  t			0.3271
	Week 144	n	11	4	
		LS Mean	-9.383	1.868	-11.25
		SEM	5.064	7.569	8.453
		95% CI	(-19.3, 0.6)	(-13.0, 16.7)	(-27.8, 5.3)
		Pr >  t			0.1836
	Week 156	n	8	3	
		LS Mean	-9.849	-3.491	-6.358
		SEM	5.680	8.546	9.676

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.0, 1.3)	(-20.3,13.3)	(-25.4,12.6)
		Pr >  t			0.5113
	Week 168	n	4	2	
		LS Mean	-8.630	2.651	-11.28
		SEM	7.475	10.22	12.20
		95% CI	(-23.3, 6.0)	(-17.4,22.7)	(-35.2,12.7)
		Pr >  t			0.3553
	Week 180	n	1	1	
		LS Mean	5.959	4.269	1.690
		SEM	14.05	14.09	19.60
		95% CI	(-21.6,33.5)	(-23.4,31.9)	(-36.8,40.2)
		Pr >  t			0.9313
	Week 192	n	1	1	
		LS Mean	-10.70	4.269	-14.97
		SEM	14.05	14.09	19.60
		95% CI	(-38.3,16.9)	(-23.4,31.9)	(-53.5,23.5)
		Pr >  t			0.4453

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 10.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64	
			LS Mean	-7.973	2.642	-10.62
			SEM	3.150	3.303	3.162
			95% CI	(-14.2,-1.8)	(-3.9, 9.2)	(-16.8,-4.4)
		Pr >  t			0.0009	
		Week 16	n	70	52	
			LS Mean	-6.481	2.950	-9.431
			SEM	3.243	3.492	3.396
			95% CI	(-12.9,-0.1)	(-3.9, 9.8)	(-16.1,-2.8)
		Pr >  t			0.0058	
		Week 24	n	54	40	
			LS Mean	-5.998	0.921	-6.919
			SEM	3.395	3.714	3.735
			95% CI	(-12.7, 0.7)	(-6.4, 8.2)	(-14.3, 0.4)
		Pr >  t			0.0646	
		Week 32	n	50	36	
			LS Mean	-4.730	-3.296	-1.434
			SEM	3.459	3.789	3.854
			95% CI	(-11.5, 2.1)	(-10.8, 4.2)	(-9.0, 6.1)
		Pr >  t			0.7100	
		Week 40	n	42	28	
			LS Mean	-4.587	0.609	-5.195
			SEM	3.570	4.018	4.160
			95% CI	(-11.6, 2.4)	(-7.3, 8.5)	(-13.4, 3.0)
Pr >  t			0.2122			
Week 48	n	38	24			
	LS Mean	-4.736	1.823	-6.559		
	SEM	3.639	4.166	4.362		
	95% CI	(-11.9, 2.4)	(-6.4,10.0)	(-15.1, 2.0)		
Pr >  t			0.1332			
Week 56	n	33	24			
	LS Mean	-6.774	0.337	-7.111		
	SEM	3.745	4.170	4.460		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.1, 0.6)	(-7.9, 8.5)	(-15.9, 1.6)
		Pr >  t			0.1114
	Week 64	n	27	19	
		LS Mean	-6.543	0.777	-7.320
		SEM	3.913	4.424	4.836
		95% CI	(-14.2, 1.1)	(-7.9, 9.5)	(-16.8, 2.2)
		Pr >  t			0.1305
	Week 72	n	26	17	
		LS Mean	-7.339	1.602	-8.941
		SEM	3.948	4.554	4.982
		95% CI	(-15.1, 0.4)	(-7.3, 10.5)	(-18.7, 0.8)
		Pr >  t			0.0731
	Week 84	n	18	16	
		LS Mean	-13.05	-0.703	-12.34
		SEM	4.367	4.634	5.374
		95% CI	(-21.6, -4.5)	(-9.8, 8.4)	(-22.9, -1.8)
		Pr >  t			0.0219
	Week 96	n	20	10	
		LS Mean	-7.520	-0.343	-7.177
		SEM	4.233	5.357	5.920
		95% CI	(-15.8, 0.8)	(-10.9, 10.2)	(-18.8, 4.4)
		Pr >  t			0.2257
	Week 108	n	14	10	
		LS Mean	-4.659	3.012	-7.671
		SEM	4.707	5.360	6.263
		95% CI	(-13.9, 4.6)	(-7.5, 13.5)	(-20.0, 4.6)
		Pr >  t			0.2210
	Week 120	n	14	7	
		LS Mean	-5.968	1.731	-7.700
		SEM	4.689	6.074	6.881
		95% CI	(-15.2, 3.2)	(-10.2, 13.7)	(-21.2, 5.8)
		Pr >  t			0.2635
	Week 132	n	12	5	
		LS Mean	-5.908	1.719	-7.628
		SEM	4.939	6.913	7.779
		95% CI	(-15.6, 3.8)	(-11.8, 15.3)	(-22.9, 7.6)
		Pr >  t			0.3271
	Week 144	n	11	4	
		LS Mean	-9.383	1.868	-11.25
		SEM	5.064	7.569	8.453

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	(-19.3, 0.6)	(-13.0,16.7)	(-27.8, 5.3)
		Pr >  t			0.1836
		n	8	3	
		LS Mean	-9.849	-3.491	-6.358
		SEM	5.680	8.546	9.676
	Week 168	95% CI	(-21.0, 1.3)	(-20.3,13.3)	(-25.4,12.6)
		Pr >  t			0.5113
		n	4	2	
		LS Mean	-8.630	2.651	-11.28
		SEM	7.475	10.22	12.20
	Week 180	95% CI	(-23.3, 6.0)	(-17.4,22.7)	(-35.2,12.7)
		Pr >  t			0.3553
		n	1	1	
		LS Mean	5.959	4.269	1.690
		SEM	14.05	14.09	19.60
Week 192	95% CI	(-21.6,33.5)	(-23.4,31.9)	(-36.8,40.2)	
	Pr >  t			0.9313	
	n	1	1		
	LS Mean	-10.70	4.269	-14.97	
	SEM	14.05	14.09	19.60	
Week 8	95% CI	(-38.3,16.9)	(-23.4,31.9)	(-53.5,23.5)	
	Pr >  t			0.4453	
	n	53	64		
	LS Mean	-3.060	4.592	-7.652	
	SEM	5.222	5.586	3.546	
	Week 16	95% CI	(-13.4, 7.3)	(-6.5,15.6)	(-14.6,-0.7)
		Pr >  t			0.0321
		n	48	48	
		LS Mean	0.578	0.851	-0.273
		SEM	5.337	5.700	3.791
Week 24	95% CI	(-10.0,11.1)	(-10.4,12.1)	(-7.7, 7.2)	
	Pr >  t			0.9426	
	n	46	36		
	LS Mean	-7.327	3.938	-11.26	
	SEM	5.353	5.827	4.020	
Week 32	95% CI	(-17.9, 3.3)	(-7.6,15.5)	(-19.2,-3.4)	
	Pr >  t			0.0054	
	n	31	33		
		LS Mean	-3.281	2.638	-5.920
		SEM	5.627	5.875	4.336

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-14.4, 7.8)	(-9.0, 14.2)	(-14.4, 2.6)
	Pr >  t			0.1730
	n	28	30	
	LS Mean	-0.580	-0.984	0.404
	SEM	5.690	5.926	4.481
Week 48	95% CI	(-11.8, 10.6)	(-12.7, 10.7)	(-8.4, 9.2)
	Pr >  t			0.9283
	n	26	23	
	LS Mean	-3.033	-1.861	-1.171
	SEM	5.731	6.086	4.748
Week 56	95% CI	(-14.3, 8.3)	(-13.9, 10.2)	(-10.5, 8.2)
	Pr >  t			0.8053
	n	22	17	
	LS Mean	1.636	1.731	-0.095
	SEM	5.838	6.318	5.165
Week 64	95% CI	(-9.9, 13.1)	(-10.7, 14.2)	(-10.2, 10.1)
	Pr >  t			0.9854
	n	17	19	
	LS Mean	-0.923	-0.555	-0.368
	SEM	6.039	6.227	5.286
Week 72	95% CI	(-12.8, 11.0)	(-12.8, 11.7)	(-10.8, 10.0)
	Pr >  t			0.9446
	n	20	14	
	LS Mean	-1.636	4.102	-5.738
	SEM	5.913	6.499	5.466
Week 84	95% CI	(-13.3, 10.0)	(-8.7, 16.9)	(-16.5, 5.0)
	Pr >  t			0.2942
	n	19	13	
	LS Mean	-4.008	-2.170	-1.838
	SEM	5.945	6.575	5.593
Week 96	95% CI	(-15.7, 7.7)	(-15.1, 10.8)	(-12.8, 9.1)
	Pr >  t			0.7425
	n	12	12	
	LS Mean	-1.408	-5.706	4.298
	SEM	6.387	6.663	6.157
Week 108	95% CI	(-14.0, 11.2)	(-18.8, 7.4)	(-7.8, 16.4)
	Pr >  t			0.4854
	n	9	9	
Week 108	LS Mean	-4.152	-1.507	-2.645
	SEM	6.762	7.024	6.912



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-17.5, 9.2)	(-15.3,12.3)	(-16.2,10.9)
		Pr >  t			0.7021
	Week 120	n	12	7	
		LS Mean	-3.455	6.772	-10.23
		SEM	6.404	7.416	6.975
		95% CI	(-16.1, 9.2)	(-7.8,21.4)	(-23.9, 3.5)
		Pr >  t			0.1431
	Week 132	n	5	2	
		LS Mean	-14.97	-19.93	4.954
		SEM	7.820	10.82	11.45
		95% CI	(-30.3, 0.4)	(-41.2, 1.3)	(-17.5,27.4)
		Pr >  t			0.6654
	Week 144	n	3	1	
		LS Mean	-8.285	2.411	-10.70
		SEM	9.204	14.34	15.59
		95% CI	(-26.4, 9.8)	(-25.8,30.6)	(-41.3,19.9)
		Pr >  t			0.4931
	Week 156	n	2		
		LS Mean	1.503		
		SEM	10.68		
		95% CI	(-19.5,22.5)		
		Pr >  t			

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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#### 4.8.4 Patientenberichtete Endpunkte: Linear mixed effects model-Subgruppenanalysen bei nicht signifikantem Interaktionstest – 2. Datenschnitt

##### 4.8.4.1 Krankheitssymptomatik: EORTC QLQ-C30 – 2. Datenschnitt

Tabelle 4H-41: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Fatigue“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

Table 11.2-21i  
Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score  
in subgroups i  
(Full Analysis Set, PIK3CA mutant cohort)

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Presence of Liver Metastases (L)	No	Week 8	n	104	98	
			LS Mean	9.274	2.473	6.801
			SEM	3.162	3.145	2.657
		95% CI	( 3.0,15.5)	( -3.7, 8.7)	( 1.6,12.0)	
		Pr >  t			0.0108	
		Week 16	n	92	77	
	LS Mean		6.874	4.346	2.528	
	SEM		3.202	3.311	2.842	
	Week 24	95% CI	( 0.6,13.2)	( -2.2,10.9)	( -3.1, 8.1)	
		Pr >  t			0.3742	
		n	83	66		
			LS Mean	5.583	5.500	0.083

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	3.256	3.380	2.977
	95% CI	(-0.8,12.0)	(-1.1,12.1)	(-5.8, 5.9)
	Pr >  t			0.9777
Week 32	n	72	60	
	LS Mean	7.559	4.319	3.240
	SEM	3.325	3.442	3.099
	95% CI	( 1.0,14.1)	(-2.4,11.1)	(-2.8, 9.3)
	Pr >  t			0.2961
Week 40	n	64	51	
	LS Mean	5.194	2.987	2.206
	SEM	3.378	3.541	3.251
	95% CI	(-1.4,11.8)	(-4.0, 9.9)	(-4.2, 8.6)
	Pr >  t			0.4977
Week 48	n	58	45	
	LS Mean	7.995	2.806	5.189
	SEM	3.423	3.615	3.380
	95% CI	( 1.3,14.7)	(-4.3, 9.9)	(-1.4,11.8)
	Pr >  t			0.1251
Week 56	n	49	38	
	LS Mean	6.683	4.738	1.945
	SEM	3.510	3.727	3.588
	95% CI	(-0.2,13.6)	(-2.6,12.1)	(-5.1, 9.0)
	Pr >  t			0.5879
Week 64	n	39	37	
	LS Mean	8.253	6.687	1.566
	SEM	3.646	3.746	3.745
	95% CI	( 1.1,15.4)	(-0.7,14.0)	(-5.8, 8.9)
	Pr >  t			0.6760
Week 72	n	41	32	
	LS Mean	6.843	5.551	1.292
	SEM	3.616	3.853	3.822
	95% CI	(-0.3,13.9)	(-2.0,13.1)	(-6.2, 8.8)
	Pr >  t			0.7354
Week 84	n	33	29	
	LS Mean	11.239	4.884	6.355
	SEM	3.782	3.933	4.044
	95% CI	( 3.8,18.7)	(-2.8,12.6)	(-1.6,14.3)
	Pr >  t			0.1163
Week 96	n	31	21	
	LS Mean	10.582	4.799	5.783

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	3.822	4.239	4.385
	95% CI	( 3.1,18.1)	( -3.5,13.1)	( -2.8,14.4)
	Pr >  t			0.1875
Week 108	n	23	18	
	LS Mean	4.776	13.533	-8.757
	SEM	4.098	4.413	4.780
	95% CI	( -3.3,12.8)	( 4.9,22.2)	(-18.1, 0.6)
	Pr >  t			0.0672
Week 120	n	25	15	
	LS Mean	7.927	0.502	7.426
	SEM	4.010	4.644	4.930
	95% CI	( 0.1,15.8)	( -8.6, 9.6)	( -2.2,17.1)
	Pr >  t			0.1323
Week 132	n	17	8	
	LS Mean	9.020	7.118	1.902
	SEM	4.433	5.693	6.217
	95% CI	( 0.3,17.7)	( -4.1,18.3)	(-10.3,14.1)
	Pr >  t			0.7597
Week 144	n	15	5	
	LS Mean	16.320	2.029	14.291
	SEM	4.579	6.814	7.357
	95% CI	( 7.3,25.3)	(-11.3,15.4)	( -0.1,28.7)
	Pr >  t			0.0523
Week 156	n	10	3	
	LS Mean	2.816	-0.025	2.841
	SEM	5.225	8.431	9.218
	95% CI	( -7.4,13.1)	(-16.6,16.5)	(-15.2,20.9)
	Pr >  t			0.7580
Week 168	n	4	2	
	LS Mean	7.361	-15.09	22.452
	SEM	7.421	10.10	11.98
	95% CI	( -7.2,21.9)	(-34.9, 4.7)	( -1.1,46.0)
	Pr >  t			0.0613
Week 180	n	1	1	
	LS Mean	17.206	3.819	13.388
	SEM	13.92	13.93	19.35
	95% CI	(-10.1,44.5)	(-23.5,31.2)	(-24.6,51.4)
	Pr >  t			0.4892
Week 192	n	1	1	
	LS Mean	6.096	-18.40	24.498

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	13.92	13.93	19.35
		95% CI	(-21.2,33.4)	(-45.7, 8.9)	(-13.5,62.5)
		Pr >  t			0.2058
Yes	Week 8	n	38	42	
		LS Mean	10.299	1.231	9.068
		SEM	4.336	4.673	4.446
		95% CI	( 1.7,18.9)	( -8.0,10.5)	( 0.3,17.9)
		Pr >  t			0.0432
	Week 16	n	32	30	
		LS Mean	6.874	3.312	3.563
		SEM	4.625	4.908	4.884
		95% CI	( -2.3,16.0)	( -6.4,13.0)	( -6.1,13.2)
		Pr >  t			0.4667
	Week 24	n	22	15	
		LS Mean	11.193	0.331	10.862
		SEM	4.945	5.810	6.046
		95% CI	( 1.4,21.0)	(-11.1,11.8)	( -1.0,22.8)
		Pr >  t			0.0736
	Week 32	n	14	13	
		LS Mean	2.175	-1.847	4.022
		SEM	5.639	6.019	6.726
		95% CI	( -8.9,13.3)	(-13.7,10.0)	( -9.2,17.3)
		Pr >  t			0.5504
	Week 40	n	11	11	
		LS Mean	4.392	2.191	2.201
		SEM	6.022	6.274	7.262
		95% CI	( -7.5,16.3)	(-10.2,14.6)	(-12.1,16.5)
		Pr >  t			0.7620
	Week 48	n	11	6	
		LS Mean	6.412	15.770	-9.358
		SEM	6.022	7.497	8.349
		95% CI	( -5.4,18.3)	( 1.0,30.5)	(-25.8, 7.1)
		Pr >  t			0.2633
	Week 56	n	10	7	
		LS Mean	3.632	0.553	3.078
		SEM	6.186	7.142	8.155
		95% CI	( -8.5,15.8)	(-13.5,14.6)	(-13.0,19.1)
		Pr >  t			0.7061
	Week 64	n	8	5	
		LS Mean	3.933	0.329	3.604

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	6.599	7.949	9.160
		95% CI	(-9.1,16.9)	(-15.3,16.0)	(-14.4,21.6)
		Pr >  t			0.6943
	Week 72	n	7	3	
		LS Mean	5.357	-7.366	12.723
		SEM	6.881	9.532	10.74
		95% CI	(-8.2,18.9)	(-26.1,11.4)	(-8.4,33.9)
		Pr >  t			0.2372
	Week 84	n	7	4	
		LS Mean	6.944	-1.139	8.082
		SEM	6.881	8.575	9.900
		95% CI	(-6.6,20.5)	(-18.0,15.7)	(-11.4,27.6)
		Pr >  t			0.4150
	Week 96	n	4	3	
		LS Mean	1.851	-7.366	9.217
		SEM	8.338	9.532	11.73
		95% CI	(-14.6,18.3)	(-26.1,11.4)	(-13.9,32.3)
		Pr >  t			0.4326
	Week 108	n	3	3	
		LS Mean	7.508	-0.104	7.612
		SEM	9.302	9.536	12.44
		95% CI	(-10.8,25.8)	(-18.9,18.7)	(-16.9,32.1)
		Pr >  t			0.5411
	Week 120	n	3	1	
		LS Mean	13.280	-0.497	13.777
		SEM	9.302	15.08	17.06
		95% CI	(-5.0,31.6)	(-30.2,29.2)	(-19.8,47.4)
		Pr >  t			0.4201
	Week 132	n	3		
		LS Mean	15.367	NE	NE
		SEM	9.304	NE	NE
		95% CI	(-2.9,33.7)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	7.954	0.401	7.553		
			SEM	1.625	1.637	2.312		
			95% CI	( 4.8,11.1)	( -2.8, 3.6)	( 3.0,12.1)		
					Pr >  t			0.0011
		Week 16	n	118	104			
			LS Mean	5.250	1.852	3.398		
			SEM	1.701	1.798	2.477		
			95% CI	( 1.9, 8.6)	( -1.7, 5.4)	( -1.5, 8.3)		
					Pr >  t			0.1705
		Week 24	n	100	79			
			LS Mean	5.113	2.241	2.873		
			SEM	1.804	1.988	2.685		
			95% CI	( 1.6, 8.7)	( -1.7, 6.1)	( -2.4, 8.1)		
					Pr >  t			0.2850
		Week 32	n	84	72			
			LS Mean	5.064	1.095	3.969		
			SEM	1.917	2.056	2.811		
			95% CI	( 1.3, 8.8)	( -2.9, 5.1)	( -1.5, 9.5)		
					Pr >  t			0.1583
		Week 40	n	73	62			
			LS Mean	3.706	0.638	3.068		
			SEM	2.014	2.165	2.956		
			95% CI	( -0.2, 7.7)	( -3.6, 4.9)	( -2.7, 8.9)		
					Pr >  t			0.2997
		Week 48	n	67	51			
			LS Mean	6.141	1.926	4.214		
			SEM	2.075	2.323	3.114		
95% CI	( 2.1,10.2)		( -2.6, 6.5)	( -1.9,10.3)				
			Pr >  t			0.1762		
Week 56	n	57	45					
	LS Mean	3.927	1.731	2.196				
	SEM	2.198	2.433	3.279				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( -0.4, 8.2)	( -3.0, 6.5)	( -4.2, 8.6)
	Pr >  t			0.5031
	n	45	42	
	LS Mean	5.928	3.510	2.418
	SEM	2.395	2.497	3.460
Week 72	95% CI	( 1.2,10.6)	( -1.4, 8.4)	( -4.4, 9.2)
	Pr >  t			0.4848
	n	46	35	
	LS Mean	4.480	1.934	2.546
	SEM	2.377	2.676	3.579
Week 84	95% CI	( -0.2, 9.1)	( -3.3, 7.2)	( -4.5, 9.6)
	Pr >  t			0.4770
	n	40	33	
	LS Mean	8.828	1.776	7.051
	SEM	2.504	2.738	3.710
Week 96	95% CI	( 3.9,13.7)	( -3.6, 7.1)	( -0.2,14.3)
	Pr >  t			0.0576
	n	34	24	
	LS Mean	8.292	0.887	7.406
	SEM	2.668	3.110	4.098
Week 108	95% CI	( 3.1,13.5)	( -5.2, 7.0)	( -0.6,15.4)
	Pr >  t			0.0709
	n	26	21	
	LS Mean	3.370	9.186	-5.817
	SEM	2.973	3.288	4.432
Week 120	95% CI	( -2.5, 9.2)	( 2.7,15.6)	( -14.5, 2.9)
	Pr >  t			0.1896
	n	27	16	
	LS Mean	6.906	-2.251	9.157
	SEM	2.930	3.693	4.713
Week 132	95% CI	( 1.2,12.7)	( -9.5, 5.0)	( -0.1,18.4)
	Pr >  t			0.0522
	n	20	8	
	LS Mean	8.318	4.207	4.111
	SEM	3.318	5.035	6.029
Week 144	95% CI	( 1.8,14.8)	( -5.7,14.1)	( -7.7,15.9)
	Pr >  t			0.4954
	n	14	5	
	LS Mean	14.480	-0.945	15.425
	SEM	3.877	6.282	7.381

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( -6.9,22.1)	( -13.3,11.4)	( 0.9,29.9)
		Pr >  t			0.0368
	Week 156	n	10	3	
		LS Mean	1.009	-2.987	3.996
		SEM	4.514	8.019	9.201
		95% CI	( -7.8, 9.9)	(-18.7,12.7)	(-14.1,22.0)
		Pr >  t			0.6641
	Week 168	n	4	2	
		LS Mean	5.565	-18.03	23.592
		SEM	6.953	9.768	11.99
		95% CI	( -8.1,19.2)	(-37.2, 1.1)	( 0.1,47.1)
		Pr >  t			0.0493
	Week 180	n	1	1	
		LS Mean	15.395	0.909	14.486
		SEM	13.72	13.72	19.40
		95% CI	(-11.5,42.3)	(-26.0,27.8)	(-23.6,52.5)
		Pr >  t			0.4553
	Week 192	n	1	1	
		LS Mean	4.285	-21.31	25.596
		SEM	13.72	13.72	19.40
		95% CI	(-22.6,31.2)	(-48.2, 5.6)	(-12.5,63.6)
		Pr >  t			0.1872
Prior use	Week 8	n	8	6	
		LS Mean	8.329	0.942	7.387
		SEM	8.796	10.30	13.54
		95% CI	(-11.1,27.7)	(-21.4,23.3)	(-22.2,37.0)
		Pr >  t			0.5957
	Week 16	n	6	3	
		LS Mean	8.211	18.261	-10.05
		SEM	9.845	14.35	17.44
		95% CI	(-12.8,29.2)	(-11.4,47.9)	(-46.3,26.2)
		Pr >  t			0.5706
	Week 24	n	5	2	
		LS Mean	7.410	16.634	-9.224
		SEM	10.45	16.09	19.20
		95% CI	(-14.5,29.4)	(-16.3,49.6)	(-48.6,30.2)
		Pr >  t			0.6348
	Week 32	n	2	1	
		LS Mean	9.564	5.359	4.205
		SEM	14.39	20.48	25.07

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-19.9,39.1)	(-36.8,47.5)	(-47.3,55.7)
	Pr >  t			0.8681
Week 40	n	2		
	LS Mean	-1.546	NE	NE
	SEM	14.39	NE	NE
	95% CI	(-31.0,27.9)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	9.564	NE	NE
	SEM	14.39	NE	NE
	95% CI	(-19.9,39.1)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	26.234	NE	NE
	SEM	14.39	NE	NE
	95% CI	(-3.3,55.7)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	9.564	NE	NE
	SEM	14.39	NE	NE
	95% CI	(-19.9,39.1)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	20.674	NE	NE
	SEM	14.39	NE	NE
	95% CI	(-8.8,50.2)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	-3.456	NE	NE
	SEM	18.48	NE	NE
	95% CI	(-41.6,34.7)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	7.654	NE	NE
	SEM	18.48	NE	NE
	95% CI	(-30.5,45.8)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	18.764	NE	NE
	SEM	18.48	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-19.4,56.9)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	9.858	1.891	7.967		
			SEM	2.584	2.651	2.353		
			95% CI	( 4.8,14.9)	( -3.3, 7.1)	( 3.3,12.6)		
					Pr >  t			0.0008
		Week 16	n	119	97			
			LS Mean	7.523	4.145	3.378		
			SEM	2.652	2.798	2.546		
			95% CI	( 2.3,12.7)	( -1.4, 9.6)	( -1.6, 8.4)		
					Pr >  t			0.1850
		Week 24	n	100	75			
			LS Mean	7.053	5.135	1.917		
			SEM	2.724	2.933	2.753		
			95% CI	( 1.7,12.4)	( -0.6,10.9)	( -3.5, 7.3)		
					Pr >  t			0.4863
		Week 32	n	82	69			
			LS Mean	7.396	3.064	4.333		
			SEM	2.831	2.986	2.885		
			95% CI	( 1.8,13.0)	( -2.8, 8.9)	( -1.3,10.0)		
					Pr >  t			0.1334
		Week 40	n	73	58			
			LS Mean	5.614	2.794	2.821		
			SEM	2.886	3.088	3.035		
			95% CI	( -0.1,11.3)	( -3.3, 8.9)	( -3.1, 8.8)		
					Pr >  t			0.3530
		Week 48	n	66	48			
			LS Mean	8.966	2.958	6.008		
			SEM	2.935	3.205	3.201		
95% CI	( 3.2,14.7)		( -3.3, 9.2)	( -0.3,12.3)				
			Pr >  t			0.0607		
Week 56	n	56	43					
	LS Mean	7.034	3.522	3.512				
	SEM	3.024	3.280	3.359				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 1.1,13.0)	( -2.9,10.0)	( -3.1,10.1)
		Pr >  t			0.2959
	Week 64	n	45	41	
		LS Mean	8.153	5.537	2.615
		SEM	3.158	3.315	3.515
		95% CI	( 2.0,14.4)	( -1.0,12.0)	( -4.3, 9.5)
		Pr >  t			0.4570
	Week 72	n	46	34	
		LS Mean	7.196	3.940	3.255
		SEM	3.145	3.459	3.640
		95% CI	( 1.0,13.4)	( -2.8,10.7)	( -3.9,10.4)
		Pr >  t			0.3713
	Week 84	n	37	32	
		LS Mean	12.723	3.427	9.296
		SEM	3.311	3.510	3.823
		95% CI	( 6.2,19.2)	( -3.5,10.3)	( 1.8,16.8)
		Pr >  t			0.0151
	Week 96	n	33	23	
		LS Mean	10.224	2.375	7.849
		SEM	3.400	3.830	4.195
		95% CI	( 3.6,16.9)	( -5.1, 9.9)	( -0.4,16.1)
		Pr >  t			0.0615
	Week 108	n	24	20	
		LS Mean	5.075	10.467	-5.392
		SEM	3.710	3.991	4.583
		95% CI	( -2.2,12.4)	( 2.6,18.3)	( -14.4, 3.6)
		Pr >  t			0.2396
	Week 120	n	25	16	
		LS Mean	8.843	-0.375	9.218
		SEM	3.663	4.278	4.805
		95% CI	( 1.7,16.0)	( -8.8, 8.0)	( -0.2,18.6)
		Pr >  t			0.0552
	Week 132	n	19	8	
		LS Mean	12.337	6.070	6.267
		SEM	3.977	5.481	6.098
		95% CI	( 4.5,20.1)	( -4.7,16.8)	( -5.7,18.2)
		Pr >  t			0.3042
	Week 144	n	14	5	
		LS Mean	16.311	0.962	15.348
		SEM	4.389	6.648	7.407

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 7.7,24.9)	(-12.1,14.0)	( 0.8,29.9)
		Pr >  t			0.0384
	Week 156	n	10	3	
		LS Mean	3.399	-1.106	4.505
		SEM	4.971	8.312	9.226
		95% CI	( -6.4,13.2)	(-17.4,15.2)	(-13.6,22.6)
		Pr >  t			0.6254
	Week 168	n	4	2	
		LS Mean	7.945	-16.16	24.102
		SEM	7.263	10.01	12.01
		95% CI	( -6.3,22.2)	(-35.8, 3.5)	( 0.5,47.7)
		Pr >  t			0.0450
	Week 180	n	1	1	
		LS Mean	17.738	2.765	14.973
		SEM	13.89	13.90	19.43
		95% CI	( -9.5,45.0)	(-24.5,30.0)	(-23.1,53.1)
		Pr >  t			0.4410
	Week 192	n	1	1	
		LS Mean	6.628	-19.46	26.083
		SEM	13.89	13.90	19.43
		95% CI	(-20.6,33.9)	(-46.7, 7.8)	(-12.0,64.2)
		Pr >  t			0.1796
Yes	Week 8	n	5	9	
		LS Mean	5.153	3.465	1.688
		SEM	6.683	4.906	8.360
		95% CI	( -8.3,18.7)	( -6.4,13.3)	(-15.2,18.5)
		Pr >  t			0.8409
	Week 16	n	5	9	
		LS Mean	-3.739	-0.466	-3.273
		SEM	6.683	4.879	8.321
		95% CI	(-17.2, 9.8)	(-10.3, 9.3)	(-20.1,13.5)
		Pr >  t			0.6960
	Week 24	n	5	5	
		LS Mean	2.927	-13.10	16.030
		SEM	6.683	6.776	9.611
		95% CI	(-10.6,16.4)	(-26.7, 0.5)	( -3.3,35.4)
		Pr >  t			0.1025
	Week 32	n	4	3	
		LS Mean	-3.595	0.429	-4.024
		SEM	7.532	9.236	11.94

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-18.8,11.6)	(-18.1,19.0)	(-28.0,20.0)
		Pr >  t			0.7374
	Week 40	n	2	3	
		LS Mean	2.484	-4.425	6.909
		SEM	11.54	8.967	14.59
		95% CI	(-20.7,25.7)	(-22.4,13.6)	(-22.4,36.2)
		Pr >  t			0.6378
	Week 48	n	3	2	
		LS Mean	-11.01	6.356	-17.37
		SEM	8.886	11.28	14.15
		95% CI	(-28.9, 6.9)	(-16.3,29.0)	(-45.8,11.0)
		Pr >  t			0.2254
	Week 56	n	3	1	
		LS Mean	-3.603	-3.767	0.164
		SEM	8.886	17.08	19.48
		95% CI	(-21.5,14.3)	(-38.1,30.5)	(-39.0,39.3)
		Pr >  t			0.9933
	Week 64	n	2		
		LS Mean	2.484	NE	NE
		SEM	11.54	NE	NE
		95% CI	(-20.7,25.7)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	2.624	NE	NE
		SEM	11.55	NE	NE
		95% CI	(-20.6,25.8)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	-14.71	NE	NE
		SEM	8.886	NE	NE
		95% CI	(-32.6, 3.2)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	2.484	NE	NE
		SEM	11.54	NE	NE
		95% CI	(-20.7,25.7)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	6.304	NE	NE
		SEM	11.04	NE	NE



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-15.9,28.5)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	3.804	NE	NE
	SEM	8.886	NE	NE
	95% CI	(-14.1,21.7)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-27.17	NE	NE
	SEM	17.29	NE	NE
	95% CI	(-61.9, 7.5)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	17.274	NE	NE
	SEM	17.29	NE	NE
	95% CI	(-17.4,52.0)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	8.858	1.824	7.034		
			SEM	2.608	2.666	2.452		
			95% CI	( 3.7,14.0)	( -3.4, 7.1)	( 2.2,11.9)		
					Pr >  t			0.0043
		Week 16	n	111	91			
			LS Mean	6.937	4.565	2.372		
			SEM	2.675	2.827	2.644		
			95% CI	( 1.7,12.2)	( -1.0,10.1)	( -2.8, 7.6)		
					Pr >  t			0.3700
		Week 24	n	96	70			
			LS Mean	6.165	4.619	1.546		
			SEM	2.743	2.978	2.856		
			95% CI	( 0.8,11.6)	( -1.2,10.5)	( -4.1, 7.2)		
					Pr >  t			0.5885
		Week 32	n	77	61			
			LS Mean	7.044	3.779	3.265		
			SEM	2.870	3.067	3.037		
			95% CI	( 1.4,12.7)	( -2.2, 9.8)	( -2.7, 9.2)		
					Pr >  t			0.2826
		Week 40	n	69	52			
			LS Mean	5.126	3.320	1.806		
			SEM	2.927	3.177	3.191		
			95% CI	( -0.6,10.9)	( -2.9, 9.6)	( -4.5, 8.1)		
			Pr >  t			0.5715		
Week 48	n	62	41					
	LS Mean	6.665	4.228	2.437				
	SEM	2.984	3.344	3.409				
	95% CI	( 0.8,12.5)	( -2.3,10.8)	( -4.3, 9.1)				
			Pr >  t			0.4748		
Week 56	n	53	35					
	LS Mean	5.975	4.340	1.635				
	SEM	3.075	3.472	3.616				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-0.1,12.0)	(-2.5,11.2)	(-5.5, 8.7)
		Pr >  t			0.6512
	Week 64	n	44	33	
		LS Mean	6.544	4.154	2.389
		SEM	3.196	3.524	3.770
		95% CI	( 0.3,12.8)	(-2.8,11.1)	(-5.0, 9.8)
		Pr >  t			0.5264
	Week 72	n	45	28	
		LS Mean	5.838	4.032	1.806
		SEM	3.183	3.676	3.901
		95% CI	(-0.4,12.1)	(-3.2,11.2)	(-5.8, 9.5)
		Pr >  t			0.6434
	Week 84	n	39	27	
		LS Mean	10.665	4.362	6.303
		SEM	3.298	3.712	4.021
		95% CI	( 4.2,17.1)	(-2.9,11.6)	(-1.6,14.2)
		Pr >  t			0.1173
	Week 96	n	34	19	
		LS Mean	9.713	2.911	6.801
		SEM	3.406	4.112	4.479
		95% CI	( 3.0,16.4)	(-5.2,11.0)	(-2.0,15.6)
		Pr >  t			0.1291
	Week 108	n	26	17	
		LS Mean	4.739	10.084	-5.345
		SEM	3.667	4.261	4.806
		95% CI	(-2.5,11.9)	( 1.7,18.4)	(-14.8, 4.1)
		Pr >  t			0.2663
	Week 120	n	27	11	
		LS Mean	8.222	0.310	7.912
		SEM	3.623	4.953	5.404
		95% CI	( 1.1,15.3)	(-9.4,10.0)	(-2.7,18.5)
		Pr >  t			0.1434
	Week 132	n	20	6	
		LS Mean	9.680	5.828	3.851
		SEM	3.964	6.281	6.831
		95% CI	( 1.9,17.5)	(-6.5,18.2)	(-9.5,17.3)
		Pr >  t			0.5730
	Week 144	n	15	4	
		LS Mean	15.845	-0.589	16.434
		SEM	4.348	7.480	8.151

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 7.3,24.4)	(-15.3,14.1)	( 0.4,32.4)
		Pr >  t			0.0440
	Week 156	n	10	2	
		LS Mean	2.370	-5.234	7.604
		SEM	5.053	10.24	11.04
		95% CI	( -7.5,12.3)	(-25.3,14.9)	(-14.1,29.3)
		Pr >  t			0.4912
	Week 168	n	4	2	
		LS Mean	6.906	-16.34	23.250
		SEM	7.408	10.24	12.30
		95% CI	( -7.6,21.4)	(-36.4, 3.7)	( -0.9,47.4)
		Pr >  t			0.0590
	Week 180	n	1	1	
		LS Mean	16.736	2.575	14.160
		SEM	14.20	14.22	19.88
		95% CI	(-11.1,44.6)	(-25.3,30.5)	(-24.8,53.2)
		Pr >  t			0.4765
	Week 192	n	1	1	
		LS Mean	5.626	-19.64	25.270
		SEM	14.20	14.22	19.88
		95% CI	(-22.2,33.5)	(-47.5, 8.3)	(-13.7,64.3)
		Pr >  t			0.2040
>= 75 Years	Week 8	n	17	19	
		LS Mean	13.146	3.748	9.398
		SEM	4.425	4.082	5.965
		95% CI	( 4.3,22.0)	( -4.4,11.9)	( -2.6,21.4)
		Pr >  t			0.1209
	Week 16	n	13	16	
		LS Mean	4.983	0.450	4.533
		SEM	4.816	4.284	6.420
		95% CI	( -4.6,14.6)	( -8.1, 9.0)	( -8.3,17.3)
		Pr >  t			0.4826
	Week 24	n	9	11	
		LS Mean	10.738	2.083	8.655
		SEM	5.360	4.781	7.160
		95% CI	( 0.1,21.4)	( -7.4,11.6)	( -5.6,22.9)
		Pr >  t			0.2299
	Week 32	n	9	12	
		LS Mean	2.246	-1.665	3.911
		SEM	5.360	4.684	7.094

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.4,12.9)	(-11.0, 7.6)	(-10.2,18.0)
		Pr >  t			0.5828
	Week 40	n	6	10	
		LS Mean	2.213	-1.787	4.000
		SEM	6.066	4.918	7.784
		95% CI	(-9.8,14.2)	(-11.5, 8.0)	(-11.4,19.4)
		Pr >  t			0.6084
	Week 48	n	7	10	
		LS Mean	16.080	1.677	14.403
		SEM	5.785	4.927	7.566
		95% CI	( 4.6,27.5)	(-8.1,11.5)	(-0.6,29.4)
		Pr >  t			0.0597
	Week 56	n	6	10	
		LS Mean	6.673	0.305	6.368
		SEM	6.057	4.932	7.772
		95% CI	(-5.3,18.7)	(-9.5,10.1)	(-9.0,21.8)
		Pr >  t			0.4143
	Week 64	n	3	9	
		LS Mean	19.253	9.265	9.988
		SEM	7.700	5.084	9.187
		95% CI	( 4.1,34.5)	(-0.8,19.3)	(-8.2,28.1)
		Pr >  t			0.2787
	Week 72	n	3	7	
		LS Mean	15.550	2.425	13.125
		SEM	7.700	5.495	9.418
		95% CI	( 0.3,30.8)	(-8.4,13.3)	(-5.5,31.7)
		Pr >  t			0.1654
	Week 84	n	1	6	
		LS Mean	-7.433	0.188	-7.621
		SEM	12.14	5.771	13.41
		95% CI	(-31.4,16.5)	(-11.2,11.6)	(-34.1,18.8)
		Pr >  t			0.5706
	Week 96	n	1	5	
		LS Mean	-7.433	1.842	-9.275
		SEM	12.14	6.144	13.58
		95% CI	(-31.4,16.5)	(-10.3,14.0)	(-36.1,17.5)
		Pr >  t			0.4955
	Week 108	n		4	
		LS Mean	NE	14.700	NE
		SEM	NE	6.655	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	( -1.6,27.8)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	10.403	-2.602
		SEM	12.17	6.144
		95% CI	(-13.6,34.4)	(-14.7, 9.5)
		Pr >  t		0.3403
	Week 132	n		2
		LS Mean	NE	6.118
		SEM	NE	8.713
		95% CI	NE	(-11.1,23.3)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	6.525
		SEM	NE	11.81
		95% CI	NE	(-16.8,29.9)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	6.525
		SEM	NE	11.81
		95% CI	NE	(-16.8,29.9)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	4.276	-1.616	5.893		
			SEM	8.221	8.456	3.228		
			95% CI	(-12.0,20.5)	(-18.3,15.1)	(-0.5,12.2)		
					Pr >  t			0.0688
		Week 16	n	69	55			
			LS Mean	4.077	-0.009	4.087		
			SEM	8.231	8.526	3.447		
			95% CI	(-12.2,20.3)	(-16.8,16.8)	(-2.7,10.9)		
					Pr >  t			0.2366
		Week 24	n	54	46			
			LS Mean	2.374	2.774	-0.400		
			SEM	8.267	8.577	3.710		
			95% CI	(-13.9,18.7)	(-14.2,19.7)	(-7.7, 6.9)		
					Pr >  t			0.9142
		Week 32	n	49	41			
			LS Mean	3.833	0.360	3.473		
			SEM	8.365	8.611	3.848		
			95% CI	(-12.7,20.3)	(-16.6,17.4)	(-4.1,11.0)		
					Pr >  t			0.3672
		Week 40	n	40	33			
			LS Mean	-0.264	-1.450	1.186		
			SEM	8.427	8.684	4.137		
			95% CI	(-16.9,16.4)	(-18.6,15.7)	(-6.9, 9.3)		
					Pr >  t			0.7745
		Week 48	n	38	28			
			LS Mean	4.285	-1.442	5.727		
			SEM	8.444	8.751	4.309		
95% CI	(-12.4,20.9)		(-18.7,15.8)	(-2.7,14.2)				
			Pr >  t			0.1844		
Week 56	n	32	28					
	LS Mean	2.000	-1.202	3.202				
	SEM	8.506	8.751	4.430				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-14.8,18.8)	(-18.5,16.1)	(-5.5,11.9)
	Pr >  t			0.4700
	n	23	26	
	LS Mean	4.463	1.215	3.248
	SEM	8.653	8.783	4.767
Week 72	95% CI	(-12.6,21.5)	(-16.1,18.5)	(-6.1,12.6)
	Pr >  t			0.4958
	n	27	25	
	LS Mean	1.390	0.509	0.881
	SEM	8.576	8.800	4.661
Week 84	95% CI	(-15.5,18.3)	(-16.8,17.9)	(-8.3,10.0)
	Pr >  t			0.8501
	n	23	22	
	LS Mean	8.560	-0.957	9.518
	SEM	8.652	8.863	4.915
Week 96	95% CI	(-8.5,25.6)	(-18.4,16.5)	(-0.1,19.2)
	Pr >  t			0.0532
	n	20	16	
	LS Mean	13.439	-1.964	15.403
	SEM	8.728	9.058	5.382
Week 108	95% CI	(-3.8,30.6)	(-19.8,15.9)	(4.8,26.0)
	Pr >  t			0.0043
	n	20	14	
	LS Mean	1.713	7.736	-6.023
	SEM	8.730	9.157	5.550
Week 120	95% CI	(-15.5,18.9)	(-10.3,25.8)	(-16.9, 4.9)
	Pr >  t			0.2781
	n	17	11	
	LS Mean	4.745	-1.875	6.621
	SEM	8.830	9.367	6.040
Week 132	95% CI	(-12.7,22.1)	(-20.3,16.6)	(-5.2,18.5)
	Pr >  t			0.2733
	n	13	6	
	LS Mean	2.864	6.786	-3.922
	SEM	9.033	10.14	7.427
Week 144	95% CI	(-14.9,20.7)	(-13.2,26.7)	(-18.5,10.7)
	Pr >  t			0.5976
	n	10	5	
	LS Mean	13.955	-2.425	16.380
	SEM	9.283	10.46	8.151



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.3,32.2)	(-23.0,18.2)	( 0.4,32.4)
		Pr >  t			0.0448
	Week 156	n	7	3	
		LS Mean	1.083	-4.477	5.560
		SEM	9.731	11.66	10.07
		95% CI	(-18.1,20.2)	(-27.4,18.4)	(-14.2,25.3)
		Pr >  t			0.5809
	Week 168	n	3	2	
		LS Mean	0.452	-19.55	20.001
		SEM	11.51	13.00	13.12
		95% CI	(-22.2,23.1)	(-45.1, 6.0)	(-5.8,45.8)
		Pr >  t			0.1278
	Week 180	n		1	
		LS Mean	NE	-0.479	NE
		SEM	NE	16.36	NE
		95% CI	NE	(-32.6,31.6)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-22.70	NE
		SEM	NE	16.36	NE
		95% CI	NE	(-54.8, 9.4)	NE
		Pr >  t			NE
Second Line	Week 8	n	66	67	
		LS Mean	11.836	2.737	9.099
		SEM	2.948	2.983	3.219
		95% CI	( 6.0,17.7)	(-3.1, 8.6)	( 2.8,15.4)
		Pr >  t			0.0051
	Week 16	n	54	52	
		LS Mean	7.150	4.963	2.188
		SEM	3.100	3.193	3.488
		95% CI	( 1.0,13.3)	(-1.3,11.3)	(-4.7, 9.1)
		Pr >  t			0.5310
	Week 24	n	49	35	
		LS Mean	8.841	2.238	6.603
		SEM	3.179	3.501	3.822
		95% CI	( 2.6,15.1)	(-4.7, 9.1)	(-0.9,14.1)
		Pr >  t			0.0849
	Week 32	n	36	32	
		LS Mean	7.014	2.336	4.678
		SEM	3.418	3.586	4.073

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	( 0.3,13.7)	( -4.7, 9.4)	( -3.3,12.7)
	Pr >  t			0.2514
	n	33	29	
	LS Mean	8.590	3.642	4.948
	SEM	3.485	3.689	4.207
Week 48	95% CI	( 1.7,15.4)	( -3.6,10.9)	( -3.3,13.2)
	Pr >  t			0.2401
	n	29	23	
	LS Mean	9.999	6.530	3.469
	SEM	3.591	3.904	4.486
Week 56	95% CI	( 2.9,17.1)	( -1.1,14.2)	( -5.3,12.3)
	Pr >  t			0.4397
	n	25	17	
	LS Mean	9.332	6.396	2.936
	SEM	3.720	4.241	4.888
Week 64	95% CI	( 2.0,16.6)	( -1.9,14.7)	( -6.7,12.5)
	Pr >  t			0.5484
	n	22	16	
	LS Mean	8.128	7.089	1.039
	SEM	3.845	4.317	5.049
Week 72	95% CI	( 0.6,15.7)	( -1.4,15.6)	( -8.9,11.0)
	Pr >  t			0.8370
	n	20	10	
	LS Mean	8.464	3.800	4.664
	SEM	3.947	5.022	5.735
Week 84	95% CI	( 0.7,16.2)	( -6.1,13.7)	( -6.6,15.9)
	Pr >  t			0.4163
	n	16	11	
	LS Mean	8.312	6.412	1.900
	SEM	4.225	4.862	5.785
Week 96	95% CI	( 0.0,16.6)	( -3.1,16.0)	( -9.5,13.3)
	Pr >  t			0.7426
	n	15	8	
	LS Mean	0.560	6.005	-5.446
	SEM	4.302	5.429	6.328
Week 108	95% CI	( -7.9, 9.0)	( -4.7,16.7)	(-17.9, 7.0)
	Pr >  t			0.3898
	n	6	7	
	LS Mean	5.576	11.275	-5.700
	SEM	5.967	5.705	7.753

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	( -6.1,17.3)	( 0.1,22.5)	(-20.9, 9.5)
	Pr >  t			0.4625
Week 120	n	11	5	
	LS Mean	9.969	-4.179	14.148
	SEM	4.771	6.503	7.557
	95% CI	( 0.6,19.3)	(-16.9, 8.6)	( -0.7,29.0)
	Pr >  t			0.0616
Week 132	n	7	2	
	LS Mean	17.858	-6.111	23.969
	SEM	5.619	9.653	10.80
	95% CI	( 6.8,28.9)	(-25.1,12.8)	( 2.8,45.2)
	Pr >  t			0.0269
Week 144	n	5		
	LS Mean	14.808	NE	NE
	SEM	6.407	NE	NE
	95% CI	( 2.2,27.4)	NE	NE
	Pr >  t			NE
Week 156	n	3		
	LS Mean	-0.586	NE	NE
	SEM	7.987	NE	NE
	95% CI	(-16.3,15.1)	NE	NE
	Pr >  t			NE
Week 168	n	1		
	LS Mean	18.454	NE	NE
	SEM	13.28	NE	NE
	95% CI	( -7.6,44.5)	NE	NE
	Pr >  t			NE
Week 180	n	1		
	LS Mean	18.454	NE	NE
	SEM	13.28	NE	NE
	95% CI	( -7.6,44.5)	NE	NE
	Pr >  t			NE
Week 192	n	1		
	LS Mean	7.344	NE	NE
	SEM	13.28	NE	NE
	95% CI	(-18.7,33.4)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	10.470	5.967	4.503		
			SEM	4.654	4.566	3.476		
			95% CI	( 1.3,19.6)	( -3.0,15.0)	( -2.3,11.3)		
					Pr >  t			0.1963
		Week 16	n	60	51			
			LS Mean	7.401	9.202	-1.801		
			SEM	4.729	4.768	3.679		
			95% CI	( -1.9,16.7)	( -0.2,18.6)	( -9.0, 5.4)		
					Pr >  t			0.6249
		Week 24	n	51	42			
			LS Mean	7.397	6.159	1.239		
			SEM	4.789	4.855	3.880		
			95% CI	( -2.0,16.8)	( -3.4,15.7)	( -6.4, 8.9)		
					Pr >  t			0.7497
		Week 32	n	46	36			
			LS Mean	8.632	9.151	-0.519		
			SEM	4.859	4.967	4.037		
			95% CI	( -0.9,18.2)	( -0.6,18.9)	( -8.5, 7.4)		
					Pr >  t			0.8977
		Week 40	n	40	33			
			LS Mean	7.487	6.262	1.224		
			SEM	4.926	5.015	4.171		
			95% CI	( -2.2,17.2)	( -3.6,16.1)	( -7.0, 9.4)		
			Pr >  t			0.7693		
Week 48	n	37	28					
	LS Mean	7.162	8.923	-1.761				
	SEM	4.963	5.114	4.332				
	95% CI	( -2.6,16.9)	( -1.1,19.0)	( -10.3, 6.8)				
			Pr >  t			0.6845		
Week 56	n	33	23					
	LS Mean	4.486	7.052	-2.566				
	SEM	5.024	5.250	4.561				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-5.4,14.4)	(-3.3,17.4)	(-11.5, 6.4)
	Pr >  t			0.5738
	n	26	20	
	LS Mean	9.927	6.557	3.370
	SEM	5.165	5.360	4.837
Week 72	95% CI	(-0.2,20.1)	(-4.0,17.1)	(-6.1,12.9)
	Pr >  t			0.4863
	n	28	17	
	LS Mean	8.141	5.870	2.271
	SEM	5.120	5.500	4.945
Week 84	95% CI	(-1.9,18.2)	(-4.9,16.7)	(-7.4,12.0)
	Pr >  t			0.6462
	n	23	17	
	LS Mean	12.746	4.018	8.728
	SEM	5.248	5.502	5.081
Week 96	95% CI	( 2.4,23.1)	(-6.8,14.8)	(-1.2,18.7)
	Pr >  t			0.0863
	n	23	11	
	LS Mean	8.834	3.529	5.305
	SEM	5.250	5.990	5.606
Week 108	95% CI	(-1.5,19.2)	(-8.2,15.3)	(-5.7,16.3)
	Pr >  t			0.3443
	n	15	13	
	LS Mean	6.459	13.805	-7.345
	SEM	5.620	5.786	5.747
Week 120	95% CI	(-4.6,17.5)	( 2.4,25.2)	(-18.6, 3.9)
	Pr >  t			0.2016
	n	16	9	
	LS Mean	7.751	2.995	4.756
	SEM	5.559	6.276	6.184
Week 132	95% CI	(-3.2,18.7)	(-9.3,15.3)	(-7.4,16.9)
	Pr >  t			0.4421
	n	14	5	
	LS Mean	14.251	4.354	9.897
	SEM	5.691	7.387	7.411
Week 144	95% CI	( 3.1,25.4)	(-10.1,18.9)	(-4.6,24.4)
	Pr >  t			0.1821
	n	8	3	
	LS Mean	8.861	3.274	5.586
	SEM	6.445	8.793	9.316

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-3.8,21.5)	(-14.0,20.5)	(-12.7,23.9)
		Pr >  t			0.5489
		n	7	2	
	Week 168	LS Mean	5.992	-2.541	8.533
		SEM	6.675	10.28	10.87
		95% CI	(-7.1,19.1)	(-22.7,17.6)	(-12.8,29.9)
	Week 180	Pr >  t			0.4327
		n	4	2	
		LS Mean	8.274	-13.65	21.925
	Week 192	SEM	7.920	10.28	11.68
		95% CI	(-7.3,23.8)	(-33.8, 6.5)	(-1.0,44.8)
		Pr >  t			0.0608
	Week 8	n	1	1	
		LS Mean	17.706	5.413	12.292
		SEM	13.78	13.79	18.65
	Week 16	95% CI	(-9.3,44.8)	(-21.7,32.5)	(-24.3,48.9)
		Pr >  t			0.5101
		n	1	1	
	Week 24	LS Mean	6.596	-16.81	23.402
		SEM	13.78	13.79	18.65
		95% CI	(-20.5,33.6)	(-43.9,10.3)	(-13.2,60.0)
	Week 32	Pr >  t			0.2100
		n	18	17	
		LS Mean	8.093	3.484	4.610
Week 8	SEM	4.767	4.979	6.903	
	95% CI	(-1.4,17.5)	(-6.4,13.4)	(-9.1,18.3)	
	Pr >  t			0.5059	
Week 16	n	17	11		
	LS Mean	6.460	2.236	4.224	
	SEM	4.887	6.031	7.758	
Week 24	95% CI	(-3.2,16.1)	(-9.7,14.2)	(-11.1,19.6)	
	Pr >  t			0.5872	
	n	15	5		
Week 32	LS Mean	4.408	11.930	-7.522	
	SEM	5.152	8.585	10.01	
	95% CI	(-5.8,14.6)	(-5.0,28.9)	(-27.3,12.3)	
Week 8	Pr >  t			0.4535	
	n	13	5		
	LS Mean	4.679	-3.626	8.305	
		SEM	5.477	8.585	10.19

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-6.2,15.5)	(-20.6,13.3)	(-11.8,28.4)	
	Pr >  t			0.4165	
	n	11	5		
	LS Mean	2.988	-1.404	4.392	
	SEM	5.866	8.585	10.42	
Week 48	95% CI	(-8.6,14.6)	(-18.4,15.5)	(-16.2,25.0)	
	Pr >  t			0.6738	
	n	11	2		
	LS Mean	14.066	15.240	-1.174	
	SEM	5.863	12.76	14.04	
Week 56	95% CI	( 2.5,25.7)	(-9.9,40.4)	(-28.9,26.5)	
	Pr >  t			0.9335	
	n	8	2		
	LS Mean	6.308	4.130	2.177	
	SEM	6.662	12.76	14.40	
Week 64	95% CI	(-6.8,19.5)	(-21.0,29.3)	(-26.2,30.6)	
	Pr >  t			0.8800	
	n	7	3		
	LS Mean	2.838	1.092	1.746	
	SEM	7.030	10.69	12.80	
Week 72	95% CI	(-11.0,16.7)	(-20.0,22.2)	(-23.5,27.0)	
	Pr >  t			0.8917	
	n	7	3		
	LS Mean	0.481	-2.611	3.092	
	SEM	7.049	10.69	12.81	
Week 84	95% CI	(-13.4,14.4)	(-23.7,18.5)	(-22.2,28.4)	
	Pr >  t			0.8096	
	n	7	2		
	LS Mean	13.179	-1.425	14.604	
	SEM	7.049	12.76	14.58	
Week 96	95% CI	(-0.7,27.1)	(-26.6,23.8)	(-14.2,43.4)	
	Pr >  t			0.3179	
	n	6	3		
	LS Mean	17.528	1.092	16.436	
	SEM	7.513	10.69	13.07	
Week 108	95% CI	( 2.7,32.4)	(-20.0,22.2)	(-9.4,42.2)	
	Pr >  t			0.2103	
	n	7	2		
	LS Mean	0.481	8.595	-8.114	
	SEM	7.049	12.74	14.56	



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-13.4,14.4)	(-16.5,33.7)	(-36.9,20.6)
		Pr >  t			0.5781
		n	6	1	
	Week 132	LS Mean	15.677	-4.983	20.659
		SEM	7.513	17.54	19.09
		95% CI	( 0.8,30.5)	(-39.6,29.7)	(-17.0,58.3)
	Week 144	Pr >  t			0.2806
		n	4		
		LS Mean	9.934	NE	NE
	Week 156	SEM	8.939	NE	NE
		95% CI	( -7.7,27.6)	NE	NE
		Pr >  t			NE
	Week 8	n	5		
		LS Mean	27.588	NE	NE
		SEM	8.116	NE	NE
	Week 16	95% CI	( 11.6,43.6)	NE	NE
		Pr >  t			NE
		n	3		
	Week 24	LS Mean	-2.854	NE	NE
		SEM	10.17	NE	NE
		95% CI	(-22.9,17.2)	NE	NE
	Week 32	Pr >  t			NE
		n	59	57	
		LS Mean	10.230	-0.977	11.207
Week 8	SEM	3.101	3.270	3.348	
	95% CI	( 4.1,16.4)	( -7.4, 5.5)	( 4.6,17.8)	
	Pr >  t			0.0009	
Week 16	n	47	44		
	LS Mean	7.920	0.088	7.832	
	SEM	3.267	3.469	3.684	
Week 24	95% CI	( 1.5,14.4)	( -6.8, 6.9)	( 0.6,15.1)	
	Pr >  t			0.0344	
	n	39	34		
Week 32	LS Mean	8.360	3.339	5.021	
	SEM	3.428	3.718	4.026	
	95% CI	( 1.6,15.1)	( -4.0,10.7)	( -2.9,12.9)	
Week 8	Pr >  t			0.2132	
	n	27	32		
	LS Mean	6.165	-1.036	7.201	
Week 16	SEM	3.793	3.770	4.361	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.3,13.6)	(-8.5, 6.4)	(-1.4,15.8)
		Pr >  t			0.0995
	Week 40	n	24	24	
		LS Mean	3.438	1.177	2.261
		SEM	3.913	4.061	4.703
		95% CI	(-4.3,11.1)	(-6.8, 9.2)	(-7.0,11.5)
		Pr >  t			0.6310
	Week 48	n	21	21	
		LS Mean	7.138	-1.131	8.269
		SEM	4.060	4.207	4.956
		95% CI	(-0.8,15.1)	(-9.4, 7.1)	(-1.5,18.0)
		Pr >  t			0.0959
	Week 56	n	18	20	
		LS Mean	11.099	1.769	9.330
		SEM	4.240	4.265	5.161
		95% CI	( 2.8,19.4)	(-6.6,10.2)	(-0.8,19.5)
		Pr >  t			0.0712
	Week 64	n	14	19	
		LS Mean	7.147	6.294	0.853
		SEM	4.578	4.326	5.498
		95% CI	(-1.9,16.1)	(-2.2,14.8)	(-9.9,11.7)
		Pr >  t			0.8768
	Week 72	n	13	15	
		LS Mean	9.139	4.661	4.479
		SEM	4.691	4.631	5.832
		95% CI	(-0.1,18.4)	(-4.4,13.8)	(-7.0,15.9)
		Pr >  t			0.4429
	Week 84	n	10	14	
		LS Mean	5.814	6.181	-0.368
		SEM	5.170	4.726	6.269
		95% CI	(-4.3,16.0)	(-3.1,15.5)	(-12.7,11.9)
		Pr >  t			0.9532
	Week 96	n	6	10	
		LS Mean	8.034	3.925	4.109
		SEM	6.251	5.269	7.579
		95% CI	(-4.2,20.3)	(-6.4,14.3)	(-10.8,19.0)
		Pr >  t			0.5879
	Week 108	n	4	6	
		LS Mean	11.188	11.025	0.163
		SEM	7.421	6.351	9.254

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-3.4,25.8)	(-1.4,23.5)	(-18.0,18.3)
	Pr >  t			0.9860
	n	6	6	
	LS Mean	5.954	-1.838	7.792
	SEM	6.253	6.354	8.368
Week 132	95% CI	(-6.3,18.2)	(-14.3,10.6)	(-8.6,24.2)
	Pr >  t			0.3522
	n	2	3	
	LS Mean	-13.34	12.940	-26.28
	SEM	10.08	8.441	12.77
Week 144	95% CI	(-33.1, 6.5)	(-3.6,29.5)	(-51.4,-1.2)
	Pr >  t			0.0401
	n	2	2	
	LS Mean	19.993	0.865	19.129
	SEM	10.04	10.13	13.95
Week 156	95% CI	( 0.3,39.7)	(-19.0,20.8)	(-8.3,46.5)
	Pr >  t			0.1710
	n		1	
	LS Mean	NE	6.391	NE
	SEM	NE	13.95	NE
	95% CI	NE	(-21.0,33.8)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35			
			LS Mean	9.627	5.514	4.113		
			SEM	4.681	5.089	4.862		
			95% CI	( 0.3,18.9)	( -4.6,15.6)	( -5.5,13.7)		
					Pr >  t			0.3993
		Week 16	n	35	22			
			LS Mean	10.076	1.813	8.263		
			SEM	4.861	5.697	5.472		
			95% CI	( 0.4,19.7)	( -9.5,13.1)	( -2.5,19.1)		
					Pr >  t			0.1330
		Week 24	n	28	16			
			LS Mean	7.653	12.581	-4.928		
			SEM	5.028	6.060	6.024		
			95% CI	( -2.3,17.6)	( 0.6,24.6)	(-16.8, 6.9)		
					Pr >  t			0.4143
		Week 32	n	22	16			
			LS Mean	5.766	6.477	-0.711		
			SEM	5.305	6.076	6.211		
			95% CI	( -4.7,16.3)	( -5.5,18.5)	(-13.0,11.5)		
					Pr >  t			0.9090
		Week 40	n	19	12			
			LS Mean	4.801	2.141	2.660		
			SEM	5.454	6.449	6.706		
			95% CI	( -6.0,15.6)	(-10.6,14.9)	(-10.5,15.9)		
					Pr >  t			0.6919
		Week 48	n	16	10			
			LS Mean	13.403	3.880	9.522		
			SEM	5.643	6.736	7.134		
95% CI	( 2.3,24.5)		( -9.4,17.2)	( -4.5,23.6)				
			Pr >  t			0.1830		
Week 56	n	14	7					
	LS Mean	13.452	4.833	8.619				
	SEM	5.813	7.396	7.894				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 2.0,24.9)	( -9.7,19.4)	( -6.9,24.1)
		Pr >  t			0.2757
	Week 64	n	8	7	
		LS Mean	6.272	7.109	-0.837
		SEM	6.674	7.395	8.561
		95% CI	( -6.9,19.4)	( -7.5,21.7)	(-17.7,16.0)
		Pr >  t			0.9222
	Week 72	n	12	6	
		LS Mean	9.891	6.625	3.265
		SEM	6.019	7.733	8.365
		95% CI	( -2.0,21.8)	( -8.6,21.8)	(-13.2,19.7)
		Pr >  t			0.6965
	Week 84	n	8	5	
		LS Mean	9.361	5.599	3.762
		SEM	6.715	8.174	9.247
		95% CI	( -3.9,22.6)	(-10.5,21.7)	(-14.4,22.0)
		Pr >  t			0.6844
	Week 96	n	5	5	
		LS Mean	17.313	3.377	13.936
		SEM	7.763	8.174	10.03
		95% CI	( 2.0,32.6)	(-12.7,19.5)	( -5.8,33.7)
		Pr >  t			0.1658
	Week 108	n	7	5	
		LS Mean	8.456	14.487	-6.031
		SEM	6.984	8.174	9.445
		95% CI	( -5.3,22.2)	( -1.6,30.6)	(-24.6,12.5)
		Pr >  t			0.5236
	Week 120	n	5	3	
		LS Mean	21.648	-4.230	25.878
		SEM	7.771	9.707	11.32
		95% CI	( 6.4,36.9)	(-23.3,14.9)	( 3.6,48.2)
		Pr >  t			0.0229
	Week 132	n	2	2	
		LS Mean	17.806	19.457	-1.651
		SEM	10.98	11.25	14.86
		95% CI	( -3.8,39.4)	( -2.7,41.6)	(-30.9,27.6)
		Pr >  t			0.9116
	Week 144	n	2		
		LS Mean	43.173	NE	NE
		SEM	10.99	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv		Treatment difference
		N=169	N=172	N=172	N=169	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive	Week 156	95% CI	( 21.6,64.8)	NE	NE	NE
		Pr >  t				NE
		n	2			
		LS Mean	5.920	NE	NE	NE
		SEM	11.00	NE	NE	NE
	Week 168	95% CI	(-15.7,27.6)	NE	NE	NE
		Pr >  t				NE
		n	1			
		LS Mean	19.443	NE	NE	NE
		SEM	14.88	NE	NE	NE
	Week 8	95% CI	( -9.8,48.7)	NE	NE	NE
		Pr >  t				NE
		n	98	104		
		LS Mean	9.403	0.947		8.456
		SEM	3.168	3.158		2.630
	Week 16	95% CI	( 3.2,15.6)	( -5.3, 7.2)		( 3.3,13.6)
		Pr >  t				0.0014
		n	87	84		
		LS Mean	5.446	4.593		0.853
		SEM	3.233	3.246		2.785
	Week 24	95% CI	( -0.9,11.8)	( -1.8,11.0)		( -4.6, 6.3)
		Pr >  t				0.7595
		n	76	65		
		LS Mean	6.327	2.283		4.043
		SEM	3.306	3.385		2.993
	Week 32	95% CI	( -0.2,12.8)	( -4.4, 8.9)		( -1.8, 9.9)
		Pr >  t				0.1772
		n	62	57		
LS Mean		7.285	2.037		5.248	
SEM		3.412	3.466		3.172	
Week 40	95% CI	( 0.6,14.0)	( -4.8, 8.8)		( -1.0,11.5)	
	Pr >  t				0.0985	
	n	54	50			
	LS Mean	5.376	2.629		2.747	
	SEM	3.483	3.549		3.324	
Week 48	95% CI	( -1.5,12.2)	( -4.3, 9.6)		( -3.8, 9.3)	
	Pr >  t				0.4088	
	n	52	41			
	LS Mean	5.995	3.830		2.164	
	SEM	3.503	3.670		3.474	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	( -0.9,12.9)	( -3.4,11.0)	( -4.7, 9.0)
	Pr >  t			0.5334
Week 56	n	44	38	
	LS Mean	4.170	3.300	0.870
	SEM	3.596	3.722	3.625
	95% CI	( -2.9,11.2)	( -4.0,10.6)	( -6.2, 8.0)
	Pr >  t			0.8104
Week 64	n	39	35	
	LS Mean	7.566	4.989	2.578
	SEM	3.673	3.780	3.761
	95% CI	( 0.3,14.8)	( -2.4,12.4)	( -4.8,10.0)
	Pr >  t			0.4932
Week 72	n	36	29	
	LS Mean	5.700	3.215	2.485
	SEM	3.728	3.926	3.960
	95% CI	( -1.6,13.0)	( -4.5,10.9)	( -5.3,10.3)
	Pr >  t			0.5305
Week 84	n	32	28	
	LS Mean	10.734	3.236	7.498
	SEM	3.822	3.955	4.071
	95% CI	( 3.2,18.2)	( -4.5,11.0)	( -0.5,15.5)
	Pr >  t			0.0657
Week 96	n	30	19	
	LS Mean	7.919	2.747	5.172
	SEM	3.864	4.340	4.490
	95% CI	( 0.3,15.5)	( -5.8,11.3)	( -3.6,14.0)
	Pr >  t			0.2497
Week 108	n	18	16	
	LS Mean	3.959	10.199	-6.240
	SEM	4.376	4.551	5.115
	95% CI	( -4.6,12.5)	( 1.3,19.1)	( -16.3, 3.8)
	Pr >  t			0.2227
Week 120	n	23	13	
	LS Mean	5.422	0.571	4.852
	SEM	4.104	4.838	5.161
	95% CI	( -2.6,13.5)	( -8.9,10.1)	( -5.3,15.0)
	Pr >  t			0.3474
Week 132	n	18	6	
	LS Mean	8.640	1.814	6.826
	SEM	4.377	6.330	6.748

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 144	95% CI	( 0.0,17.2)	(-10.6,14.2)	( -6.4,20.1)
	Pr >  t			0.3119
	n	13	5	
	LS Mean	11.592	0.363	11.229
	SEM	4.791	6.802	7.463
Week 156	95% CI	( 2.2,21.0)	(-13.0,13.7)	( -3.4,25.9)
	Pr >  t			0.1327
	n	8	3	
	LS Mean	1.844	-1.742	3.586
	SEM	5.654	8.415	9.439
Week 168	95% CI	( -9.2,12.9)	(-18.3,14.8)	(-14.9,22.1)
	Pr >  t			0.7040
	n	3	2	
	LS Mean	3.469	-16.81	20.281
	SEM	8.382	10.08	12.57
Week 180	95% CI	(-13.0,19.9)	(-36.6, 3.0)	( -4.4,45.0)
	Pr >  t			0.1070
	n	1	1	
	LS Mean	15.804	2.200	13.604
	SEM	13.90	13.90	19.31
Week 192	95% CI	(-11.5,43.1)	(-25.1,29.5)	(-24.3,51.5)
	Pr >  t			0.4812
	n	1	1	
	LS Mean	4.694	-20.02	24.714
	SEM	13.90	13.90	19.31
	95% CI	(-22.6,32.0)	(-47.3, 7.3)	(-13.2,62.6)
	Pr >  t			0.2008

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-21i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Fatigue score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	9.602	0.866	8.736		
			SEM	3.162	3.145	2.636		
			95% CI	( 3.4,15.8)	( -5.3, 7.1)	( 3.6,13.9)		
					Pr >  t			0.0010
		Week 16	n	85	84			
			LS Mean	5.684	4.494	1.190		
			SEM	3.231	3.233	2.794		
			95% CI	( -0.7,12.0)	( -1.9,10.9)	( -4.3, 6.7)		
					Pr >  t			0.6703
		Week 24	n	75	65			
			LS Mean	6.671	2.181	4.490		
			SEM	3.301	3.374	2.999		
			95% CI	( 0.2,13.2)	( -4.5, 8.8)	( -1.4,10.4)		
					Pr >  t			0.1348
		Week 32	n	61	57			
			LS Mean	7.683	1.935	5.748		
			SEM	3.412	3.455	3.182		
			95% CI	( 1.0,14.4)	( -4.9, 8.7)	( -0.5,12.0)		
					Pr >  t			0.0713
		Week 40	n	53	50			
			LS Mean	5.825	2.526	3.300		
			SEM	3.486	3.539	3.337		
			95% CI	( -1.0,12.7)	( -4.4, 9.5)	( -3.3, 9.9)		
					Pr >  t			0.3231
		Week 48	n	51	41			
			LS Mean	6.243	3.728	2.514		
			SEM	3.506	3.661	3.488		
95% CI	( -0.6,13.1)		( -3.5,10.9)	( -4.3, 9.4)				
			Pr >  t			0.4712		
Week 56	n	43	38					
	LS Mean	4.891	3.199	1.692				
	SEM	3.604	3.713	3.644				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-2.2,12.0)	(-4.1,10.5)	(-5.5, 8.8)
	Pr >  t			0.6426
	n	39	35	
	LS Mean	7.926	4.891	3.035
	SEM	3.668	3.772	3.765
Week 72	95% CI	( 0.7,15.1)	(-2.5,12.3)	(-4.4,10.4)
	Pr >  t			0.4204
	n	35	29	
	LS Mean	6.155	3.115	3.040
	SEM	3.743	3.918	3.985
Week 84	95% CI	(-1.2,13.5)	(-4.6,10.8)	(-4.8,10.9)
	Pr >  t			0.4458
	n	31	28	
	LS Mean	11.364	3.139	8.225
	SEM	3.842	3.948	4.100
Week 96	95% CI	( 3.8,18.9)	(-4.6,10.9)	( 0.2,16.3)
	Pr >  t			0.0451
	n	29	19	
	LS Mean	8.475	2.651	5.824
	SEM	3.888	4.336	4.523
Week 108	95% CI	( 0.8,16.1)	(-5.9,11.2)	(-3.0,14.7)
	Pr >  t			0.1981
	n	18	16	
	LS Mean	4.335	10.106	-5.772
	SEM	4.375	4.548	5.126
Week 120	95% CI	(-4.3,12.9)	( 1.2,19.0)	(-15.8, 4.3)
	Pr >  t			0.2604
	n	23	13	
	LS Mean	5.788	0.483	5.305
	SEM	4.101	4.836	5.172
Week 132	95% CI	(-2.3,13.8)	(-9.0,10.0)	(-4.8,15.5)
	Pr >  t			0.3053
	n	18	6	
	LS Mean	9.018	1.726	7.291
	SEM	4.376	6.337	6.764
Week 144	95% CI	( 0.4,17.6)	(-10.7,14.2)	(-6.0,20.6)
	Pr >  t			0.2812
	n	13	5	
	LS Mean	11.968	0.263	11.705
	SEM	4.793	6.811	7.482

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	( 2.6,21.4)	(-13.1,13.6)	( -3.0,26.4)
		Pr >  t			0.1180
		n	8	3	
	Week 168	LS Mean	2.232	-1.836	4.068
		SEM	5.660	8.431	9.464
		95% CI	( -8.9,13.3)	(-18.4,14.7)	(-14.5,22.6)
	Week 180	Pr >  t			0.6674
		n	3	2	
		LS Mean	3.855	-16.91	20.765
	Week 192	SEM	8.400	10.10	12.61
		95% CI	(-12.6,20.3)	(-36.7, 2.9)	( -4.0,45.5)
		Pr >  t			0.0999
	Week 8	n	1	1	
		LS Mean	16.189	2.115	14.074
		SEM	13.93	13.94	19.36
	Week 16	95% CI	(-11.2,43.5)	(-25.2,29.5)	(-23.9,52.1)
		Pr >  t			0.4674
		n	1	1	
	Week 24	LS Mean	5.079	-20.11	25.184
		SEM	13.93	13.94	19.36
		95% CI	(-22.3,32.4)	(-47.4, 7.2)	(-12.8,63.2)
	Week 32	Pr >  t			0.1936
		n	42	35	
		LS Mean	9.627	5.514	4.113
Week 8	SEM	4.681	5.089	4.862	
	95% CI	( 0.3,18.9)	( -4.6,15.6)	( -5.5,13.7)	
	Pr >  t			0.3993	
Week 16	n	35	22		
	LS Mean	10.076	1.813	8.263	
	SEM	4.861	5.697	5.472	
Week 24	95% CI	( 0.4,19.7)	( -9.5,13.1)	( -2.5,19.1)	
	Pr >  t			0.1330	
	n	28	16		
Week 32	LS Mean	7.653	12.581	-4.928	
	SEM	5.028	6.060	6.024	
	95% CI	( -2.3,17.6)	( 0.6,24.6)	(-16.8, 6.9)	
Week 8	Pr >  t			0.4143	
	n	22	16		
	LS Mean	5.766	6.477	-0.711	
Week 16	SEM	5.305	6.076	6.211	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-4.7,16.3)	(-5.5,18.5)	(-13.0,11.5)
	Pr >  t			0.9090
	n	19	12	
	LS Mean	4.801	2.141	2.660
	SEM	5.454	6.449	6.706
Week 48	95% CI	(-6.0,15.6)	(-10.6,14.9)	(-10.5,15.9)
	Pr >  t			0.6919
	n	16	10	
	LS Mean	13.403	3.880	9.522
	SEM	5.643	6.736	7.134
Week 56	95% CI	( 2.3,24.5)	(-9.4,17.2)	(-4.5,23.6)
	Pr >  t			0.1830
	n	14	7	
	LS Mean	13.452	4.833	8.619
	SEM	5.813	7.396	7.894
Week 64	95% CI	( 2.0,24.9)	(-9.7,19.4)	(-6.9,24.1)
	Pr >  t			0.2757
	n	8	7	
	LS Mean	6.272	7.109	-0.837
	SEM	6.674	7.395	8.561
Week 72	95% CI	(-6.9,19.4)	(-7.5,21.7)	(-17.7,16.0)
	Pr >  t			0.9222
	n	12	6	
	LS Mean	9.891	6.625	3.265
	SEM	6.019	7.733	8.365
Week 84	95% CI	(-2.0,21.8)	(-8.6,21.8)	(-13.2,19.7)
	Pr >  t			0.6965
	n	8	5	
	LS Mean	9.361	5.599	3.762
	SEM	6.715	8.174	9.247
Week 96	95% CI	(-3.9,22.6)	(-10.5,21.7)	(-14.4,22.0)
	Pr >  t			0.6844
	n	5	5	
	LS Mean	17.313	3.377	13.936
	SEM	7.763	8.174	10.03
Week 108	95% CI	( 2.0,32.6)	(-12.7,19.5)	(-5.8,33.7)
	Pr >  t			0.1658
	n	7	5	
	LS Mean	8.456	14.487	-6.031
	SEM	6.984	8.174	9.445

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-5.3,22.2)	(-1.6,30.6)	(-24.6,12.5)
	Pr >  t			0.5236
	n	5	3	
	LS Mean	21.648	-4.230	25.878
	SEM	7.771	9.707	11.32
Week 132	95% CI	( 6.4,36.9)	(-23.3,14.9)	( 3.6,48.2)
	Pr >  t			0.0229
	n	2	2	
	LS Mean	17.806	19.457	-1.651
	SEM	10.98	11.25	14.86
Week 144	95% CI	(-3.8,39.4)	(-2.7,41.6)	(-30.9,27.6)
	Pr >  t			0.9116
	n	2		
	LS Mean	43.173	NE	NE
	SEM	10.99	NE	NE
Week 156	95% CI	( 21.6,64.8)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	5.920	NE	NE
	SEM	11.00	NE	NE
Week 168	95% CI	(-15.7,27.6)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	19.443	NE	NE
	SEM	14.88	NE	NE
	95% CI	(-9.8,48.7)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-42: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Übelkeit/Erbrechen“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73	
			LS Mean	11.660	7.645	4.015
			SEM	2.240	2.248	2.047
			95% CI	( 7.2,16.1)	( 3.2,12.1)	( -0.0, 8.0)
			Pr >  t			0.0508
	Week 16	n	67	56		
		LS Mean	10.433	5.330	5.104	
		SEM	2.282	2.389	2.232	
		95% CI	( 5.9,14.9)	( 0.6,10.0)	( 0.7, 9.5)	
		Pr >  t			0.0228	
	Week 24	n	61	46		
		LS Mean	8.723	5.570	3.153	
		SEM	2.329	2.473	2.363	
		95% CI	( 4.1,13.3)	( 0.7,10.4)	( -1.5, 7.8)	
		Pr >  t			0.1829	
	Week 32	n	52	41		
		LS Mean	10.785	6.249	4.536	
		SEM	2.418	2.542	2.482	
		95% CI	( 6.0,15.6)	( 1.2,11.3)	( -0.3, 9.4)	
		Pr >  t			0.0683	
Week 40	n	45	36			
	LS Mean	7.607	7.840	-0.233		
	SEM	2.476	2.622	2.610		
	95% CI	( 2.7,12.5)	( 2.7,13.0)	( -5.4, 4.9)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.9289
	Week 48	n	42	30
		LS Mean	8.690	5.185
		SEM	2.507	2.723
		95% CI	( 3.8,13.6)	( -0.2,10.5)
		Pr >  t		( -1.9, 8.9)
	Week 56	n	35	24
		LS Mean	8.869	8.177
		SEM	2.594	2.869
		95% CI	( 3.8,14.0)	( 2.5,13.8)
		Pr >  t		( -5.1, 6.5)
	Week 64	n	25	25
		LS Mean	11.129	5.512
		SEM	2.789	2.842
		95% CI	( 5.6,16.6)	( -0.1,11.1)
		Pr >  t		( -0.5,11.7)
	Week 72	n	27	20
		LS Mean	9.639	5.795
		SEM	2.742	3.004
		95% CI	( 4.2,15.0)	( -0.1,11.7)
		Pr >  t		( -2.5,10.2)
	Week 84	n	23	19
		LS Mean	8.231	7.201
		SEM	2.859	3.045
		95% CI	( 2.6,13.9)	( 1.2,13.2)
		Pr >  t		( -5.5, 7.6)
	Week 96	n	20	13
		LS Mean	9.706	5.745
		SEM	2.964	3.396
		95% CI	( 3.9,15.5)	( -0.9,12.4)
		Pr >  t		( -3.4,11.3)
	Week 108	n	17	13
		LS Mean	9.705	5.777
		SEM	3.100	3.397
		95% CI	( 3.6,15.8)	( -0.9,12.4)
		Pr >  t		( -3.7,11.5)
	Week 120	n	17	12
		LS Mean	5.298	7.136
		SEM	3.099	3.484
		95% CI	( -0.8,11.4)	( 0.3,14.0)
				( -9.6, 5.9)

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.6409
	Week 132	n	13	6	
		LS Mean	5.095	6.007	-0.912
		SEM	3.356	4.445	4.980
		95% CI	(-1.5,11.7)	(-2.7,14.7)	(-10.7, 8.9)
		Pr >  t			0.8548
	Week 144	n	11	4	
		LS Mean	6.169	3.758	2.412
		SEM	3.543	5.237	5.810
		95% CI	(-0.8,13.1)	(-6.5,14.0)	(-9.0,13.8)
		Pr >  t			0.6782
	Week 156	n	7	2	
		LS Mean	5.616	2.728	2.889
		SEM	4.156	7.080	7.823
		95% CI	(-2.5,13.8)	(-11.2,16.6)	(-12.5,18.2)
		Pr >  t			0.7121
	Week 168	n	3	1	
		LS Mean	5.880	-0.366	6.246
		SEM	5.877	9.779	11.13
		95% CI	(-5.7,17.4)	(-19.6,18.8)	(-15.6,28.1)
		Pr >  t			0.5750
	Week 180	n	1	1	
		LS Mean	4.922	-0.366	5.288
		SEM	9.758	9.779	13.59
		95% CI	(-14.2,24.1)	(-19.6,18.8)	(-21.4,32.0)
		Pr >  t			0.6973
	Week 192	n	1	1	
		LS Mean	4.922	-0.366	5.288
		SEM	9.758	9.779	13.59
		95% CI	(-14.2,24.1)	(-19.6,18.8)	(-21.4,32.0)
		Pr >  t			0.6973
Present	Week 8	n	65	67	
		LS Mean	4.970	2.948	2.022
		SEM	2.429	2.501	2.172
		95% CI	( 0.2, 9.8)	( -2.0, 7.9)	( -2.3, 6.3)
		Pr >  t			0.3529
	Week 16	n	57	51	
		LS Mean	4.547	2.143	2.405
		SEM	2.544	2.641	2.368
		95% CI	(-0.5, 9.6)	(-3.1, 7.4)	(-2.3, 7.1)



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.3106
Week 24	n	44	35	
	LS Mean	4.096	2.979	1.118
	SEM	2.653	2.880	2.716
	95% CI	(-1.1, 9.3)	(-2.7, 8.7)	(-4.2, 6.5)
	Pr >  t			0.6810
Week 32	n	34	32	
	LS Mean	3.733	1.022	2.711
	SEM	2.816	2.940	2.919
	95% CI	(-1.8, 9.3)	(-4.8, 6.8)	(-3.0, 8.4)
	Pr >  t			0.3535
Week 40	n	30	26	
	LS Mean	4.531	0.895	3.636
	SEM	2.895	3.077	3.133
	95% CI	(-1.2, 10.2)	(-5.2, 7.0)	(-2.5, 9.8)
	Pr >  t			0.2462
Week 48	n	27	21	
	LS Mean	2.844	5.289	-2.445
	SEM	2.960	3.241	3.354
	95% CI	(-3.0, 8.7)	(-1.1, 11.7)	(-9.0, 4.1)
	Pr >  t			0.4663
Week 56	n	24	21	
	LS Mean	0.317	2.895	-2.578
	SEM	3.043	3.241	3.429
	95% CI	(-5.7, 6.3)	(-3.5, 9.3)	(-9.3, 4.2)
	Pr >  t			0.4525
Week 64	n	22	17	
	LS Mean	3.744	2.524	1.220
	SEM	3.108	3.426	3.661
	95% CI	(-2.4, 9.9)	(-4.2, 9.3)	(-6.0, 8.4)
	Pr >  t			0.7391
Week 72	n	21	15	
	LS Mean	1.154	0.552	0.602
	SEM	3.147	3.548	3.809
	95% CI	(-5.0, 7.3)	(-6.4, 7.5)	(-6.9, 8.1)
	Pr >  t			0.8745
Week 84	n	17	14	
	LS Mean	3.400	1.703	1.698
	SEM	3.342	3.618	4.022
	95% CI	(-3.2, 10.0)	(-5.4, 8.8)	(-6.2, 9.6)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.6731
	Week 96	n	15	11	
		LS Mean	3.075	1.678	1.396
		SEM	3.446	3.896	4.373
		95% CI	(-3.7, 9.8)	(-6.0, 9.3)	(-7.2,10.0)
		Pr >  t			0.7495
	Week 108	n	9	8	
		LS Mean	3.680	-1.736	5.416
		SEM	4.083	4.336	5.236
		95% CI	(-4.3,11.7)	(-10.3, 6.8)	(-4.9,15.7)
		Pr >  t			0.3014
	Week 120	n	11	4	
		LS Mean	0.410	-0.383	0.794
		SEM	3.801	5.661	6.215
		95% CI	(-7.1, 7.9)	(-11.5,10.7)	(-11.4,13.0)
		Pr >  t			0.8984
	Week 132	n	7	2	
		LS Mean	0.984	-3.591	4.576
		SEM	4.471	7.616	8.362
		95% CI	(-7.8, 9.8)	(-18.5,11.4)	(-11.9,21.0)
		Pr >  t			0.5845
	Week 144	n	4	1	
		LS Mean	8.345	1.246	7.099
		SEM	5.536	10.50	11.55
		95% CI	(-2.5,19.2)	(-19.4,21.9)	(-15.6,29.8)
		Pr >  t			0.5391
	Week 156	n	3	1	
		LS Mean	0.043	1.246	-1.204
		SEM	6.312	10.50	11.92
		95% CI	(-12.4,12.4)	(-19.4,21.9)	(-24.6,22.2)
		Pr >  t			0.9196
	Week 168	n	1	1	
		LS Mean	1.200	1.246	-0.047
		SEM	10.48	10.50	14.56
		95% CI	(-19.4,21.8)	(-19.4,21.9)	(-28.7,28.6)
		Pr >  t			0.9974

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	9.737	5.178	4.559		
			SEM	1.797	1.905	1.833		
			95% CI	( 6.2,13.3)	( 1.4, 8.9)	( 1.0, 8.2)		
					Pr >  t			0.0133
		Week 16	n	86	68			
			LS Mean	8.428	3.368	5.061		
			SEM	1.849	2.003	1.978		
			95% CI	( 4.8,12.1)	( -0.6, 7.3)	( 1.2, 8.9)		
					Pr >  t			0.0108
		Week 24	n	73	48			
			LS Mean	6.790	3.290	3.500		
			SEM	1.916	2.187	2.213		
			95% CI	( 3.0,10.6)	( -1.0, 7.6)	( -0.8, 7.8)		
					Pr >  t			0.1143
		Week 32	n	60	43			
			LS Mean	8.054	3.113	4.941		
			SEM	2.025	2.259	2.346		
			95% CI	( 4.1,12.0)	( -1.3, 7.6)	( 0.3, 9.5)		
					Pr >  t			0.0355
		Week 40	n	50	38			
			LS Mean	5.985	5.080	0.905		
			SEM	2.110	2.340	2.491		
			95% CI	( 1.8,10.1)	( 0.5, 9.7)	( -4.0, 5.8)		
			Pr >  t			0.7166		
Week 48	n	48	31					
	LS Mean	6.249	2.603	3.646				
	SEM	2.131	2.471	2.632				
	95% CI	( 2.1,10.4)	( -2.3, 7.5)	( -1.5, 8.8)				
			Pr >  t			0.1664		
Week 56	n	41	25					
	LS Mean	6.656	6.127	0.529				
	SEM	2.214	2.631	2.850				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 2.3,11.0)	( 1.0,11.3)	( -5.1, 6.1)
	Pr >  t			0.8527
	n	30	24	
	LS Mean	8.537	2.909	5.627
	SEM	2.406	2.664	3.035
Week 72	95% CI	( 3.8,13.3)	( -2.3, 8.1)	( -0.3,11.6)
	Pr >  t			0.0640
	n	32	19	
	LS Mean	7.338	3.185	4.153
	SEM	2.363	2.867	3.182
Week 84	95% CI	( 2.7,12.0)	( -2.4, 8.8)	( -2.1,10.4)
	Pr >  t			0.1921
	n	26	19	
	LS Mean	6.198	4.612	1.586
	SEM	2.525	2.867	3.294
Week 96	95% CI	( 1.2,11.2)	( -1.0,10.2)	( -4.9, 8.0)
	Pr >  t			0.6304
	n	23	14	
	LS Mean	8.187	3.145	5.042
	SEM	2.616	3.181	3.641
Week 108	95% CI	( 3.1,13.3)	( -3.1, 9.4)	( -2.1,12.2)
	Pr >  t			0.1664
	n	19	13	
	LS Mean	7.463	3.116	4.347
	SEM	2.793	3.267	3.837
Week 120	95% CI	( 2.0,12.9)	( -3.3, 9.5)	( -3.2,11.9)
	Pr >  t			0.2575
	n	19	11	
	LS Mean	3.402	4.712	-1.310
	SEM	2.784	3.476	4.017
Week 132	95% CI	( -2.1, 8.9)	( -2.1,11.5)	( -9.2, 6.6)
	Pr >  t			0.7445
	n	15	5	
	LS Mean	2.469	3.509	-1.040
	SEM	3.032	4.785	5.324
Week 144	95% CI	( -3.5, 8.4)	( -5.9,12.9)	( -11.5, 9.4)
	Pr >  t			0.8452
	n	12	3	
	LS Mean	5.510	0.471	5.040
	SEM	3.283	6.014	6.579

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.9,12.0)	(-11.3,12.3)	(-7.9,18.0)
		Pr >  t			0.4439
	Week 156	n	7	2	
		LS Mean	3.561	0.209	3.352
		SEM	4.090	7.249	8.096
		95% CI	(-4.5,11.6)	(-14.0,14.4)	(-12.5,19.2)
		Pr >  t			0.6790
	Week 168	n	3	1	
		LS Mean	3.877	-2.818	6.695
		SEM	5.953	10.09	11.56
		95% CI	(-7.8,15.6)	(-22.6,17.0)	(-16.0,29.4)
		Pr >  t			0.5625
	Week 180	n	1	1	
		LS Mean	2.835	-2.818	5.653
		SEM	10.06	10.09	14.12
		95% CI	(-16.9,22.6)	(-22.6,17.0)	(-22.1,33.4)
		Pr >  t			0.6890
	Week 192	n	1	1	
		LS Mean	2.835	-2.818	5.653
		SEM	10.06	10.09	14.12
		95% CI	(-16.9,22.6)	(-22.6,17.0)	(-22.1,33.4)
		Pr >  t			0.6890
Yes	Week 8	n	44	56	
		LS Mean	10.247	9.834	0.413
		SEM	4.250	4.052	2.679
		95% CI	( 1.8,18.7)	( 1.8,17.9)	(-4.9, 5.7)
		Pr >  t			0.8778
	Week 16	n	38	39	
		LS Mean	10.505	8.925	1.580
		SEM	4.374	4.294	2.922
		95% CI	( 1.8,19.2)	( 0.4,17.4)	(-4.2, 7.4)
		Pr >  t			0.5896
	Week 24	n	32	33	
		LS Mean	10.226	10.330	-0.104
		SEM	4.440	4.350	3.101
		95% CI	( 1.4,19.0)	( 1.7,18.9)	(-6.2, 6.0)
		Pr >  t			0.9733
	Week 32	n	26	30	
		LS Mean	10.791	9.470	1.321
		SEM	4.524	4.391	3.275

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	( 1.8,19.7)	( 0.8,18.1)	( -5.1, 7.8)
	Pr >  t			0.6870
	n	25	24	
	LS Mean	10.194	8.727	1.467
	SEM	4.544	4.485	3.426
Week 48	95% CI	( 1.2,19.2)	( -0.1,17.6)	( -5.3, 8.2)
	Pr >  t			0.6688
	n	21	20	
	LS Mean	9.568	13.309	-3.741
	SEM	4.620	4.575	3.642
Week 56	95% CI	( 0.4,18.7)	( 4.3,22.3)	( -10.9, 3.4)
	Pr >  t			0.3051
	n	18	20	
	LS Mean	5.613	9.955	-4.343
	SEM	4.701	4.575	3.744
Week 64	95% CI	( -3.7,14.9)	( 0.9,19.0)	( -11.7, 3.0)
	Pr >  t			0.2469
	n	17	18	
	LS Mean	10.084	10.201	-0.117
	SEM	4.734	4.633	3.854
Week 72	95% CI	( 0.7,19.4)	( 1.1,19.3)	( -7.7, 7.5)
	Pr >  t			0.9759
	n	16	16	
	LS Mean	6.699	8.394	-1.695
	SEM	4.773	4.703	3.983
Week 84	95% CI	( -2.7,16.1)	( -0.9,17.7)	( -9.5, 6.1)
	Pr >  t			0.6706
	n	14	14	
	LS Mean	9.531	9.433	0.098
	SEM	4.853	4.788	4.179
Week 96	95% CI	( -0.0,19.1)	( -0.0,18.9)	( -8.1, 8.3)
	Pr >  t			0.9813
	n	12	10	
	LS Mean	7.783	9.469	-1.686
	SEM	4.965	5.053	4.602
Week 108	95% CI	( -2.0,17.6)	( -0.5,19.4)	( -10.7, 7.4)
	Pr >  t			0.7142
	n	7	8	
	SEM	5.480	5.274	5.369

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.7,20.9)	(-4.3,16.5)	(-6.5,14.5)
		Pr >  t			0.4570
	Week 120	n	9	5	
		LS Mean	6.183	7.601	-1.418
		SEM	5.224	5.882	5.732
		95% CI	(-4.1,16.5)	(-4.0,19.2)	(-12.7, 9.8)
		Pr >  t			0.8046
	Week 132	n	5	3	
		LS Mean	9.266	5.598	3.667
		SEM	5.927	6.812	7.246
		95% CI	(-2.4,20.9)	(-7.8,19.0)	(-10.6,17.9)
		Pr >  t			0.6130
	Week 144	n	3	2	
		LS Mean	11.128	8.971	2.156
		SEM	6.849	7.829	8.898
		95% CI	(-2.3,24.6)	(-6.4,24.3)	(-15.3,19.6)
		Pr >  t			0.8086
	Week 156	n	3	1	
		LS Mean	6.075	9.034	-2.959
		SEM	6.856	10.28	11.12
		95% CI	(-7.4,19.5)	(-11.2,29.2)	(-24.8,18.9)
		Pr >  t			0.7903
	Week 168	n	1	1	
		LS Mean	7.405	9.034	-1.629
		SEM	10.33	10.28	13.54
		95% CI	(-12.9,27.7)	(-11.2,29.2)	(-28.2,25.0)
		Pr >  t			0.9043

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	10.570	6.856	3.714		
			SEM	1.940	1.929	1.667		
			95% CI	( 6.7,14.4)	( 3.1,10.7)	( 0.4, 7.0)		
					Pr >  t			0.0264
		Week 16	n	92	77			
			LS Mean	9.262	5.008	4.254		
			SEM	1.969	2.046	1.799		
			95% CI	( 5.4,13.1)	( 1.0, 9.0)	( 0.7, 7.8)		
					Pr >  t			0.0184
		Week 24	n	83	66			
			LS Mean	7.369	6.317	1.051		
			SEM	2.008	2.096	1.893		
			95% CI	( 3.4,11.3)	( 2.2,10.4)	( -2.7, 4.8)		
					Pr >  t			0.5789
		Week 32	n	72	60			
			LS Mean	10.493	6.008	4.485		
			SEM	2.058	2.142	1.979		
			95% CI	( 6.4,14.5)	( 1.8,10.2)	( 0.6, 8.4)		
					Pr >  t			0.0238
		Week 40	n	64	51			
			LS Mean	7.795	6.601	1.194		
			SEM	2.095	2.214	2.087		
			95% CI	( 3.7,11.9)	( 2.2,11.0)	( -2.9, 5.3)		
					Pr >  t			0.5675
		Week 48	n	58	45			
			LS Mean	8.573	5.275	3.298		
			SEM	2.128	2.267	2.178		
95% CI	( 4.4,12.8)		( 0.8, 9.7)	( -1.0, 7.6)				
			Pr >  t			0.1303		
Week 56	n	49	38					
	LS Mean	7.305	7.668	-0.363				
	SEM	2.192	2.348	2.324				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 3.0,11.6)	( 3.1,12.3)	( -4.9, 4.2)
	Pr >  t			0.8760
	n	39	37	
	LS Mean	10.592	6.063	4.530
	SEM	2.290	2.362	2.434
Week 72	95% CI	( 6.1,15.1)	( 1.4,10.7)	( -0.2, 9.3)
	Pr >  t			0.0630
	n	41	32	
	LS Mean	7.703	5.342	2.361
	SEM	2.268	2.439	2.488
Week 84	95% CI	( 3.2,12.2)	( 0.5,10.1)	( -2.5, 7.2)
	Pr >  t			0.3429
	n	33	29	
	LS Mean	7.439	6.849	0.590
	SEM	2.389	2.496	2.642
Week 96	95% CI	( 2.7,12.1)	( 1.9,11.8)	( -4.6, 5.8)
	Pr >  t			0.8233
	n	31	21	
	LS Mean	8.062	5.237	2.826
	SEM	2.418	2.715	2.879
Week 108	95% CI	( 3.3,12.8)	( -0.1,10.6)	( -2.8, 8.5)
	Pr >  t			0.3266
	n	23	18	
	LS Mean	8.514	4.620	3.894
	SEM	2.615	2.838	3.152
Week 120	95% CI	( 3.4,13.6)	( -1.0,10.2)	( -2.3,10.1)
	Pr >  t			0.2170
	n	25	15	
	LS Mean	5.215	5.542	-0.327
	SEM	2.552	3.001	3.256
Week 132	95% CI	( 0.2,10.2)	( -0.3,11.4)	( -6.7, 6.1)
	Pr >  t			0.9200
	n	17	8	
	LS Mean	5.550	4.320	1.230
	SEM	2.853	3.734	4.139
Week 144	95% CI	( -0.1,11.1)	( -3.0,11.6)	( -6.9, 9.3)
	Pr >  t			0.7664
	n	15	5	
	LS Mean	7.569	3.746	3.823
	SEM	2.956	4.508	4.917

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.8,13.4)	( -5.1,12.6)	( -5.8,13.5)
		Pr >  t			0.4370
	Week 156	n	10	3	
		LS Mean	4.983	3.340	1.643
		SEM	3.409	5.617	6.183
		95% CI	( -1.7,11.7)	( -7.7,14.4)	( -10.5,13.8)
		Pr >  t			0.7905
	Week 168	n	4	2	
		LS Mean	5.565	2.313	3.252
		SEM	4.926	6.754	8.058
		95% CI	( -4.1,15.2)	( -10.9,15.6)	( -12.6,19.1)
		Pr >  t			0.6866
	Week 180	n	1	1	
		LS Mean	4.360	-0.580	4.941
		SEM	9.351	9.358	13.04
		95% CI	( -14.0,22.7)	( -18.9,17.8)	( -20.6,30.5)
		Pr >  t			0.7049
	Week 192	n	1	1	
		LS Mean	4.360	-0.580	4.941
		SEM	9.351	9.358	13.04
		95% CI	( -14.0,22.7)	( -18.9,17.8)	( -20.6,30.5)
		Pr >  t			0.7049
Yes	Week 8	n	38	42	
		LS Mean	5.473	3.001	2.471
		SEM	3.245	3.464	3.305
		95% CI	( -1.0,11.9)	( -3.9, 9.9)	( -4.1, 9.0)
		Pr >  t			0.4559
	Week 16	n	32	30	
		LS Mean	5.837	2.124	3.713
		SEM	3.500	3.682	3.686
		95% CI	( -1.1,12.8)	( -5.2, 9.4)	( -3.6,11.0)
		Pr >  t			0.3152
	Week 24	n	22	15	
		LS Mean	7.886	-0.387	8.273
		SEM	3.795	4.494	4.717
		95% CI	( 0.4,15.4)	( -9.3, 8.5)	( -1.0,17.6)
		Pr >  t			0.0807
	Week 32	n	14	13	
		LS Mean	-0.769	-1.537	0.768
		SEM	4.443	4.687	5.324

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-9.5, 8.0)	(-10.8, 7.7)	(-9.7,11.2)
	Pr >  t			0.8854
	n	11	11	
	LS Mean	3.405	0.718	2.687
	SEM	4.797	4.925	5.821
Week 48	95% CI	(-6.0,12.9)	(-9.0,10.4)	(-8.8,14.1)
	Pr >  t			0.6447
	n	11	6	
	LS Mean	-1.140	12.903	-14.04
	SEM	4.797	6.029	6.780
Week 56	95% CI	(-10.6, 8.3)	(-1.0,24.8)	(-27.4,-0.7)
	Pr >  t			0.0392
	n	10	7	
	LS Mean	-0.214	1.414	-1.628
	SEM	4.946	5.709	6.609
Week 64	95% CI	(-10.0, 9.5)	(-9.8,12.7)	(-14.6,11.4)
	Pr >  t			0.8056
	n	8	5	
	LS Mean	-0.720	-1.514	0.794
	SEM	5.324	6.446	7.518
Week 72	95% CI	(-11.2, 9.8)	(-14.2,11.2)	(-14.0,15.6)
	Pr >  t			0.9160
	n	7	3	
	LS Mean	2.032	-2.372	4.404
	SEM	5.578	7.877	8.931
Week 84	95% CI	(-8.9,13.0)	(-17.9,13.1)	(-13.2,22.0)
	Pr >  t			0.6224
	n	7	4	
	LS Mean	4.412	-1.832	6.244
	SEM	5.578	7.023	8.188
Week 96	95% CI	(-6.6,15.4)	(-15.7,12.0)	(-9.9,22.4)
	Pr >  t			0.4465
	n	4	3	
	LS Mean	7.191	3.185	4.007
	SEM	6.883	7.877	9.800
Week 108	95% CI	(-6.4,20.7)	(-12.3,18.7)	(-15.3,23.3)
	Pr >  t			0.6830
	n	3	3	
Week 108	LS Mean	6.188	-2.394	8.583
	SEM	7.739	7.872	10.42

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.1,21.4)	(-17.9,13.1)	(-11.9,29.1)
		Pr >  t			0.4108
	Week 120	n	3	1	
		LS Mean	-3.319	9.036	-12.36
		SEM	7.739	12.74	14.45
		95% CI	(-18.6,11.9)	(-16.1,34.2)	(-40.9,16.1)
		Pr >  t			0.3936
	Week 132	n	3		
		LS Mean	-3.903	NE	NE
		SEM	7.740	NE	NE
		95% CI	(-19.1,11.3)	NE	NE
		Pr >  t			NE

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	6.987	4.567	2.420		
			SEM	2.016	2.016	1.788		
			95% CI	( 3.0,11.0)	( 0.6, 8.5)	( -1.1, 5.9)		
					Pr >  t			0.1767
				Week 16	n	92	83	
					LS Mean	5.993	2.479	3.514
					SEM	2.075	2.139	1.934
					95% CI	( 1.9,10.1)	( -1.7, 6.7)	( -0.3, 7.3)
					Pr >  t			0.0699
				Week 24	n	77	59	
					LS Mean	6.220	3.342	2.878
					SEM	2.125	2.279	2.137
					95% CI	( 2.0,10.4)	( -1.1, 7.8)	( -1.3, 7.1)
					Pr >  t			0.1785
				Week 32	n	57	53	
					LS Mean	5.832	3.474	2.358
					SEM	2.261	2.325	2.297
					95% CI	( 1.4,10.3)	( -1.1, 8.0)	( -2.2, 6.9)
					Pr >  t			0.3050
				Week 40	n	50	44	
					LS Mean	5.112	2.183	2.929
					SEM	2.318	2.419	2.440
					95% CI	( 0.6, 9.7)	( -2.6, 6.9)	( -1.9, 7.7)
			Pr >  t			0.2304		
		Week 48	n	47	37			
			LS Mean	4.660	5.052	-0.392		
			SEM	2.344	2.510	2.555		
			95% CI	( 0.1, 9.3)	( 0.1,10.0)	( -5.4, 4.6)		
			Pr >  t			0.8780		
		Week 56	n	40	32			
			LS Mean	3.652	4.430	-0.779		
			SEM	2.422	2.594	2.707		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.1, 8.4)	(-0.7, 9.5)	(-6.1, 4.5)
		Pr >  t			0.7736
	Week 64	n	32	27	
		LS Mean	5.780	3.097	2.683
		SEM	2.544	2.702	2.918
		95% CI	( 0.8,10.8)	(-2.2, 8.4)	(-3.0, 8.4)
		Pr >  t			0.3581
	Week 72	n	31	23	
		LS Mean	4.556	1.764	2.792
		SEM	2.565	2.818	3.043
		95% CI	(-0.5, 9.6)	(-3.8, 7.3)	(-3.2, 8.8)
		Pr >  t			0.3591
	Week 84	n	27	21	
		LS Mean	5.819	4.060	1.759
		SEM	2.656	2.888	3.179
		95% CI	( 0.6,11.0)	(-1.6, 9.7)	(-4.5, 8.0)
		Pr >  t			0.5801
	Week 96	n	23	16	
		LS Mean	7.021	2.290	4.731
		SEM	2.764	3.126	3.488
		95% CI	( 1.6,12.4)	(-3.8, 8.4)	(-2.1,11.6)
		Pr >  t			0.1752
	Week 108	n	15	14	
		LS Mean	5.471	1.434	4.037
		SEM	3.143	3.260	3.902
		95% CI	(-0.7,11.6)	(-5.0, 7.8)	(-3.6,11.7)
		Pr >  t			0.3011
	Week 120	n	18	8	
		LS Mean	3.305	0.519	2.786
		SEM	2.968	3.968	4.395
		95% CI	(-2.5, 9.1)	(-7.3, 8.3)	(-5.8,11.4)
		Pr >  t			0.5264
	Week 132	n	12	4	
		LS Mean	2.082	2.418	-0.337
		SEM	3.385	5.240	5.801
		95% CI	(-4.6, 8.7)	(-7.9,12.7)	(-11.7,11.0)
		Pr >  t			0.9537
	Week 144	n	8	3	
		LS Mean	6.538	1.907	4.631
		SEM	3.908	5.949	6.746

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-1.1,14.2)	(-9.8,13.6)	(-8.6,17.9)
		Pr >  t			0.4926
	Week 156	n	5	1	
		LS Mean	2.261	2.893	-0.631
		SEM	4.736	9.896	10.73
		95% CI	(-7.0,11.6)	(-16.5,22.3)	(-21.7,20.4)
		Pr >  t			0.9531
	Week 168	n	2	1	
		LS Mean	11.286	2.893	8.393
		SEM	7.122	9.896	11.97
		95% CI	(-2.7,25.3)	(-16.5,22.3)	(-15.1,31.9)
		Pr >  t			0.4835
	Week 180	n	1		
		LS Mean	1.918	NE	NE
		SEM	9.868	NE	NE
		95% CI	(-17.4,21.3)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	1.918	NE	NE
		SEM	9.868	NE	NE
		95% CI	(-17.4,21.3)	NE	NE
		Pr >  t			NE
Yes	Week 8	n	38	30	
		LS Mean	14.667	9.953	4.713
		SEM	2.776	3.000	2.752
		95% CI	( 9.2,20.2)	( 4.0,15.9)	(-0.7,10.1)
		Pr >  t			0.0880
	Week 16	n	32	24	
		LS Mean	14.259	10.269	3.991
		SEM	2.854	3.148	3.032
		95% CI	( 8.6,19.9)	( 4.0,16.5)	(-2.0,10.0)
		Pr >  t			0.1891
	Week 24	n	28	22	
		LS Mean	9.204	9.596	-0.393
		SEM	2.988	3.202	3.170
		95% CI	( 3.3,15.1)	( 3.3,15.9)	(-6.6, 5.8)
		Pr >  t			0.9015
	Week 32	n	29	20	
		LS Mean	13.831	7.632	6.199
		SEM	2.969	3.340	3.229



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 8.0,19.7)	( 1.0,14.2)	( -0.2,12.6)
		Pr >  t			0.0558
	Week 40	n	25	18	
		LS Mean	10.474	14.056	-3.583
		SEM	3.058	3.428	3.406
		95% CI	( 4.4,16.5)	( 7.3,20.8)	(-10.3, 3.1)
		Pr >  t			0.2936
	Week 48	n	22	14	
		LS Mean	11.135	7.722	3.413
		SEM	3.143	3.651	3.704
		95% CI	( 4.9,17.3)	( 0.5,14.9)	( -3.9,10.7)
		Pr >  t			0.3574
	Week 56	n	19	13	
		LS Mean	10.613	11.910	-1.297
		SEM	3.249	3.729	3.874
		95% CI	( 4.2,17.0)	( 4.6,19.3)	( -8.9, 6.3)
		Pr >  t			0.7380
	Week 64	n	15	15	
		LS Mean	14.369	9.355	5.013
		SEM	3.444	3.591	3.920
		95% CI	( 7.6,21.2)	( 2.3,16.4)	( -2.7,12.7)
		Pr >  t			0.2016
	Week 72	n	17	12	
		LS Mean	10.896	9.993	0.903
		SEM	3.337	3.812	4.031
		95% CI	( 4.3,17.5)	( 2.5,17.5)	( -7.0, 8.8)
		Pr >  t			0.8228
	Week 84	n	13	12	
		LS Mean	8.895	9.470	-0.575
		SEM	3.625	3.813	4.244
		95% CI	( 1.8,16.0)	( 2.0,17.0)	( -8.9, 7.8)
		Pr >  t			0.8923
	Week 96	n	12	8	
		LS Mean	9.131	10.404	-1.272
		SEM	3.709	4.312	4.763
		95% CI	( 1.8,16.4)	( 1.9,18.9)	(-10.6, 8.1)
		Pr >  t			0.7895
	Week 108	n	11	7	
		LS Mean	12.615	8.192	4.424
		SEM	3.808	4.508	5.015

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( -5.1,20.1)	( -0.7,17.1)	( -5.4,14.3)
		Pr >  t			0.3782
	Week 120	n	10	8	
		LS Mean	5.461	12.515	-7.054
		SEM	3.919	4.313	4.930
		95% CI	( -2.3,13.2)	( 4.0,21.0)	(-16.7, 2.6)
		Pr >  t			0.1532
	Week 132	n	8	4	
		LS Mean	7.708	7.344	0.364
		SEM	4.214	5.531	6.220
		95% CI	( -0.6,16.0)	( -3.5,18.2)	(-11.9,12.6)
		Pr >  t			0.9534
	Week 144	n	7	2	
		LS Mean	8.212	6.276	1.937
		SEM	4.413	7.383	8.020
		95% CI	( -0.5,16.9)	( -8.2,20.8)	(-13.8,17.7)
		Pr >  t			0.8093
	Week 156	n	5	2	
		LS Mean	7.846	6.276	1.570
		SEM	4.993	7.383	8.352
		95% CI	( -2.0,17.7)	( -8.2,20.8)	(-14.8,18.0)
		Pr >  t			0.8510
	Week 168	n	2	1	
		LS Mean	0.211	3.381	-3.170
		SEM	7.304	10.11	12.08
		95% CI	(-14.1,14.6)	(-16.5,23.2)	(-26.9,20.6)
		Pr >  t			0.7930
	Week 180	n		1	
		LS Mean	NE	3.381	NE
		SEM	NE	10.11	NE
		95% CI	NE	(-16.5,23.2)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	3.381	NE
		SEM	NE	10.11	NE
		95% CI	NE	(-16.5,23.2)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	8.912	5.865	3.046		
			SEM	1.715	1.756	1.564		
			95% CI	( 5.5,12.3)	( 2.4, 9.3)	( -0.0, 6.1)		
					Pr >  t			0.0520
		Week 16	n	119	97			
			LS Mean	8.485	4.713	3.773		
			SEM	1.763	1.861	1.704		
			95% CI	( 5.0,12.0)	( 1.1, 8.4)	( 0.4, 7.1)		
					Pr >  t			0.0272
		Week 24	n	100	75			
			LS Mean	6.757	5.459	1.298		
			SEM	1.814	1.956	1.850		
			95% CI	( 3.2,10.3)	( 1.6, 9.3)	( -2.3, 4.9)		
					Pr >  t			0.4830
		Week 32	n	82	69			
			LS Mean	8.262	4.954	3.308		
			SEM	1.891	1.995	1.944		
			95% CI	( 4.5,12.0)	( 1.0, 8.9)	( -0.5, 7.1)		
					Pr >  t			0.0892
		Week 40	n	73	58			
			LS Mean	6.888	5.742	1.146		
			SEM	1.930	2.068	2.051		
			95% CI	( 3.1,10.7)	( 1.7, 9.8)	( -2.9, 5.2)		
					Pr >  t			0.5765
		Week 48	n	66	48			
			LS Mean	6.836	6.038	0.798		
			SEM	1.965	2.151	2.168		
95% CI	( 3.0,10.7)		( 1.8,10.3)	( -3.5, 5.1)				
			Pr >  t			0.7128		
Week 56	n	56	43					
	LS Mean	5.913	6.768	-0.855				
	SEM	2.028	2.205	2.279				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.9, 9.9)	( -5.3, 3.6)
		Pr >  t		0.7076
	Week 64	n	45	41
		LS Mean	8.764	4.970
		SEM	2.124	2.230
		95% CI	( 4.6,12.9)	( 0.6, 9.3)
		Pr >  t		0.1127
	Week 72	n	46	34
		LS Mean	6.620	4.293
		SEM	2.115	2.333
		95% CI	( 2.5,10.8)	( -0.3, 8.9)
		Pr >  t		0.3478
	Week 84	n	37	32
		LS Mean	6.071	5.641
		SEM	2.233	2.369
		95% CI	( 1.7,10.5)	( 1.0,10.3)
		Pr >  t		0.8689
	Week 96	n	33	23
		LS Mean	7.294	4.780
		SEM	2.296	2.596
		95% CI	( 2.8,11.8)	( -0.3, 9.9)
		Pr >  t		0.3809
	Week 108	n	24	20
		LS Mean	7.732	3.391
		SEM	2.515	2.709
		95% CI	( 2.8,12.7)	( -1.9, 8.7)
		Pr >  t		0.1670
	Week 120	n	25	16
		LS Mean	3.093	5.211
		SEM	2.482	2.912
		95% CI	( -1.8, 8.0)	( -0.5,10.9)
		Pr >  t		0.5205
	Week 132	n	19	8
		LS Mean	3.647	3.504
		SEM	2.704	3.755
		95% CI	( -1.7, 9.0)	( -3.9,10.9)
		Pr >  t		0.9728
	Week 144	n	14	5
		LS Mean	6.470	2.942
		SEM	2.994	4.570
				3.527
				5.108

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.6,12.3)	( -6.0,11.9)	( -6.5,13.5)
		Pr >  t			0.4899
	Week 156	n	10	3	
		LS Mean	3.634	2.547	1.087
		SEM	3.402	5.729	6.371
		95% CI	( -3.0,10.3)	( -8.7,13.8)	(-11.4,13.6)
		Pr >  t			0.8646
	Week 168	n	4	2	
		LS Mean	4.173	1.523	2.651
		SEM	5.001	6.911	8.305
		95% CI	( -5.6,14.0)	(-12.0,15.1)	(-13.6,18.9)
		Pr >  t			0.7497
	Week 180	n	1	1	
		LS Mean	2.943	-1.440	4.383
		SEM	9.600	9.610	13.44
		95% CI	(-15.9,21.8)	(-20.3,17.4)	(-22.0,30.8)
		Pr >  t			0.7444
	Week 192	n	1	1	
		LS Mean	2.943	-1.440	4.383
		SEM	9.600	9.610	13.44
		95% CI	(-15.9,21.8)	(-20.3,17.4)	(-22.0,30.8)
		Pr >  t			0.7444
Yes	Week 8	n	5	9	
		LS Mean	7.088	-1.316	8.404
		SEM	6.722	4.915	8.369
		95% CI	( -6.4,20.6)	(-11.2, 8.6)	( -8.4,25.2)
		Pr >  t			0.3202
	Week 16	n	5	9	
		LS Mean	-2.910	-6.931	4.021
		SEM	6.722	4.909	8.365
		95% CI	(-16.4,10.6)	(-16.8, 2.9)	(-12.8,20.8)
		Pr >  t			0.6328
	Week 24	n	5	5	
		LS Mean	7.088	-10.01	17.096
		SEM	6.722	6.671	9.484
		95% CI	( -6.4,20.6)	(-23.4, 3.4)	( -2.0,36.1)
		Pr >  t			0.0775
	Week 32	n	4	3	
		LS Mean	1.918	-11.73	13.646
		SEM	7.486	8.836	11.53

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.1,17.0)	(-29.5, 6.0)	(-9.5,36.8)
		Pr >  t			0.2421
	Week 40	n	2	3	
		LS Mean	-9.442	-8.439	-1.003
		SEM	10.55	8.599	13.59
		95% CI	(-30.6,11.7)	(-25.7, 8.8)	(-28.3,26.3)
		Pr >  t			0.9414
	Week 48	n	3	2	
		LS Mean	-3.421	-6.421	3.001
		SEM	8.574	10.72	13.60
		95% CI	(-20.6,13.8)	(-27.9,15.1)	(-24.3,30.3)
		Pr >  t			0.8263
	Week 56	n	3	1	
		LS Mean	-3.421	-12.47	9.052
		SEM	8.574	15.12	17.49
		95% CI	(-20.6,13.8)	(-42.8,17.9)	(-26.1,44.2)
		Pr >  t			0.6071
	Week 64	n	2		
		LS Mean	-9.442	NE	NE
		SEM	10.55	NE	NE
		95% CI	(-30.6,11.7)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	-2.218	NE	NE
		SEM	10.55	NE	NE
		95% CI	(-23.4,19.0)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	7.689	NE	NE
		SEM	8.574	NE	NE
		95% CI	(-9.5,24.9)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	-1.107	NE	NE
		SEM	10.55	NE	NE
		95% CI	(-22.3,20.1)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	1.398	NE	NE
		SEM	10.62	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.9,22.7)	NE
		Pr >  t		NE
	Week 120	n	3	
		LS Mean	2.133	NE
		SEM	8.574	NE
		95% CI	(-15.1,19.4)	NE
		Pr >  t		NE
	Week 132	n	1	
		LS Mean	-5.825	NE
		SEM	15.12	NE
		95% CI	(-36.2,24.5)	NE
		Pr >  t		NE
	Week 144	n	1	
		LS Mean	-5.825	NE
		SEM	15.12	NE
		95% CI	(-36.2,24.5)	NE
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	8.385	6.209	2.175		
			SEM	1.717	1.751	1.633		
			95% CI	( 5.0,11.8)	( 2.8, 9.7)	( -1.0, 5.4)		
					Pr >  t			0.1833
		Week 16	n	111	91			
			LS Mean	8.279	4.135	4.145		
			SEM	1.767	1.873	1.781		
			95% CI	( 4.8,11.8)	( 0.5, 7.8)	( 0.6, 7.6)		
					Pr >  t			0.0203
		Week 24	n	96	70			
			LS Mean	6.996	4.825	2.171		
			SEM	1.819	1.987	1.938		
			95% CI	( 3.4,10.6)	( 0.9, 8.7)	( -1.6, 6.0)		
					Pr >  t			0.2629
		Week 32	n	77	61			
			LS Mean	7.837	4.371	3.466		
			SEM	1.917	2.055	2.075		
			95% CI	( 4.1,11.6)	( 0.3, 8.4)	( -0.6, 7.5)		
					Pr >  t			0.0951
		Week 40	n	69	52			
			LS Mean	6.157	5.491	0.666		
			SEM	1.960	2.140	2.191		
			95% CI	( 2.3,10.0)	( 1.3, 9.7)	( -3.6, 5.0)		
			Pr >  t			0.7611		
Week 48	n	62	41					
	LS Mean	5.597	5.444	0.154				
	SEM	2.004	2.267	2.354				
	95% CI	( 1.7, 9.5)	( 1.0, 9.9)	( -4.5, 4.8)				
			Pr >  t			0.9479		
Week 56	n	53	35					
	LS Mean	5.432	6.304	-0.872				
	SEM	2.074	2.364	2.508				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.4, 9.5)	( -5.8, 4.0)
		Pr >  t		0.7281
	Week 64	n	44	33
		LS Mean	7.128	4.088
		SEM	2.166	2.404
		95% CI	( 2.9,11.4)	( -0.6, 8.8)
		Pr >  t		0.2468
	Week 72	n	45	28
		LS Mean	6.233	4.313
		SEM	2.156	2.519
		95% CI	( 2.0,10.5)	( -0.6, 9.3)
		Pr >  t		0.4805
	Week 84	n	39	27
		LS Mean	6.101	4.735
		SEM	2.244	2.547
		95% CI	( 1.7,10.5)	( -0.3, 9.7)
		Pr >  t		0.6269
	Week 96	n	34	19
		LS Mean	6.801	5.231
		SEM	2.326	2.847
		95% CI	( 2.2,11.4)	( -0.4,10.8)
		Pr >  t		0.6180
	Week 108	n	26	17
		LS Mean	7.091	3.737
		SEM	2.523	2.958
		95% CI	( 2.1,12.0)	( -2.1, 9.5)
		Pr >  t		0.3224
	Week 120	n	27	11
		LS Mean	3.047	6.465
		SEM	2.489	3.472
		95% CI	( -1.8, 7.9)	( -0.3,13.3)
		Pr >  t		0.3719
	Week 132	n	20	6
		LS Mean	3.127	4.524
		SEM	2.746	4.448
		95% CI	( -2.3, 8.5)	( -4.2,13.3)
		Pr >  t		0.7742
	Week 144	n	15	4
		LS Mean	5.707	2.283
		SEM	3.032	5.323
				3.424
				5.826

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.2,11.7)	(-8.2,12.7)	(-8.0,14.9)
		Pr >  t			0.5568
	Week 156	n	10	2	
		LS Mean	3.154	1.289	1.864
		SEM	3.554	7.329	7.919
		95% CI	(-3.8,10.1)	(-13.1,15.7)	(-13.7,17.4)
		Pr >  t			0.8139
	Week 168	n	4	2	
		LS Mean	3.724	1.289	2.435
		SEM	5.276	7.329	8.827
		95% CI	(-6.6,14.1)	(-13.1,15.7)	(-14.9,19.8)
		Pr >  t			0.7827
	Week 180	n	1	1	
		LS Mean	2.407	-1.605	4.012
		SEM	10.19	10.21	14.30
		95% CI	(-17.6,22.4)	(-21.6,18.4)	(-24.0,32.1)
		Pr >  t			0.7790
	Week 192	n	1	1	
		LS Mean	2.407	-1.605	4.012
		SEM	10.19	10.21	14.30
		95% CI	(-17.6,22.4)	(-21.6,18.4)	(-24.0,32.1)
		Pr >  t			0.7790
>= 75 Years	Week 8	n	17	19	
		LS Mean	5.817	-1.382	7.199
		SEM	2.127	1.955	2.910
		95% CI	( 1.6,10.1)	( -5.3, 2.5)	( 1.4,13.0)
		Pr >  t			0.0162
	Week 16	n	13	16	
		LS Mean	-0.957	-1.137	0.179
		SEM	2.370	2.074	3.137
		95% CI	(-5.7, 3.8)	(-5.3, 3.0)	(-6.1, 6.4)
		Pr >  t			0.9546
	Week 24	n	9	11	
		LS Mean	-2.361	-1.655	-0.706
		SEM	2.737	2.425	3.651
		95% CI	(-7.8, 3.1)	(-6.5, 3.2)	(-7.9, 6.5)
		Pr >  t			0.8470
	Week 32	n	9	12	
		LS Mean	1.440	-1.979	3.418
		SEM	2.737	2.359	3.608

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.0, 6.9)	(-6.7, 2.7)	(-3.7,10.6)
		Pr >  t			0.3457
	Week 40	n	6	10	
		LS Mean	0.503	-2.041	2.544
		SEM	3.206	2.517	4.071
		95% CI	(-5.8, 6.8)	(-7.0, 2.9)	(-5.5,10.6)
		Pr >  t			0.5330
	Week 48	n	7	10	
		LS Mean	5.111	-0.314	5.425
		SEM	3.021	2.526	3.931
		95% CI	(-0.9,11.1)	(-5.3, 4.7)	(-2.4,13.2)
		Pr >  t			0.1701
	Week 56	n	6	10	
		LS Mean	-2.458	-0.110	-2.348
		SEM	3.201	2.530	4.070
		95% CI	(-8.8, 3.9)	(-5.1, 4.9)	(-10.4, 5.7)
		Pr >  t			0.5650
	Week 64	n	3	9	
		LS Mean	12.859	0.097	12.762
		SEM	4.255	2.633	4.996
		95% CI	( 4.5,21.3)	(-5.1, 5.3)	( 2.9,22.6)
		Pr >  t			0.0115
	Week 72	n	3	7	
		LS Mean	-3.808	-3.971	0.163
		SEM	4.255	2.906	5.145
		95% CI	(-12.2, 4.6)	(-9.7, 1.8)	(-10.0,10.3)
		Pr >  t			0.9748
	Week 84	n	1	6	
		LS Mean	1.008	1.223	-0.215
		SEM	6.984	3.088	7.631
		95% CI	(-12.8,14.8)	(-4.9, 7.3)	(-15.3,14.9)
		Pr >  t			0.9776
	Week 96	n	1	5	
		LS Mean	1.008	-4.912	5.920
		SEM	6.984	3.328	7.733
		95% CI	(-12.8,14.8)	(-11.5, 1.7)	(-9.4,21.2)
		Pr >  t			0.4451
	Week 108	n		4	
		LS Mean	NE	-5.667	NE
		SEM	NE	3.656	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	NE	(-12.9, 1.5)	NE
		Pr >  t			NE
	Week 120	n	1	5	
		LS Mean	-0.575	-4.912	4.337
		SEM	6.997	3.328	7.750
		95% CI	(-14.4,13.2)	(-11.5, 1.7)	(-11.0,19.6)
		Pr >  t			0.5765
	Week 132	n		2	
		LS Mean	NE	-7.435	NE
		SEM	NE	4.937	NE
		95% CI	NE	(-17.2, 2.3)	NE
		Pr >  t			NE
	Week 144	n		1	
		LS Mean	NE	-2.509	NE
		SEM	NE	6.825	NE
		95% CI	NE	(-16.0,11.0)	NE
		Pr >  t			NE
	Week 156	n		1	
		LS Mean	NE	-2.509	NE
		SEM	NE	6.825	NE
		95% CI	NE	(-16.0,11.0)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Geographic Region 1 (L)	Asia	Week 8	n	30	35	
			LS Mean	6.114	0.024	6.090
		SEM	2.102	1.999	2.024	
		95% CI	( 2.0,10.3)	( -3.9, 4.0)	( 2.1,10.1)	
		Pr >  t			0.0029	
		Week 16	n	28	29	
			LS Mean	4.941	0.808	4.133
		SEM	2.132	2.137	2.152	
		95% CI	( 0.7, 9.2)	( -3.4, 5.0)	( -0.1, 8.4)	
		Pr >  t			0.0558	
		Week 24	n	21	25	
			LS Mean	0.613	1.764	-1.151
		SEM	2.285	2.204	2.380	
		95% CI	( -3.9, 5.1)	( -2.6, 6.1)	( -5.8, 3.5)	
		Pr >  t			0.6290	
		Week 32	n	19	23	
			LS Mean	0.975	2.869	-1.895
		SEM	2.342	2.250	2.489	
		95% CI	( -3.7, 5.6)	( -1.6, 7.3)	( -6.8, 3.0)	
		Pr >  t			0.4471	
		Week 40	n	16	18	
			LS Mean	1.163	0.514	0.649
		SEM	2.452	2.444	2.738	
		95% CI	( -3.7, 6.0)	( -4.3, 5.3)	( -4.7, 6.0)	
Pr >  t			0.8127			
Week 48	n	16	17			
	LS Mean	0.121	0.439	-0.318		
SEM	2.452	2.481	2.773			
95% CI	( -4.7, 5.0)	( -4.5, 5.3)	( -5.8, 5.1)			
Pr >  t			0.9089			
Week 56	n	12	14			
	LS Mean	2.273	2.841	-0.568		
SEM	2.670	2.620	3.100			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-3.0, 7.5)	(-2.3, 8.0)	(-6.7, 5.5)
	Pr >  t			0.8546
	n	12	11	
	LS Mean	5.050	2.193	2.857
	SEM	2.670	2.828	3.277
Week 72	95% CI	(-0.2, 10.3)	(-3.4, 7.8)	(-3.6, 9.3)
	Pr >  t			0.3838
	n	10	8	
	LS Mean	4.487	-1.125	5.612
	SEM	2.831	3.157	3.693
Week 84	95% CI	(-1.1, 10.1)	(-7.3, 5.1)	(-1.6, 12.9)
	Pr >  t			0.1295
	n	8	8	
	LS Mean	5.878	3.042	2.836
	SEM	3.110	3.157	3.874
Week 96	95% CI	(-0.2, 12.0)	(-3.2, 9.3)	(-4.8, 10.5)
	Pr >  t			0.4647
	n	6	6	
	LS Mean	3.983	-1.784	5.768
	SEM	3.461	3.511	4.437
Week 108	95% CI	(-2.8, 10.8)	(-8.7, 5.1)	(-3.0, 14.5)
	Pr >  t			0.1944
	n	4	5	
	LS Mean	5.106	-2.296	7.402
	SEM	4.071	3.772	5.117
Week 120	95% CI	(-2.9, 13.1)	(-9.7, 5.1)	(-2.7, 17.5)
	Pr >  t			0.1489
	n	4	4	
	LS Mean	5.106	-3.014	8.120
	SEM	4.071	4.132	5.386
Week 132	95% CI	(-2.9, 13.1)	(-11.1, 5.1)	(-2.5, 18.7)
	Pr >  t			0.1325
	n	3	2	
	LS Mean	6.564	-4.210	10.774
	SEM	4.598	5.520	6.855
Week 144	95% CI	(-2.5, 15.6)	(-15.1, 6.6)	(-2.7, 24.3)
	Pr >  t			0.1170
	n	3	1	
	LS Mean	6.564	-0.060	6.624
	SEM	4.598	7.605	8.621

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Europe	Week 156	95% CI	(-2.5,15.6)	(-15.0,14.9)	(-10.3,23.6)
		Pr >  t			0.4428
		n	2	1	
	Week 168	LS Mean	1.278	-0.060	1.338
		SEM	5.497	7.605	9.131
		95% CI	(-9.5,12.1)	(-15.0,14.9)	(-16.6,19.3)
	Week 8	Pr >  t			0.8836
		n	1		
		LS Mean	2.894	NE	NE
	Week 16	SEM	7.575	NE	NE
		95% CI	(-12.0,17.8)	NE	NE
		Pr >  t			NE
	Week 8	n	66	68	
		LS Mean	11.533	9.494	2.040
		SEM	4.872	4.867	2.634
	Week 16	95% CI	( 1.9,21.2)	(-0.2,19.1)	(-3.2, 7.2)
		Pr >  t			0.4396
		n	58	48	
	Week 24	LS Mean	10.932	6.752	4.180
		SEM	4.899	4.951	2.890
		95% CI	( 1.2,20.6)	(-3.1,16.6)	(-1.5, 9.9)
	Week 32	Pr >  t			0.1491
		n	51	36	
		LS Mean	9.004	6.474	2.529
Week 40	SEM	4.931	5.038	3.123	
	95% CI	(-0.8,18.8)	(-3.5,16.5)	(-3.6, 8.7)	
	Pr >  t			0.4185	
Week 48	n	43	30		
	LS Mean	8.992	5.501	3.491	
	SEM	5.021	5.160	3.321	
Week 8	95% CI	(-1.0,18.9)	(-4.7,15.7)	(-3.0,10.0)	
	Pr >  t			0.2938	
	n	37	25		
Week 16	LS Mean	8.642	6.530	2.112	
	SEM	5.069	5.244	3.518	
	95% CI	(-1.4,18.7)	(-3.8,16.9)	(-4.8, 9.0)	
Week 24	Pr >  t			0.5485	
	n	33	21		
	LS Mean	10.131	9.939	0.192	
Week 32	SEM	5.110	5.335	3.708	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	( 0.0,20.2)	( -0.6,20.5)	( -7.1, 7.5)
	Pr >  t			0.9587
	n	29	20	
	LS Mean	6.775	5.967	0.808
	SEM	5.159	5.363	3.817
Week 64	95% CI	( -3.4,17.0)	( -4.6,16.6)	( -6.7, 8.3)
	Pr >  t			0.8325
	n	23	20	
	LS Mean	10.532	6.013	4.518
	SEM	5.262	5.365	3.957
Week 72	95% CI	( 0.1,20.9)	( -4.6,16.6)	( -3.3,12.3)
	Pr >  t			0.2540
	n	25	19	
	LS Mean	7.870	6.317	1.553
	SEM	5.224	5.393	3.945
Week 84	95% CI	( -2.5,18.2)	( -4.3,17.0)	( -6.2, 9.3)
	Pr >  t			0.6940
	n	22	17	
	LS Mean	5.460	7.876	-2.416
	SEM	5.285	5.462	4.117
Week 96	95% CI	( -5.0,15.9)	( -2.9,18.7)	( -10.5, 5.7)
	Pr >  t			0.5576
	n	20	13	
	LS Mean	11.053	7.441	3.612
	SEM	5.336	5.656	4.434
Week 108	95% CI	( 0.5,21.6)	( -3.7,18.6)	( -5.1,12.3)
	Pr >  t			0.4155
	n	15	11	
	LS Mean	10.397	4.847	5.550
	SEM	5.520	5.802	4.829
Week 120	95% CI	( -0.5,21.3)	( -6.6,16.3)	( -3.9,15.0)
	Pr >  t			0.2508
	n	16	8	
	LS Mean	4.845	10.550	-5.704
	SEM	5.478	6.140	5.185
Week 132	95% CI	( -6.0,15.7)	( -1.5,22.6)	( -15.9, 4.5)
	Pr >  t			0.2716
	n	12	3	
	LS Mean	3.600	4.267	-0.667
	SEM	5.693	7.884	7.332

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.6,14.8)	(-11.2,19.8)	(-15.1,13.7)
		Pr >  t			0.9275
	Week 144	n	7	4	
		LS Mean	4.980	4.234	0.746
		SEM	6.273	7.242	7.140
		95% CI	(-7.4,17.3)	(-10.0,18.5)	(-13.3,14.8)
		Pr >  t			0.9168
	Week 156	n	5	2	
		LS Mean	4.341	3.135	1.206
		SEM	6.785	9.034	9.319
		95% CI	(-9.0,17.7)	(-14.6,20.9)	(-17.1,19.5)
		Pr >  t			0.8971
	Week 168	n	2	2	
		LS Mean	-3.619	3.135	-6.754
		SEM	9.002	9.034	11.04
		95% CI	(-21.3,14.1)	(-14.6,20.9)	(-28.4,14.9)
		Pr >  t			0.5408
	Week 180	n		1	
		LS Mean	NE	0.251	NE
		SEM	NE	11.81	NE
		95% CI	NE	(-22.9,23.4)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	0.251	NE
		SEM	NE	11.81	NE
		95% CI	NE	(-22.9,23.4)	NE
		Pr >  t			NE
Latin America	Week 8	n	14	13	
		LS Mean	2.655	-1.922	4.577
		SEM	3.043	3.102	4.351
		95% CI	(-3.4, 8.7)	(-8.1, 4.2)	(-4.0,13.2)
		Pr >  t			0.2949
	Week 16	n	13	12	
		LS Mean	-0.835	-1.898	1.063
		SEM	3.147	3.229	4.499
		95% CI	(-7.1, 5.4)	(-8.3, 4.5)	(-7.8,10.0)
		Pr >  t			0.8136
	Week 24	n	12	10	
		LS Mean	0.635	-1.862	2.497
		SEM	3.264	3.524	4.807

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-5.8, 7.1)	(-8.8, 5.1)	(-7.0,12.0)
	Pr >  t			0.6043
	n	9	10	
	LS Mean	12.646	-1.862	14.508
	SEM	3.756	3.524	5.155
Week 40	95% CI	(-5.2,20.1)	(-8.8, 5.1)	(-4.3,24.7)
	Pr >  t			0.0056
	n	7	10	
	LS Mean	2.944	-1.862	4.806
	SEM	4.188	3.524	5.475
Week 48	95% CI	(-5.3,11.2)	(-8.8, 5.1)	(-6.0,15.6)
	Pr >  t			0.3816
	n	7	7	
	LS Mean	-1.818	-0.724	-1.094
	SEM	4.188	4.176	5.902
Week 56	95% CI	(-10.1, 6.5)	(-9.0, 7.5)	(-12.8,10.6)
	Pr >  t			0.8532
	n	6	7	
	LS Mean	-2.179	3.680	-5.859
	SEM	4.517	4.170	6.142
Week 64	95% CI	(-11.1, 6.7)	(-4.6,11.9)	(-18.0, 6.3)
	Pr >  t			0.3417
	n	4	7	
	LS Mean	0.870	-0.614	1.484
	SEM	5.465	4.175	6.868
Week 72	95% CI	(-9.9,11.7)	(-8.9, 7.6)	(-12.1,15.1)
	Pr >  t			0.8292
	n	4	4	
	LS Mean	0.870	0.382	0.488
	SEM	5.465	5.449	7.707
Week 84	95% CI	(-9.9,11.7)	(-10.4,11.1)	(-14.7,15.7)
	Pr >  t			0.9496
	n	4	5	
	LS Mean	4.124	-3.442	7.566
	SEM	5.460	4.894	7.328
Week 96	95% CI	(-6.7,14.9)	(-13.1, 6.2)	(-6.9,22.0)
	Pr >  t			0.3035
	n	3	2	
	LS Mean	-4.423	3.396	-7.819
	SEM	6.278	7.604	9.855

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-16.8, 8.0)	(-11.6,18.4)	(-27.3,11.7)
		Pr >  t			0.4288
		n	2	3	
		LS Mean	-6.365	-2.661	-3.704
		SEM	7.625	6.255	9.858
	Week 120	95% CI	(-21.4, 8.7)	(-15.0, 9.7)	(-23.2,15.8)
		Pr >  t			0.7076
		n	2	2	
		LS Mean	-8.565	-2.575	-5.990
		SEM	7.629	7.614	10.77
	Week 132	95% CI	(-23.6, 6.5)	(-17.6,12.5)	(-27.3,15.3)
		Pr >  t			0.5788
		n	1	2	
		LS Mean	-6.223	-2.575	-3.648
		SEM	10.71	7.614	13.12
	Week 8	95% CI	(-27.4,14.9)	(-17.6,12.5)	(-29.6,22.3)
		Pr >  t			0.7813
		n	16	19	
		LS Mean	4.142	4.736	-0.595
		SEM	3.200	3.105	3.896
	Week 16	95% CI	(-2.3,10.6)	(-1.5,11.0)	(-8.4, 7.3)
		Pr >  t			0.8794
		n	12	14	
		LS Mean	3.525	1.804	1.721
		SEM	3.512	3.410	4.311
	Week 24	95% CI	(-3.5,10.6)	(-5.0, 8.6)	(-6.9,10.3)
		Pr >  t			0.6912
		n	12	8	
LS Mean		3.579	4.352	-0.772	
SEM		3.515	4.116	4.845	
Week 32	95% CI	(-3.5,10.6)	(-3.8,12.5)	(-10.4, 8.9)	
	Pr >  t			0.8737	
	n	9	7		
	LS Mean	6.580	2.186	4.394	
	SEM	3.829	4.284	5.195	
Week 40	95% CI	(-1.1,14.2)	(-6.3,10.7)	(-5.9,14.7)	
	Pr >  t			0.3998	
	n	9	7		
		LS Mean	5.010	11.711	-6.700
		SEM	3.842	4.284	5.213

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-2.7,12.7)	( 3.2,20.2)	(-17.0, 3.6)
	Pr >  t			0.2017
	n	8	5	
	LS Mean	5.142	0.245	4.896
	SEM	3.976	4.756	5.700
Week 56	95% CI	(-2.8,13.1)	(-9.2, 9.7)	(-6.4,16.2)
	Pr >  t			0.3921
	n	7	3	
	LS Mean	4.984	11.648	-6.664
	SEM	4.132	5.677	6.589
Week 64	95% CI	(-3.2,13.2)	( 0.4,22.9)	(-19.7, 6.4)
	Pr >  t			0.3136
	n	5	3	
	LS Mean	6.187	0.535	5.652
	SEM	4.596	5.677	6.896
Week 72	95% CI	(-2.9,15.3)	(-10.7,11.8)	(-8.0,19.3)
	Pr >  t			0.4138
	n	5	3	
	LS Mean	2.855	0.770	2.084
	SEM	4.580	5.677	6.877
Week 84	95% CI	(-6.2,11.9)	(-10.5,12.0)	(-11.5,15.7)
	Pr >  t			0.7623
	n	2	2	
	LS Mean	19.960	-0.388	20.348
	SEM	6.492	6.628	8.944
Week 96	95% CI	( 7.1,32.8)	(-13.5,12.7)	( 2.7,38.0)
	Pr >  t			0.0245
	n	3	2	
	LS Mean	-0.646	-0.388	-0.258
	SEM	5.483	6.628	8.267
Week 108	95% CI	(-11.5,10.2)	(-13.5,12.7)	(-16.6,16.1)
	Pr >  t			0.9752
	n	1	2	
	LS Mean	11.129	7.947	3.182
	SEM	8.713	6.628	10.67
Week 120	95% CI	(-6.1,28.4)	(-5.2,21.1)	(-17.9,24.3)
	Pr >  t			0.7659
	n	3	2	
	LS Mean	-0.646	-0.388	-0.258
	SEM	5.483	6.628	8.267

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.5,10.2)	(-13.5,12.7)	(-16.6,16.1)
		Pr >  t			0.9752
	Week 132	n	1	1	
		LS Mean	1.413	12.736	-11.32
		SEM	8.712	8.828	12.16
		95% CI	(-15.8,18.7)	(-4.7,30.2)	(-35.4,12.8)
		Pr >  t			0.3537
	Week 144	n	2		
		LS Mean	10.136	NE	NE
		SEM	6.435	NE	NE
		95% CI	(-2.6,22.9)	NE	NE
		Pr >  t			NE
	Week 156	n	1		
		LS Mean	1.413	NE	NE
		SEM	8.712	NE	NE
		95% CI	(-15.8,18.7)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	18.083	NE	NE
		SEM	8.712	NE	NE
		95% CI	( 0.8,35.3)	NE	NE
		Pr >  t			NE
	Week 180	n	1		
		LS Mean	1.413	NE	NE
		SEM	8.712	NE	NE
		95% CI	(-15.8,18.7)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	1.413	NE	NE
		SEM	8.712	NE	NE
		95% CI	(-15.8,18.7)	NE	NE
		Pr >  t			NE
Other	Week 8	n	16	5	
		LS Mean	14.657	13.197	1.460
		SEM	4.038	5.544	6.118
		95% CI	( 5.9,23.4)	( 1.5,24.9)	(-11.4,14.4)
		Pr >  t			0.8142
	Week 16	n	13	4	
		LS Mean	15.828	14.291	1.537
		SEM	4.089	6.219	6.574

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	( 7.0,24.6)	( 1.4,27.1)	(-12.1,15.2)
	Pr >  t			0.8173
	n	9	2	
	LS Mean	23.210	18.389	4.820
	SEM	4.470	7.674	8.101
Week 32	95% CI	( 13.9,32.6)	( 2.9,33.8)	(-11.5,21.2)
	Pr >  t			0.5549
	n	6	3	
	LS Mean	17.684	10.981	6.703
	SEM	4.998	6.785	7.575
Week 40	95% CI	( 7.5,27.9)	( -2.9,24.8)	( -8.7,22.1)
	Pr >  t			0.3823
	n	6	2	
	LS Mean	13.609	12.944	0.664
	SEM	5.077	7.674	8.401
Week 48	95% CI	( 3.3,24.0)	( -2.5,28.4)	(-16.2,17.6)
	Pr >  t			0.9373
	n	5	1	
	LS Mean	13.198	12.833	0.365
	SEM	5.314	9.854	10.59
Week 56	95% CI	( 2.4,24.0)	( -6.8,32.5)	(-20.7,21.5)
	Pr >  t			0.9726
	n	5	1	
	LS Mean	16.532	12.833	3.699
	SEM	5.314	9.854	10.59
Week 64	95% CI	( 5.8,27.3)	( -6.8,32.5)	(-17.4,24.8)
	Pr >  t			0.7280
	n	3	1	
	LS Mean	12.804	12.833	-0.030
	SEM	6.130	9.854	11.02
Week 72	95% CI	( 0.5,25.1)	( -6.8,32.5)	(-22.0,21.9)
	Pr >  t			0.9979
	n	4	1	
	LS Mean	12.878	12.833	0.045
	SEM	5.653	9.854	10.77
Week 84	95% CI	( 1.5,24.3)	( -6.8,32.5)	(-21.4,21.5)
	Pr >  t			0.9967
	n	4	1	
	LS Mean	12.878	12.833	0.045
	SEM	5.653	9.854	10.77

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	( 1.5,24.3)	( -6.8,32.5)	(-21.4,21.5)
	Pr >  t			0.9967
	n	3	1	
	LS Mean	12.804	12.833	-0.030
	SEM	6.130	9.854	11.02
Week 108	95% CI	( 0.5,25.1)	( -6.8,32.5)	(-22.0,21.9)
	Pr >  t			0.9979
	n	4		
	LS Mean	12.878	NE	NE
	SEM	5.653	NE	NE
Week 120	95% CI	( 1.5,24.3)	NE	NE
	Pr >  t		NE	NE
	n	3		
	LS Mean	12.804	NE	NE
	SEM	6.130	NE	NE
Week 132	95% CI	( 0.5,25.1)	NE	NE
	Pr >  t		NE	NE
	n	3		
	LS Mean	12.804	NE	NE
	SEM	6.130	NE	NE
Week 144	95% CI	( 0.5,25.1)	NE	NE
	Pr >  t		NE	NE
	n	3		
	LS Mean	12.710	NE	NE
	SEM	6.140	NE	NE
Week 156	95% CI	( 0.4,25.0)	NE	NE
	Pr >  t		NE	NE
	n	2		
	LS Mean	12.393	NE	NE
	SEM	6.957	NE	NE
	95% CI	( -1.5,26.3)	NE	NE
	Pr >  t		NE	NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final





**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	6.154	3.352	2.802	
		SEM	2.012	1.970	1.668	
		95% CI	( 2.2,10.1)	( -0.5, 7.2)	( -0.5, 6.1)	
			Pr >  t			0.0936
	Week 16	n	88	71		
		LS Mean	5.143	2.730	2.413	
		SEM	2.061	2.133	1.807	
		95% CI	( 1.1, 9.2)	( -1.5, 6.9)	( -1.1, 6.0)	
			Pr >  t			0.1822
	Week 24	n	75	54		
		LS Mean	6.365	3.001	3.365	
		SEM	2.106	2.237	1.990	
		95% CI	( 2.2,10.5)	( -1.4, 7.4)	( -0.5, 7.3)	
			Pr >  t			0.0912
	Week 32	n	62	52		
		LS Mean	8.401	2.557	5.843	
		SEM	2.184	2.254	2.081	
		95% CI	( 4.1,12.7)	( -1.9, 7.0)	( 1.8, 9.9)	
			Pr >  t			0.0051
	Week 40	n	51	46		
		LS Mean	6.007	3.394	2.613	
		SEM	2.260	2.325	2.222	
		95% CI	( 1.6,10.5)	( -1.2, 8.0)	( -1.7, 7.0)	
			Pr >  t			0.2399
	Week 48	n	50	37		
		LS Mean	4.853	3.501	1.352	
		SEM	2.269	2.434	2.345	
		95% CI	( 0.4, 9.3)	( -1.3, 8.3)	( -3.2, 6.0)	
			Pr >  t			0.5645
	Week 56	n	43	33		
		LS Mean	4.523	3.806	0.717	
		SEM	2.336	2.500	2.478	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-0.1, 9.1)	(-1.1, 8.7)	(-4.1, 5.6)
		Pr >  t			0.7723
	Week 64	n	35	33	
		LS Mean	8.479	1.344	7.135
		SEM	2.440	2.500	2.579
		95% CI	( 3.7,13.3)	( -3.6, 6.3)	( 2.1,12.2)
		Pr >  t			0.0058
	Week 72	n	35	31	
		LS Mean	5.029	0.913	4.116
		SEM	2.440	2.537	2.615
		95% CI	( 0.2, 9.8)	( -4.1, 5.9)	( -1.0, 9.2)
		Pr >  t			0.1157
	Week 84	n	31	29	
		LS Mean	4.760	2.946	1.815
		SEM	2.519	2.578	2.719
		95% CI	( -0.2, 9.7)	( -2.1, 8.0)	( -3.5, 7.1)
		Pr >  t			0.5046
	Week 96	n	27	22	
		LS Mean	6.245	1.717	4.528
		SEM	2.596	2.771	2.980
		95% CI	( 1.1,11.3)	( -3.7, 7.2)	( -1.3,10.4)
		Pr >  t			0.1289
	Week 108	n	19	20	
		LS Mean	7.760	0.805	6.956
		SEM	2.873	2.847	3.281
		95% CI	( 2.1,13.4)	( -4.8, 6.4)	( 0.5,13.4)
		Pr >  t			0.0342
	Week 120	n	20	15	
		LS Mean	3.775	2.673	1.101
		SEM	2.815	3.109	3.476
		95% CI	( -1.8, 9.3)	( -3.4, 8.8)	( -5.7, 7.9)
		Pr >  t			0.7514
	Week 132	n	15	7	
		LS Mean	2.583	0.838	1.746
		SEM	3.090	4.089	4.548
		95% CI	( -3.5, 8.6)	( -7.2, 8.9)	( -7.2,10.7)
		Pr >  t			0.7011
	Week 144	n	10	5	
		LS Mean	6.501	0.378	6.122
		SEM	3.532	4.694	5.393

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.4,13.4)	(-8.8, 9.6)	(-4.5,16.7)
		Pr >  t			0.2565
	Week 156	n	6	3	
		LS Mean	2.632	-0.005	2.637
		SEM	4.337	5.857	6.895
		95% CI	(-5.9,11.1)	(-11.5,11.5)	(-10.9,16.2)
		Pr >  t			0.7022
	Week 168	n	3	2	
		LS Mean	2.594	-0.980	3.574
		SEM	5.847	7.048	8.847
		95% CI	(-8.9,14.1)	(-14.8,12.8)	(-13.8,20.9)
		Pr >  t			0.6863
	Week 180	n	1	1	
		LS Mean	1.785	-3.741	5.526
		SEM	9.774	9.773	13.62
		95% CI	(-17.4,21.0)	(-22.9,15.4)	(-21.2,32.3)
		Pr >  t			0.6850
	Week 192	n	1	1	
		LS Mean	1.785	-3.741	5.526
		SEM	9.774	9.773	13.62
		95% CI	(-17.4,21.0)	(-22.9,15.4)	(-21.2,32.3)
		Pr >  t			0.6850
1	Week 8	n	43	50	
		LS Mean	12.094	7.350	4.744
		SEM	3.141	3.298	3.192
		95% CI	( 5.9,18.3)	( 0.8,13.9)	(-1.6,11.1)
		Pr >  t			0.1399
	Week 16	n	35	35	
		LS Mean	11.937	4.231	7.706
		SEM	3.278	3.405	3.487
		95% CI	( 5.4,18.4)	(-2.5,11.0)	( 0.8,14.6)
		Pr >  t			0.0286
	Week 24	n	29	26	
		LS Mean	4.794	5.142	-0.348
		SEM	3.402	3.634	3.764
		95% CI	(-1.9,11.5)	(-2.1,12.3)	(-7.8, 7.1)
		Pr >  t			0.9263
	Week 32	n	23	21	
		LS Mean	2.987	4.609	-1.622
		SEM	3.585	3.813	4.032

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.1,10.1)	(-2.9,12.1)	(-9.6, 6.3)
		Pr >  t			0.6877
	Week 40	n	23	16	
		LS Mean	3.620	5.499	-1.879
		SEM	3.593	4.017	4.235
		95% CI	(-3.5,10.7)	(-2.4,13.4)	(-10.2, 6.5)
		Pr >  t			0.6576
	Week 48	n	18	14	
		LS Mean	6.417	6.467	-0.051
		SEM	3.763	4.139	4.503
		95% CI	(-1.0,13.8)	(-1.7,14.6)	(-8.9, 8.8)
		Pr >  t			0.9910
	Week 56	n	15	12	
		LS Mean	3.617	8.315	-4.698
		SEM	3.921	4.291	4.779
		95% CI	(-4.1,11.3)	(-0.1,16.8)	(-14.1, 4.7)
		Pr >  t			0.3262
	Week 64	n	11	9	
		LS Mean	2.300	9.829	-7.529
		SEM	4.221	4.625	5.321
		95% CI	(-6.0,10.6)	( 0.7,18.9)	(-18.0, 2.9)
		Pr >  t			0.1579
	Week 72	n	12	4	
		LS Mean	4.973	11.887	-6.914
		SEM	4.140	6.005	6.502
		95% CI	(-3.2,13.1)	( 0.1,23.7)	(-19.7, 5.9)
		Pr >  t			0.2883
	Week 84	n	8	4	
		LS Mean	6.787	7.720	-0.933
		SEM	4.645	6.005	6.824
		95% CI	(-2.4,15.9)	(-4.1,19.5)	(-14.3,12.5)
		Pr >  t			0.8914
	Week 96	n	8	2	
		LS Mean	4.704	11.756	-7.052
		SEM	4.645	7.861	8.503
		95% CI	(-4.4,13.8)	(-3.7,27.2)	(-23.8, 9.7)
		Pr >  t			0.4074
	Week 108	n	6	1	
		LS Mean	1.456	7.066	-5.610
		SEM	5.085	10.63	11.30

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.5,11.5)	(-13.8,28.0)	(-27.8,16.6)
		Pr >  t			0.6199
	Week 120	n	8	1	
		LS Mean	-2.010	7.066	-9.075
		SEM	4.658	10.63	11.11
		95% CI	(-11.2, 7.2)	(-13.8,28.0)	(-30.9,12.8)
		Pr >  t			0.4148
	Week 132	n	5	1	
		LS Mean	1.188	7.066	-5.878
		SEM	5.406	10.63	11.45
		95% CI	(-9.4,11.8)	(-13.8,28.0)	(-28.4,16.6)
		Pr >  t			0.6080
	Week 144	n	5		
		LS Mean	1.188	NE	NE
		SEM	5.406	NE	NE
		95% CI	(-9.4,11.8)	NE	NE
		Pr >  t			NE
	Week 156	n	4		
		LS Mean	1.298	NE	NE
		SEM	5.851	NE	NE
		95% CI	(-10.2,12.8)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	4.025	NE	NE
		SEM	10.45	NE	NE
		95% CI	(-16.5,24.6)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73	
			LS Mean	2.212	-1.058	3.270
		SEM	5.500	5.640	2.127	
		95% CI	(-8.7,13.1)	(-12.2,10.1)	(-0.9, 7.5)	
		Pr >  t			0.1256	
		Week 16	n	69	55	
			LS Mean	1.952	-2.989	4.941
		SEM	5.506	5.688	2.270	
		95% CI	(-9.0,12.9)	(-14.3, 8.3)	( 0.5, 9.4)	
		Pr >  t			0.0304	
		Week 24	n	54	46	
			LS Mean	-0.690	-2.384	1.695
		SEM	5.528	5.719	2.437	
		95% CI	(-11.6,10.3)	(-13.7, 8.9)	(-3.1, 6.5)	
		Pr >  t			0.4873	
		Week 32	n	49	41	
			LS Mean	0.270	-3.494	3.764
		SEM	5.588	5.741	2.528	
		95% CI	(-10.8,11.3)	(-14.9, 7.9)	(-1.2, 8.7)	
		Pr >  t			0.1373	
		Week 40	n	40	33	
			LS Mean	0.635	-2.461	3.097
		SEM	5.627	5.788	2.711	
		95% CI	(-10.5,11.8)	(-13.9, 9.0)	(-2.2, 8.4)	
		Pr >  t			0.2539	
		Week 48	n	38	28	
			LS Mean	1.197	-3.842	5.039
		SEM	5.638	5.829	2.820	
95% CI	(-10.0,12.4)	(-15.4, 7.7)	(-0.5,10.6)			
Pr >  t			0.0746			
Week 56	n	32	28			
	LS Mean	-1.343	-1.773	0.430		
SEM	5.677	5.829	2.897			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-12.6, 9.9)	(-13.3, 9.8)	(-5.3, 6.1)
	Pr >  t			0.8821
	n	23	26	
	LS Mean	0.929	-2.867	3.796
	SEM	5.768	5.850	3.110
Week 72	95% CI	(-10.5,12.3)	(-14.4, 8.7)	(-2.3, 9.9)
	Pr >  t			0.2228
	n	27	25	
	LS Mean	-1.258	-3.227	1.968
	SEM	5.720	5.861	3.044
Week 84	95% CI	(-12.6,10.1)	(-14.8, 8.4)	(-4.0, 7.9)
	Pr >  t			0.5181
	n	23	22	
	LS Mean	-2.618	-2.005	-0.613
	SEM	5.767	5.900	3.205
Week 96	95% CI	(-14.0, 8.8)	(-13.7, 9.7)	(-6.9, 5.7)
	Pr >  t			0.8483
	n	20	16	
	LS Mean	3.782	-3.777	7.560
	SEM	5.814	6.020	3.501
Week 108	95% CI	(-7.7,15.3)	(-15.7, 8.1)	( 0.7,14.4)
	Pr >  t			0.0311
	n	20	14	
	LS Mean	1.918	-3.287	5.205
	SEM	5.815	6.082	3.608
Week 120	95% CI	(-9.6,13.4)	(-15.3, 8.7)	(-1.9,12.3)
	Pr >  t			0.1495
	n	17	11	
	LS Mean	-2.240	-1.828	-0.412
	SEM	5.877	6.213	3.921
Week 132	95% CI	(-13.9, 9.4)	(-14.1,10.4)	(-8.1, 7.3)
	Pr >  t			0.9163
	n	13	6	
	LS Mean	-3.187	-2.644	-0.543
	SEM	6.003	6.695	4.804
Week 144	95% CI	(-15.0, 8.7)	(-15.8,10.6)	(-10.0, 8.9)
	Pr >  t			0.9100
	n	10	5	
	LS Mean	-1.073	-4.855	3.782
	SEM	6.158	6.899	5.267



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Second Line	Week 156	95% CI	(-13.2,11.1)	(-18.4, 8.7)	(-6.6,14.1)
		Pr >  t			0.4729
		n	7	3	
	Week 168	LS Mean	-3.388	-5.248	1.860
		SEM	6.438	7.649	6.494
		95% CI	(-16.1, 9.3)	(-20.3, 9.8)	(-10.9,14.6)
	Week 180	Pr >  t			0.7746
		n	3	2	
		LS Mean	-8.111	-6.303	-1.808
	Week 192	SEM	7.551	8.496	8.450
		95% CI	(-23.0, 6.7)	(-23.0,10.4)	(-18.4,14.8)
		Pr >  t			0.8306
	Week 8	n		1	
		LS Mean	NE	-9.255	NE
		SEM	NE	10.62	NE
	Week 16	95% CI	NE	(-30.1,11.6)	NE
		Pr >  t			NE
		n		1	
	Week 24	LS Mean	NE	-9.255	NE
		SEM	NE	10.62	NE
		95% CI	NE	(-30.1,11.6)	NE
	Week 32	Pr >  t			NE
		n	66	67	
		LS Mean	8.710	6.202	2.507
Week 8	SEM	1.923	1.923	2.165	
	95% CI	( 4.9,12.5)	( 2.4,10.0)	(-1.8, 6.8)	
	Pr >  t			0.2477	
Week 16	n	54	52		
	LS Mean	7.463	4.881	2.581	
	SEM	2.058	2.113	2.412	
Week 24	95% CI	( 3.4,11.5)	( 0.7, 9.0)	(-2.2, 7.3)	
	Pr >  t			0.2852	
	n	49	35		
Week 32	LS Mean	8.024	5.304	2.719	
	SEM	2.130	2.397	2.704	
	95% CI	( 3.8,12.2)	( 0.6,10.0)	(-2.6, 8.0)	
Week 8	Pr >  t			0.3150	
	n	36	32		
	LS Mean	9.593	5.670	3.924	
Week 16	SEM	2.359	2.481	2.932	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	( 5.0,14.2)	( 0.8,10.5)	( -1.8, 9.7)
	Pr >  t			0.1813
	n	33	29	
	LS Mean	5.366	6.323	-0.957
	SEM	2.423	2.580	3.054
Week 48	95% CI	( 0.6,10.1)	( 1.3,11.4)	( -7.0, 5.0)
	Pr >  t			0.7541
	n	29	23	
	LS Mean	4.381	8.613	-4.233
	SEM	2.520	2.783	3.303
Week 56	95% CI	( -0.6, 9.3)	( 3.1,14.1)	( -10.7, 2.3)
	Pr >  t			0.2006
	n	25	17	
	LS Mean	5.513	7.955	-2.442
	SEM	2.644	3.095	3.666
Week 64	95% CI	( 0.3,10.7)	( 1.9,14.0)	( -9.6, 4.8)
	Pr >  t			0.5056
	n	22	16	
	LS Mean	8.707	5.343	3.364
	SEM	2.761	3.167	3.813
Week 72	95% CI	( 3.3,14.1)	( -0.9,11.6)	( -4.1,10.9)
	Pr >  t			0.3779
	n	20	10	
	LS Mean	7.231	3.973	3.258
	SEM	2.852	3.802	4.416
Week 84	95% CI	( 1.6,12.8)	( -3.5,11.4)	( -5.4,11.9)
	Pr >  t			0.4609
	n	16	11	
	LS Mean	9.716	5.608	4.108
	SEM	3.116	3.659	4.460
Week 96	95% CI	( 3.6,15.8)	( -1.6,12.8)	( -4.6,12.9)
	Pr >  t			0.3574
	n	15	8	
	LS Mean	2.344	6.779	-4.435
	SEM	3.184	4.165	4.936
Week 108	95% CI	( -3.9, 8.6)	( -1.4,15.0)	( -14.1, 5.3)
	Pr >  t			0.3692
	n	6	7	
	LS Mean	2.998	1.814	1.184
	SEM	4.661	4.406	6.158

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-6.2,12.2)	(-6.8,10.5)	(-10.9,13.3)
	Pr >  t			0.8476
	n	11	5	
	LS Mean	1.550	4.074	-2.524
	SEM	3.601	5.100	5.989
Week 132	95% CI	(-5.5, 8.6)	(-5.9,14.1)	(-14.3, 9.2)
	Pr >  t			0.6736
	n	7	2	
	LS Mean	3.008	-0.963	3.971
	SEM	4.358	7.775	8.731
Week 144	95% CI	(-5.5,11.6)	(-16.2,14.3)	(-13.2,21.1)
	Pr >  t			0.6494
	n	5		
	LS Mean	6.539	NE	NE
	SEM	5.035	NE	NE
Week 156	95% CI	(-3.3,16.4)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	3.393	NE	NE
	SEM	6.389	NE	NE
Week 168	95% CI	(-9.2,15.9)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	19.941	NE	NE
	SEM	10.82	NE	NE
Week 180	95% CI	(-1.3,41.2)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	3.271	NE	NE
	SEM	10.82	NE	NE
Week 192	95% CI	(-18.0,24.5)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	3.271	NE	NE
	SEM	10.82	NE	NE
	95% CI	(-18.0,24.5)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	11.682	9.262	2.419		
			SEM	3.313	3.244	2.475		
			95% CI	( 5.1,18.2)	( 2.9,15.7)	( -2.5, 7.3)		
					Pr >  t			0.3295
		Week 16	n	60	51			
			LS Mean	11.458	7.123	4.335		
			SEM	3.373	3.402	2.630		
			95% CI	( 4.8,18.1)	( 0.4,13.8)	( -0.8, 9.5)		
					Pr >  t			0.1006
		Week 24	n	51	42			
			LS Mean	10.054	8.074	1.979		
			SEM	3.423	3.473	2.794		
			95% CI	( 3.3,16.8)	( 1.2,14.9)	( -3.5, 7.5)		
					Pr >  t			0.4791
		Week 32	n	46	36			
			LS Mean	11.445	6.637	4.807		
			SEM	3.481	3.565	2.923		
			95% CI	( 4.6,18.3)	( -0.4,13.7)	( -0.9,10.6)		
					Pr >  t			0.1009
		Week 40	n	40	33			
			LS Mean	10.259	8.863	1.397		
			SEM	3.536	3.605	3.035		
			95% CI	( 3.3,17.2)	( 1.8,16.0)	( -4.6, 7.4)		
			Pr >  t			0.6456		
Week 48	n	37	28					
	LS Mean	9.121	8.748	0.373				
	SEM	3.565	3.686	3.164				
	95% CI	( 2.1,16.2)	( 1.5,16.0)	( -5.8, 6.6)				
			Pr >  t			0.9061		
Week 56	n	33	23					
	LS Mean	8.503	10.031	-1.528				
	SEM	3.615	3.796	3.347				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 1.4,15.6)	( 2.6,17.5)	( -8.1, 5.0)	
	Pr >  t				0.6482
	n	26	20		
	LS Mean	10.616	6.541		4.075
	SEM	3.729	3.886		3.569
Week 72	95% CI	( 3.3,18.0)	( -1.1,14.2)	( -2.9,11.1)	
	Pr >  t				0.2539
	n	28	17		
	LS Mean	8.590	5.925		2.665
	SEM	3.692	4.001		3.657
Week 84	95% CI	( 1.3,15.9)	( -1.9,13.8)	( -4.5, 9.8)	
	Pr >  t				0.4664
	n	23	17		
	LS Mean	7.232	6.543		0.689
	SEM	3.796	4.002		3.763
Week 96	95% CI	( -0.2,14.7)	( -1.3,14.4)	( -6.7, 8.1)	
	Pr >  t				0.8548
	n	23	11		
	LS Mean	9.303	6.261		3.042
	SEM	3.798	4.393		4.177
Week 108	95% CI	( 1.8,16.8)	( -2.4,14.9)	( -5.2,11.2)	
	Pr >  t				0.4667
	n	15	13		
	LS Mean	10.852	6.158		4.693
	SEM	4.097	4.228		4.286
Week 120	95% CI	( 2.8,18.9)	( -2.2,14.5)	( -3.7,13.1)	
	Pr >  t				0.2739
	n	16	9		
	LS Mean	7.096	9.580		-2.484
	SEM	4.048	4.621		4.631
Week 132	95% CI	( -0.9,15.1)	( 0.5,18.7)	( -11.6, 6.6)	
	Pr >  t				0.5918
	n	14	5		
	LS Mean	5.817	7.308		-1.491
	SEM	4.154	5.498		5.585
Week 144	95% CI	( -2.4,14.0)	( -3.5,18.1)	( -12.5, 9.5)	
	Pr >  t				0.7896
	n	8	3		
	LS Mean	6.886	5.103		1.782
	SEM	4.756	6.601		7.063

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-2.5,16.2)	(-7.9,18.1)	(-12.1,15.6)
		Pr >  t			0.8009
		n	7	2	
	Week 168	LS Mean	6.619	3.928	2.691
		SEM	4.939	7.757	8.264
		95% CI	(-3.1,16.3)	(-11.3,19.2)	(-13.5,18.9)
	Week 180	Pr >  t			0.7448
		n	4	2	
		LS Mean	6.781	3.928	2.853
	Week 192	SEM	5.920	7.757	8.885
		95% CI	(-4.8,18.4)	(-11.3,19.2)	(-14.6,20.3)
		Pr >  t			0.7482
	Week 8	n	1	1	
		LS Mean	5.618	1.123	4.495
		SEM	10.47	10.47	14.24
	Week 16	95% CI	(-14.9,26.2)	(-19.4,21.7)	(-23.5,32.5)
		Pr >  t			0.7524
		n	1	1	
	Week 24	LS Mean	5.618	1.123	4.495
		SEM	10.47	10.47	14.24
		95% CI	(-14.9,26.2)	(-19.4,21.7)	(-23.5,32.5)
	Week 32	Pr >  t			0.7524
		n	18	17	
		LS Mean	4.586	2.100	2.486
Week 8	SEM	2.009	2.069	2.884	
	95% CI	( 0.6, 8.6)	(-2.0, 6.2)	(-3.2, 8.2)	
	Pr >  t			0.3900	
Week 16	n	17	11		
	LS Mean	1.459	1.953	-0.494	
	SEM	2.076	2.577	3.299	
Week 24	95% CI	(-2.6, 5.6)	(-3.1, 7.0)	(-7.0, 6.0)	
	Pr >  t			0.8811	
	n	15	5		
Week 32	LS Mean	-0.686	2.927	-3.612	
	SEM	2.210	3.817	4.417	
	95% CI	(-5.0, 3.7)	(-4.6,10.5)	(-12.3, 5.1)	
Week 8	Pr >  t			0.4147	
	n	13	5		
	LS Mean	6.772	-0.407	7.179	
Week 16	SEM	2.367	3.817	4.497	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	( 2.1,11.4)	( -7.9, 7.1)	( -1.7,16.1)	
	Pr >  t			0.1122	
	n	11	5		
	LS Mean	3.496	-0.407	3.903	
	SEM	2.572	3.817	4.609	
Week 48	95% CI	( -1.6, 8.6)	( -7.9, 7.1)	( -5.2,13.0)	
	Pr >  t			0.3983	
	n	11	2		
	LS Mean	6.377	-0.583	6.961	
	SEM	2.572	5.978	6.509	
Week 56	95% CI	( 1.3,11.5)	(-12.4,11.2)	( -5.9,19.8)	
	Pr >  t			0.2863	
	n	8	2		
	LS Mean	-0.584	-0.583	-0.001	
	SEM	3.001	5.978	6.691	
Week 64	95% CI	( -6.5, 5.3)	(-12.4,11.2)	(-13.2,13.2)	
	Pr >  t			0.9999	
	n	7	3		
	LS Mean	8.133	-0.512	8.645	
	SEM	3.197	4.905	5.854	
Week 72	95% CI	( 1.8,14.4)	(-10.2, 9.2)	( -2.9,20.2)	
	Pr >  t			0.1415	
	n	7	3		
	LS Mean	-0.847	-0.512	-0.335	
	SEM	3.205	4.905	5.860	
Week 84	95% CI	( -7.2, 5.5)	(-10.2, 9.2)	(-11.9,11.2)	
	Pr >  t			0.9544	
	n	7	2		
	LS Mean	1.534	-0.583	2.118	
	SEM	3.205	5.978	6.785	
Week 96	95% CI	( -4.8, 7.9)	(-12.4,11.2)	(-11.3,15.5)	
	Pr >  t			0.7553	
	n	6	3		
	LS Mean	1.813	-0.512	2.325	
	SEM	3.452	4.905	5.999	
Week 108	95% CI	( -5.0, 8.6)	(-10.2, 9.2)	( -9.5,14.2)	
	Pr >  t			0.6989	
	n	7	2		
	LS Mean	1.534	-0.385	1.919	
	SEM	3.205	5.978	6.780	



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-4.8, 7.9)	(-12.2,11.4)	(-11.5,15.3)
		Pr >  t			0.7775
		n	6	1	
	Week 132	LS Mean	-3.744	-0.369	-3.375
		SEM	3.452	8.419	9.098
		95% CI	(-10.6, 3.1)	(-17.0,16.2)	(-21.3,14.6)
	Week 144	Pr >  t			0.7112
		n	4		
		LS Mean	3.136	NE	NE
	Week 156	SEM	4.202	NE	NE
		95% CI	(-5.2,11.4)	NE	NE
		Pr >  t			NE
	Week 8	n	5		
		LS Mean	2.481	NE	NE
		SEM	3.771	NE	NE
	Week 16	95% CI	(-5.0, 9.9)	NE	NE
		Pr >  t			NE
		n	3		
	Week 24	LS Mean	-1.547	NE	NE
		SEM	4.839	NE	NE
		95% CI	(-11.1, 8.0)	NE	NE
	Week 32	Pr >  t			NE
		n	59	57	
		LS Mean	7.675	3.242	4.433
Week 8	SEM	1.987	2.086	2.196	
	95% CI	( 3.7,11.6)	(-0.9, 7.4)	( 0.1, 8.8)	
	Pr >  t			0.0445	
Week 16	n	47	44		
	LS Mean	6.805	2.001	4.804	
	SEM	2.113	2.243	2.457	
Week 24	95% CI	( 2.6,11.0)	(-2.4, 6.4)	(-0.0, 9.6)	
	Pr >  t			0.0514	
	n	39	34		
Week 32	LS Mean	6.396	2.034	4.362	
	SEM	2.238	2.435	2.713	
	95% CI	( 2.0,10.8)	(-2.8, 6.8)	(-1.0, 9.7)	
Week 8	Pr >  t			0.1088	
	n	27	32		
	LS Mean	4.508	3.130	1.378	
Week 16	SEM	2.527	2.476	2.970	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI			
Week 40		Pr >  t	(-0.5, 9.5)	(-1.7, 8.0)	(-4.5, 7.2)
		n	24	24	0.6428
		LS Mean	3.129	2.558	0.572
		SEM	2.620	2.709	3.233
		95% CI	(-2.0, 8.3)	(-2.8, 7.9)	(-5.8, 6.9)
Week 48		Pr >  t			0.8597
		n	21	21	
		LS Mean	3.460	3.260	0.200
		SEM	2.733	2.824	3.424
		95% CI	(-1.9, 8.8)	(-2.3, 8.8)	(-6.5, 6.9)
Week 56		Pr >  t			0.9534
		n	18	20	
		LS Mean	5.091	3.409	1.681
		SEM	2.873	2.869	3.581
		95% CI	(-0.6, 10.7)	(-2.2, 9.1)	(-5.4, 8.7)
Week 64		Pr >  t			0.6389
		n	14	19	
		LS Mean	5.750	3.437	2.313
		SEM	3.136	2.917	3.838
		95% CI	(-0.4, 11.9)	(-2.3, 9.2)	(-5.2, 9.9)
Week 72		Pr >  t			0.5470
		n	13	15	
		LS Mean	7.741	2.782	4.959
		SEM	3.223	3.155	4.091
		95% CI	( 1.4, 14.1)	(-3.4, 9.0)	(-3.1, 13.0)
Week 84		Pr >  t			0.2260
		n	10	14	
		LS Mean	10.844	5.154	5.690
		SEM	3.594	3.230	4.420
		95% CI	( 3.8, 17.9)	(-1.2, 11.5)	(-3.0, 14.4)
Week 96		Pr >  t			0.1985
		n	6	10	
		LS Mean	10.149	3.443	6.706
		SEM	4.411	3.649	5.402
		95% CI	( 1.5, 18.8)	(-3.7, 10.6)	(-3.9, 17.3)
Week 108		Pr >  t			0.2150
		n	4	6	
		LS Mean	7.881	-0.004	7.885
	SEM	5.289	4.471	6.645	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-2.5,18.3)	(-8.8, 8.8)	(-5.2,20.9)
	Pr >  t			0.2360
	n	6	6	
	LS Mean	3.599	-0.133	3.732
	SEM	4.412	4.474	5.988
Week 132	95% CI	(-5.1,12.3)	(-8.9, 8.7)	(-8.0,15.5)
	Pr >  t			0.5334
	n	2	3	
	LS Mean	-2.399	-1.110	-1.289
	SEM	7.258	6.037	9.238
Week 144	95% CI	(-16.7,11.9)	(-13.0,10.7)	(-19.4,16.9)
	Pr >  t			0.8891
	n	2	2	
	LS Mean	11.268	0.701	10.567
	SEM	7.229	7.285	10.11
Week 156	95% CI	(-2.9,25.5)	(-13.6,15.0)	(-9.3,30.4)
	Pr >  t			0.2964
	n		1	
	LS Mean	NE	1.770	NE
	SEM	NE	10.10	NE
	95% CI	NE	(-18.1,21.6)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	9.307	4.449	4.858		
			SEM	2.078	2.081	1.741		
			95% CI	( 5.2,13.4)	( 0.3, 8.6)	( 1.4, 8.3)		
					Pr >  t			0.0055
		Week 16	n	79	68			
			LS Mean	7.176	3.500	3.677		
			SEM	2.106	2.217	1.910		
			95% CI	( 3.0,11.3)	( -0.9, 7.9)	( -0.1, 7.4)		
					Pr >  t			0.0548
		Week 24	n	64	55			
			LS Mean	5.435	3.004	2.430		
			SEM	2.189	2.325	2.088		
			95% CI	( 1.1, 9.7)	( -1.6, 7.6)	( -1.7, 6.5)		
					Pr >  t			0.2449
		Week 32	n	49	53			
			LS Mean	6.548	2.755	3.793		
			SEM	2.323	2.342	2.219		
			95% CI	( 2.0,11.1)	( -1.9, 7.4)	( -0.6, 8.1)		
					Pr >  t			0.0878
		Week 40	n	44	45			
			LS Mean	5.051	3.065	1.986		
			SEM	2.372	2.412	2.343		
			95% CI	( 0.4, 9.7)	( -1.7, 7.8)	( -2.6, 6.6)		
					Pr >  t			0.3969
		Week 48	n	41	36			
			LS Mean	6.234	5.078	1.156		
			SEM	2.405	2.521	2.486		
95% CI	( 1.5,11.0)		( 0.1,10.0)	( -3.7, 6.0)				
			Pr >  t			0.6421		
Week 56	n	33	32					
	LS Mean	5.712	3.799	1.913				
	SEM	2.516	2.586	2.661				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 0.8,10.7)	( -1.3, 8.9)	( -3.3, 7.1)
		Pr >  t			0.4723
	Week 64	n	27	31	
		LS Mean	7.339	3.421	3.918
		SEM	2.634	2.605	2.794
		95% CI	( 2.2,12.5)	( -1.7, 8.5)	( -1.6, 9.4)
		Pr >  t			0.1611
	Week 72	n	26	26	
		LS Mean	6.397	2.363	4.033
		SEM	2.659	2.715	2.919
		95% CI	( 1.2,11.6)	( -3.0, 7.7)	( -1.7, 9.8)
		Pr >  t			0.1673
	Week 84	n	22	23	
		LS Mean	5.694	3.762	1.932
		SEM	2.790	2.798	3.102
		95% CI	( 0.2,11.2)	( -1.7, 9.3)	( -4.2, 8.0)
		Pr >  t			0.5335
	Week 96	n	18	18	
		LS Mean	5.305	3.920	1.386
		SEM	2.951	2.990	3.415
		95% CI	( -0.5,11.1)	( -2.0, 9.8)	( -5.3, 8.1)
		Pr >  t			0.6850
	Week 108	n	14	14	
		LS Mean	8.034	2.515	5.519
		SEM	3.190	3.225	3.817
		95% CI	( 1.8,14.3)	( -3.8, 8.8)	( -2.0,13.0)
		Pr >  t			0.1486
	Week 120	n	12	12	
		LS Mean	0.402	2.388	-1.986
		SEM	3.352	3.389	4.089
		95% CI	( -6.2, 7.0)	( -4.3, 9.0)	( -10.0, 6.0)
		Pr >  t			0.6273
	Week 132	n	9	5	
		LS Mean	3.106	4.953	-1.847
		SEM	3.706	4.686	5.449
		95% CI	( -4.2,10.4)	( -4.2,14.1)	( -12.5, 8.8)
		Pr >  t			0.7347
	Week 144	n	7	4	
		LS Mean	2.105	2.558	-0.452
		SEM	4.073	5.148	6.090

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.9,10.1)	(-7.5,12.7)	(-12.4,11.5)
		Pr >  t			0.9408
	Week 156	n	4	2	
		LS Mean	1.747	3.233	-1.486
		SEM	5.114	6.988	8.307
		95% CI	(-8.3,11.8)	(-10.5,16.9)	(-17.8,14.8)
		Pr >  t			0.8580
	Week 168	n	2	1	
		LS Mean	-5.530	3.304	-8.834
		SEM	6.959	9.674	11.66
		95% CI	(-19.2, 8.1)	(-15.7,22.3)	(-31.7,14.1)
		Pr >  t			0.4490
Yes	Week 8	n	53	48	
		LS Mean	7.183	6.772	0.411
		SEM	2.757	2.886	2.745
		95% CI	( 1.7,12.6)	( 1.1,12.5)	(-5.0, 5.8)
		Pr >  t			0.8812
	Week 16	n	45	39	
		LS Mean	8.402	4.135	4.267
		SEM	2.893	3.017	2.948
		95% CI	( 2.7,14.1)	(-1.8,10.1)	(-1.5,10.1)
		Pr >  t			0.1492
	Week 24	n	41	26	
		LS Mean	8.069	6.537	1.532
		SEM	2.936	3.261	3.266
		95% CI	( 2.3,13.9)	( 0.1,13.0)	(-4.9, 8.0)
		Pr >  t			0.6394
	Week 32	n	37	20	
		LS Mean	8.853	5.943	2.910
		SEM	3.010	3.487	3.520
		95% CI	( 2.9,14.8)	(-0.9,12.8)	(-4.0, 9.8)
		Pr >  t			0.4091
	Week 40	n	31	17	
		LS Mean	7.161	8.197	-1.036
		SEM	3.107	3.661	3.750
		95% CI	( 1.0,13.3)	( 1.0,15.4)	(-8.4, 6.3)
		Pr >  t			0.7825
	Week 48	n	28	15	
		LS Mean	5.343	4.097	1.246
		SEM	3.165	3.781	3.918

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-0.9,11.6)	(-3.3,11.5)	(-6.5, 8.9)
	Pr >  t			0.7506
	n	26	13	
	LS Mean	4.139	9.656	-5.518
	SEM	3.211	3.930	4.102
Week 64	95% CI	(-2.2,10.5)	(-1.9,17.4)	(-13.6, 2.5)
	Pr >  t			0.1793
	n	20	11	
	LS Mean	8.059	4.668	3.392
	SEM	3.397	4.121	4.431
Week 72	95% CI	(-1.4,14.8)	(-3.4,12.8)	(-5.3,12.1)
	Pr >  t			0.4444
	n	22	9	
	LS Mean	5.048	5.304	-0.256
	SEM	3.329	4.377	4.620
Week 84	95% CI	(-1.5,11.6)	(-3.3,13.9)	(-9.3, 8.8)
	Pr >  t			0.9559
	n	18	10	
	LS Mean	6.166	6.228	-0.062
	SEM	3.495	4.240	4.606
Week 96	95% CI	(-0.7,13.0)	(-2.1,14.6)	(-9.1, 9.0)
	Pr >  t			0.9892
	n	17	6	
	LS Mean	8.091	2.462	5.629
	SEM	3.533	5.011	5.359
Week 108	95% CI	(-1.1,15.0)	(-7.4,12.3)	(-4.9,16.2)
	Pr >  t			0.2940
	n	12	7	
	LS Mean	5.475	2.272	3.204
	SEM	3.895	4.749	5.363
Week 120	95% CI	(-2.2,13.1)	(-7.1,11.6)	(-7.3,13.7)
	Pr >  t			0.5505
	n	16	4	
	LS Mean	4.963	8.677	-3.714
	SEM	3.592	5.830	6.166
Week 132	95% CI	(-2.1,12.0)	(-2.8,20.1)	(-15.8, 8.4)
	Pr >  t			0.5472
	n	11	3	
	LS Mean	2.961	-1.364	4.325
	SEM	3.997	6.544	7.060

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-4.9,10.8)	(-14.2,11.5)	(-9.5,18.2)
		Pr >  t			0.5404
	Week 144	n	8	1	
		LS Mean	8.640	-2.122	10.762
		SEM	4.404	10.65	11.14
		95% CI	(-0.0,17.3)	(-23.0,18.8)	(-11.1,32.6)
		Pr >  t			0.3343
	Week 156	n	6	1	
		LS Mean	4.031	-2.122	6.154
		SEM	4.897	10.65	11.33
		95% CI	(-5.6,13.7)	(-23.0,18.8)	(-16.1,28.4)
		Pr >  t			0.5873
	Week 168	n	2	1	
		LS Mean	12.822	-2.122	14.944
		SEM	7.692	10.65	12.79
		95% CI	(-2.3,27.9)	(-23.0,18.8)	(-10.2,40.1)
		Pr >  t			0.2432
	Week 180	n	1	1	
		LS Mean	3.468	-2.122	5.590
		SEM	10.56	10.65	14.69
		95% CI	(-17.3,24.2)	(-23.0,18.8)	(-23.3,34.5)
		Pr >  t			0.7038
	Week 192	n	1	1	
		LS Mean	3.468	-2.122	5.590
		SEM	10.56	10.65	14.69
		95% CI	(-17.3,24.2)	(-23.0,18.8)	(-23.3,34.5)
		Pr >  t			0.7038

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
95% CI	NE		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	NE	NE	NE			
	SEM	NE	NE	NE			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	NE
		Pr >  t		NE
	Week 72	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
	Week 84	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
	Week 96	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
Positive	Week 8	n	140	140
		LS Mean	8.943	5.662
		SEM	1.655	1.680
		95% CI	( 5.7,12.2)	( 2.4, 9.0)
		Pr >  t		( 0.3, 6.2)
				0.0290
	Week 16	n	122	107
		LS Mean	8.114	4.050
		SEM	1.705	1.779
		95% CI	( 4.8,11.5)	( 0.6, 7.5)
		Pr >  t		( 0.9, 7.3)
				0.0129
	Week 24	n	104	81
		LS Mean	6.876	4.560
		SEM	1.755	1.881
		95% CI	( 3.4,10.3)	( 0.9, 8.3)
		Pr >  t		( -1.2, 5.8)
				0.1942
	Week 32	n	85	73
		LS Mean	7.983	4.103
	SEM	1.837	1.928	
	95% CI	( 4.4,11.6)	( 0.3, 7.9)	
	Pr >  t		( 0.2, 7.6)	
			0.0402	
Week 40	n	74	62	
	LS Mean	6.355	4.981	
	SEM	1.886	1.999	
			1.375	
			2.003	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 2.7,10.1)	( -1.1, 8.9)	( -2.6, 5.3)
		Pr >  t			0.4927
	Week 48	n	68	51	
		LS Mean	6.296	5.260	1.036
		SEM	1.917	2.087	2.120
		95% CI	( 2.5,10.1)	( 1.2, 9.4)	( -3.1, 5.2)
		Pr >  t			0.6251
	Week 56	n	58	45	
		LS Mean	5.361	5.965	-0.604
		SEM	1.981	2.150	2.241
		95% CI	( 1.5, 9.3)	( 1.7,10.2)	( -5.0, 3.8)
		Pr >  t			0.7876
	Week 64	n	47	42	
		LS Mean	8.011	4.267	3.744
		SEM	2.077	2.187	2.363
		95% CI	( 3.9,12.1)	( -0.0, 8.6)	( -0.9, 8.4)
		Pr >  t			0.1132
	Week 72	n	47	35	
		LS Mean	6.077	3.604	2.473
		SEM	2.078	2.293	2.461
		95% CI	( 2.0,10.2)	( -0.9, 8.1)	( -2.4, 7.3)
		Pr >  t			0.3152
	Week 84	n	39	33	
		LS Mean	6.280	4.921	1.359
		SEM	2.185	2.329	2.579
		95% CI	( 2.0,10.6)	( 0.3, 9.5)	( -3.7, 6.4)
		Pr >  t			0.5982
	Week 96	n	34	24	
		LS Mean	6.989	4.091	2.897
		SEM	2.263	2.557	2.851
		95% CI	( 2.5,11.4)	( -0.9, 9.1)	( -2.7, 8.5)
		Pr >  t			0.3097
	Week 108	n	26	21	
		LS Mean	7.261	2.771	4.490
		SEM	2.454	2.668	3.096
		95% CI	( 2.4,12.1)	( -2.5, 8.0)	( -1.6,10.6)
		Pr >  t			0.1473
	Week 120	n	28	16	
		LS Mean	3.263	4.521	-1.258
		SEM	2.395	2.926	3.282

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.4, 8.0)	(-1.2, 10.3)	(-7.7, 5.2)
		Pr >  t			0.7015
	Week 132	n	20	8	
		LS Mean	3.305	2.842	0.462
		SEM	2.669	3.813	4.256
		95% CI	(-1.9, 8.5)	(-4.6, 10.3)	(-7.9, 8.8)
		Pr >  t			0.9135
	Week 144	n	15	5	
		LS Mean	5.896	2.258	3.638
		SEM	2.945	4.663	5.188
		95% CI	(0.1, 11.7)	(-6.9, 11.4)	(-6.5, 13.8)
		Pr >  t			0.4833
	Week 156	n	10	3	
		LS Mean	3.315	1.877	1.438
		SEM	3.450	5.867	6.541
		95% CI	(-3.5, 10.1)	(-9.6, 13.4)	(-11.4, 14.3)
		Pr >  t			0.8260
	Week 168	n	4	2	
		LS Mean	3.879	0.869	3.009
		SEM	5.117	7.092	8.540
		95% CI	(-6.2, 13.9)	(-13.0, 14.8)	(-13.7, 19.8)
		Pr >  t			0.7246
	Week 180	n	1	1	
		LS Mean	2.592	-2.053	4.645
		SEM	9.876	9.884	13.84
		95% CI	(-16.8, 22.0)	(-21.4, 17.3)	(-22.5, 31.8)
		Pr >  t			0.7373
	Week 192	n	1	1	
		LS Mean	2.592	-2.053	4.645
		SEM	9.876	9.884	13.84
		95% CI	(-16.8, 22.0)	(-21.4, 17.3)	(-22.5, 31.8)
		Pr >  t			0.7373

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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Final



**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	10.785	6.214	4.570
			SEM	3.039	3.317	3.183
			95% CI	( 4.7,16.8)	( -0.4,12.8)	( -1.7,10.9)
		Pr >  t			0.1537	
		Week 16	n	35	22	
			LS Mean	10.308	3.936	6.372
			SEM	3.158	3.720	3.596
			95% CI	( 4.0,16.6)	( -3.4,11.3)	( -0.7,13.5)
		Pr >  t			0.0783	
		Week 24	n	28	16	
			LS Mean	7.888	8.142	-0.254
			SEM	3.274	3.975	3.978
			95% CI	( 1.4,14.4)	( 0.3,16.0)	( -8.1, 7.6)
		Pr >  t			0.9491	
		Week 32	n	22	16	
			LS Mean	5.096	5.623	-0.527
			SEM	3.467	3.985	4.105
			95% CI	( -1.8,12.0)	( -2.3,13.5)	( -8.6, 7.6)
		Pr >  t			0.8979	
		Week 40	n	19	12	
			LS Mean	6.265	5.069	1.196
			SEM	3.573	4.247	4.446
			95% CI	( -0.8,13.3)	( -3.3,13.4)	( -7.6,10.0)
Pr >  t			0.7882			
Week 48	n	16	10			
	LS Mean	8.903	6.852	2.051		
	SEM	3.703	4.445	4.739		
	95% CI	( 1.6,16.2)	( -1.9,15.6)	( -7.3,11.4)		
Pr >  t			0.6655			
Week 56	n	14	7			
	LS Mean	8.584	10.185	-1.601		
	SEM	3.821	4.900	5.259		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 1.0,16.1)	( 0.5,19.8)	(-11.9, 8.7)
		Pr >  t			0.7610
	Week 64	n	8	7	
		LS Mean	9.031	5.671	3.360
		SEM	4.411	4.900	5.714
		95% CI	( 0.3,17.7)	( -4.0,15.3)	( -7.9,14.6)
		Pr >  t			0.5569
	Week 72	n	12	6	
		LS Mean	9.276	2.927	6.349
		SEM	3.964	5.132	5.581
		95% CI	( 1.5,17.1)	( -7.2,13.0)	( -4.6,17.3)
		Pr >  t			0.2561
	Week 84	n	8	5	
		LS Mean	9.764	9.042	0.721
		SEM	4.442	5.435	6.182
		95% CI	( 1.0,18.5)	( -1.7,19.7)	(-11.4,12.9)
		Pr >  t			0.9072
	Week 96	n	5	5	
		LS Mean	7.269	2.374	4.894
		SEM	5.162	5.435	6.718
		95% CI	( -2.9,17.4)	( -8.3,13.1)	( -8.3,18.1)
		Pr >  t			0.4668
	Week 108	n	7	5	
		LS Mean	7.434	2.374	5.060
		SEM	4.628	5.435	6.317
		95% CI	( -1.7,16.5)	( -8.3,13.1)	( -7.4,17.5)
		Pr >  t			0.4237
	Week 120	n	5	3	
		LS Mean	7.518	0.330	7.187
		SEM	5.169	6.485	7.595
		95% CI	( -2.7,17.7)	(-12.4,13.1)	( -7.8,22.1)
		Pr >  t			0.3447
	Week 132	n	2	2	
		LS Mean	7.076	-0.371	7.448
		SEM	7.356	7.532	9.989
		95% CI	( -7.4,21.5)	(-15.2,14.4)	(-12.2,27.1)
		Pr >  t			0.4565
	Week 144	n	2		
		LS Mean	7.121	NE	NE
		SEM	7.361	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Positive	Week 156	95% CI	(-7.4,21.6)	NE	NE
		Pr >  t			NE
		n	2		
		LS Mean	6.383	NE	NE
		SEM	7.371	NE	NE
	Week 168	95% CI	(-8.1,20.9)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	6.339	NE	NE
		SEM	10.00	NE	NE
	Week 8	95% CI	(-13.3,26.0)	NE	NE
		Pr >  t			NE
		n	98	104	
		LS Mean	7.909	5.290	2.619
		SEM	1.958	1.936	1.674
	Week 16	95% CI	( 4.1,11.8)	( 1.5, 9.1)	(-0.7, 5.9)
		Pr >  t			0.1183
		n	87	84	
		LS Mean	6.817	3.712	3.105
		SEM	2.009	2.011	1.801
	Week 24	95% CI	( 2.9,10.8)	(-0.2, 7.7)	(-0.4, 6.6)
		Pr >  t			0.0852
		n	76	65	
		LS Mean	5.986	3.286	2.700
SEM		2.067	2.120	1.960	
Week 32	95% CI	( 1.9,10.1)	(-0.9, 7.5)	(-1.1, 6.5)	
	Pr >  t			0.1687	
	n	62	57		
	LS Mean	8.669	3.261	5.408	
	SEM	2.154	2.188	2.099	
Week 40	95% CI	( 4.4,12.9)	(-1.0, 7.6)	( 1.3, 9.5)	
	Pr >  t			0.0102	
	n	54	50		
	LS Mean	6.027	4.597	1.431	
	SEM	2.210	2.258	2.219	
Week 48	95% CI	( 1.7,10.4)	( 0.2, 9.0)	(-2.9, 5.8)	
	Pr >  t			0.5192	
	n	52	41		
	LS Mean	5.123	4.517	0.606	
	SEM	2.226	2.356	2.335	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	( 0.7, 9.5)	( -0.1, 9.1)	( -4.0, 5.2)
	Pr >  t			0.7953
	n	44	38	
	LS Mean	4.038	4.751	-0.713
	SEM	2.303	2.398	2.452
Week 64	95% CI	( -0.5, 8.6)	( 0.0, 9.5)	( -5.5, 4.1)
	Pr >  t			0.7713
	n	39	35	
	LS Mean	7.234	3.630	3.604
	SEM	2.365	2.446	2.557
Week 72	95% CI	( 2.6,11.9)	( -1.2, 8.4)	( -1.4, 8.6)
	Pr >  t			0.1590
	n	36	29	
	LS Mean	4.684	3.372	1.312
	SEM	2.409	2.564	2.710
Week 84	95% CI	( -0.1, 9.4)	( -1.7, 8.4)	( -4.0, 6.6)
	Pr >  t			0.6284
	n	32	28	
	LS Mean	4.875	3.802	1.074
	SEM	2.486	2.588	2.794
Week 96	95% CI	( -0.0, 9.8)	( -1.3, 8.9)	( -4.4, 6.6)
	Pr >  t			0.7009
	n	30	19	
	LS Mean	6.287	4.294	1.993
	SEM	2.519	2.893	3.112
Week 108	95% CI	( 1.3,11.2)	( -1.4,10.0)	( -4.1, 8.1)
	Pr >  t			0.5221
	n	18	16	
	LS Mean	5.393	2.748	2.644
	SEM	2.926	3.057	3.582
Week 120	95% CI	( -0.3,11.1)	( -3.3, 8.7)	( -4.4, 9.7)
	Pr >  t			0.4605
	n	23	13	
	LS Mean	1.788	5.264	-3.475
	SEM	2.709	3.280	3.617
Week 132	95% CI	( -3.5, 7.1)	( -1.2,11.7)	(-10.6, 3.6)
	Pr >  t			0.3368
	n	18	6	
	LS Mean	2.169	3.577	-1.408
	SEM	2.926	4.415	4.794

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-3.6, 7.9)	(-5.1,12.2)	(-10.8, 8.0)
	Pr >  t			0.7689
Week 144	n	13	5	
	LS Mean	5.012	1.843	3.169
	SEM	3.246	4.769	5.321
	95% CI	(-1.4,11.4)	(-7.5,11.2)	(-7.3,13.6)
	Pr >  t			0.5516
Week 156	n	8	3	
	LS Mean	2.049	1.491	0.558
	SEM	3.909	5.968	6.770
	95% CI	(-5.6, 9.7)	(-10.2,13.2)	(-12.7,13.8)
	Pr >  t			0.9343
Week 168	n	3	2	
	LS Mean	2.764	0.504	2.260
	SEM	5.947	7.192	9.057
	95% CI	(-8.9,14.4)	(-13.6,14.6)	(-15.5,20.0)
	Pr >  t			0.8030
Week 180	n	1	1	
	LS Mean	1.707	-2.335	4.041
	SEM	9.991	9.992	13.95
	95% CI	(-17.9,21.3)	(-21.9,17.3)	(-23.3,31.4)
	Pr >  t			0.7721
Week 192	n	1	1	
	LS Mean	1.707	-2.335	4.041
	SEM	9.991	9.992	13.95
	95% CI	(-17.9,21.3)	(-21.9,17.3)	(-23.3,31.4)
	Pr >  t			0.7721

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	7.986	5.262	2.724		
			SEM	1.972	1.944	1.690		
			95% CI	( 4.1,11.9)	( 1.4, 9.1)	( -0.6, 6.0)		
					Pr >  t			0.1076
		Week 16	n	85	84			
			LS Mean	6.877	3.681	3.196		
			SEM	2.024	2.020	1.819		
			95% CI	( 2.9,10.9)	( -0.3, 7.7)	( -0.4, 6.8)		
					Pr >  t			0.0795
		Week 24	n	75	65			
			LS Mean	6.018	3.257	2.761		
			SEM	2.081	2.129	1.975		
			95% CI	( 1.9,10.1)	( -0.9, 7.4)	( -1.1, 6.6)		
					Pr >  t			0.1627
		Week 32	n	61	57			
			LS Mean	8.748	3.232	5.516		
			SEM	2.171	2.197	2.117		
			95% CI	( 4.5,13.0)	( -1.1, 7.6)	( 1.4, 9.7)		
					Pr >  t			0.0094
		Week 40	n	53	50			
			LS Mean	6.072	4.566	1.506		
			SEM	2.230	2.268	2.240		
			95% CI	( 1.7,10.5)	( 0.1, 9.0)	( -2.9, 5.9)		
			Pr >  t			0.5016		
Week 48	n	51	41					
	LS Mean	5.150	4.487	0.663				
	SEM	2.246	2.367	2.356				
	95% CI	( 0.7, 9.6)	( -0.2, 9.1)	( -4.0, 5.3)				
			Pr >  t			0.7785		
Week 56	n	43	38					
	LS Mean	4.038	4.720	-0.682				
	SEM	2.326	2.409	2.476				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-0.5, 8.6)	(-0.0, 9.5)	(-5.5, 4.2)
	Pr >  t			0.7831
	n	39	35	
	LS Mean	7.260	3.601	3.659
	SEM	2.377	2.457	2.571
Week 72	95% CI	( 2.6,11.9)	(-1.2, 8.4)	(-1.4, 8.7)
	Pr >  t			0.1550
	n	35	29	
	LS Mean	4.679	3.342	1.337
	SEM	2.438	2.575	2.739
Week 84	95% CI	(-0.1, 9.5)	(-1.7, 8.4)	(-4.0, 6.7)
	Pr >  t			0.6255
	n	31	28	
	LS Mean	4.874	3.773	1.102
	SEM	2.519	2.599	2.827
Week 96	95% CI	(-0.1, 9.8)	(-1.3, 8.9)	(-4.4, 6.6)
	Pr >  t			0.6968
	n	29	19	
	LS Mean	6.334	4.265	2.069
	SEM	2.554	2.906	3.147
Week 108	95% CI	( 1.3,11.4)	(-1.4,10.0)	(-4.1, 8.2)
	Pr >  t			0.5111
	n	18	16	
	LS Mean	5.420	2.720	2.699
	SEM	2.940	3.071	3.601
Week 120	95% CI	(-0.4,11.2)	(-3.3, 8.7)	(-4.4, 9.8)
	Pr >  t			0.4536
	n	23	13	
	LS Mean	1.814	5.237	-3.423
	SEM	2.723	3.295	3.635
Week 132	95% CI	(-3.5, 7.2)	(-1.2,11.7)	(-10.6, 3.7)
	Pr >  t			0.3466
	n	18	6	
	LS Mean	2.196	3.550	-1.355
	SEM	2.941	4.435	4.817
Week 144	95% CI	(-3.6, 8.0)	(-5.2,12.3)	(-10.8, 8.1)
	Pr >  t			0.7786
	n	13	5	
	LS Mean	5.040	1.815	3.224
	SEM	3.263	4.791	5.347

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive Negative	Week 156	95% CI	(-1.4,11.4)	(-7.6,11.2)	(-7.3,13.7)
		Pr >  t			0.5466
		n	8	3	
	Week 168	LS Mean	2.077	1.462	0.614
		SEM	3.928	5.996	6.803
		95% CI	(-5.6, 9.8)	(-10.3,13.2)	(-12.7,14.0)
		Pr >  t			0.9281
		n	3	2	
	Week 180	LS Mean	2.795	0.475	2.321
		SEM	5.975	7.226	9.100
		95% CI	(-8.9,14.5)	(-13.7,14.7)	(-15.5,20.2)
		Pr >  t			0.7988
		n	1	1	
	Week 192	LS Mean	1.739	-2.359	4.098
		SEM	10.04	10.04	14.01
		95% CI	(-18.0,21.4)	(-22.1,17.3)	(-23.4,31.6)
		Pr >  t			0.7700
		n	1	1	
	Week 8	LS Mean	1.739	-2.359	4.098
		SEM	10.04	10.04	14.01
		95% CI	(-18.0,21.4)	(-22.1,17.3)	(-23.4,31.6)
		Pr >  t			0.7700
		n	42	35	
	Week 16	LS Mean	10.785	6.214	4.570
SEM		3.039	3.317	3.183	
95% CI		( 4.7,16.8)	(-0.4,12.8)	(-1.7,10.9)	
Pr >  t				0.1537	
n		35	22		
Week 24	LS Mean	10.308	3.936	6.372	
	SEM	3.158	3.720	3.596	
	95% CI	( 4.0,16.6)	(-3.4,11.3)	(-0.7,13.5)	
	Pr >  t			0.0783	
	n	28	16		
Week 32	LS Mean	7.888	8.142	-0.254	
	SEM	3.274	3.975	3.978	
	95% CI	( 1.4,14.4)	( 0.3,16.0)	(-8.1, 7.6)	
	Pr >  t			0.9491	
	n	22	16		
Week 32	LS Mean	5.096	5.623	-0.527	
	SEM	3.467	3.985	4.105	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-1.8,12.0)	(-2.3,13.5)	(-8.6, 7.6)
	Pr >  t			0.8979
	n	19	12	
	LS Mean	6.265	5.069	1.196
	SEM	3.573	4.247	4.446
Week 48	95% CI	(-0.8,13.3)	(-3.3,13.4)	(-7.6,10.0)
	Pr >  t			0.7882
	n	16	10	
	LS Mean	8.903	6.852	2.051
	SEM	3.703	4.445	4.739
Week 56	95% CI	( 1.6,16.2)	(-1.9,15.6)	(-7.3,11.4)
	Pr >  t			0.6655
	n	14	7	
	LS Mean	8.584	10.185	-1.601
	SEM	3.821	4.900	5.259
Week 64	95% CI	( 1.0,16.1)	( 0.5,19.8)	(-11.9, 8.7)
	Pr >  t			0.7610
	n	8	7	
	LS Mean	9.031	5.671	3.360
	SEM	4.411	4.900	5.714
Week 72	95% CI	( 0.3,17.7)	(-4.0,15.3)	(-7.9,14.6)
	Pr >  t			0.5569
	n	12	6	
	LS Mean	9.276	2.927	6.349
	SEM	3.964	5.132	5.581
Week 84	95% CI	( 1.5,17.1)	(-7.2,13.0)	(-4.6,17.3)
	Pr >  t			0.2561
	n	8	5	
	LS Mean	9.764	9.042	0.721
	SEM	4.442	5.435	6.182
Week 96	95% CI	( 1.0,18.5)	(-1.7,19.7)	(-11.4,12.9)
	Pr >  t			0.9072
	n	5	5	
	LS Mean	7.269	2.374	4.894
	SEM	5.162	5.435	6.718
Week 108	95% CI	(-2.9,17.4)	(-8.3,13.1)	(-8.3,18.1)
	Pr >  t			0.4668
	n	7	5	
	LS Mean	7.434	2.374	5.060
	SEM	4.628	5.435	6.317

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-1.7,16.5)	(-8.3,13.1)	(-7.4,17.5)
	Pr >  t			0.4237
	n	5	3	
	LS Mean	7.518	0.330	7.187
	SEM	5.169	6.485	7.595
Week 132	95% CI	(-2.7,17.7)	(-12.4,13.1)	(-7.8,22.1)
	Pr >  t			0.3447
	n	2	2	
	LS Mean	7.076	-0.371	7.448
	SEM	7.356	7.532	9.989
Week 144	95% CI	(-7.4,21.5)	(-15.2,14.4)	(-12.2,27.1)
	Pr >  t			0.4565
	n	2		
	LS Mean	7.121	NE	NE
	SEM	7.361	NE	NE
Week 156	95% CI	(-7.4,21.6)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	6.383	NE	NE
	SEM	7.371	NE	NE
Week 168	95% CI	(-8.1,20.9)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	6.339	NE	NE
	SEM	10.00	NE	NE
	95% CI	(-13.3,26.0)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	5.619	0.103	5.516		
			SEM	3.909	4.047	2.036		
			95% CI	(-2.2,13.4)	(-8.0, 8.2)	( 1.5, 9.5)		
					Pr >  t			0.0071
		Week 16	n	59	49			
			LS Mean	3.956	-1.612	5.568		
			SEM	3.935	4.102	2.208		
			95% CI	(-3.9,11.8)	(-9.8, 6.6)	( 1.2, 9.9)		
					Pr >  t			0.0121
		Week 24	n	54	41			
			LS Mean	0.572	-1.306	1.878		
			SEM	3.951	4.153	2.341		
			95% CI	(-7.3, 8.4)	(-9.6, 7.0)	(-2.7, 6.5)		
					Pr >  t			0.4228
		Week 32	n	48	37			
			LS Mean	4.139	-1.065	5.204		
			SEM	3.975	4.185	2.447		
			95% CI	(-3.8,12.1)	(-9.4, 7.3)	( 0.4,10.0)		
					Pr >  t			0.0339
		Week 40	n	43	33			
			LS Mean	0.798	0.913	-0.114		
			SEM	4.000	4.224	2.561		
			95% CI	(-7.2, 8.8)	(-7.5, 9.3)	(-5.1, 4.9)		
			Pr >  t			0.9644		
Week 48	n	41	28					
	LS Mean	1.910	-1.979	3.889				
	SEM	4.012	4.285	2.681				
	95% CI	(-6.1, 9.9)	(-10.5, 6.5)	(-1.4, 9.2)				
			Pr >  t			0.1475		
Week 56	n	35	22					
	LS Mean	2.085	1.262	0.822				
	SEM	4.056	4.394	2.922				



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.0,10.2)	(-7.5,10.0)	(-4.9, 6.6)
		Pr >  t			0.7785
	Week 64	n	26	23	
		LS Mean	4.238	-1.653	5.891
		SEM	4.157	4.373	3.047
		95% CI	(-4.0,12.5)	(-10.3, 7.0)	(-0.1,11.9)
		Pr >  t			0.0536
	Week 72	n	28	18	
		LS Mean	2.848	-1.353	4.201
		SEM	4.130	4.501	3.188
		95% CI	(-5.4,11.1)	(-10.3, 7.6)	(-2.1,10.5)
		Pr >  t			0.1880
	Week 84	n	22	18	
		LS Mean	1.503	0.158	1.345
		SEM	4.265	4.501	3.326
		95% CI	(-7.0,10.0)	(-8.8, 9.1)	(-5.2, 7.9)
		Pr >  t			0.6861
	Week 96	n	21	13	
		LS Mean	2.896	-1.370	4.266
		SEM	4.249	4.716	3.642
		95% CI	(-5.5,11.3)	(-10.7, 8.0)	(-2.9,11.4)
		Pr >  t			0.2418
	Week 108	n	17	12	
		LS Mean	3.056	-1.356	4.413
		SEM	4.408	4.778	3.857
		95% CI	(-5.7,11.8)	(-10.8, 8.1)	(-3.2,12.0)
		Pr >  t			0.2529
	Week 120	n	18	11	
		LS Mean	-1.243	0.128	-1.371
		SEM	4.327	4.851	3.910
		95% CI	(-9.8, 7.3)	(-9.5, 9.7)	(-9.0, 6.3)
		Pr >  t			0.7260
	Week 132	n	13	5	
		LS Mean	-1.616	-1.072	-0.544
		SEM	4.588	5.785	5.212
		95% CI	(-10.7, 7.5)	(-12.5,10.3)	(-10.8, 9.7)
		Pr >  t			0.9169
	Week 144	n	12	3	
		LS Mean	0.967	-4.061	5.028
		SEM	4.589	6.759	6.324

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.1,10.0)	(-17.3, 9.2)	(-7.4,17.4)
		Pr >  t			0.4268
	Week 156	n	7	2	
		LS Mean	-1.043	-4.331	3.288
		SEM	5.201	7.794	7.774
		95% CI	(-11.3, 9.2)	(-19.6,11.0)	(-12.0,18.5)
		Pr >  t			0.6725
	Week 168	n	3	1	
		LS Mean	-0.676	-7.313	6.637
		SEM	6.652	10.30	11.09
		95% CI	(-13.7,12.4)	(-27.5,12.9)	(-15.1,28.4)
		Pr >  t			0.5497
	Week 180	n	1	1	
		LS Mean	-1.785	-7.313	5.528
		SEM	10.23	10.30	13.54
		95% CI	(-21.9,18.3)	(-27.5,12.9)	(-21.1,32.1)
		Pr >  t			0.6833
	Week 192	n	1	1	
		LS Mean	-1.785	-7.313	5.528
		SEM	10.23	10.30	13.54
		95% CI	(-21.9,18.3)	(-27.5,12.9)	(-21.1,32.1)
		Pr >  t			0.6833
Yes	Week 8	n	73	80	
		LS Mean	9.315	8.181	1.134
		SEM	2.864	2.889	2.200
		95% CI	( 3.7,15.0)	( 2.5,13.9)	(-3.2, 5.5)
		Pr >  t			0.6068
	Week 16	n	65	58	
		LS Mean	9.355	6.834	2.522
		SEM	2.950	3.033	2.391
		95% CI	( 3.5,15.2)	( 0.8,12.8)	(-2.2, 7.2)
		Pr >  t			0.2925
	Week 24	n	51	40	
		LS Mean	10.289	7.697	2.592
		SEM	3.023	3.216	2.689
		95% CI	( 4.3,16.3)	( 1.4,14.0)	(-2.7, 7.9)
		Pr >  t			0.3357
	Week 32	n	38	36	
		LS Mean	8.677	6.491	2.186
		SEM	3.192	3.273	2.893

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 2.4,15.0)	( 0.0,12.9)	(-3.5, 7.9)
		Pr >  t			0.4503
	Week 40	n	32	29	
		LS Mean	9.411	6.142	3.268
		SEM	3.287	3.388	3.116
		95% CI	( 2.9,15.9)	(-0.5,12.8)	(-2.9, 9.4)
		Pr >  t			0.2947
	Week 48	n	28	23	
		LS Mean	7.819	10.184	-2.365
		SEM	3.359	3.535	3.344
		95% CI	( 1.2,14.4)	( 3.2,17.1)	(-8.9, 4.2)
		Pr >  t			0.4796
	Week 56	n	24	23	
		LS Mean	5.389	8.000	-2.611
		SEM	3.458	3.535	3.438
		95% CI	(-1.4,12.2)	( 1.0,15.0)	(-9.4, 4.1)
		Pr >  t			0.4480
	Week 64	n	21	19	
		LS Mean	8.842	7.607	1.235
		SEM	3.551	3.670	3.666
		95% CI	( 1.9,15.8)	( 0.4,14.8)	(-6.0, 8.4)
		Pr >  t			0.7362
	Week 72	n	20	17	
		LS Mean	6.113	5.876	0.237
		SEM	3.590	3.758	3.790
		95% CI	(-0.9,13.2)	(-1.5,13.3)	(-7.2, 7.7)
		Pr >  t			0.9501
	Week 84	n	18	15	
		LS Mean	8.351	6.877	1.474
		SEM	3.660	3.867	3.966
		95% CI	( 1.2,15.5)	(-0.7,14.5)	(-6.3, 9.3)
		Pr >  t			0.7102
	Week 96	n	14	11	
		LS Mean	8.197	6.892	1.305
		SEM	3.883	4.182	4.461
		95% CI	( 0.6,15.8)	(-1.3,15.1)	(-7.5,10.1)
		Pr >  t			0.7699
	Week 108	n	9	9	
		LS Mean	8.655	3.785	4.870
		SEM	4.375	4.421	5.104

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.1,17.2)	( -4.9,12.5)	( -5.1,14.9)
		Pr >  t			0.3403
	Week 120	n	10	5	
		LS Mean	5.255	5.089	0.167
		SEM	4.258	5.353	5.845
		95% CI	( -3.1,13.6)	( -5.4,15.6)	(-11.3,11.6)
		Pr >  t			0.9773
	Week 132	n	7	3	
		LS Mean	5.869	3.091	2.777
		SEM	4.729	6.484	7.201
		95% CI	( -3.4,15.2)	( -9.6,15.8)	(-11.4,16.9)
		Pr >  t			0.6999
	Week 144	n	3	2	
		LS Mean	9.992	6.388	3.604
		SEM	6.447	7.676	9.381
		95% CI	( -2.7,22.6)	( -8.7,21.5)	(-14.8,22.0)
		Pr >  t			0.7009
	Week 156	n	3	1	
		LS Mean	4.950	6.569	-1.620
		SEM	6.455	10.47	11.77
		95% CI	( -7.7,17.6)	(-14.0,27.1)	(-24.7,21.5)
		Pr >  t			0.8906
	Week 168	n	1	1	
		LS Mean	6.296	6.569	-0.273
		SEM	10.47	10.47	14.37
		95% CI	(-14.3,26.9)	(-14.0,27.1)	(-28.5,28.0)
		Pr >  t			0.9849

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-2.605	-3.043	0.438
			SEM	6.543	7.208	6.058
			95% CI	(-15.9,10.7)	(-17.7,11.6)	(-11.8,12.6)
		Pr >  t			0.9426	
		Week 16	n	14	17	
			LS Mean	1.436	-7.164	8.601
			SEM	6.608	7.403	6.426
			95% CI	(-12.0,14.8)	(-22.2, 7.9)	(-4.3,21.5)
		Pr >  t			0.1863	
		Week 24	n	14	11	
			LS Mean	-2.135	-6.631	4.496
			SEM	6.608	7.724	6.786
			95% CI	(-15.5,11.3)	(-22.2, 9.0)	(-9.1,18.0)
		Pr >  t			0.5099	
		Week 32	n	10	10	
			LS Mean	-9.359	-7.082	-2.277
			SEM	7.073	7.818	7.126
			95% CI	(-23.6, 4.9)	(-22.9, 8.7)	(-16.5,11.9)
		Pr >  t			0.7501	
		Week 40	n	8	10	
			LS Mean	-6.391	-7.112	0.721
			SEM	7.288	7.817	7.333
			95% CI	(-21.0, 8.2)	(-22.9, 8.7)	(-13.9,15.3)
		Pr >  t			0.9219	
		Week 48	n	7	11	
			LS Mean	-6.717	-0.927	-5.790
			SEM	7.428	7.747	7.417
			95% CI	(-21.6, 8.2)	(-16.6,14.7)	(-20.5, 8.9)
		Pr >  t			0.4370	
		Week 56	n	6	9	
			LS Mean	-6.913	-5.380	-1.534
			SEM	7.609	7.908	7.770

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.1, 8.3)	(-21.3,10.6)	(-16.9,13.9)
		Pr >  t			0.8439
	Week 64	n	5	8	
		LS Mean	-4.152	-7.368	3.215
		SEM	7.855	8.014	8.113
		95% CI	(-19.8,11.5)	(-23.5, 8.8)	(-12.8,19.3)
		Pr >  t			0.6926
	Week 72	n	7	7	
		LS Mean	-6.652	-9.679	3.027
		SEM	7.421	8.150	7.837
		95% CI	(-21.5, 8.2)	(-26.0, 6.7)	(-12.5,18.6)
		Pr >  t			0.7001
	Week 84	n	7	7	
		LS Mean	-6.652	-2.536	-4.116
		SEM	7.421	8.150	7.837
		95% CI	(-21.5, 8.2)	(-18.9,13.8)	(-19.7,11.4)
		Pr >  t			0.6005
	Week 96	n	5	6	
		LS Mean	-7.523	-7.557	0.034
		SEM	7.853	8.322	8.416
		95% CI	(-23.2, 8.1)	(-24.2, 9.1)	(-16.6,16.7)
		Pr >  t			0.9968
	Week 108	n	4	6	
		LS Mean	-1.587	-7.557	5.970
		SEM	8.214	8.322	8.755
		95% CI	(-17.9,14.7)	(-24.2, 9.1)	(-11.3,23.3)
		Pr >  t			0.4964
	Week 120	n	4	4	
		LS Mean	-3.623	-8.253	4.630
		SEM	8.217	8.891	9.301
		95% CI	(-20.0,12.7)	(-26.0, 9.5)	(-13.7,23.0)
		Pr >  t			0.6193
	Week 132	n	3	1	
		LS Mean	-9.035	2.743	-11.78
		SEM	8.772	12.78	13.43
		95% CI	(-26.4, 8.4)	(-22.5,28.0)	(-38.2,14.7)
		Pr >  t			0.3813
	Week 144	n	1	1	
		LS Mean	-5.325	-9.286	3.960
		SEM	12.34	12.83	16.02

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-29.7,19.0)	(-34.6,16.0)	(-27.6,35.5)
		Pr >  t			0.8050
		n	35	37	
	Week 16	LS Mean	5.193	1.501	3.692
		SEM	5.147	5.383	2.377
		95% CI	(-4.9,15.3)	(-9.1,12.1)	(-1.0, 8.4)
	Week 24	Pr >  t			0.1214
		n	34	30	
		LS Mean	4.505	2.019	2.486
	Week 32	SEM	5.379	5.431	2.506
		95% CI	(-6.1,15.1)	(-8.7,12.7)	(-2.4, 7.4)
		Pr >  t			0.3220
	Week 40	n	32	23	
		LS Mean	4.181	3.929	0.252
		SEM	5.398	5.521	2.722
	Week 48	95% CI	(-6.4,14.8)	(-6.9,14.8)	(-5.1, 5.6)
		Pr >  t			0.9264
		n	21	22	
	Week 56	LS Mean	1.841	2.651	-0.810
		SEM	5.518	5.529	3.019
		95% CI	(-9.0,12.7)	(-8.2,13.5)	(-6.7, 5.1)
	Week 64	Pr >  t			0.7885
		n	20	20	
		LS Mean	1.444	4.542	-3.098
	Week 8	SEM	5.533	5.566	3.118
		95% CI	(-9.4,12.3)	(-6.4,15.5)	(-9.2, 3.0)
		Pr >  t			0.3210
	Week 16	n	19	12	
		LS Mean	3.601	2.990	0.611
		SEM	5.554	5.822	3.591
	Week 24	95% CI	(-7.3,14.5)	(-8.5,14.4)	(-6.4, 7.7)
		Pr >  t			0.8649
		n	16	8	
	Week 32	LS Mean	4.030	4.422	-0.391
		SEM	5.633	6.131	4.176
		95% CI	(-7.1,15.1)	(-7.6,16.5)	(-8.6, 7.8)
	Week 40	Pr >  t			0.9254
		n	12	11	
		LS Mean	10.131	2.158	7.972
	Week 48	SEM	5.789	5.884	4.032

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.3,21.5)	(-9.4,13.7)	(0.0,15.9)
		Pr >  t			0.0487
	Week 72	n	13	7	
		LS Mean	4.200	0.049	4.151
		SEM	5.748	6.256	4.502
		95% CI	(-7.1,15.5)	(-12.3,12.4)	(-4.7,13.0)
		Pr >  t			0.3571
	Week 84	n	12	6	
		LS Mean	10.328	2.660	7.668
		SEM	5.794	6.422	4.786
		95% CI	(-1.1,21.7)	(-10.0,15.3)	(-1.7,17.1)
		Pr >  t			0.1099
	Week 96	n	7	6	
		LS Mean	1.902	2.522	-0.620
		SEM	6.226	6.420	5.295
		95% CI	(-10.3,14.1)	(-10.1,15.1)	(-11.0, 9.8)
		Pr >  t			0.9068
	Week 108	n	5	3	
		LS Mean	4.089	-1.448	5.537
		SEM	6.601	7.450	6.869
		95% CI	(-8.9,17.1)	(-16.1,13.2)	(-8.0,19.0)
		Pr >  t			0.4207
	Week 120	n	8	3	
		LS Mean	-2.761	-1.448	-1.313
		SEM	6.107	7.450	6.389
		95% CI	(-14.8, 9.2)	(-16.1,13.2)	(-13.9,11.2)
		Pr >  t			0.8373
	Week 132	n	2	1	
		LS Mean	1.650	-7.107	8.757
		SEM	8.298	10.59	11.36
		95% CI	(-14.7,18.0)	(-27.9,13.7)	(-13.6,31.1)
		Pr >  t			0.4413
	Week 144	n	2		
		LS Mean	1.460	NE	NE
		SEM	8.310	NE	NE
		95% CI	(-14.9,17.8)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	1.460	NE	NE
		SEM	8.310	NE	NE



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
H1047X	Week 8	95% CI	(-14.9,17.8)	NE	NE	
		Pr >  t			NE	
	Week 16	n	81	64		
		LS Mean	10.886	6.480	4.405	
	Week 24	SEM	1.875	1.975	1.934	
		95% CI	( 7.2,14.6)	( 2.6,10.4)	( 0.6, 8.2)	
	Week 32	Pr >  t			0.0233	
		n	70	52		
	Week 40	LS Mean	9.027	5.007	4.020	
		SEM	1.942	2.113	2.097	
	Week 48	95% CI	( 5.2,12.9)	( 0.8, 9.2)	( -0.1, 8.1)	
		Pr >  t			0.0559	
	Week 56	n	54	40		
		LS Mean	7.989	4.344	3.645	
	Week 64	SEM	2.060	2.278	2.345	
		95% CI	( 3.9,12.0)	( -0.1, 8.8)	( -1.0, 8.3)	
	Week 8	Pr >  t			0.1207	
		n	50	36		
	Week 16	LS Mean	11.572	4.522	7.050	
		SEM	2.110	2.340	2.438	
	Week 24	95% CI	( 7.4,15.7)	( -0.1, 9.1)	( 2.3,11.8)	
		Pr >  t			0.0040	
	Week 32	n	42	28		
		LS Mean	8.383	4.823	3.560	
	Week 40	SEM	2.197	2.517	2.671	
		95% CI	( 4.1,12.7)	( -0.1, 9.8)	( -1.7, 8.8)	
	Week 48	Pr >  t			0.1831	
		n	38	24		
Week 56	LS Mean	7.340	3.781	3.559		
	SEM	2.250	2.631	2.822		
Week 64	95% CI	( 2.9,11.8)	( -1.4, 9.0)	( -2.0, 9.1)		
	Pr >  t			0.2076		
Week 8	n	33	24			
	LS Mean	6.549	5.853	0.696		
Week 16	SEM	2.332	2.632	2.893		
	95% CI	( 2.0,11.1)	( 0.7,11.0)	( -5.0, 6.4)		
Week 24	Pr >  t			0.8100		
	n	27	19			
Week 32	LS Mean	8.019	4.764	3.255		
	SEM	2.461	2.827	3.174		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 3.2,12.9)	( -0.8,10.3)	( -3.0, 9.5)
		Pr >  t			0.3054
	Week 72	n	26	17	
		LS Mean	5.761	5.178	0.584
		SEM	2.489	2.928	3.286
		95% CI	( 0.9,10.7)	( -0.6,10.9)	( -5.9, 7.0)
		Pr >  t			0.8590
	Week 84	n	18	16	
		LS Mean	3.526	4.896	-1.370
		SEM	2.809	2.989	3.571
		95% CI	( -2.0, 9.0)	( -1.0,10.8)	( -8.4, 5.6)
		Pr >  t			0.7012
	Week 96	n	20	10	
		LS Mean	7.159	3.927	3.232
		SEM	2.707	3.528	3.970
		95% CI	( 1.8,12.5)	( -3.0,10.9)	( -4.6,11.0)
		Pr >  t			0.4158
	Week 108	n	14	10	
		LS Mean	8.021	3.724	4.297
		SEM	3.065	3.528	4.215
		95% CI	( 2.0,14.0)	( -3.2,10.6)	( -4.0,12.6)
		Pr >  t			0.3083
	Week 120	n	14	7	
		LS Mean	5.452	8.456	-3.004
		SEM	3.050	4.055	4.664
		95% CI	( -0.5,11.4)	( 0.5,16.4)	( -12.2, 6.2)
		Pr >  t			0.5197
	Week 132	n	12	5	
		LS Mean	5.025	3.322	1.703
		SEM	3.238	4.663	5.306
		95% CI	( -1.3,11.4)	( -5.8,12.5)	( -8.7,12.1)
		Pr >  t			0.7484
	Week 144	n	11	4	
		LS Mean	7.471	2.978	4.493
		SEM	3.329	5.135	5.787
		95% CI	( 0.9,14.0)	( -7.1,13.1)	( -6.9,15.9)
		Pr >  t			0.4378
	Week 156	n	8	3	
		LS Mean	4.179	2.426	1.753
		SEM	3.785	5.834	6.655

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168	95% CI	(-3.2,11.6)	(-9.0,13.9)	(-11.3,14.8)
	Pr >  t			0.7923
	n	4	2	
	LS Mean	5.099	1.403	3.696
	SEM	5.082	7.027	8.434
Week 180	95% CI	(-4.9,15.1)	(-12.4,15.2)	(-12.9,20.3)
	Pr >  t			0.6614
	n	1	1	
	LS Mean	3.871	-1.360	5.230
	SEM	9.736	9.757	13.63
Week 192	95% CI	(-15.2,23.0)	(-20.5,17.8)	(-21.5,32.0)
	Pr >  t			0.7014
	n	1	1	
	LS Mean	3.871	-1.360	5.230
	SEM	9.736	9.757	13.63
	95% CI	(-15.2,23.0)	(-20.5,17.8)	(-21.5,32.0)
	Pr >  t			0.7014

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-22i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Nausea and vomiting score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64	
			LS Mean	10.886	6.480	4.405
			SEM	1.875	1.975	1.934
			95% CI	( 7.2,14.6)	( 2.6,10.4)	( 0.6, 8.2)
			Pr >  t			0.0233
		Week 16	n	70	52	
			LS Mean	9.027	5.007	4.020
			SEM	1.942	2.113	2.097
			95% CI	( 5.2,12.9)	( 0.8, 9.2)	( -0.1, 8.1)
			Pr >  t			0.0559
		Week 24	n	54	40	
			LS Mean	7.989	4.344	3.645
			SEM	2.060	2.278	2.345
			95% CI	( 3.9,12.0)	( -0.1, 8.8)	( -1.0, 8.3)
			Pr >  t			0.1207
		Week 32	n	50	36	
			LS Mean	11.572	4.522	7.050
			SEM	2.110	2.340	2.438
			95% CI	( 7.4,15.7)	( -0.1, 9.1)	( 2.3,11.8)
			Pr >  t			0.0040
Week 40	n	42	28			
	LS Mean	8.383	4.823	3.560		
	SEM	2.197	2.517	2.671		
	95% CI	( 4.1,12.7)	( -0.1, 9.8)	( -1.7, 8.8)		
	Pr >  t			0.1831		
Week 48	n	38	24			
	LS Mean	7.340	3.781	3.559		
	SEM	2.250	2.631	2.822		
	95% CI	( 2.9,11.8)	( -1.4, 9.0)	( -2.0, 9.1)		
	Pr >  t			0.2076		
Week 56	n	33	24			
	LS Mean	6.549	5.853	0.696		
	SEM	2.332	2.632	2.893		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 2.0,11.1)	( 0.7,11.0)	( -5.0, 6.4)
	Pr >  t			0.8100
	n	27	19	
	LS Mean	8.019	4.764	3.255
	SEM	2.461	2.827	3.174
Week 72	95% CI	( 3.2,12.9)	( -0.8,10.3)	( -3.0, 9.5)
	Pr >  t			0.3054
	n	26	17	
	LS Mean	5.761	5.178	0.584
	SEM	2.489	2.928	3.286
Week 84	95% CI	( 0.9,10.7)	( -0.6,10.9)	( -5.9, 7.0)
	Pr >  t			0.8590
	n	18	16	
	LS Mean	3.526	4.896	-1.370
	SEM	2.809	2.989	3.571
Week 96	95% CI	( -2.0, 9.0)	( -1.0,10.8)	( -8.4, 5.6)
	Pr >  t			0.7012
	n	20	10	
	LS Mean	7.159	3.927	3.232
	SEM	2.707	3.528	3.970
Week 108	95% CI	( 1.8,12.5)	( -3.0,10.9)	( -4.6,11.0)
	Pr >  t			0.4158
	n	14	10	
	LS Mean	8.021	3.724	4.297
	SEM	3.065	3.528	4.215
Week 120	95% CI	( 2.0,14.0)	( -3.2,10.6)	( -4.0,12.6)
	Pr >  t			0.3083
	n	14	7	
	LS Mean	5.452	8.456	-3.004
	SEM	3.050	4.055	4.664
Week 132	95% CI	( -0.5,11.4)	( 0.5,16.4)	( -12.2, 6.2)
	Pr >  t			0.5197
	n	12	5	
	LS Mean	5.025	3.322	1.703
	SEM	3.238	4.663	5.306
Week 144	95% CI	( -1.3,11.4)	( -5.8,12.5)	( -8.7,12.1)
	Pr >  t			0.7484
	n	11	4	
	LS Mean	7.471	2.978	4.493
	SEM	3.329	5.135	5.787

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.9,14.0)	( -7.1,13.1)	( -6.9,15.9)
		Pr >  t			0.4378
	Week 156	n	8	3	
		LS Mean	4.179	2.426	1.753
		SEM	3.785	5.834	6.655
		95% CI	( -3.2,11.6)	( -9.0,13.9)	(-11.3,14.8)
		Pr >  t			0.7923
	Week 168	n	4	2	
		LS Mean	5.099	1.403	3.696
		SEM	5.082	7.027	8.434
		95% CI	( -4.9,15.1)	(-12.4,15.2)	(-12.9,20.3)
		Pr >  t			0.6614
	Week 180	n	1	1	
		LS Mean	3.871	-1.360	5.230
		SEM	9.736	9.757	13.63
		95% CI	(-15.2,23.0)	(-20.5,17.8)	(-21.5,32.0)
		Pr >  t			0.7014
	Week 192	n	1	1	
		LS Mean	3.871	-1.360	5.230
		SEM	9.736	9.757	13.63
		95% CI	(-15.2,23.0)	(-20.5,17.8)	(-21.5,32.0)
		Pr >  t			0.7014
Exon 9	Week 8	n	53	64	
		LS Mean	1.284	-1.636	2.920
		SEM	3.312	3.552	2.349
		95% CI	( -5.3, 7.8)	( -8.7, 5.4)	( -1.7, 7.5)
		Pr >  t			0.2150
	Week 16	n	48	48	
		LS Mean	1.739	-3.295	5.034
		SEM	3.398	3.635	2.528
		95% CI	( -5.0, 8.5)	(-10.5, 3.9)	( 0.1,10.0)
		Pr >  t			0.0474
	Week 24	n	46	36	
		LS Mean	0.389	-1.992	2.381
		SEM	3.411	3.746	2.706
		95% CI	( -6.4, 7.1)	( -9.4, 5.4)	( -2.9, 7.7)
		Pr >  t			0.3796
	Week 32	n	31	33	
		LS Mean	-3.567	-2.584	-0.984
		SEM	3.646	3.786	2.959

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.8, 3.6)	(-10.1, 4.9)	(-6.8, 4.8)
		Pr >  t			0.7398
	Week 40	n	28	30	
		LS Mean	-3.039	-1.666	-1.373
		SEM	3.697	3.829	3.073
		95% CI	(-10.3, 4.3)	(-9.2, 5.9)	(-7.4, 4.7)
		Pr >  t			0.6552
	Week 48	n	26	23	
		LS Mean	-1.520	0.016	-1.536
		SEM	3.732	3.966	3.286
		95% CI	(-8.9, 5.8)	(-7.8, 7.8)	(-8.0, 4.9)
		Pr >  t			0.6404
	Week 56	n	22	17	
		LS Mean	-1.254	-1.458	0.204
		SEM	3.823	4.161	3.617
		95% CI	(-8.8, 6.3)	(-9.7, 6.7)	(-6.9, 7.3)
		Pr >  t			0.9550
	Week 64	n	17	19	
		LS Mean	3.712	-3.315	7.027
		SEM	3.992	4.084	3.712
		95% CI	(-4.2, 11.6)	(-11.4, 4.7)	(-0.3, 14.3)
		Pr >  t			0.0588
	Week 72	n	20	14	
		LS Mean	-1.353	-5.725	4.372
		SEM	3.886	4.312	3.851
		95% CI	(-9.0, 6.3)	(-14.2, 2.8)	(-3.2, 11.9)
		Pr >  t			0.2568
	Week 84	n	19	13	
		LS Mean	2.523	-0.725	3.248
		SEM	3.915	4.374	3.952
		95% CI	(-5.2, 10.2)	(-9.3, 7.9)	(-4.5, 11.0)
		Pr >  t			0.4114
	Week 96	n	12	12	
		LS Mean	-3.008	-3.449	0.441
		SEM	4.283	4.448	4.390
		95% CI	(-11.4, 5.4)	(-12.2, 5.3)	(-8.2, 9.1)
		Pr >  t			0.9200
	Week 108	n	9	9	
		LS Mean	0.817	-5.120	5.937
		SEM	4.587	4.746	4.971

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.2, 9.8)	(-14.5, 4.2)	(-3.8,15.7)
		Pr >  t			0.2328
	Week 120	n	12	7	
		LS Mean	-4.794	-5.773	0.979
		SEM	4.292	5.065	5.018
		95% CI	(-13.2, 3.7)	(-15.7, 4.2)	(-8.9,10.8)
		Pr >  t			0.8453
	Week 132	n	5	2	
		LS Mean	-4.030	-3.716	-0.314
		SEM	5.441	7.746	8.411
		95% CI	(-14.7, 6.7)	(-18.9,11.5)	(-16.8,16.2)
		Pr >  t			0.9702
	Week 144	n	3	1	
		LS Mean	-2.522	-5.720	3.198
		SEM	6.525	10.43	11.51
		95% CI	(-15.3,10.3)	(-26.2,14.8)	(-19.4,25.8)
		Pr >  t			0.7813
	Week 156	n	2		
		LS Mean	-3.100	NE	NE
		SEM	7.669	NE	NE
		95% CI	(-18.2,12.0)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



Tabelle 4H-43: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schmerzen“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference			
			N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv			
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73			
			LS Mean	-5.140	1.139	-6.279		
			SEM	3.961	3.992	3.509		
			95% CI	(-13.0, 2.7)	(-6.7, 9.0)	(-13.2, 0.6)		
							Pr >  t	0.0746
		Week 16	n	67	56			
			LS Mean	-3.670	5.499	-9.169		
			SEM	4.016	4.197	3.771		
			95% CI	(-11.6, 4.2)	(-2.8, 13.8)	(-16.6, -1.8)		
							Pr >  t	0.0155
		Week 24	n	61	46			
			LS Mean	-1.589	3.180	-4.769		
			SEM	4.079	4.310	3.957		
			95% CI	(-9.6, 6.4)	(-5.3, 11.7)	(-12.5, 3.0)		
							Pr >  t	0.2288
		Week 32	n	52	41			
			LS Mean	0.423	5.054	-4.630		
			SEM	4.193	4.399	4.121		
			95% CI	(-7.8, 8.7)	(-3.6, 13.7)	(-12.7, 3.5)		
							Pr >  t	0.2617
		Week 40	n	45	36			
			LS Mean	-0.227	4.542	-4.770		
			SEM	4.272	4.505	4.298		
			95% CI	(-8.6, 8.2)	(-4.3, 13.4)	(-13.2, 3.7)		
					Pr >  t	0.2676		
Week 48	n	42	30					
	LS Mean	-0.355	2.590	-2.946				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	4.316	4.639	4.480
		95% CI	(-8.9, 8.1)	(-6.5, 11.7)	(-11.7, 5.9)
		Pr >  t			0.5111
	Week 56	n	35	24	
		LS Mean	0.645	2.678	-2.033
		SEM	4.432	4.832	4.790
		95% CI	(-8.1, 9.4)	(-6.8, 12.2)	(-11.4, 7.4)
		Pr >  t			0.6713
	Week 64	n	25	25	
		LS Mean	2.927	-0.107	3.034
		SEM	4.691	4.796	5.001
		95% CI	(-6.3, 12.2)	(-9.5, 9.3)	(-6.8, 12.9)
		Pr >  t			0.5443
	Week 72	n	27	20	
		LS Mean	-0.351	4.747	-5.098
		SEM	4.627	5.014	5.152
		95% CI	(-9.5, 8.7)	(-5.1, 14.6)	(-15.2, 5.0)
		Pr >  t			0.3228
	Week 84	n	23	19	
		LS Mean	3.385	7.705	-4.320
		SEM	4.783	5.069	5.333
		95% CI	(-6.0, 12.8)	(-2.3, 17.7)	(-14.8, 6.1)
		Pr >  t			0.4181
	Week 96	n	20	13	
		LS Mean	2.041	4.015	-1.974
		SEM	4.924	5.547	5.906
		95% CI	(-7.6, 11.7)	(-6.9, 14.9)	(-13.6, 9.6)
		Pr >  t			0.7383
	Week 108	n	17	13	
		LS Mean	1.960	2.755	-0.796
		SEM	5.108	5.549	6.063
		95% CI	(-8.1, 12.0)	(-8.1, 13.7)	(-12.7, 11.1)
		Pr >  t			0.8956
	Week 120	n	17	12	
		LS Mean	-1.844	-2.144	0.300
		SEM	5.107	5.669	6.172
		95% CI	(-11.9, 8.2)	(-13.3, 9.0)	(-11.8, 12.4)
		Pr >  t			0.9613
	Week 132	n	13	6	
		LS Mean	-1.021	1.684	-2.706

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 144	SEM	5.460	7.015	7.674
		95% CI	(-11.7, 9.7)	(-12.1,15.5)	(-17.8,12.4)
		Pr >  t			0.7245
		n	11	4	
		LS Mean	6.403	-0.893	7.296
		SEM	5.718	8.152	8.889
	Week 156	95% CI	(-4.8,17.6)	(-16.9,15.1)	(-10.2,24.7)
		Pr >  t			0.4120
		n	7	2	
		LS Mean	-3.095	14.355	-17.45
		SEM	6.581	10.83	11.86
		95% CI	(-16.0, 9.8)	(-6.9,35.6)	(-40.7, 5.8)
	Week 168	Pr >  t			0.1414
		n	3	1	
		LS Mean	2.238	9.409	-7.171
		SEM	9.057	14.81	16.77
		95% CI	(-15.5,20.0)	(-19.7,38.5)	(-40.1,25.8)
		Pr >  t			0.6691
	Week 180	n	1	1	
		LS Mean	-11.62	9.409	-21.03
		SEM	14.77	14.81	20.43
		95% CI	(-40.6,17.4)	(-19.7,38.5)	(-61.1,19.1)
		Pr >  t			0.3038
		n	1	1	
Week 192	LS Mean	21.714	9.409	12.305	
	SEM	14.77	14.81	20.43	
	95% CI	(-7.3,50.7)	(-19.7,38.5)	(-27.8,52.4)	
	Pr >  t			0.5472	
	n	65	67		
	LS Mean	2.286	4.838	-2.552	
Week 8	SEM	4.064	4.189	3.480	
	95% CI	(-5.7,10.3)	(-3.4,13.1)	(-9.4, 4.3)	
	Pr >  t			0.4639	
	n	57	51		
	LS Mean	1.576	4.354	-2.777	
	SEM	4.210	4.373	3.751	
Week 16	95% CI	(-6.7, 9.9)	(-4.3,13.0)	(-10.2, 4.6)	
	Pr >  t			0.4596	
	n	44	35		
	LS Mean	4.081	8.558	-4.477	
	SEM				
	95% CI				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.347	4.671	4.203
		95% CI	(-4.5,12.6)	(-0.6,17.8)	(-12.7, 3.8)
		Pr >  t			0.2875
	Week 32	n	34	32	
		LS Mean	2.282	3.492	-1.210
		SEM	4.537	4.743	4.467
		95% CI	(-6.6,11.2)	(-5.8,12.8)	(-10.0, 7.6)
		Pr >  t			0.7866
	Week 40	n	30	26	
		LS Mean	2.392	3.499	-1.107
		SEM	4.636	4.910	4.745
		95% CI	(-6.7,11.5)	(-6.2,13.2)	(-10.4, 8.2)
		Pr >  t			0.8155
	Week 48	n	27	21	
		LS Mean	4.243	10.024	-5.780
		SEM	4.714	5.118	5.032
		95% CI	(-5.0,13.5)	(-0.0,20.1)	(-15.7, 4.1)
		Pr >  t			0.2512
	Week 56	n	24	21	
		LS Mean	2.013	9.467	-7.454
		SEM	4.819	5.118	5.131
		95% CI	(-7.5,11.5)	(-0.6,19.5)	(-17.5, 2.6)
		Pr >  t			0.1468
	Week 64	n	22	17	
		LS Mean	2.577	12.543	-9.966
		SEM	4.901	5.344	5.435
		95% CI	(-7.1,12.2)	( 2.0,23.0)	(-20.6, 0.7)
		Pr >  t			0.0672
	Week 72	n	21	15	
		LS Mean	1.095	6.843	-5.748
		SEM	4.948	5.496	5.629
		95% CI	(-8.6,10.8)	(-4.0,17.6)	(-16.8, 5.3)
		Pr >  t			0.3076
	Week 84	n	17	14	
		LS Mean	8.199	7.604	0.595
		SEM	5.187	5.582	5.911
		95% CI	(-2.0,18.4)	(-3.4,18.6)	(-11.0,12.2)
		Pr >  t			0.9199
	Week 96	n	15	11	
		LS Mean	4.748	14.258	-9.509

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	SEM	5.321	5.936	6.377
	95% CI	(-5.7,15.2)	(2.6,25.9)	(-22.0, 3.0)
	Pr >  t			0.1364
	n	9	8	
	LS Mean	8.400	16.997	-8.597
Week 120	SEM	6.132	6.508	7.535
	95% CI	(-3.6,20.4)	(4.2,29.8)	(-23.4, 6.2)
	Pr >  t			0.2543
	n	11	4	
	LS Mean	7.863	18.936	-11.07
Week 132	SEM	5.777	8.249	8.864
	95% CI	(-3.5,19.2)	(2.7,35.1)	(-28.5, 6.3)
	Pr >  t			0.2121
	n	7	2	
	LS Mean	7.596	-0.473	8.070
Week 144	SEM	6.637	10.88	11.80
	95% CI	(-5.4,20.6)	(-21.8,20.9)	(-15.1,31.3)
	Pr >  t			0.4945
	n	4	1	
	LS Mean	22.557	6.924	15.633
Week 156	SEM	8.056	14.83	16.21
	95% CI	(6.7,38.4)	(-22.2,36.0)	(-16.2,47.5)
	Pr >  t			0.3351
	n	3	1	
	LS Mean	12.714	6.924	5.790
Week 168	SEM	9.092	14.83	16.72
	95% CI	(-5.1,30.6)	(-22.2,36.0)	(-27.0,38.6)
	Pr >  t			0.7292
	n	1	1	
	LS Mean	2.945	6.924	-3.979
Week 168	SEM	14.78	14.83	20.38
	95% CI	(-26.1,32.0)	(-22.2,36.0)	(-44.0,36.0)
	Pr >  t			0.8452

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	-2.721	0.551	-3.272		
			SEM	3.172	3.351	3.098		
			95% CI	(-9.0, 3.5)	(-6.0, 7.1)	(-9.4, 2.8)		
					Pr >  t			0.2915
		Week 16	n	86	68			
			LS Mean	-2.357	4.361	-6.718		
			SEM	3.241	3.482	3.300		
			95% CI	(-8.7, 4.0)	(-2.5, 11.2)	(-13.2, -0.2)		
					Pr >  t			0.0423
		Week 24	n	73	48			
			LS Mean	-0.466	2.862	-3.328		
			SEM	3.326	3.721	3.617		
			95% CI	(-7.0, 6.1)	(-4.5, 10.2)	(-10.4, 3.8)		
					Pr >  t			0.3579
		Week 32	n	60	43			
			LS Mean	0.715	4.301	-3.586		
			SEM	3.462	3.812	3.793		
			95% CI	(-6.1, 7.5)	(-3.2, 11.8)	(-11.0, 3.9)		
					Pr >  t			0.3449
		Week 40	n	50	38			
			LS Mean	-0.202	1.498	-1.700		
			SEM	3.570	3.916	3.986		
			95% CI	(-7.2, 6.8)	(-6.2, 9.2)	(-9.5, 6.1)		
			Pr >  t			0.6699		
Week 48	n	48	31					
	LS Mean	-0.443	1.564	-2.007				
	SEM	3.598	4.083	4.175				
	95% CI	(-7.5, 6.6)	(-6.5, 9.6)	(-10.2, 6.2)				
			Pr >  t			0.6308		
Week 56	n	41	25					
	LS Mean	1.158	1.018	0.140				
	SEM	3.703	4.290	4.467				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-6.1, 8.4)	(-7.4, 9.4)	(-8.6, 8.9)
	Pr >  t			0.9750
	n	30	24	
	LS Mean	2.026	0.427	1.599
	SEM	3.948	4.333	4.717
Week 72	95% CI	(-5.7, 9.8)	(-8.1, 8.9)	(-7.7,10.9)
	Pr >  t			0.7347
	n	32	19	
	LS Mean	-0.120	4.161	-4.282
	SEM	3.894	4.598	4.918
Week 84	95% CI	(-7.8, 7.5)	(-4.9,13.2)	(-13.9, 5.4)
	Pr >  t			0.3842
	n	26	19	
	LS Mean	4.378	7.296	-2.918
	SEM	4.099	4.599	5.071
Week 96	95% CI	(-3.7,12.4)	(-1.7,16.3)	(-12.9, 7.0)
	Pr >  t			0.5652
	n	23	14	
	LS Mean	1.346	2.455	-1.109
	SEM	4.219	5.015	5.549
Week 108	95% CI	(-6.9, 9.6)	(-7.4,12.3)	(-12.0, 9.8)
	Pr >  t			0.8416
	n	19	13	
	LS Mean	1.618	1.675	-0.057
	SEM	4.452	5.130	5.821
Week 120	95% CI	(-7.1,10.4)	(-8.4,11.7)	(-11.5,11.4)
	Pr >  t			0.9922
	n	19	11	
	LS Mean	-1.779	-3.598	1.819
	SEM	4.440	5.411	6.071
Week 132	95% CI	(-10.5, 6.9)	(-14.2, 7.0)	(-10.1,13.7)
	Pr >  t			0.7645
	n	15	5	
	LS Mean	0.613	0.543	0.070
	SEM	4.768	7.212	7.907
Week 144	95% CI	(-8.7,10.0)	(-13.6,14.7)	(-15.4,15.6)
	Pr >  t			0.9929
	n	12	3	
Week 144	LS Mean	6.043	-3.123	9.166
	SEM	5.108	8.942	9.693



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-4.0,16.1)	(-20.7,14.4)	(-9.9,28.2)
		Pr >  t			0.3446
	Week 156	n	7	2	
		LS Mean	-2.703	13.192	-15.90
		SEM	6.212	10.69	11.86
		95% CI	(-14.9, 9.5)	(-7.8,34.2)	(-39.2, 7.4)
		Pr >  t			0.1806
	Week 168	n	3	1	
		LS Mean	2.649	8.301	-5.652
		SEM	8.826	14.77	16.84
		95% CI	(-14.7,20.0)	(-20.7,37.3)	(-38.7,27.4)
		Pr >  t			0.7373
	Week 180	n	1	1	
		LS Mean	-11.31	8.301	-19.61
		SEM	14.70	14.77	20.54
		95% CI	(-40.2,17.5)	(-20.7,37.3)	(-59.9,20.7)
		Pr >  t			0.3401
	Week 192	n	1	1	
		LS Mean	22.023	8.301	13.722
		SEM	14.70	14.77	20.54
		95% CI	(-6.8,50.9)	(-20.7,37.3)	(-26.6,54.0)
		Pr >  t			0.5043
Yes	Week 8	n	44	56	
		LS Mean	3.251	10.114	-6.863
		SEM	6.526	6.230	4.082
		95% CI	(-9.6,16.1)	(-2.2,22.4)	(-14.9, 1.2)
		Pr >  t			0.0943
	Week 16	n	38	39	
		LS Mean	3.889	9.376	-5.487
		SEM	6.709	6.575	4.461
		95% CI	(-9.3,17.1)	(-3.6,22.3)	(-14.3, 3.3)
		Pr >  t			0.2199
	Week 24	n	32	33	
		LS Mean	7.065	13.460	-6.396
		SEM	6.804	6.654	4.721
		95% CI	(-6.3,20.5)	( 0.3,26.6)	(-15.7, 2.9)
		Pr >  t			0.1766
	Week 32	n	26	30	
		LS Mean	5.987	8.649	-2.662
		SEM	6.921	6.713	4.971

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( -7.7,19.6)	( -4.6,21.9)	(-12.4, 7.1)
		Pr >  t			0.5927
	Week 40	n	25	24	
		LS Mean	7.028	12.201	-5.173
		SEM	6.949	6.849	5.189
		95% CI	( -6.7,20.7)	( -1.3,25.7)	(-15.4, 5.0)
		Pr >  t			0.3195
	Week 48	n	21	20	
		LS Mean	9.565	16.052	-6.488
		SEM	7.059	6.980	5.502
		95% CI	( -4.3,23.5)	( 2.3,29.8)	(-17.3, 4.3)
		Pr >  t			0.2391
	Week 56	n	18	20	
		LS Mean	4.883	16.290	-11.41
		SEM	7.176	6.980	5.651
		95% CI	( -9.2,19.0)	( 2.5,30.0)	(-22.5,-0.3)
		Pr >  t			0.0442
	Week 64	n	17	18	
		LS Mean	7.617	15.827	-8.211
		SEM	7.223	7.063	5.814
		95% CI	( -6.6,21.8)	( 1.9,29.7)	(-19.6, 3.2)
		Pr >  t			0.1586
	Week 72	n	16	16	
		LS Mean	4.773	12.345	-7.572
		SEM	7.276	7.163	6.001
		95% CI	( -9.6,19.1)	( -1.8,26.4)	(-19.4, 4.2)
		Pr >  t			0.2076
	Week 84	n	14	14	
		LS Mean	11.385	12.682	-1.298
		SEM	7.393	7.286	6.289
		95% CI	( -3.2,25.9)	( -1.7,27.0)	(-13.7,11.1)
		Pr >  t			0.8366
	Week 96	n	12	10	
		LS Mean	10.655	21.490	-10.83
		SEM	7.555	7.671	6.909
		95% CI	( -4.2,25.5)	( 6.4,36.6)	(-24.4, 2.7)
		Pr >  t			0.1174
	Week 108	n	7	8	
		LS Mean	15.484	22.949	-7.465
		SEM	8.301	7.992	8.035

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( -0.8,31.8)	( 7.2,38.7)	(-23.2, 8.3)
		Pr >  t			0.3533
	Week 120	n	9	5	
		LS Mean	14.175	22.379	-8.203
		SEM	7.929	8.878	8.568
		95% CI	( -1.4,29.8)	( 4.9,39.8)	(-25.0, 8.6)
		Pr >  t			0.3388
	Week 132	n	5	3	
		LS Mean	10.004	8.045	1.959
		SEM	8.955	10.24	10.81
		95% CI	( -7.6,27.6)	(-12.1,28.2)	(-19.3,23.2)
		Pr >  t			0.8562
	Week 144	n	3	2	
		LS Mean	33.823	13.137	20.686
		SEM	10.30	11.73	13.25
		95% CI	( 13.6,54.1)	( -9.9,36.2)	( -5.3,46.7)
		Pr >  t			0.1191
	Week 156	n	3	1	
		LS Mean	17.031	12.977	4.054
		SEM	10.32	15.34	16.54
		95% CI	( -3.2,37.3)	(-17.2,43.1)	(-28.4,36.6)
		Pr >  t			0.8065
	Week 168	n	1	1	
		LS Mean	7.188	12.977	-5.789
		SEM	15.43	15.34	20.13
		95% CI	(-23.1,37.5)	(-17.2,43.1)	(-45.3,33.8)
		Pr >  t			0.7738

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	-2.289	2.276	-4.565		
			SEM	3.560	3.530	2.934		
			95% CI	(-9.3, 4.7)	(-4.7, 9.2)	(-10.3, 1.2)		
					Pr >  t			0.1205
				Week 16	n	92	77	
					LS Mean	-2.045	5.683	-7.728
					SEM	3.599	3.703	3.133
					95% CI	(-9.1, 5.0)	(-1.6,13.0)	(-13.9,-1.6)
					Pr >  t			0.0140
				Week 24	n	83	66	
					LS Mean	0.563	6.085	-5.522
					SEM	3.652	3.771	3.269
					95% CI	(-6.6, 7.8)	(-1.3,13.5)	(-11.9, 0.9)
					Pr >  t			0.0917
				Week 32	n	72	60	
					LS Mean	2.372	5.476	-3.104
					SEM	3.720	3.834	3.391
					95% CI	(-4.9, 9.7)	(-2.1,13.0)	(-9.8, 3.6)
					Pr >  t			0.3604
				Week 40	n	64	51	
					LS Mean	1.807	5.660	-3.853
					SEM	3.771	3.932	3.547
					95% CI	(-5.6, 9.2)	(-2.1,13.4)	(-10.8, 3.1)
			Pr >  t			0.2776		
		Week 48	n	58	45			
			LS Mean	2.067	4.077	-2.010		
			SEM	3.816	4.005	3.675		
			95% CI	(-5.4, 9.6)	(-3.8,11.9)	(-9.2, 5.2)		
			Pr >  t			0.5846		
		Week 56	n	49	38			
			LS Mean	1.149	4.631	-3.482		
			SEM	3.902	4.115	3.885		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-6.5, 8.8)	(-3.5,12.7)	(-11.1, 4.1)
	Pr >  t			0.3704
	n	39	37	
	LS Mean	3.084	4.126	-1.041
	SEM	4.036	4.135	4.043
Week 72	95% CI	(-4.8,11.0)	(-4.0,12.3)	(-9.0, 6.9)
	Pr >  t			0.7968
	n	41	32	
	LS Mean	0.489	5.967	-5.478
	SEM	4.006	4.241	4.122
Week 84	95% CI	(-7.4, 8.4)	(-2.4,14.3)	(-13.6, 2.6)
	Pr >  t			0.1842
	n	33	29	
	LS Mean	5.361	8.775	-3.415
	SEM	4.169	4.321	4.346
Week 96	95% CI	(-2.8,13.6)	( 0.3,17.3)	(-11.9, 5.1)
	Pr >  t			0.4322
	n	31	21	
	LS Mean	4.270	8.625	-4.354
	SEM	4.210	4.625	4.693
Week 108	95% CI	(-4.0,12.5)	(-0.5,17.7)	(-13.6, 4.9)
	Pr >  t			0.3537
	n	23	18	
	LS Mean	5.554	7.071	-1.517
	SEM	4.484	4.800	5.098
Week 120	95% CI	(-3.3,14.4)	(-2.4,16.5)	(-11.5, 8.5)
	Pr >  t			0.7660
	n	25	15	
	LS Mean	1.475	2.472	-0.997
	SEM	4.396	5.032	5.251
Week 132	95% CI	(-7.2,10.1)	(-7.4,12.3)	(-11.3, 9.3)
	Pr >  t			0.8495
	n	17	8	
	LS Mean	1.622	1.947	-0.325
	SEM	4.818	6.094	6.573
Week 144	95% CI	(-7.8,11.1)	(-10.0,13.9)	(-13.2,12.6)
	Pr >  t			0.9606
	n	15	5	
	LS Mean	11.597	1.889	9.708
	SEM	4.967	7.242	7.753

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.8,21.3)	(-12.3,16.1)	( -5.5,24.9)
		Pr >  t			0.2107
	Week 156	n	10	3	
		LS Mean	2.321	12.455	-10.13
		SEM	5.618	8.907	9.683
		95% CI	( -8.7,13.3)	( -5.0,29.9)	(-29.1, 8.9)
		Pr >  t			0.2955
	Week 168	n	4	2	
		LS Mean	3.550	8.096	-4.546
		SEM	7.864	10.63	12.56
		95% CI	(-11.9,19.0)	(-12.8,29.0)	(-29.2,20.1)
		Pr >  t			0.7174
	Week 180	n	1	1	
		LS Mean	-9.306	11.147	-20.45
		SEM	14.60	14.61	20.24
		95% CI	(-37.9,19.3)	(-17.5,39.8)	(-60.2,19.2)
		Pr >  t			0.3124
	Week 192	n	1	1	
		LS Mean	24.024	11.147	12.877
		SEM	14.60	14.61	20.24
		95% CI	( -4.6,52.7)	(-17.5,39.8)	(-26.8,52.6)
		Pr >  t			0.5247
Yes	Week 8	n	38	42	
		LS Mean	0.138	4.232	-4.093
		SEM	4.679	5.011	4.616
		95% CI	( -9.1, 9.4)	( -5.7,14.2)	(-13.2, 5.0)
		Pr >  t			0.3767
	Week 16	n	32	30	
		LS Mean	0.819	3.095	-2.276
		SEM	4.946	5.260	5.069
		95% CI	( -9.0,10.6)	( -7.3,13.5)	(-12.3, 7.7)
		Pr >  t			0.6540
	Week 24	n	22	15	
		LS Mean	2.427	3.627	-1.200
		SEM	5.254	6.120	6.193
		95% CI	( -7.9,12.8)	( -8.4,15.7)	(-13.4,11.0)
		Pr >  t			0.8466
	Week 32	n	14	13	
		LS Mean	-3.927	-0.109	-3.818
		SEM	5.915	6.326	6.869

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-15.6, 7.7)	(-12.6,12.4)	(-17.3, 9.7)
	Pr >  t			0.5788
	n	11	11	
	LS Mean	-3.673	-2.140	-1.533
	SEM	6.294	6.574	7.417
Week 48	95% CI	(-16.1, 8.7)	(-15.1,10.8)	(-16.1,13.1)
	Pr >  t			0.8364
	n	11	6	
	LS Mean	-0.642	19.866	-20.51
	SEM	6.294	7.773	8.494
Week 56	95% CI	(-13.0,11.8)	( 4.6,35.2)	(-37.2,-3.8)
	Pr >  t			0.0164
	n	10	7	
	LS Mean	2.112	13.230	-11.12
	SEM	6.454	7.426	8.300
Week 64	95% CI	(-10.6,14.8)	( -1.4,27.9)	(-27.5, 5.2)
	Pr >  t			0.1815
	n	8	5	
	LS Mean	0.233	13.730	-13.50
	SEM	6.861	8.210	9.305
Week 72	95% CI	(-13.3,13.7)	( -2.4,29.9)	(-31.8, 4.8)
	Pr >  t			0.1480
	n	7	3	
	LS Mean	-1.115	4.431	-5.546
	SEM	7.133	9.784	10.90
Week 84	95% CI	(-15.2,12.9)	(-14.8,23.7)	(-27.0,15.9)
	Pr >  t			0.6114
	n	7	4	
	LS Mean	6.027	0.640	5.387
	SEM	7.133	8.832	10.06
Week 96	95% CI	( -8.0,20.1)	(-16.7,18.0)	(-14.4,25.2)
	Pr >  t			0.5927
	n	4	3	
	LS Mean	-4.416	9.988	-14.40
	SEM	8.570	9.784	11.89
Week 108	95% CI	(-21.3,12.5)	( -9.3,29.2)	(-37.8, 9.0)
	Pr >  t			0.2270
	n	3	3	
Week 108	LS Mean	-2.999	18.006	-21.00
	SEM	9.527	9.796	12.61

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.8,15.8)	(-1.3,37.3)	(-45.8, 3.8)
		Pr >  t			0.0969
	Week 120	n	3	1	
		LS Mean	7.900	26.242	-18.34
		SEM	9.529	15.32	17.26
		95% CI	(-10.9,26.7)	(-3.9,56.4)	(-52.3,15.7)
		Pr >  t			0.2889
	Week 132	n	3		
		LS Mean	6.122	NE	NE
		SEM	9.529	NE	NE
		95% CI	(-12.6,24.9)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134	
			LS Mean	-4.855	-0.658	-4.197
		SEM	1.791	1.788	2.529	
		95% CI	(-8.4,-1.3)	(-4.2, 2.9)	(-9.2, 0.8)	
		Pr >  t			0.0976	
		Week 16	n	118	104	
			LS Mean	-4.449	1.156	-5.605
		SEM	1.869	1.962	2.709	
		95% CI	(-8.1,-0.8)	(-2.7, 5.0)	(-10.9,-0.3)	
		Pr >  t			0.0389	
		Week 24	n	100	79	
			LS Mean	-2.292	1.282	-3.574
		SEM	1.974	2.153	2.920	
		95% CI	(-6.2, 1.6)	(-2.9, 5.5)	(-9.3, 2.2)	
		Pr >  t			0.2213	
		Week 32	n	84	72	
			LS Mean	-1.597	0.466	-2.063
		SEM	2.086	2.223	3.047	
		95% CI	(-5.7, 2.5)	(-3.9, 4.8)	(-8.0, 3.9)	
		Pr >  t			0.4986	
		Week 40	n	73	62	
			LS Mean	-1.920	0.283	-2.202
		SEM	2.185	2.335	3.196	
		95% CI	(-6.2, 2.4)	(-4.3, 4.9)	(-8.5, 4.1)	
		Pr >  t			0.4909	
		Week 48	n	67	51	
			LS Mean	-1.494	1.807	-3.301
		SEM	2.246	2.495	3.355	
95% CI	(-5.9, 2.9)	(-3.1, 6.7)	(-9.9, 3.3)			
Pr >  t			0.3254			
Week 56	n	57	45			
	LS Mean	-2.116	1.886	-4.002		
SEM	2.370	2.607	3.522			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-6.8, 2.5)	(-3.2, 7.0)	(-10.9, 2.9)
	Pr >  t			0.2561
	n	45	42	
	LS Mean	-0.844	1.262	-2.106
	SEM	2.569	2.673	3.706
Week 72	95% CI	(-5.9, 4.2)	(-4.0, 6.5)	(-9.4, 5.2)
	Pr >  t			0.5701
	n	46	35	
	LS Mean	-3.298	1.813	-5.112
	SEM	2.552	2.856	3.829
Week 84	95% CI	(-8.3, 1.7)	(-3.8, 7.4)	(-12.6, 2.4)
	Pr >  t			0.1820
	n	40	33	
	LS Mean	2.379	3.825	-1.446
	SEM	2.680	2.919	3.962
Week 96	95% CI	(-2.9, 7.6)	(-1.9, 9.6)	(-9.2, 6.3)
	Pr >  t			0.7152
	n	34	24	
	LS Mean	0.210	4.750	-4.540
	SEM	2.848	3.300	4.358
Week 108	95% CI	(-5.4, 5.8)	(-1.7, 11.2)	(-13.1, 4.0)
	Pr >  t			0.2977
	n	26	21	
	LS Mean	1.432	4.489	-3.057
	SEM	3.160	3.483	4.701
Week 120	95% CI	(-4.8, 7.6)	(-2.3, 11.3)	(-12.3, 6.2)
	Pr >  t			0.5156
	n	27	16	
	LS Mean	-0.882	-0.038	-0.844
	SEM	3.116	3.900	4.990
Week 132	95% CI	(-7.0, 5.2)	(-7.7, 7.6)	(-10.6, 8.9)
	Pr >  t			0.8657
	n	20	8	
	LS Mean	-0.778	-1.812	1.034
	SEM	3.513	5.287	6.346
Week 144	95% CI	(-7.7, 6.1)	(-12.2, 8.6)	(-11.4, 13.5)
	Pr >  t			0.8706
	n	14	5	
	LS Mean	9.193	-1.954	11.147
	SEM	4.089	6.582	7.748

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 1.2,17.2)	(-14.9,11.0)	(-4.1,26.3)
		Pr >  t			0.1504
	Week 156	n	10	3	
		LS Mean	-0.882	8.667	-9.549
		SEM	4.748	8.388	9.637
		95% CI	(-10.2, 8.4)	(-7.8,25.1)	(-28.5, 9.4)
		Pr >  t			0.3219
	Week 168	n	4	2	
		LS Mean	0.291	4.335	-4.044
		SEM	7.278	10.21	12.54
		95% CI	(-14.0,14.6)	(-15.7,24.4)	(-28.6,20.5)
		Pr >  t			0.7471
	Week 180	n	1	1	
		LS Mean	-12.59	7.446	-20.04
		SEM	14.32	14.32	20.25
		95% CI	(-40.7,15.5)	(-20.7,35.5)	(-59.8,19.7)
		Pr >  t			0.3226
	Week 192	n	1	1	
		LS Mean	20.736	7.446	13.290
		SEM	14.32	14.32	20.25
		95% CI	(-7.4,48.8)	(-20.7,35.5)	(-26.4,53.0)
		Pr >  t			0.5118
Prior use	Week 8	n	8	6	
		LS Mean	-3.021	3.249	-6.270
		SEM	8.364	9.614	12.41
		95% CI	(-21.2,15.1)	(-17.3,23.8)	(-32.9,20.4)
		Pr >  t			0.6213
	Week 16	n	6	3	
		LS Mean	-1.584	14.976	-16.56
		SEM	9.256	12.89	15.42
		95% CI	(-21.2,18.0)	(-11.7,41.7)	(-48.7,15.5)
		Pr >  t			0.2953
	Week 24	n	5	2	
		LS Mean	3.430	34.578	-31.15
		SEM	9.688	14.53	17.08
		95% CI	(-16.9,23.8)	( 4.8,64.4)	(-66.3, 4.0)
		Pr >  t			0.0797
	Week 32	n	2	1	
		LS Mean	-3.028	24.319	-27.35
		SEM	13.10	18.44	22.47

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-29.9,23.8)	(-13.5,62.2)	(-73.4,18.7)
	Pr >  t			0.2341
Week 40	n	2		
	LS Mean	-3.028	NE	NE
	SEM	13.10	NE	NE
	95% CI	(-29.9,23.8)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	5.307	NE	NE
	SEM	13.10	NE	NE
	95% CI	(-21.5,32.1)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	13.637	NE	NE
	SEM	13.10	NE	NE
	95% CI	(-13.2,40.5)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	13.637	NE	NE
	SEM	13.10	NE	NE
	95% CI	(-13.2,40.5)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	13.637	NE	NE
	SEM	13.10	NE	NE
	95% CI	(-13.2,40.5)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	2.017	NE	NE
	SEM	16.80	NE	NE
	95% CI	(-32.6,36.6)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	2.017	NE	NE
	SEM	16.80	NE	NE
	95% CI	(-32.6,36.6)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	2.017	NE	NE
	SEM	16.80	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-32.6,36.6)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-2.045	2.199	-4.245		
			SEM	2.895	2.953	2.582		
			95% CI	(-7.7, 3.6)	(-3.6, 8.0)	(-9.3, 0.8)		
					Pr >  t			0.1008
		Week 16	n	119	97			
			LS Mean	-1.745	3.929	-5.674		
			SEM	2.964	3.108	2.790		
			95% CI	(-7.6, 4.1)	(-2.2, 10.0)	(-11.2, -0.2)		
					Pr >  t			0.0424
		Week 24	n	100	75			
			LS Mean	0.649	6.118	-5.469		
			SEM	3.036	3.242	2.999		
			95% CI	(-5.3, 6.6)	(-0.3, 12.5)	(-11.4, 0.4)		
					Pr >  t			0.0686
		Week 32	n	82	69			
			LS Mean	1.557	3.463	-1.906		
			SEM	3.141	3.295	3.133		
			95% CI	(-4.6, 7.7)	(-3.0, 9.9)	(-8.1, 4.2)		
					Pr >  t			0.5431
		Week 40	n	73	58			
			LS Mean	0.747	3.403	-2.656		
			SEM	3.196	3.397	3.287		
			95% CI	(-5.5, 7.0)	(-3.3, 10.1)	(-9.1, 3.8)		
			Pr >  t			0.4193		
Week 48	n	66	48					
	LS Mean	1.893	5.035	-3.141				
	SEM	3.244	3.513	3.453				
	95% CI	(-4.5, 8.3)	(-1.9, 11.9)	(-9.9, 3.6)				
			Pr >  t			0.3632		
Week 56	n	56	43					
	LS Mean	1.036	4.968	-3.933				
	SEM	3.332	3.589	3.614				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.5, 7.6)	(-2.1, 12.0)	(-11.0, 3.2)
		Pr >  t			0.2767
	Week 64	n	45	41	
		LS Mean	2.375	4.788	-2.413
		SEM	3.465	3.624	3.774
		95% CI	(-4.4, 9.2)	(-2.3, 11.9)	(-9.8, 5.0)
		Pr >  t			0.5226
	Week 72	n	46	34	
		LS Mean	0.119	5.413	-5.294
		SEM	3.453	3.768	3.902
		95% CI	(-6.7, 6.9)	(-2.0, 12.8)	(-12.9, 2.4)
		Pr >  t			0.1751
	Week 84	n	37	32	
		LS Mean	5.933	7.497	-1.565
		SEM	3.617	3.820	4.087
		95% CI	(-1.2, 13.0)	( 0.0, 15.0)	(-9.6, 6.5)
		Pr >  t			0.7019
	Week 96	n	33	23	
		LS Mean	3.477	8.582	-5.105
		SEM	3.706	4.142	4.469
		95% CI	(-3.8, 10.8)	( 0.5, 16.7)	(-13.9, 3.7)
		Pr >  t			0.2534
	Week 108	n	24	20	
		LS Mean	4.130	8.373	-4.242
		SEM	4.018	4.304	4.867
		95% CI	(-3.8, 12.0)	(-0.1, 16.8)	(-13.8, 5.3)
		Pr >  t			0.3836
	Week 120	n	25	16	
		LS Mean	1.008	3.426	-2.417
		SEM	3.971	4.596	5.096
		95% CI	(-6.8, 8.8)	(-5.6, 12.4)	(-12.4, 7.6)
		Pr >  t			0.6353
	Week 132	n	19	8	
		LS Mean	2.516	1.629	0.887
		SEM	4.288	5.825	6.430
		95% CI	(-5.9, 10.9)	(-9.8, 13.1)	(-11.7, 13.5)
		Pr >  t			0.8903
	Week 144	n	14	5	
		LS Mean	9.985	1.533	8.453
		SEM	4.707	7.028	7.789

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.8,19.2)	(-12.3,15.3)	( -6.8,23.7)
		Pr >  t			0.2780
	Week 156	n	10	3	
		LS Mean	1.985	12.128	-10.14
		SEM	5.301	8.749	9.679
		95% CI	( -8.4,12.4)	( -5.0,29.3)	(-29.1, 8.8)
		Pr >  t			0.2948
	Week 168	n	4	2	
		LS Mean	3.178	7.770	-4.592
		SEM	7.661	10.52	12.58
		95% CI	(-11.8,18.2)	(-12.9,28.4)	(-29.3,20.1)
		Pr >  t			0.7152
	Week 180	n	1	1	
		LS Mean	-9.707	10.884	-20.59
		SEM	14.54	14.56	20.31
		95% CI	(-38.2,18.8)	(-17.7,39.5)	(-60.4,19.3)
		Pr >  t			0.3109
	Week 192	n	1	1	
		LS Mean	23.623	10.884	12.739
		SEM	14.54	14.56	20.31
		95% CI	( -4.9,52.2)	(-17.7,39.5)	(-27.1,52.6)
		Pr >  t			0.5307
Yes	Week 8	n	5	9	
		LS Mean	-9.222	3.111	-12.33
		SEM	6.022	4.495	7.580
		95% CI	(-21.3, 2.9)	( -5.9,12.1)	(-27.6, 2.9)
		Pr >  t			0.1099
	Week 16	n	5	9	
		LS Mean	-5.888	12.251	-18.14
		SEM	6.022	4.587	7.648
		95% CI	(-18.0, 6.2)	( 3.0,21.5)	(-33.5,-2.8)
		Pr >  t			0.0216
	Week 24	n	5	5	
		LS Mean	-5.888	-12.91	7.020
		SEM	6.022	6.078	8.648
		95% CI	(-18.0, 6.2)	(-25.1,-0.7)	(-10.3,24.4)
		Pr >  t			0.4208
	Week 32	n	4	3	
		LS Mean	-12.15	8.392	-20.54
		SEM	6.728	8.103	10.73



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-25.7, 1.4)	(-7.9, 24.7)	(-42.1, 1.0)
		Pr >  t			0.0611
	Week 40	n	2	3	
		LS Mean	0.244	0.859	-0.615
		SEM	9.722	7.744	12.41
		95% CI	(-19.3, 19.8)	(-14.7, 16.4)	(-25.5, 24.3)
		Pr >  t			0.9607
	Week 48	n	3	2	
		LS Mean	-13.74	-13.25	-0.487
		SEM	7.772	9.724	12.31
		95% CI	(-29.3, 1.9)	(-32.8, 6.3)	(-25.2, 24.2)
		Pr >  t			0.9686
	Week 56	n	3	1	
		LS Mean	-2.628	29.079	-31.71
		SEM	7.772	13.80	15.95
		95% CI	(-18.2, 13.0)	( 1.4, 56.8)	(-63.7, 0.3)
		Pr >  t			0.0522
	Week 64	n	2		
		LS Mean	0.244	NE	NE
		SEM	9.722	NE	NE
		95% CI	(-19.3, 19.8)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	-8.779	NE	NE
		SEM	9.716	NE	NE
		95% CI	(-28.3, 10.7)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	-8.185	NE	NE
		SEM	7.772	NE	NE
		95% CI	(-23.8, 7.4)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	-8.086	NE	NE
		SEM	9.722	NE	NE
		95% CI	(-27.6, 11.4)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	0.650	NE	NE
		SEM	9.660	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-18.7,20.0)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	2.925	NE	NE
	SEM	7.772	NE	NE
	95% CI	(-12.7,18.5)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-6.986	NE	NE
	SEM	14.12	NE	NE
	95% CI	(-35.3,21.4)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	26.344	NE	NE
	SEM	14.12	NE	NE
	95% CI	( -2.0,54.7)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-2.172	2.521	-4.693		
			SEM	2.913	2.965	2.678		
			95% CI	(-7.9, 3.6)	(-3.3, 8.4)	(-10.0, 0.6)		
					Pr >  t			0.0803
		Week 16	n	111	91			
			LS Mean	-1.695	4.156	-5.851		
			SEM	2.980	3.128	2.881		
			95% CI	(-7.6, 4.2)	(-2.0, 10.3)	(-11.5, -0.2)		
					Pr >  t			0.0427
		Week 24	n	96	70			
			LS Mean	0.580	4.588	-4.008		
			SEM	3.046	3.274	3.090		
			95% CI	(-5.4, 6.6)	(-1.8, 11.0)	(-10.1, 2.1)		
					Pr >  t			0.1951
		Week 32	n	77	61			
			LS Mean	0.419	4.654	-4.236		
			SEM	3.167	3.361	3.270		
			95% CI	(-5.8, 6.6)	(-1.9, 11.3)	(-10.7, 2.2)		
					Pr >  t			0.1956
		Week 40	n	69	52			
			LS Mean	0.508	4.637	-4.130		
			SEM	3.222	3.468	3.425		
			95% CI	(-5.8, 6.8)	(-2.2, 11.4)	(-10.9, 2.6)		
			Pr >  t			0.2283		
Week 48	n	62	41					
	LS Mean	2.014	6.259	-4.245				
	SEM	3.277	3.631	3.639				
	95% CI	(-4.4, 8.5)	(-0.9, 13.4)	(-11.4, 2.9)				
			Pr >  t			0.2437		
Week 56	n	53	35					
	LS Mean	1.752	4.420	-2.668				
	SEM	3.366	3.756	3.845				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 64	95% CI	(-4.9, 8.4)	(-3.0,11.8)	(-10.2, 4.9)
	Pr >  t			0.4880
	n	44	33	
	LS Mean	1.719	4.659	-2.941
	SEM	3.483	3.808	3.999
Week 72	95% CI	(-5.1, 8.6)	(-2.8,12.1)	(-10.8, 4.9)
	Pr >  t			0.4623
	n	45	28	
	LS Mean	0.345	6.647	-6.302
	SEM	3.470	3.957	4.131
Week 84	95% CI	(-6.5, 7.2)	(-1.1,14.4)	(-14.4, 1.8)
	Pr >  t			0.1273
	n	39	27	
	LS Mean	5.735	7.050	-1.315
	SEM	3.581	3.993	4.250
Week 96	95% CI	(-1.3,12.8)	(-0.8,14.9)	(-9.7, 7.0)
	Pr >  t			0.7570
	n	34	19	
	LS Mean	2.947	10.245	-7.298
	SEM	3.686	4.387	4.709
Week 108	95% CI	(-4.3,10.2)	( 1.6,18.9)	(-16.5, 1.9)
	Pr >  t			0.1215
	n	26	17	
	LS Mean	4.336	8.598	-4.263
	SEM	3.942	4.535	5.039
Week 120	95% CI	(-3.4,12.1)	(-0.3,17.5)	(-14.1, 5.6)
	Pr >  t			0.3978
	n	27	11	
	LS Mean	1.916	1.425	0.491
	SEM	3.900	5.226	5.644
Week 132	95% CI	(-5.7, 9.6)	(-8.8,11.7)	(-10.6,11.6)
	Pr >  t			0.9307
	n	20	6	
	LS Mean	2.114	0.790	1.324
	SEM	4.235	6.563	7.092
Week 144	95% CI	(-6.2,10.4)	(-12.1,13.7)	(-12.6,15.2)
	Pr >  t			0.8519
	n	15	4	
	LS Mean	11.229	1.079	10.150
	SEM	4.617	7.779	8.439

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 2.2,20.3)	(-14.2,16.3)	( -6.4,26.7)
		Pr >  t			0.2293
	Week 156	n	10	2	
		LS Mean	1.977	16.477	-14.50
		SEM	5.322	10.59	11.40
		95% CI	( -8.5,12.4)	( -4.3,37.3)	(-36.9, 7.9)
		Pr >  t			0.2035
	Week 168	n	4	2	
		LS Mean	3.155	8.142	-4.986
		SEM	7.702	10.59	12.68
		95% CI	(-12.0,18.3)	(-12.6,28.9)	(-29.9,19.9)
		Pr >  t			0.6943
	Week 180	n	1	1	
		LS Mean	-9.717	11.142	-20.86
		SEM	14.64	14.67	20.46
		95% CI	(-38.4,19.0)	(-17.6,39.9)	(-61.0,19.3)
		Pr >  t			0.3082
	Week 192	n	1	1	
		LS Mean	23.613	11.142	12.471
		SEM	14.64	14.67	20.46
		95% CI	( -5.1,52.3)	(-17.6,39.9)	(-27.7,52.6)
		Pr >  t			0.5423
>= 75 Years	Week 8	n	17	19	
		LS Mean	-3.559	-1.714	-1.844
		SEM	4.966	4.462	6.623
		95% CI	(-13.5, 6.4)	(-10.6, 7.2)	(-15.1,11.4)
		Pr >  t			0.7815
	Week 16	n	13	16	
		LS Mean	-3.966	3.520	-7.486
		SEM	5.450	4.795	7.218
		95% CI	(-14.8, 6.9)	( -6.0,13.1)	(-21.8, 6.9)
		Pr >  t			0.3028
	Week 24	n	9	11	
		LS Mean	-1.969	5.249	-7.218
		SEM	6.132	5.436	8.154
		95% CI	(-14.1,10.2)	( -5.5,16.0)	(-23.4, 8.9)
		Pr >  t			0.3780
	Week 32	n	9	12	
		LS Mean	4.319	-2.787	7.106
		SEM	6.134	5.311	8.073

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.8,16.5)	(-13.3, 7.7)	(-8.9,23.1)
		Pr >  t			0.3807
	Week 40	n	6	10	
		LS Mean	0.875	-4.075	4.950
		SEM	7.018	5.605	8.941
		95% CI	(-13.0,14.8)	(-15.2, 7.0)	(-12.7,22.6)
		Pr >  t			0.5808
	Week 48	n	7	10	
		LS Mean	-6.365	-2.231	-4.135
		SEM	6.665	5.623	8.673
		95% CI	(-19.6, 6.8)	(-13.4, 8.9)	(-21.3,13.0)
		Pr >  t			0.6344
	Week 56	n	6	10	
		LS Mean	-6.996	5.090	-12.09
		SEM	7.005	5.627	8.930
		95% CI	(-20.8, 6.9)	(-6.1,16.2)	(-29.8, 5.6)
		Pr >  t			0.1783
	Week 64	n	3	9	
		LS Mean	10.062	1.480	8.583
		SEM	9.039	5.822	10.70
		95% CI	(-7.8,27.9)	(-10.0,13.0)	(-12.6,29.7)
		Pr >  t			0.4238
	Week 72	n	3	7	
		LS Mean	-6.604	-3.588	-3.016
		SEM	9.039	6.340	10.99
		95% CI	(-24.4,11.2)	(-16.1, 8.9)	(-24.7,18.7)
		Pr >  t			0.7841
	Week 84	n	1	6	
		LS Mean	-14.71	4.956	-19.67
		SEM	14.46	6.682	15.90
		95% CI	(-43.3,13.8)	(-8.2,18.2)	(-51.0,11.7)
		Pr >  t			0.2177
	Week 96	n	1	5	
		LS Mean	1.959	-3.030	4.988
		SEM	14.46	7.142	16.10
		95% CI	(-26.6,30.5)	(-17.1,11.1)	(-26.8,36.8)
		Pr >  t			0.7570
	Week 108	n		4	
		LS Mean	NE	1.437	NE
		SEM	NE	7.778	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-13.9,16.8)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	0.190	3.636
		SEM	14.49	7.142
		95% CI	(-28.4,28.8)	(-10.5,17.7)
		Pr >  t		(-35.3,28.4)
	Week 132	n		2
		LS Mean	NE	0.234
		SEM	NE	10.31
		95% CI	NE	(-20.1,20.6)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	-0.541
		SEM	NE	14.08
		95% CI	NE	(-28.4,27.3)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	-0.541
		SEM	NE	14.08
		95% CI	NE	(-28.4,27.3)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	2.247	-4.651	6.898		
			SEM	5.461	5.161	4.559		
			95% CI	(-8.6,13.1)	(-14.9, 5.6)	(-2.1,15.9)		
					Pr >  t		0.1325	
		Week 16	n	30	30			
			LS Mean	-0.723	0.278	-1.001		
			SEM	5.495	5.383	4.767		
			95% CI	(-11.6,10.2)	(-10.4,11.0)	(-10.4, 8.4)		
					Pr >  t		0.8339	
		Week 24	n	21	26			
			LS Mean	3.384	-0.863	4.246		
			SEM	5.750	5.472	5.188		
			95% CI	(-8.0,14.8)	(-11.7,10.0)	(-6.0,14.5)		
					Pr >  t		0.4141	
		Week 32	n	19	24			
			LS Mean	5.259	0.581	4.678		
			SEM	5.833	5.533	5.356		
			95% CI	(-6.3,16.8)	(-10.4,11.5)	(-5.9,15.2)		
					Pr >  t		0.3835	
		Week 40	n	16	19			
			LS Mean	-1.832	3.216	-5.048		
			SEM	5.985	5.779	5.731		
			95% CI	(-13.7,10.0)	(-8.2,14.7)	(-16.3, 6.2)		
					Pr >  t		0.3793	
		Week 48	n	16	18			
			LS Mean	5.459	4.165	1.294		
			SEM	5.985	5.828	5.782		
95% CI	(-6.4,17.3)		(-7.4,15.7)	(-10.1,12.7)				
			Pr >  t		0.8231			
Week 56	n	12	14					
	LS Mean	7.309	6.421	0.888				
	SEM	6.288	6.079	6.355				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.1,19.7)	(-5.6,18.4)	(-11.6,13.4)
		Pr >  t			0.8890
	Week 64	n	12	11	
		LS Mean	4.532	6.165	-1.633
		SEM	6.288	6.374	6.635
		95% CI	(-7.9,17.0)	(-6.4,18.7)	(-14.7,11.4)
		Pr >  t			0.8057
	Week 72	n	10	9	
		LS Mean	3.004	3.505	-0.500
		SEM	6.523	6.661	7.131
		95% CI	(-9.9,15.9)	(-9.6,16.6)	(-14.5,13.5)
		Pr >  t			0.9441
	Week 84	n	8	8	
		LS Mean	7.350	8.233	-0.884
		SEM	6.917	6.853	7.618
		95% CI	(-6.3,21.0)	(-5.3,21.7)	(-15.9,14.1)
		Pr >  t			0.9077
	Week 96	n	6	6	
		LS Mean	7.807	6.337	1.470
		SEM	7.442	7.388	8.558
		95% CI	(-6.9,22.5)	(-8.2,20.9)	(-15.4,18.3)
		Pr >  t			0.8637
	Week 108	n	4	5	
		LS Mean	15.731	5.068	10.663
		SEM	8.385	7.789	9.709
		95% CI	(-0.8,32.2)	(-10.3,20.4)	(-8.4,29.8)
		Pr >  t			0.2728
	Week 120	n	4	4	
		LS Mean	15.728	9.846	5.882
		SEM	8.385	8.352	10.17
		95% CI	(-0.8,32.2)	(-6.6,26.3)	(-14.1,25.9)
		Pr >  t			0.5633
	Week 132	n	3	2	
		LS Mean	8.972	3.099	5.873
		SEM	9.225	10.66	12.73
		95% CI	(-9.2,27.1)	(-17.9,24.1)	(-19.2,30.9)
		Pr >  t			0.6449
	Week 144	n	3	1	
		LS Mean	25.639	2.297	23.341
		SEM	9.225	14.22	15.83

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 7.5,43.8)	(-25.7,30.3)	( -7.8,54.5)
		Pr >  t			0.1412
	Week 156	n	2	1	
		LS Mean	19.530	2.297	17.233
		SEM	10.70	14.22	16.73
		95% CI	( -1.5,40.6)	(-25.7,30.3)	(-15.7,50.1)
		Pr >  t			0.3036
	Week 168	n	1		
		LS Mean	21.584	NE	NE
		SEM	14.22	NE	NE
		95% CI	( -6.4,49.5)	NE	NE
		Pr >  t			NE
Other	Week 8	n	16	17	
		LS Mean	-16.86	0.355	-17.21
		SEM	12.19	11.71	7.495
		95% CI	(-41.2, 7.5)	(-23.0,23.7)	(-32.2,-2.2)
		Pr >  t			0.0250
	Week 16	n	15	14	
		LS Mean	-10.18	6.527	-16.70
		SEM	12.28	11.13	8.070
		95% CI	(-34.7,14.4)	(-15.7,28.8)	(-32.8,-0.6)
		Pr >  t			0.0421
	Week 24	n	12	11	
		LS Mean	-3.981	13.022	-17.00
		SEM	12.48	12.04	8.679
		95% CI	(-28.9,20.9)	(-11.0,37.0)	(-34.3, 0.3)
		Pr >  t			0.0534
	Week 32	n	8	9	
		LS Mean	-11.85	6.862	-18.71
		SEM	12.93	12.28	9.594
		95% CI	(-37.6,13.9)	(-17.6,31.3)	(-37.7, 0.3)
		Pr >  t			0.0538
	Week 40	n	6	7	
		LS Mean	10.174	0.518	9.656
		SEM	13.35	12.59	10.48
		95% CI	(-16.4,36.7)	(-24.5,25.5)	(-11.1,30.4)
		Pr >  t			0.3588
	Week 48	n	4	6	
		LS Mean	-5.686	0.265	-5.951
		SEM	14.11	12.82	11.71

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-33.7,22.3)	(-25.2,25.7)	(-29.1,17.2)
		Pr >  t			0.6122
	Week 56	n	4	6	
		LS Mean	-12.80	4.277	-17.08
		SEM	14.10	12.84	11.71
		95% CI	(-40.8,15.2)	(-21.2,29.8)	(-40.2, 6.1)
		Pr >  t			0.1470
	Week 64	n	4	4	
		LS Mean	-6.106	-1.264	-4.842
		SEM	14.12	13.60	12.53
		95% CI	(-34.2,21.9)	(-28.2,25.7)	(-29.6,19.9)
		Pr >  t			0.6997
	Week 72	n	4	4	
		LS Mean	-1.936	7.068	-9.005
		SEM	14.12	13.60	12.53
		95% CI	(-30.0,26.1)	(-19.9,34.0)	(-33.8,15.8)
		Pr >  t			0.4735
	Week 84	n	4	4	
		LS Mean	6.814	2.901	3.914
		SEM	14.11	13.60	12.54
		95% CI	(-21.2,34.8)	(-24.1,29.9)	(-20.9,28.7)
		Pr >  t			0.7554
	Week 96	n	3	2	
		LS Mean	-11.46	-1.882	-9.578
		SEM	14.81	15.62	15.37
		95% CI	(-40.8,17.9)	(-32.8,29.0)	(-40.0,20.8)
		Pr >  t			0.5342
	Week 108	n	3	3	
		LS Mean	-0.346	11.678	-12.02
		SEM	14.81	14.32	14.07
		95% CI	(-29.7,29.0)	(-16.7,40.1)	(-39.8,15.8)
		Pr >  t			0.3941
	Week 120	n	2	1	
		LS Mean	-7.989	-21.92	13.934
		SEM	16.10	18.99	19.82
		95% CI	(-39.9,23.9)	(-59.5,15.6)	(-25.2,53.1)
		Pr >  t			0.4831
	Week 132	n	2	1	
		LS Mean	21.353	-5.253	26.606
		SEM	16.08	18.99	19.81

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.5,53.2)	(-42.8,32.3)	(-12.6,65.8)
		Pr >  t			0.1816
	Week 156	n	1		
		LS Mean	-5.564	NE	NE
		SEM	19.41	NE	NE
		95% CI	(-43.9,32.8)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-5.564	NE	NE
		SEM	19.41	NE	NE
		95% CI	(-43.9,32.8)	NE	NE
		Pr >  t			NE
White	Week 8	n	93	85	
		LS Mean	-1.109	6.167	-7.276
		SEM	3.430	3.604	3.196
		95% CI	(-7.9, 5.6)	(-0.9,13.3)	(-13.6,-1.0)
		Pr >  t			0.0234
	Week 16	n	79	61	
		LS Mean	-0.774	5.757	-6.532
		SEM	3.537	3.859	3.507
		95% CI	(-7.7, 6.2)	(-1.8,13.4)	(-13.4, 0.4)
		Pr >  t			0.0632
	Week 24	n	71	43	
		LS Mean	0.091	6.299	-6.208
		SEM	3.599	4.079	3.806
		95% CI	(-7.0, 7.2)	(-1.7,14.3)	(-13.7, 1.3)
		Pr >  t			0.1035
	Week 32	n	59	39	
		LS Mean	1.473	4.905	-3.432
		SEM	3.728	4.169	3.970
		95% CI	(-5.9, 8.8)	(-3.3,13.1)	(-11.2, 4.4)
		Pr >  t			0.3877
	Week 40	n	52	35	
		LS Mean	-0.029	4.855	-4.884
		SEM	3.800	4.252	4.124
		95% CI	(-7.5, 7.4)	(-3.5,13.2)	(-13.0, 3.2)
		Pr >  t			0.2367
	Week 48	n	48	26	
		LS Mean	1.375	7.049	-5.673
		SEM	3.847	4.505	4.424

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.2, 8.9)	(-1.8, 15.9)	(-14.4, 3.0)
		Pr >  t			0.2001
	Week 56	n	42	24	
		LS Mean	1.282	6.032	-4.750
		SEM	3.928	4.582	4.576
		95% CI	(-6.4, 9.0)	(-3.0, 15.0)	(-13.7, 4.2)
		Pr >  t			0.2996
	Week 64	n	30	26	
		LS Mean	2.495	6.307	-3.812
		SEM	4.175	4.507	4.721
		95% CI	(-5.7, 10.7)	(-2.5, 15.2)	(-13.1, 5.5)
		Pr >  t			0.4196
	Week 72	n	34	21	
		LS Mean	-0.441	4.736	-5.176
		SEM	4.079	4.720	4.843
		95% CI	(-8.5, 7.6)	(-4.5, 14.0)	(-14.7, 4.3)
		Pr >  t			0.2855
	Week 84	n	28	20	
		LS Mean	4.450	6.992	-2.542
		SEM	4.243	4.772	5.028
		95% CI	(-3.9, 12.8)	(-2.4, 16.4)	(-12.4, 7.3)
		Pr >  t			0.6132
	Week 96	n	26	15	
		LS Mean	3.597	10.354	-6.758
		SEM	4.303	5.128	5.420
		95% CI	(-4.9, 12.0)	( 0.3, 20.4)	(-17.4, 3.9)
		Pr >  t			0.2128
	Week 108	n	19	12	
		LS Mean	2.447	8.224	-5.777
		SEM	4.646	5.461	5.990
		95% CI	(-6.7, 11.6)	(-2.5, 18.9)	(-17.5, 6.0)
		Pr >  t			0.3351
	Week 120	n	22	10	
		LS Mean	0.248	4.553	-4.305
		SEM	4.474	5.771	6.156
		95% CI	(-8.5, 9.0)	(-6.8, 15.9)	(-16.4, 7.8)
		Pr >  t			0.4845
	Week 132	n	15	4	
		LS Mean	-2.008	-0.427	-1.581
		SEM	4.946	8.028	8.567

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.7, 7.7)	(-16.2,15.3)	(-18.4,15.2)
		Pr >  t			0.8536
	Week 144	n	12	4	
		LS Mean	8.336	1.956	6.381
		SEM	5.272	8.033	8.773
		95% CI	(-2.0,18.7)	(-13.8,17.7)	(-10.8,23.6)
		Pr >  t			0.4672
	Week 156	n	7	2	
		LS Mean	-1.863	17.310	-19.17
		SEM	6.343	10.77	11.86
		95% CI	(-14.3,10.6)	(-3.8,38.4)	(-42.5, 4.1)
		Pr >  t			0.1064
	Week 168	n	2	2	
		LS Mean	-2.262	8.975	-11.24
		SEM	10.66	10.77	14.63
		95% CI	(-23.2,18.7)	(-12.2,30.1)	(-40.0,17.5)
		Pr >  t			0.4427
	Week 180	n	1	1	
		LS Mean	-10.64	12.163	-22.81
		SEM	14.72	14.78	20.48
		95% CI	(-39.5,18.2)	(-16.8,41.2)	(-63.0,17.4)
		Pr >  t			0.2658
	Week 192	n	1	1	
		LS Mean	22.687	12.163	10.524
		SEM	14.72	14.78	20.48
		95% CI	(-6.2,51.6)	(-16.8,41.2)	(-29.7,50.7)
		Pr >  t			0.6075

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	3.238	5.556	-2.318		
			SEM	4.856	4.756	3.605		
					95% CI	(-6.3,12.8)	(-3.8,14.9)	(-9.4, 4.8)
					Pr >  t			0.5209
				Week 16	n	60	51	
					LS Mean	-0.042	6.892	-6.934
					SEM	4.936	4.973	3.820
					95% CI	(-9.8, 9.7)	(-2.9,16.7)	(-14.5, 0.6)
					Pr >  t			0.0705
				Week 24	n	51	42	
					LS Mean	4.103	7.426	-3.323
					SEM	5.001	5.066	4.037
					95% CI	(-5.8,14.0)	(-2.6,17.4)	(-11.3, 4.6)
					Pr >  t			0.4110
				Week 32	n	46	36	
					LS Mean	3.976	6.108	-2.132
					SEM	5.078	5.187	4.210
					95% CI	(-6.0,14.0)	(-4.1,16.3)	(-10.4, 6.1)
					Pr >  t			0.6128
				Week 40	n	40	33	
					LS Mean	4.618	8.256	-3.638
					SEM	5.151	5.239	4.358
					95% CI	(-5.5,14.8)	(-2.1,18.6)	(-12.2, 4.9)
			Pr >  t			0.4042		
		Week 48	n	37	28			
			LS Mean	7.300	10.912	-3.612		
			SEM	5.190	5.347	4.532		
			95% CI	(-2.9,17.5)	( 0.4,21.4)	(-12.5, 5.3)		
			Pr >  t			0.4258		
		Week 56	n	33	23			
			LS Mean	3.945	6.462	-2.517		
			SEM	5.256	5.496	4.781		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 64	95% CI	(-6.4,14.3)	(-4.3,17.3)	(-11.9, 6.9)
	Pr >  t			0.5988
	n	26	20	
	LS Mean	3.542	6.435	-2.893
	SEM	5.408	5.614	5.077
Week 72	95% CI	(-7.1,14.2)	(-4.6,17.5)	(-12.9, 7.1)
	Pr >  t			0.5690
	n	28	17	
	LS Mean	4.612	8.816	-4.204
	SEM	5.359	5.765	5.193
Week 84	95% CI	(-5.9,15.2)	(-2.5,20.2)	(-14.4, 6.0)
	Pr >  t			0.4185
	n	23	17	
	LS Mean	7.581	7.201	0.380
	SEM	5.497	5.767	5.339
Week 96	95% CI	(-3.2,18.4)	(-4.1,18.5)	(-10.1,10.9)
	Pr >  t			0.9433
	n	23	11	
	LS Mean	6.306	11.340	-5.034
	SEM	5.499	6.292	5.903
Week 108	95% CI	(-4.5,17.1)	(-1.0,23.7)	(-16.6, 6.6)
	Pr >  t			0.3940
	n	15	13	
	LS Mean	8.386	13.587	-5.201
	SEM	5.898	6.073	6.054
Week 120	95% CI	(-3.2,20.0)	( 1.7,25.5)	(-17.1, 6.7)
	Pr >  t			0.3905
	n	16	9	
	LS Mean	4.606	9.895	-5.289
	SEM	5.833	6.598	6.522
Week 132	95% CI	(-6.9,16.1)	(-3.1,22.9)	(-18.1, 7.5)
	Pr >  t			0.4176
	n	14	5	
	LS Mean	7.856	4.378	3.478
	SEM	5.975	7.791	7.833
Week 144	95% CI	(-3.9,19.6)	(-10.9,19.7)	(-11.9,18.9)
	Pr >  t			0.6572
	n	8	3	
	LS Mean	6.210	4.211	1.999
	SEM	6.785	9.295	9.868



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-7.1,19.5)	(-14.0,22.5)	(-17.4,21.4)
		Pr >  t			0.8395
		n	7	2	
		LS Mean	9.369	19.459	-10.09
	Week 168	SEM	7.032	10.88	11.53
		95% CI	(-4.4,23.2)	(-1.9,40.8)	(-32.7,12.5)
		Pr >  t			0.3816
		n	4	2	
	Week 180	LS Mean	6.626	11.124	-4.498
		SEM	8.366	10.88	12.39
		95% CI	(-9.8,23.0)	(-10.2,32.5)	(-28.8,19.8)
		Pr >  t			0.7166
	Week 192	n	1	1	
		LS Mean	-6.330	14.398	-20.73
		SEM	14.62	14.63	19.81
		95% CI	(-35.0,22.4)	(-14.3,43.1)	(-59.6,18.2)
	Week 8	Pr >  t			0.2958
		n	1	1	
		LS Mean	27.000	14.398	12.602
		SEM	14.62	14.63	19.81
	Week 16	95% CI	(-1.7,55.7)	(-14.3,43.1)	(-26.3,51.5)
		Pr >  t			0.5249
		n	18	17	
		LS Mean	-6.308	0.196	-6.504
Week 24	SEM	4.963	5.226	7.214	
	95% CI	(-16.2, 3.6)	(-10.3,10.7)	(-20.9, 7.9)	
	Pr >  t			0.3707	
	n	17	11		
Week 32	LS Mean	-3.752	-4.898	1.147	
	SEM	5.074	6.201	8.035	
	95% CI	(-13.9, 6.4)	(-17.2, 7.4)	(-14.8,17.1)	
	Pr >  t			0.8869	
Week 8	n	15	5		
	LS Mean	-4.447	-1.961	-2.485	
	SEM	5.297	8.431	9.982	
	95% CI	(-15.0, 6.1)	(-18.6,14.7)	(-22.2,17.3)	
Week 16	Pr >  t			0.8038	
	n	13	5		
	LS Mean	1.477	-5.295	6.773	
Week 24	SEM	5.564	8.431	10.13	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-9.6,12.5)	(-22.0,11.4)	(-13.3,26.8)	
	Pr >  t			0.5049	
	n	11	5		
	LS Mean	4.063	-5.295	9.359	
	SEM	5.879	8.431	10.31	
Week 48	95% CI	(-7.6,15.7)	(-22.0,11.4)	(-11.0,29.7)	
	Pr >  t			0.3655	
	n	11	2		
	LS Mean	6.219	6.130	0.089	
	SEM	5.887	12.02	13.41	
Week 56	95% CI	(-5.5,17.9)	(-17.6,29.8)	(-26.4,26.6)	
	Pr >  t			0.9947	
	n	8	2		
	LS Mean	-0.729	-10.54	9.806	
	SEM	6.551	12.02	13.72	
Week 64	95% CI	(-13.7,12.2)	(-34.3,13.2)	(-17.3,36.9)	
	Pr >  t			0.4756	
	n	7	3		
	LS Mean	2.161	1.345	0.817	
	SEM	6.855	10.23	12.34	
Week 72	95% CI	(-11.4,15.7)	(-18.9,21.5)	(-23.5,25.2)	
	Pr >  t			0.9473	
	n	7	3		
	LS Mean	-0.310	-9.765	9.456	
	SEM	6.874	10.23	12.35	
Week 84	95% CI	(-13.9,13.3)	(-30.0,10.4)	(-14.9,33.8)	
	Pr >  t			0.4451	
	n	7	2		
	LS Mean	6.835	-2.200	9.035	
	SEM	6.874	12.02	13.87	
Week 96	95% CI	(-6.8,20.4)	(-25.9,21.5)	(-18.3,36.4)	
	Pr >  t			0.5156	
	n	6	3		
	LS Mean	1.468	-9.765	11.234	
	SEM	7.262	10.23	12.57	
Week 108	95% CI	(-12.9,15.8)	(-30.0,10.4)	(-13.6,36.0)	
	Pr >  t			0.3728	
	n	7	2		
	LS Mean	4.455	-9.311	13.766	
	SEM	6.874	12.00	13.85	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-9.1,18.0)	(-33.0,14.4)	(-13.6,41.1)
		Pr >  t			0.3217
		n	6	1	
		LS Mean	7.023	-8.226	15.249
		SEM	7.262	16.23	17.79
	Week 132	95% CI	(-7.3,21.4)	(-40.3,23.8)	(-19.9,50.4)
		Pr >  t			0.3926
		n	4		
		LS Mean	-1.231	NE	NE
		SEM	8.480	NE	NE
	Week 144	95% CI	(-18.0,15.5)	NE	NE
		Pr >  t			NE
		n	5		
		LS Mean	23.487	NE	NE
		SEM	7.776	NE	NE
	Week 156	95% CI	( 8.1,38.8)	NE	NE
		Pr >  t			NE
		n	3		
		LS Mean	-7.249	NE	NE
		SEM	9.551	NE	NE
	Week 8	95% CI	(-26.1,11.6)	NE	NE
		Pr >  t			NE
		n	59	57	
		LS Mean	-5.974	0.240	-6.214
SEM		3.692	3.866	3.920	
Week 16	95% CI	(-13.3, 1.3)	(-7.4, 7.9)	(-13.9, 1.5)	
	Pr >  t			0.1144	
	n	47	44		
	LS Mean	-1.614	5.006	-6.620	
	SEM	3.863	4.084	4.288	
Week 24	95% CI	(-9.2, 6.0)	(-3.1,13.1)	(-15.1, 1.8)	
	Pr >  t			0.1239	
	n	39	34		
	LS Mean	-0.690	4.897	-5.587	
	SEM	4.027	4.340	4.646	
Week 32	95% CI	(-8.6, 7.2)	(-3.7,13.4)	(-14.7, 3.6)	
	Pr >  t			0.2301	
	n	27	32		
	LS Mean	-1.449	4.202	-5.651	
	SEM	4.391	4.394	4.988	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 40	95% CI	(-10.1, 7.2)	(-4.5,12.9)	(-15.5, 4.2)
	Pr >  t			0.2579
	n	24	24	
	LS Mean	-4.851	0.892	-5.743
	SEM	4.516	4.687	5.345
Week 48	95% CI	(-13.7, 4.0)	(-8.3,10.1)	(-16.2, 4.8)
	Pr >  t			0.2832
	n	21	21	
	LS Mean	-8.860	0.030	-8.890
	SEM	4.663	4.835	5.600
Week 56	95% CI	(-18.0, 0.3)	(-9.5, 9.5)	(-19.9, 2.1)
	Pr >  t			0.1131
	n	18	20	
	LS Mean	-0.108	7.412	-7.520
	SEM	4.845	4.895	5.810
Week 64	95% CI	(-9.6, 9.4)	(-2.2,17.0)	(-18.9, 3.9)
	Pr >  t			0.1962
	n	14	19	
	LS Mean	3.621	4.245	-0.624
	SEM	5.190	4.957	6.158
Week 72	95% CI	(-6.6,13.8)	(-5.5,14.0)	(-12.7,11.5)
	Pr >  t			0.9194
	n	13	15	
	LS Mean	-5.481	5.070	-10.55
	SEM	5.308	5.268	6.509
Week 84	95% CI	(-15.9, 5.0)	(-5.3,15.4)	(-23.3, 2.2)
	Pr >  t			0.1056
	n	10	14	
	LS Mean	3.703	10.354	-6.651
	SEM	5.798	5.366	6.961
Week 96	95% CI	(-7.7,15.1)	(-0.2,20.9)	(-20.3, 7.0)
	Pr >  t			0.3398
	n	6	10	
	LS Mean	2.086	9.995	-7.908
	SEM	6.928	5.926	8.341
Week 108	95% CI	(-11.5,15.7)	(-1.6,21.6)	(-24.3, 8.5)
	Pr >  t			0.3435
	n	4	6	
	LS Mean	-1.788	4.260	-6.047
	SEM	8.159	7.052	10.12

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.8,14.2)	(-9.6,18.1)	(-25.9,13.8)
		Pr >  t			0.5503
	Week 120	n	6	6	
		LS Mean	-4.748	-2.095	-2.653
		SEM	6.931	7.055	9.180
		95% CI	(-18.4, 8.9)	(-16.0,11.8)	(-20.7,15.4)
		Pr >  t			0.7727
	Week 132	n	2	3	
		LS Mean	-11.25	1.307	-12.55
		SEM	10.98	9.251	13.86
		95% CI	(-32.8,10.3)	(-16.9,19.5)	(-39.8,14.7)
		Pr >  t			0.3657
	Week 144	n	2	2	
		LS Mean	10.915	1.184	9.731
		SEM	10.94	11.05	15.13
		95% CI	(-10.6,32.4)	(-20.5,22.9)	(-20.0,39.5)
		Pr >  t			0.5205
	Week 156	n		1	
		LS Mean	NE	2.532	NE
		SEM	NE	15.12	NE
		95% CI	NE	(-27.2,32.2)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
95% CI	NE		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	NE	NE	NE			
	SEM	NE	NE	NE			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	NE
		Pr >  t		NE
	Week 72	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
	Week 84	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
	Week 96	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
Positive	Week 8	n	140	140
		LS Mean	-2.028	2.244
		SEM	2.843	2.877
		95% CI	(-7.6, 3.6)	(-3.4, 7.9)
		Pr >  t		(-9.2, 0.6) 0.0863
	Week 16	n	122	107
		LS Mean	-1.602	4.346
		SEM	2.910	3.015
		95% CI	(-7.3, 4.1)	(-1.6, 10.3)
		Pr >  t		(-11.2, -0.7) 0.0265
	Week 24	n	104	81
		LS Mean	0.674	4.946
		SEM	2.976	3.150
		95% CI	(-5.2, 6.5)	(-1.2, 11.1)
		Pr >  t		(-9.9, 1.4) 0.1389
	Week 32	n	85	73
		LS Mean	1.182	3.776
		SEM	3.081	3.211
		95% CI	(-4.9, 7.2)	(-2.5, 10.1)
		Pr >  t		(-8.5, 3.3) 0.3920
	Week 40	n	74	62
		LS Mean	0.872	3.530
		SEM	3.146	3.305
				-2.658 3.185

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-5.3, 7.1)	(-3.0, 10.0)	(-8.9, 3.6)
	Pr >  t			0.4042
Week 48	n	68	51	
	LS Mean	1.286	5.049	-3.763
	SEM	3.186	3.420	3.344
	95% CI	(-5.0, 7.5)	(-1.7, 11.8)	(-10.3, 2.8)
	Pr >  t			0.2608
Week 56	n	58	45	
	LS Mean	1.239	5.121	-3.882
	SEM	3.270	3.503	3.510
	95% CI	(-5.2, 7.7)	(-1.8, 12.0)	(-10.8, 3.0)
	Pr >  t			0.2690
Week 64	n	47	42	
	LS Mean	2.455	4.507	-2.052
	SEM	3.395	3.553	3.678
	95% CI	(-4.2, 9.1)	(-2.5, 11.5)	(-9.3, 5.2)
	Pr >  t			0.5770
Week 72	n	47	35	
	LS Mean	0.138	5.063	-4.926
	SEM	3.398	3.693	3.815
	95% CI	(-6.5, 6.8)	(-2.2, 12.3)	(-12.4, 2.6)
	Pr >  t			0.1969
Week 84	n	39	33	
	LS Mean	5.091	7.075	-1.985
	SEM	3.537	3.742	3.979
	95% CI	(-1.9, 12.0)	(-0.3, 14.4)	(-9.8, 5.8)
	Pr >  t			0.6180
Week 96	n	34	24	
	LS Mean	3.206	7.998	-4.793
	SEM	3.642	4.049	4.360
	95% CI	(-3.9, 10.4)	(0.1, 15.9)	(-13.3, 3.8)
	Pr >  t			0.2719
Week 108	n	26	21	
	LS Mean	4.370	7.735	-3.365
	SEM	3.898	4.200	4.705
	95% CI	(-3.3, 12.0)	(-0.5, 16.0)	(-12.6, 5.9)
	Pr >  t			0.4746
Week 120	n	28	16	
	LS Mean	1.968	3.218	-1.250
	SEM	3.820	4.554	4.968



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.5, 9.5)	(-5.7, 12.2)	(-11.0, 8.5)
		Pr >  t			0.8015
	Week 132	n	20	8	
		LS Mean	2.157	1.432	0.725
		SEM	4.191	5.793	6.358
		95% CI	(-6.1, 10.4)	(-9.9, 12.8)	(-11.7, 13.2)
		Pr >  t			0.9093
	Week 144	n	15	5	
		LS Mean	11.265	1.314	9.952
		SEM	4.572	7.002	7.702
		95% CI	( 2.3, 20.2)	(-12.4, 15.0)	(-5.2, 25.1)
		Pr >  t			0.1966
	Week 156	n	10	3	
		LS Mean	2.025	11.916	-9.891
		SEM	5.275	8.731	9.662
		95% CI	(-8.3, 12.4)	(-5.2, 29.0)	(-28.8, 9.1)
		Pr >  t			0.3062
	Week 168	n	4	2	
		LS Mean	3.229	7.575	-4.346
		SEM	7.645	10.50	12.57
		95% CI	(-11.8, 18.2)	(-13.0, 28.2)	(-29.0, 20.3)
		Pr >  t			0.7296
	Week 180	n	1	1	
		LS Mean	-9.650	10.676	-20.33
		SEM	14.54	14.56	20.31
		95% CI	(-38.2, 18.9)	(-17.9, 39.2)	(-60.2, 19.5)
		Pr >  t			0.3172
	Week 192	n	1	1	
		LS Mean	23.680	10.676	13.005
		SEM	14.54	14.56	20.31
		95% CI	(-4.8, 52.2)	(-17.9, 39.2)	(-26.8, 52.9)
		Pr >  t			0.5222

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	3.073	2.616	0.456
			SEM	5.195	5.714	5.406
			95% CI	(-7.2,13.4)	(-8.7,14.0)	(-10.3,11.2)
			Pr >  t			0.9329
		Week 16	n	35	22	
			LS Mean	0.414	4.721	-4.307
			SEM	5.381	6.354	6.041
			95% CI	(-10.3,11.1)	(-7.9,17.3)	(-16.2, 7.6)
			Pr >  t			0.4770
		Week 24	n	28	16	
			LS Mean	4.481	8.630	-4.148
			SEM	5.550	6.716	6.601
			95% CI	(-6.5,15.5)	(-4.6,21.9)	(-17.2, 8.9)
			Pr >  t			0.5305
		Week 32	n	22	16	
			LS Mean	2.635	6.045	-3.410
			SEM	5.832	6.734	6.794
			95% CI	(-8.9,14.2)	(-7.3,19.4)	(-16.8,10.0)
			Pr >  t			0.6163
		Week 40	n	19	12	
			LS Mean	0.575	10.754	-10.18
			SEM	5.983	7.113	7.306
			95% CI	(-11.3,12.4)	(-3.3,24.8)	(-24.6, 4.2)
Pr >  t				0.1648		
Week 48	n	16	10			
	LS Mean	7.575	9.264	-1.689		
	SEM	6.177	7.398	7.738		
	95% CI	(-4.6,19.8)	(-5.3,23.9)	(-16.9,13.5)		
	Pr >  t			0.8274		
Week 56	n	14	7			
	LS Mean	8.313	3.868	4.445		
	SEM	6.349	8.071	8.524		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	95% CI	(-4.2,20.8)	(-12.0,19.8)	(-12.3,21.2)	
	Pr >  t			0.6025	
	n	8	7		
	LS Mean	7.123	-0.891	8.014	
	SEM	7.232	8.071	9.209	
Week 72	95% CI	(-7.1,21.4)	(-16.8,15.0)	(-10.1,26.1)	
	Pr >  t			0.3848	
	n	12	6		
	LS Mean	3.970	0.758	3.213	
	SEM	6.560	8.419	9.014	
Week 84	95% CI	(-9.0,16.9)	(-15.8,17.3)	(-14.5,20.9)	
	Pr >  t			0.7218	
	n	8	5		
	LS Mean	13.172	8.951	4.221	
	SEM	7.273	8.871	9.926	
Week 96	95% CI	(-1.2,27.5)	(-8.5,26.4)	(-15.3,23.7)	
	Pr >  t			0.6709	
	n	5	5		
	LS Mean	15.060	2.285	12.776	
	SEM	8.356	8.871	10.75	
Week 108	95% CI	(-1.4,31.5)	(-15.2,19.7)	(-8.4,33.9)	
	Pr >  t			0.2355	
	n	7	5		
	LS Mean	6.777	12.285	-5.508	
	SEM	7.551	8.871	10.14	
Week 120	95% CI	(-8.1,21.6)	(-5.2,29.7)	(-25.4,14.4)	
	Pr >  t			0.5872	
	n	5	3		
	LS Mean	10.018	6.530	3.489	
	SEM	8.366	10.45	12.09	
Week 132	95% CI	(-6.4,26.5)	(-14.0,27.1)	(-20.3,27.3)	
	Pr >  t			0.7732	
	n	2	2		
	LS Mean	7.972	2.478	5.494	
	SEM	11.71	12.05	15.79	
Week 144	95% CI	(-15.1,31.0)	(-21.2,26.2)	(-25.6,36.6)	
	Pr >  t			0.7282	
	n	2			
	LS Mean	36.386	NE	NE	
	SEM	11.72	NE	NE	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 13.3,59.4)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	-0.892	NE	NE
		SEM	11.73	NE	NE
		95% CI	(-24.0,22.2)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	4.029	NE	NE
		SEM	15.81	NE	NE
		95% CI	(-27.1,35.1)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	98	104	
		LS Mean	-4.937	1.243	-6.181
		SEM	3.508	3.466	2.830
		95% CI	(-11.8, 2.0)	( -5.6, 8.1)	(-11.7,-0.6)
		Pr >  t			0.0295
	Week 16	n	87	84	
		LS Mean	-3.381	3.269	-6.651
		SEM	3.576	3.563	3.006
		95% CI	(-10.4, 3.7)	( -3.7,10.3)	(-12.6,-0.7)
		Pr >  t			0.0274
	Week 24	n	76	65	
		LS Mean	-1.291	3.195	-4.485
		SEM	3.647	3.700	3.217
		95% CI	( -8.5, 5.9)	( -4.1,10.5)	(-10.8, 1.8)
		Pr >  t			0.1637
	Week 32	n	62	57	
		LS Mean	-0.255	2.343	-2.598
		SEM	3.751	3.780	3.398
		95% CI	( -7.6, 7.1)	( -5.1, 9.8)	( -9.3, 4.1)
		Pr >  t			0.4448
	Week 40	n	54	50	
		LS Mean	-0.282	0.930	-1.212
		SEM	3.821	3.864	3.555
		95% CI	( -7.8, 7.2)	( -6.7, 8.5)	( -8.2, 5.8)
		Pr >  t			0.7333
	Week 48	n	52	41	
		LS Mean	-1.611	3.143	-4.754
		SEM	3.840	3.985	3.706

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.2, 5.9)	(-4.7, 11.0)	(-12.0, 2.5)
		Pr >  t			0.2000
	Week 56	n	44	38	
		LS Mean	-1.881	4.360	-6.241
		SEM	3.932	4.037	3.859
		95% CI	(-9.6, 5.8)	(-3.6, 12.3)	(-13.8, 1.3)
		Pr >  t			0.1062
	Week 64	n	39	35	
		LS Mean	0.101	4.677	-4.576
		SEM	4.008	4.095	3.998
		95% CI	(-7.8, 8.0)	(-3.4, 12.7)	(-12.4, 3.3)
		Pr >  t			0.2527
	Week 72	n	36	29	
		LS Mean	-1.952	5.041	-6.993
		SEM	4.062	4.241	4.201
		95% CI	(-9.9, 6.0)	(-3.3, 13.4)	(-15.2, 1.3)
		Pr >  t			0.0963
	Week 84	n	32	28	
		LS Mean	2.280	5.820	-3.540
		SEM	4.154	4.270	4.313
		95% CI	(-5.9, 10.4)	(-2.6, 14.2)	(-12.0, 4.9)
		Pr >  t			0.4120
	Week 96	n	30	19	
		LS Mean	-0.420	8.665	-9.085
		SEM	4.197	4.656	4.741
		95% CI	(-8.7, 7.8)	(-0.5, 17.8)	(-18.4, 0.2)
		Pr >  t			0.0556
	Week 108	n	18	16	
		LS Mean	3.488	5.404	-1.916
		SEM	4.707	4.868	5.380
		95% CI	(-5.8, 12.7)	(-4.2, 15.0)	(-12.5, 8.6)
		Pr >  t			0.7219
	Week 120	n	23	13	
		LS Mean	-1.013	1.560	-2.573
		SEM	4.436	5.157	5.429
		95% CI	(-9.7, 7.7)	(-8.6, 11.7)	(-13.2, 8.1)
		Pr >  t			0.6356
	Week 132	n	18	6	
		LS Mean	-0.256	0.188	-0.444
		SEM	4.708	6.675	7.057

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-9.5, 9.0)	(-12.9,13.3)	(-14.3,13.4)
	Pr >  t			0.9499
Week 144	n	13	5	
	LS Mean	5.912	0.141	5.771
	SEM	5.125	7.158	7.797
	95% CI	(-4.1,16.0)	(-13.9,14.2)	(-9.5,21.1)
	Pr >  t			0.4593
Week 156	n	8	3	
	LS Mean	1.638	10.743	-9.106
	SEM	5.998	8.815	9.837
	95% CI	(-10.1,13.4)	(-6.5,28.0)	(-28.4,10.2)
	Pr >  t			0.3548
Week 168	n	3	2	
	LS Mean	2.080	6.406	-4.326
	SEM	8.787	10.53	13.08
	95% CI	(-15.2,19.3)	(-14.2,27.1)	(-30.0,21.3)
	Pr >  t			0.7409
Week 180	n	1	1	
	LS Mean	-11.94	9.403	-21.34
	SEM	14.48	14.48	20.06
	95% CI	(-40.3,16.5)	(-19.0,37.8)	(-60.7,18.0)
	Pr >  t			0.2876
Week 192	n	1	1	
	LS Mean	21.394	9.403	11.991
	SEM	14.48	14.48	20.06
	95% CI	(-7.0,49.8)	(-19.0,37.8)	(-27.4,51.3)
	Pr >  t			0.5501

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	-5.001	1.153	-6.154		
			SEM	3.534	3.482	2.857		
			95% CI	(-12.0, 2.0)	(-5.7, 8.0)	(-11.8,-0.5)		
					Pr >  t			0.0318
		Week 16	n	85	84			
			LS Mean	-3.405	3.180	-6.585		
			SEM	3.605	3.579	3.037		
			95% CI	(-10.5, 3.7)	(-3.9,10.2)	(-12.6,-0.6)		
					Pr >  t			0.0306
		Week 24	n	75	65			
			LS Mean	-1.316	3.106	-4.421		
			SEM	3.675	3.717	3.244		
			95% CI	(-8.5, 5.9)	(-4.2,10.4)	(-10.8, 1.9)		
					Pr >  t			0.1734
		Week 32	n	61	57			
			LS Mean	-0.256	2.254	-2.510		
			SEM	3.781	3.797	3.429		
			95% CI	(-7.7, 7.2)	(-5.2, 9.7)	(-9.2, 4.2)		
					Pr >  t			0.4644
		Week 40	n	53	50			
			LS Mean	-0.245	0.841	-1.086		
			SEM	3.854	3.881	3.589		
			95% CI	(-7.8, 7.3)	(-6.8, 8.5)	(-8.1, 6.0)		
			Pr >  t			0.7623		
Week 48	n	51	41					
	LS Mean	-1.926	3.054	-4.980				
	SEM	3.874	4.003	3.740				
	95% CI	(-9.5, 5.7)	(-4.8,10.9)	(-12.3, 2.4)				
			Pr >  t			0.1834		
Week 56	n	43	38					
	LS Mean	-1.860	4.271	-6.131				
	SEM	3.970	4.055	3.897				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.7, 5.9)	(-3.7,12.2)	(-13.8, 1.5)
	Pr >  t			0.1160
	n	39	35	
	LS Mean	0.030	4.588	-4.558
	SEM	4.032	4.113	4.022
Week 72	95% CI	(-7.9, 8.0)	(-3.5,12.7)	(-12.5, 3.3)
	Pr >  t			0.2574
	n	35	29	
	LS Mean	-1.963	4.953	-6.916
	SEM	4.107	4.259	4.245
Week 84	95% CI	(-10.0, 6.1)	(-3.4,13.3)	(-15.2, 1.4)
	Pr >  t			0.1036
	n	31	28	
	LS Mean	1.870	5.730	-3.860
	SEM	4.203	4.289	4.362
Week 96	95% CI	(-6.4,10.1)	(-2.7,14.2)	(-12.4, 4.7)
	Pr >  t			0.3763
	n	29	19	
	LS Mean	-0.366	8.576	-8.942
	SEM	4.249	4.676	4.792
Week 108	95% CI	(-8.7, 8.0)	(-0.6,17.8)	(-18.3, 0.5)
	Pr >  t			0.0623
	n	18	16	
	LS Mean	3.414	5.316	-1.902
	SEM	4.733	4.889	5.408
Week 120	95% CI	(-5.9,12.7)	(-4.3,14.9)	(-12.5, 8.7)
	Pr >  t			0.7251
	n	23	13	
	LS Mean	-1.084	1.472	-2.555
	SEM	4.461	5.179	5.456
Week 132	95% CI	(-9.8, 7.7)	(-8.7,11.6)	(-13.3, 8.1)
	Pr >  t			0.6396
	n	18	6	
	LS Mean	-0.329	0.100	-0.430
	SEM	4.734	6.702	7.090
Week 144	95% CI	(-9.6, 9.0)	(-13.0,13.2)	(-14.3,13.5)
	Pr >  t			0.9517
	n	13	5	
	LS Mean	5.842	0.054	5.788
	SEM	5.152	7.187	7.831

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	(-4.3,16.0)	(-14.0,14.2)	(-9.6,21.2)
		Pr >  t			0.4600
		n	8	3	
		LS Mean	1.566	10.656	-9.090
		SEM	6.027	8.850	9.878
	Week 168	95% CI	(-10.3,13.4)	(-6.7,28.0)	(-28.5,10.3)
		Pr >  t			0.3577
		n	3	2	
		LS Mean	2.013	6.318	-4.305
		SEM	8.824	10.57	13.13
	Week 180	95% CI	(-15.3,19.3)	(-14.4,27.1)	(-30.1,21.5)
		Pr >  t			0.7432
		n	1	1	
		LS Mean	-11.99	9.318	-21.30
		SEM	14.54	14.53	20.13
	Week 192	95% CI	(-40.5,16.5)	(-19.2,37.8)	(-60.8,18.2)
		Pr >  t			0.2902
		n	1	1	
		LS Mean	21.344	9.318	12.025
		SEM	14.54	14.53	20.13
	Week 8	95% CI	(-7.2,49.9)	(-19.2,37.8)	(-27.5,51.5)
		Pr >  t			0.5505
		n	42	35	
		LS Mean	3.073	2.616	0.456
SEM		5.195	5.714	5.406	
Week 16	95% CI	(-7.2,13.4)	(-8.7,14.0)	(-10.3,11.2)	
	Pr >  t			0.9329	
	n	35	22		
	LS Mean	0.414	4.721	-4.307	
	SEM	5.381	6.354	6.041	
Week 24	95% CI	(-10.3,11.1)	(-7.9,17.3)	(-16.2, 7.6)	
	Pr >  t			0.4770	
	n	28	16		
	LS Mean	4.481	8.630	-4.148	
	SEM	5.550	6.716	6.601	
Week 32	95% CI	(-6.5,15.5)	(-4.6,21.9)	(-17.2, 8.9)	
	Pr >  t			0.5305	
	n	22	16		
		LS Mean	2.635	6.045	-3.410
		SEM	5.832	6.734	6.794

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-8.9,14.2)	(-7.3,19.4)	(-16.8,10.0)
	Pr >  t			0.6163
	n	19	12	
	LS Mean	0.575	10.754	-10.18
	SEM	5.983	7.113	7.306
Week 48	95% CI	(-11.3,12.4)	(-3.3,24.8)	(-24.6, 4.2)
	Pr >  t			0.1648
	n	16	10	
	LS Mean	7.575	9.264	-1.689
	SEM	6.177	7.398	7.738
Week 56	95% CI	(-4.6,19.8)	(-5.3,23.9)	(-16.9,13.5)
	Pr >  t			0.8274
	n	14	7	
	LS Mean	8.313	3.868	4.445
	SEM	6.349	8.071	8.524
Week 64	95% CI	(-4.2,20.8)	(-12.0,19.8)	(-12.3,21.2)
	Pr >  t			0.6025
	n	8	7	
	LS Mean	7.123	-0.891	8.014
	SEM	7.232	8.071	9.209
Week 72	95% CI	(-7.1,21.4)	(-16.8,15.0)	(-10.1,26.1)
	Pr >  t			0.3848
	n	12	6	
	LS Mean	3.970	0.758	3.213
	SEM	6.560	8.419	9.014
Week 84	95% CI	(-9.0,16.9)	(-15.8,17.3)	(-14.5,20.9)
	Pr >  t			0.7218
	n	8	5	
	LS Mean	13.172	8.951	4.221
	SEM	7.273	8.871	9.926
Week 96	95% CI	(-1.2,27.5)	(-8.5,26.4)	(-15.3,23.7)
	Pr >  t			0.6709
	n	5	5	
	LS Mean	15.060	2.285	12.776
	SEM	8.356	8.871	10.75
Week 108	95% CI	(-1.4,31.5)	(-15.2,19.7)	(-8.4,33.9)
	Pr >  t			0.2355
	n	7	5	
	LS Mean	6.777	12.285	-5.508
	SEM	7.551	8.871	10.14

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-8.1,21.6)	(-5.2,29.7)	(-25.4,14.4)
	Pr >  t			0.5872
	n	5	3	
	LS Mean	10.018	6.530	3.489
	SEM	8.366	10.45	12.09
Week 132	95% CI	(-6.4,26.5)	(-14.0,27.1)	(-20.3,27.3)
	Pr >  t			0.7732
	n	2	2	
	LS Mean	7.972	2.478	5.494
	SEM	11.71	12.05	15.79
Week 144	95% CI	(-15.1,31.0)	(-21.2,26.2)	(-25.6,36.6)
	Pr >  t			0.7282
	n	2		
	LS Mean	36.386	NE	NE
	SEM	11.72	NE	NE
Week 156	95% CI	(13.3,59.4)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	-0.892	NE	NE
	SEM	11.73	NE	NE
Week 168	95% CI	(-24.0,22.2)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	4.029	NE	NE
	SEM	15.81	NE	NE
	95% CI	(-27.1,35.1)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-1.251	2.921	-4.171
			SEM	3.114	3.212	2.928
			95% CI	(-7.4, 4.9)	(-3.4, 9.2)	(-9.9, 1.6)
		Pr >  t			0.1550	
		Week 16	n	90	75	
			LS Mean	-0.733	5.399	-6.132
			SEM	3.180	3.345	3.123
			95% CI	(-7.0, 5.5)	(-1.2, 12.0)	(-12.3, 0.0)
		Pr >  t			0.0502	
		Week 24	n	79	62	
			LS Mean	-0.339	4.773	-5.112
			SEM	3.243	3.458	3.284
			95% CI	(-6.7, 6.0)	(-2.0, 11.6)	(-11.6, 1.3)
		Pr >  t			0.1202	
		Week 32	n	70	56	
			LS Mean	1.307	5.211	-3.904
			SEM	3.320	3.523	3.394
			95% CI	(-5.2, 7.8)	(-1.7, 12.1)	(-10.6, 2.8)
		Pr >  t			0.2506	
		Week 40	n	61	46	
			LS Mean	1.098	3.258	-2.160
			SEM	3.385	3.644	3.572
			95% CI	(-5.6, 7.8)	(-3.9, 10.4)	(-9.2, 4.9)
Pr >  t			0.5457			
Week 48	n	56	38			
	LS Mean	0.548	4.203	-3.655		
	SEM	3.427	3.768	3.738		
	95% CI	(-6.2, 7.3)	(-3.2, 11.6)	(-11.0, 3.7)		
Pr >  t			0.3285			
Week 56	n	49	33			
	LS Mean	1.871	4.302	-2.431		
	SEM	3.497	3.870	3.908		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-5.0, 8.7)	(-3.3,11.9)	(-10.1, 5.2)
	Pr >  t			0.5341
	n	37	29	
	LS Mean	2.632	2.599	0.032
	SEM	3.668	3.977	4.165
Week 72	95% CI	(-4.6, 9.8)	(-5.2,10.4)	(-8.1, 8.2)
	Pr >  t			0.9938
	n	40	25	
	LS Mean	0.597	5.470	-4.873
	SEM	3.619	4.105	4.245
Week 84	95% CI	(-6.5, 7.7)	(-2.6,13.5)	(-13.2, 3.5)
	Pr >  t			0.2514
	n	32	23	
	LS Mean	5.770	10.920	-5.150
	SEM	3.785	4.186	4.456
Week 96	95% CI	(-1.7,13.2)	( 2.7,19.1)	(-13.9, 3.6)
	Pr >  t			0.2480
	n	29	17	
	LS Mean	2.336	5.197	-2.860
	SEM	3.859	4.519	4.833
Week 108	95% CI	(-5.2, 9.9)	(-3.7,14.1)	(-12.3, 6.6)
	Pr >  t			0.5541
	n	22	15	
	LS Mean	5.199	4.919	0.280
	SEM	4.123	4.679	5.184
Week 120	95% CI	(-2.9,13.3)	(-4.3,14.1)	(-9.9,10.4)
	Pr >  t			0.9570
	n	23	13	
	LS Mean	1.763	1.449	0.314
	SEM	4.074	4.882	5.334
Week 132	95% CI	(-6.2, 9.8)	(-8.1,11.0)	(-10.2,10.8)
	Pr >  t			0.9531
	n	17	5	
	LS Mean	2.247	3.081	-0.834
	SEM	4.410	6.813	7.337
Week 144	95% CI	(-6.4,10.9)	(-10.3,16.4)	(-15.2,13.6)
	Pr >  t			0.9096
	n	14	3	
Week 144	LS Mean	11.078	-0.479	11.557
	SEM	4.656	8.428	8.987

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.9,20.2)	(-17.0,16.1)	( -6.1,29.2)
		Pr >  t			0.1987
	Week 156	n	9	2	
		LS Mean	0.602	15.851	-15.25
		SEM	5.389	10.07	10.88
		95% CI	(-10.0,11.2)	( -3.9,35.6)	(-36.6, 6.1)
		Pr >  t			0.1613
	Week 168	n	4	1	
		LS Mean	3.264	10.940	-7.676
		SEM	7.375	13.88	15.33
		95% CI	(-11.2,17.7)	(-16.3,38.2)	(-37.8,22.4)
		Pr >  t			0.6167
	Week 180	n	1	1	
		LS Mean	-9.632	10.940	-20.57
		SEM	13.83	13.88	19.28
		95% CI	(-36.8,17.5)	(-16.3,38.2)	(-58.4,17.3)
		Pr >  t			0.2863
	Week 192	n	1	1	
		LS Mean	23.698	10.940	12.758
		SEM	13.83	13.88	19.28
		95% CI	( -3.4,50.8)	(-16.3,38.2)	(-25.1,50.6)
		Pr >  t			0.5084
>= 3	Week 8	n	37	45	
		LS Mean	-5.298	-0.492	-4.806
		SEM	8.394	8.351	4.835
		95% CI	(-21.9,11.3)	(-17.0,16.0)	(-14.3, 4.7)
		Pr >  t			0.3214
	Week 16	n	34	32	
		LS Mean	-4.879	0.599	-5.478
		SEM	8.645	8.739	5.286
		95% CI	(-21.9,12.2)	(-16.6,17.8)	(-15.9, 4.9)
		Pr >  t			0.3012
	Week 24	n	26	19	
		LS Mean	2.829	4.918	-2.089
		SEM	8.827	9.137	6.202
		95% CI	(-14.6,20.2)	(-13.1,22.9)	(-14.3,10.1)
		Pr >  t			0.7365
	Week 32	n	16	17	
		LS Mean	-0.133	-1.485	1.352
		SEM	9.255	9.258	6.965

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.4,18.1)	(-19.7,16.8)	(-12.4,15.1)
		Pr >  t			0.8463
	Week 40	n	14	16	
		LS Mean	-1.010	3.610	-4.620
		SEM	9.410	9.317	7.238
		95% CI	(-19.5,17.5)	(-14.7,22.0)	(-18.9, 9.6)
		Pr >  t			0.5237
	Week 48	n	13	13	
		LS Mean	4.744	6.829	-2.084
		SEM	9.489	9.546	7.631
		95% CI	(-13.9,23.4)	(-12.0,25.6)	(-17.1,12.9)
		Pr >  t			0.7849
	Week 56	n	10	12	
		LS Mean	-2.837	6.701	-9.538
		SEM	9.850	9.652	8.179
		95% CI	(-22.2,16.6)	(-12.3,25.7)	(-25.6, 6.5)
		Pr >  t			0.2443
	Week 64	n	10	13	
		LS Mean	0.984	7.822	-6.838
		SEM	9.854	9.557	8.072
		95% CI	(-18.4,20.4)	(-11.0,26.6)	(-22.7, 9.0)
		Pr >  t			0.3975
	Week 72	n	8	10	
		LS Mean	-2.746	3.161	-5.907
		SEM	10.20	9.899	8.884
		95% CI	(-22.8,17.3)	(-16.3,22.7)	(-23.4,11.6)
		Pr >  t			0.5065
	Week 84	n	8	10	
		LS Mean	3.119	-2.782	5.901
		SEM	10.21	9.896	8.886
		95% CI	(-17.0,23.2)	(-22.3,16.7)	(-11.6,23.4)
		Pr >  t			0.5070
	Week 96	n	6	7	
		LS Mean	6.182	13.819	-7.637
		SEM	10.78	10.50	10.14
		95% CI	(-15.0,27.4)	(-6.8,34.5)	(-27.6,12.3)
		Pr >  t			0.4521
	Week 108	n	4	6	
		LS Mean	-0.167	14.013	-14.18
		SEM	11.80	10.80	11.53



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-23.4,23.0)	(-7.2,35.3)	(-36.9, 8.5)
		Pr >  t			0.2195
	Week 120	n	5	3	
		LS Mean	2.585	10.360	-7.776
		SEM	11.20	12.77	12.85
		95% CI	(-19.4,24.6)	(-14.7,35.5)	(-33.1,17.5)
		Pr >  t			0.5456
	Week 132	n	3	3	
		LS Mean	1.577	-1.960	3.537
		SEM	12.74	12.77	14.23
		95% CI	(-23.5,26.6)	(-27.1,23.2)	(-24.5,31.5)
		Pr >  t			0.8039
	Week 144	n	1	2	
		LS Mean	16.318	3.013	13.305
		SEM	18.62	14.47	20.83
		95% CI	(-20.3,52.9)	(-25.4,31.5)	(-27.7,54.3)
		Pr >  t			0.5234
	Week 156	n	1	1	
		LS Mean	16.318	3.292	13.026
		SEM	18.62	18.65	23.92
		95% CI	(-20.3,52.9)	(-33.4,40.0)	(-34.0,60.1)
		Pr >  t			0.5864
	Week 168	n		1	
		LS Mean	NE	3.292	NE
		SEM	NE	18.65	NE
		95% CI	NE	(-33.4,40.0)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-23i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Pain score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	-8.928	-4.361	-4.567		
			SEM	8.475	8.768	3.692		
			95% CI	(-25.7, 7.9)	(-21.7,13.0)	(-11.8, 2.7)		
					Pr >  t			0.2171
		Week 16	n	59	49			
			LS Mean	-8.009	1.145	-9.154		
			SEM	8.500	8.836	3.936		
			95% CI	(-24.9, 8.8)	(-16.4,18.7)	(-16.9,-1.4)		
					Pr >  t			0.0206
		Week 24	n	54	41			
			LS Mean	-7.343	-1.098	-6.245		
			SEM	8.517	8.898	4.120		
			95% CI	(-24.2, 9.5)	(-18.7,16.5)	(-14.3, 1.9)		
					Pr >  t			0.1305
		Week 32	n	48	37			
			LS Mean	-4.557	1.051	-5.608		
			SEM	8.543	8.932	4.261		
			95% CI	(-21.5,12.4)	(-16.6,18.7)	(-14.0, 2.8)		
					Pr >  t			0.1889
		Week 40	n	43	33			
			LS Mean	-5.467	-1.570	-3.897		
			SEM	8.568	8.976	4.414		
			95% CI	(-22.4,11.5)	(-19.3,16.2)	(-12.6, 4.8)		
					Pr >  t			0.3777
		Week 48	n	41	28			
			LS Mean	-5.715	-3.136	-2.578		
			SEM	8.581	9.041	4.575		
95% CI	(-22.7,11.3)		(-21.0,14.8)	(-11.6, 6.4)				
			Pr >  t			0.5733		
Week 56	n	35	22					
	LS Mean	-4.570	-2.456	-2.114				
	SEM	8.628	9.158	4.898				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.7,12.5)	(-20.6,15.7)	(-11.7, 7.5)
		Pr >  t			0.6662
	Week 64	n	26	23	
		LS Mean	-2.365	-4.755	2.390
		SEM	8.736	9.136	5.065
		95% CI	(-19.7,14.9)	(-22.8,13.3)	(-7.6,12.3)
		Pr >  t			0.6372
	Week 72	n	28	18	
		LS Mean	-5.536	0.729	-6.265
		SEM	8.704	9.276	5.261
		95% CI	(-22.8,11.7)	(-17.6,19.1)	(-16.6, 4.1)
		Pr >  t			0.2341
	Week 84	n	22	18	
		LS Mean	-2.474	3.099	-5.574
		SEM	8.851	9.276	5.448
		95% CI	(-20.0,15.0)	(-15.2,21.4)	(-16.3, 5.1)
		Pr >  t			0.3067
	Week 96	n	21	13	
		LS Mean	-3.279	-0.923	-2.356
		SEM	8.833	9.512	5.885
		95% CI	(-20.8,14.2)	(-19.7,17.9)	(-13.9, 9.2)
		Pr >  t			0.6889
	Week 108	n	17	12	
		LS Mean	-3.183	-2.158	-1.025
		SEM	9.005	9.583	6.187
		95% CI	(-21.0,14.6)	(-21.1,16.8)	(-13.2,11.1)
		Pr >  t			0.8685
	Week 120	n	18	11	
		LS Mean	-6.979	-7.490	0.510
		SEM	8.916	9.666	6.262
		95% CI	(-24.6,10.7)	(-26.6,11.6)	(-11.8,12.8)
		Pr >  t			0.9351
	Week 132	n	13	5	
		LS Mean	-6.193	-3.424	-2.770
		SEM	9.207	10.75	8.113
		95% CI	(-24.4,12.0)	(-24.6,17.8)	(-18.7,13.2)
		Pr >  t			0.7329
	Week 144	n	12	3	
		LS Mean	0.553	-7.000	7.553
		SEM	9.207	11.96	9.728

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.6,18.7)	(-30.5,16.5)	(-11.5,26.6)
		Pr >  t			0.4377
	Week 156	n	7	2	
		LS Mean	-8.286	9.250	-17.54
		SEM	9.908	13.30	11.85
		95% CI	(-27.8,11.3)	(-16.9,35.4)	(-40.8, 5.7)
		Pr >  t			0.1393
	Week 168	n	3	1	
		LS Mean	-2.885	4.286	-7.172
		SEM	11.70	16.68	16.75
		95% CI	(-25.9,20.1)	(-28.5,37.0)	(-40.1,25.7)
		Pr >  t			0.6687
	Week 180	n	1	1	
		LS Mean	-16.78	4.286	-21.06
		SEM	16.51	16.68	20.40
		95% CI	(-49.2,15.6)	(-28.5,37.0)	(-61.1,19.0)
		Pr >  t			0.3022
	Week 192	n	1	1	
		LS Mean	16.552	4.286	12.265
		SEM	16.51	16.68	20.40
		95% CI	(-15.9,49.0)	(-28.5,37.0)	(-27.8,52.3)
		Pr >  t			0.5479
Yes	Week 8	n	73	80	
		LS Mean	2.658	7.087	-4.429
		SEM	4.468	4.520	3.354
		95% CI	( -6.1,11.5)	( -1.8,16.0)	(-11.0, 2.2)
		Pr >  t			0.1877
	Week 16	n	65	58	
		LS Mean	2.703	6.176	-3.473
		SEM	4.582	4.711	3.624
		95% CI	( -6.3,11.7)	( -3.1,15.5)	(-10.6, 3.7)
		Pr >  t			0.3385
	Week 24	n	51	40	
		LS Mean	6.653	9.414	-2.760
		SEM	4.680	4.952	4.027
		95% CI	( -2.6,15.9)	( -0.3,19.2)	(-10.7, 5.2)
		Pr >  t			0.4934
	Week 32	n	38	36	
		LS Mean	4.478	4.866	-0.388
		SEM	4.895	5.025	4.304

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.2,14.1)	(-5.0,14.8)	(-8.8, 8.1)
		Pr >  t			0.9282
	Week 40	n	32	29	
		LS Mean	4.828	7.111	-2.283
		SEM	5.021	5.176	4.608
		95% CI	(-5.1,14.7)	(-3.1,17.3)	(-11.3, 6.8)
		Pr >  t			0.6204
	Week 48	n	28	23	
		LS Mean	6.699	12.495	-5.796
		SEM	5.115	5.374	4.919
		95% CI	(-3.4,16.8)	( 1.9,23.1)	(-15.5, 3.9)
		Pr >  t			0.2391
	Week 56	n	24	23	
		LS Mean	4.303	11.251	-6.948
		SEM	5.246	5.373	5.049
		95% CI	(-6.0,14.6)	( 0.7,21.8)	(-16.9, 3.0)
		Pr >  t			0.1692
	Week 64	n	21	19	
		LS Mean	4.759	13.061	-8.302
		SEM	5.371	5.550	5.362
		95% CI	(-5.8,15.3)	( 2.2,24.0)	(-18.8, 2.2)
		Pr >  t			0.1220
	Week 72	n	20	17	
		LS Mean	3.201	7.929	-4.728
		SEM	5.420	5.665	5.532
		95% CI	(-7.5,13.9)	(-3.2,19.1)	(-15.6, 6.1)
		Pr >  t			0.3930
	Week 84	n	18	15	
		LS Mean	11.201	9.291	1.909
		SEM	5.513	5.810	5.775
		95% CI	( 0.4,22.0)	(-2.1,20.7)	(-9.4,13.2)
		Pr >  t			0.7410
	Week 96	n	14	11	
		LS Mean	7.176	15.979	-8.803
		SEM	5.812	6.233	6.460
		95% CI	(-4.2,18.6)	( 3.7,28.2)	(-21.5, 3.9)
		Pr >  t			0.1734
	Week 108	n	9	9	
		LS Mean	10.728	17.636	-6.908
		SEM	6.476	6.560	7.354

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-2.0,23.4)	( 4.8,30.5)	(-21.3, 7.5)
		Pr >  t			0.3478
	Week 120	n	10	5	
		LS Mean	10.738	18.196	-7.459
		SEM	6.319	7.830	8.390
		95% CI	(-1.7,23.1)	( 2.8,33.6)	(-23.9, 9.0)
		Pr >  t			0.3743
	Week 132	n	7	3	
		LS Mean	9.961	3.900	6.062
		SEM	6.959	9.390	10.29
		95% CI	(-3.7,23.6)	(-14.5,22.3)	(-14.1,26.3)
		Pr >  t			0.5561
	Week 144	n	3	2	
		LS Mean	31.913	8.960	22.953
		SEM	9.329	11.05	13.36
		95% CI	( 13.6,50.2)	(-12.7,30.7)	(-3.3,49.2)
		Pr >  t			0.0863
	Week 156	n	3	1	
		LS Mean	15.149	8.758	6.391
		SEM	9.343	14.96	16.74
		95% CI	(-3.2,33.5)	(-20.6,38.1)	(-26.5,39.3)
		Pr >  t			0.7027
	Week 168	n	1	1	
		LS Mean	5.225	8.758	-3.533
		SEM	14.96	14.96	20.41
		95% CI	(-24.1,34.6)	(-20.6,38.1)	(-43.6,36.5)
		Pr >  t			0.8626

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-44: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Dyspnoe“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Presence of Liver Metastases (L)	No	Week 8	n	104	98	
			LS Mean	4.738	5.669	-0.931
			SEM	2.780	2.764	2.432
			95% CI	(-0.7,10.2)	( 0.2,11.1)	(-5.7, 3.8)
			Pr >  t			0.7019
		Week 16	n	92	77	
			LS Mean	4.363	6.180	-1.817
			SEM	2.824	2.945	2.631
			95% CI	(-1.2, 9.9)	( 0.4,12.0)	(-7.0, 3.3)
			Pr >  t			0.4900
		Week 24	n	83	66	
			LS Mean	4.522	10.083	-5.561
			SEM	2.885	3.022	2.776
			95% CI	(-1.2,10.2)	( 4.1,16.0)	(-11.0,-0.1)
			Pr >  t			0.0455
		Week 32	n	72	60	
			LS Mean	3.661	4.515	-0.854
			SEM	2.965	3.095	2.908
			95% CI	(-2.2, 9.5)	(-1.6,10.6)	(-6.6, 4.9)
			Pr >  t			0.7690
Week 40	n	64	51			
	LS Mean	2.317	8.762	-6.445		
	SEM	3.024	3.209	3.075		
	95% CI	(-3.6, 8.3)	( 2.5,15.1)	(-12.5,-0.4)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.0364
Week 48	n	58	45	
	LS Mean	4.837	9.000	-4.163
	SEM	3.077	3.293	3.215
	95% CI	(-1.2,10.9)	(2.5,15.5)	(-10.5, 2.1)
	Pr >  t			0.1957
Week 56	n	49	38	
	LS Mean	4.983	7.789	-2.807
	SEM	3.177	3.419	3.441
	95% CI	(-1.3,11.2)	(1.1,14.5)	(-9.6, 3.9)
	Pr >  t			0.4148
Week 64	n	39	37	
	LS Mean	3.084	7.177	-4.092
	SEM	3.332	3.441	3.610
	95% CI	(-3.5, 9.6)	(0.4,13.9)	(-11.2, 3.0)
	Pr >  t			0.2572
Week 72	n	41	32	
	LS Mean	7.691	7.444	0.246
	SEM	3.297	3.562	3.693
	95% CI	(1.2,14.2)	(0.5,14.4)	(-7.0, 7.5)
	Pr >  t			0.9469
Week 84	n	33	29	
	LS Mean	6.003	9.188	-3.185
	SEM	3.487	3.651	3.930
	95% CI	(-0.8,12.9)	(2.0,16.4)	(-10.9, 4.5)
	Pr >  t			0.4179
Week 96	n	31	21	
	LS Mean	3.789	10.513	-6.723
	SEM	3.532	3.991	4.294
	95% CI	(-3.1,10.7)	(2.7,18.3)	(-15.1, 1.7)
	Pr >  t			0.1176
Week 108	n	23	18	
	LS Mean	1.130	9.767	-8.637
	SEM	3.841	4.183	4.712
	95% CI	(-6.4, 8.7)	(1.6,18.0)	(-17.9, 0.6)
	Pr >  t			0.0670
Week 120	n	25	15	
	LS Mean	5.706	7.422	-1.716
	SEM	3.741	4.436	4.870
	95% CI	(-1.6,13.0)	(-1.3,16.1)	(-11.3, 7.8)



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.7246
	Week 132	n	17	8
		LS Mean	6.101	18.207
		SEM	4.210	5.565
		95% CI	( -2.2,14.4)	( 7.3,29.1)
		Pr >  t		0.0518
	Week 144	n	15	5
		LS Mean	9.330	7.277
		SEM	4.369	6.751
		95% CI	( 0.8,17.9)	( -6.0,20.5)
		Pr >  t		0.7815
	Week 156	n	10	3
		LS Mean	3.008	7.744
		SEM	5.069	8.443
		95% CI	( -6.9,13.0)	( -8.8,24.3)
		Pr >  t		0.6116
	Week 168	n	4	2
		LS Mean	8.538	7.750
		SEM	7.391	10.17
		95% CI	( -6.0,23.0)	( -12.2,27.7)
		Pr >  t		0.9484
	Week 180	n	1	1
		LS Mean	33.848	7.749
		SEM	14.11	14.12
		95% CI	( 6.2,61.5)	( -20.0,35.5)
		Pr >  t		0.1858
	Week 192	n	1	1
		LS Mean	33.848	7.749
		SEM	14.11	14.12
		95% CI	( 6.2,61.5)	( -20.0,35.5)
		Pr >  t		0.1858
Yes	Week 8	n	38	42
		LS Mean	-3.830	-4.310
		SEM	3.928	4.188
		95% CI	( -11.6, 4.0)	( -12.6, 4.0)
		Pr >  t		0.9028
	Week 16	n	32	30
		LS Mean	-4.508	-5.638
		SEM	4.202	4.420
		95% CI	( -12.8, 3.8)	( -14.4, 3.1)
				( -7.4, 9.7)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.7947
Week 24	n	22	15	
	LS Mean	-6.808	-4.776	-2.032
	SEM	4.505	5.253	5.419
	95% CI	(-15.7, 2.1)	(-15.1, 5.6)	(-12.7, 8.6)
	Pr >  t			0.7080
Week 32	n	14	13	
	LS Mean	-7.467	-6.033	-1.434
	SEM	5.164	5.450	6.059
	95% CI	(-17.6, 2.7)	(-16.8, 4.7)	(-13.4,10.5)
	Pr >  t			0.8131
Week 40	n	11	11	
	LS Mean	0.409	-6.875	7.284
	SEM	5.525	5.703	6.587
	95% CI	(-10.5,11.3)	(-18.1, 4.4)	(-5.7,20.2)
	Pr >  t			0.2697
Week 48	n	11	6	
	LS Mean	-5.651	2.170	-7.821
	SEM	5.525	6.846	7.603
	95% CI	(-16.5, 5.2)	(-11.3,15.6)	(-22.8, 7.1)
	Pr >  t			0.3045
Week 56	n	10	7	
	LS Mean	-11.07	-8.634	-2.434
	SEM	5.681	6.513	7.420
	95% CI	(-22.3, 0.1)	(-21.5, 4.2)	(-17.0,12.2)
	Pr >  t			0.7432
Week 64	n	8	5	
	LS Mean	-1.472	-3.292	1.820
	SEM	6.073	7.283	8.388
	95% CI	(-13.4,10.5)	(-17.6,11.0)	(-14.7,18.3)
	Pr >  t			0.8284
Week 72	n	7	3	
	LS Mean	-1.106	-10.18	9.069
	SEM	6.339	8.797	9.896
	95% CI	(-13.6,11.4)	(-27.5, 7.1)	(-10.4,28.6)
	Pr >  t			0.3603
Week 84	n	7	4	
	LS Mean	-5.868	-17.83	11.966
	SEM	6.339	7.894	9.102
	95% CI	(-18.3, 6.6)	(-33.4,-2.3)	(-6.0,29.9)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.1898
	Week 96	n	4	3	
		LS Mean	-6.251	0.935	-7.186
		SEM	7.711	8.797	10.83
		95% CI	(-21.4, 8.9)	(-16.4, 18.3)	(-28.5, 14.1)
		Pr >  t			0.5075
	Week 108	n	3	3	
		LS Mean	-5.726	-5.391	-0.335
		SEM	8.621	8.792	11.49
		95% CI	(-22.7, 11.2)	(-22.7, 11.9)	(-23.0, 22.3)
		Pr >  t			0.9768
	Week 120	n	3	1	
		LS Mean	-1.616	-37.61	35.994
		SEM	8.618	14.01	15.84
		95% CI	(-18.6, 15.4)	(-65.2, -10)	( 4.8, 67.2)
		Pr >  t			0.0241
	Week 132	n	3		
		LS Mean	0.457	NE	NE
		SEM	8.622	NE	NE
		95% CI	(-16.5, 17.4)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Bone Lesions Only (L)	No	Week 8	n	104	110	
			LS Mean	0.548	1.470	-0.922
			SEM	2.719	2.712	2.428
			95% CI	(-4.8, 5.9)	(-3.9, 6.8)	(-5.7, 3.8)
		Pr >  t			0.7044	
		Week 16	n	92	83	
			LS Mean	-2.017	0.303	-2.319
			SEM	2.803	2.893	2.640
			95% CI	(-7.5, 3.5)	(-5.4, 6.0)	(-7.5, 2.9)
		Pr >  t			0.3801	
		Week 24	n	77	59	
			LS Mean	-0.403	4.558	-4.961
			SEM	2.876	3.095	2.933
			95% CI	(-6.1, 5.3)	(-1.5, 10.6)	(-10.7, 0.8)
		Pr >  t			0.0912	
		Week 32	n	57	53	
			LS Mean	-2.027	-0.579	-1.447
			SEM	3.077	3.162	3.164
			95% CI	(-8.1, 4.0)	(-6.8, 5.6)	(-7.7, 4.8)
		Pr >  t			0.6475	
		Week 40	n	50	44	
			LS Mean	-1.054	3.230	-4.283
			SEM	3.159	3.302	3.370
			95% CI	(-7.3, 5.2)	(-3.3, 9.7)	(-10.9, 2.3)
		Pr >  t			0.2041	
		Week 48	n	47	37	
			LS Mean	1.681	6.820	-5.139
			SEM	3.198	3.435	3.536
95% CI	(-4.6, 8.0)		( 0.1, 13.6)	(-12.1, 1.8)		
Pr >  t			0.1465			
Week 56	n	40	32			
	LS Mean	-1.174	1.069	-2.244		
	SEM	3.312	3.557	3.756		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	95% CI	(-7.7, 5.3)	(-5.9, 8.1)	(-9.6, 5.1)	
	Pr >  t			0.5504	
	n	32	27		
	LS Mean	0.316	1.482	-1.166	
	SEM	3.491	3.716	4.061	
Week 72	95% CI	(-6.5, 7.2)	(-5.8, 8.8)	(-9.1, 6.8)	
	Pr >  t			0.7741	
	n	31	23		
	LS Mean	3.201	1.541	1.660	
	SEM	3.522	3.884	4.240	
Week 84	95% CI	(-3.7,10.1)	(-6.1, 9.2)	(-6.7,10.0)	
	Pr >  t			0.6955	
	n	27	21		
	LS Mean	0.714	2.123	-1.409	
	SEM	3.655	3.986	4.437	
Week 96	95% CI	(-6.5, 7.9)	(-5.7, 9.9)	(-10.1, 7.3)	
	Pr >  t			0.7508	
	n	23	16		
	LS Mean	-0.615	9.779	-10.39	
	SEM	3.813	4.332	4.880	
Week 108	95% CI	(-8.1, 6.9)	( 1.3,18.3)	(-20.0,-0.8)	
	Pr >  t			0.0334	
	n	15	14		
	LS Mean	-1.676	7.606	-9.282	
	SEM	4.363	4.525	5.474	
Week 120	95% CI	(-10.2, 6.9)	(-1.3,16.5)	(-20.0, 1.5)	
	Pr >  t			0.0902	
	n	18	8		
	LS Mean	-0.975	-1.560	0.585	
	SEM	4.108	5.544	6.178	
Week 132	95% CI	(-9.0, 7.1)	(-12.4, 9.3)	(-11.5,12.7)	
	Pr >  t			0.9246	
	n	12	4		
	LS Mean	0.245	26.302	-26.06	
	SEM	4.712	7.369	8.184	
Week 144	95% CI	(-9.0, 9.5)	( 11.8,40.8)	(-42.1, -10)	
	Pr >  t			0.0015	
	n	8	3		
	LS Mean	7.089	2.735	4.353	
	SEM	5.465	8.381	9.529	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
	Week 156	95% CI	(-3.6,17.8)	(-13.7,19.2)	(-14.3,23.1)
		Pr >  t			0.6479
		n	5	1	
	Week 168	LS Mean	-0.244	4.058	-4.302
		SEM	6.652	14.00	15.19
		95% CI	(-13.3,12.8)	(-23.4,31.5)	(-34.1,25.5)
	Week 180	Pr >  t			0.7770
		n	2	1	
		LS Mean	-2.701	4.058	-6.759
	Week 192	SEM	10.05	14.00	16.95
		95% CI	(-22.4,17.0)	(-23.4,31.5)	(-40.0,26.5)
		Pr >  t			0.6902
Week 8	n	1			
	LS Mean	28.928	NE	NE	
	SEM	13.96	NE	NE	
Week 16	95% CI	( 1.5,56.3)	NE	NE	
	Pr >  t			NE	
	n	1			
Week 24	LS Mean	28.928	NE	NE	
	SEM	13.96	NE	NE	
	95% CI	( 1.5,56.3)	NE	NE	
Week 32	Pr >  t			NE	
	n	38	30		
	LS Mean	6.353	6.229	0.124	
Week 8	SEM	4.064	4.383	3.970	
	95% CI	(-1.7,14.4)	(-2.5,14.9)	(-7.7, 7.9)	
	Pr >  t			0.9751	
Week 16	n	32	24		
	LS Mean	11.910	10.421	1.489	
	SEM	4.174	4.577	4.347	
Week 24	95% CI	( 3.6,20.2)	( 1.4,19.5)	(-7.1,10.0)	
	Pr >  t			0.7322	
	n	28	22		
Week 32	LS Mean	5.846	11.738	-5.893	
	SEM	4.361	4.663	4.556	
	95% CI	(-2.8,14.5)	( 2.5,21.0)	(-14.9, 3.1)	
Week 8	Pr >  t			0.1968	
	n	29	20		
	LS Mean	7.109	8.128	-1.020	
Week 16	SEM	4.334	4.855	4.639	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-1.5,15.7)	(-1.5,17.7)	(-10.1, 8.1)
	Pr >  t			0.8261
	n	25	18	
	LS Mean	5.366	10.035	-4.669
	SEM	4.457	4.969	4.879
Week 48	95% CI	(-3.4,14.2)	( 0.2,19.8)	(-14.3, 4.9)
	Pr >  t			0.3392
	n	22	14	
	LS Mean	3.421	5.690	-2.269
	SEM	4.576	5.280	5.305
Week 56	95% CI	(-5.6,12.5)	(-4.7,16.1)	(-12.7, 8.2)
	Pr >  t			0.6690
	n	19	13	
	LS Mean	7.141	11.707	-4.566
	SEM	4.725	5.388	5.546
Week 64	95% CI	(-2.2,16.5)	( 1.1,22.3)	(-15.5, 6.3)
	Pr >  t			0.4109
	n	15	15	
	LS Mean	4.263	10.856	-6.593
	SEM	4.993	5.196	5.611
Week 72	95% CI	(-5.6,14.1)	( 0.6,21.1)	(-17.6, 4.4)
	Pr >  t			0.2407
	n	17	12	
	LS Mean	10.028	9.813	0.215
	SEM	4.846	5.503	5.766
Week 84	95% CI	( 0.5,19.6)	(-1.0,20.7)	(-11.1,11.5)
	Pr >  t			0.9703
	n	13	12	
	LS Mean	8.562	9.823	-1.261
	SEM	5.247	5.504	6.066
Week 96	95% CI	(-1.8,18.9)	(-1.0,20.7)	(-13.2,10.7)
	Pr >  t			0.8354
	n	12	8	
	LS Mean	5.752	4.773	0.978
	SEM	5.363	6.203	6.795
Week 108	95% CI	(-4.8,16.3)	(-7.4,17.0)	(-12.4,14.3)
	Pr >  t			0.8856
	n	11	7	
Week 108	LS Mean	1.876	4.502	-2.626
	SEM	5.501	6.478	7.151

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.0,12.7)	(-8.2,17.2)	(-16.7,11.4)
		Pr >  t			0.7136
	Week 120	n	10	8	
		LS Mean	12.642	8.418	4.224
		SEM	5.654	6.205	7.031
		95% CI	( 1.5,23.8)	( -3.8,20.6)	( -9.6,18.0)
		Pr >  t			0.5483
	Week 132	n	8	4	
		LS Mean	11.887	5.785	6.102
		SEM	6.067	7.913	8.852
		95% CI	( -0.0,23.8)	( -9.8,21.3)	(-11.3,23.5)
		Pr >  t			0.4910
	Week 144	n	7	2	
		LS Mean	9.410	7.355	2.055
		SEM	6.345	10.52	11.40
		95% CI	( -3.1,21.9)	(-13.3,28.0)	(-20.3,24.5)
		Pr >  t			0.8570
	Week 156	n	5	2	
		LS Mean	4.244	7.355	-3.111
		SEM	7.157	10.52	11.87
		95% CI	( -9.8,18.3)	(-13.3,28.0)	(-26.4,20.2)
		Pr >  t			0.7934
	Week 168	n	2	1	
		LS Mean	17.643	7.285	10.358
		SEM	10.41	14.37	17.14
		95% CI	( -2.8,38.1)	(-21.0,35.5)	(-23.3,44.0)
		Pr >  t			0.5459
	Week 180	n		1	
		LS Mean	NE	7.285	NE
		SEM	NE	14.37	NE
		95% CI	NE	(-21.0,35.5)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	7.285	NE
		SEM	NE	14.37	NE
		95% CI	NE	(-21.0,35.5)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis



-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134	
			LS Mean	1.661	1.906	-0.245
		SEM	1.480	1.479	2.089	
		95% CI	(-1.2, 4.6)	(-1.0, 4.8)	(-4.3, 3.9)	
		Pr >  t			0.9068	
		Week 16	n	118	104	
			LS Mean	1.151	2.176	-1.026
		SEM	1.560	1.651	2.270	
		95% CI	(-1.9, 4.2)	(-1.1, 5.4)	(-5.5, 3.4)	
		Pr >  t			0.6515	
		Week 24	n	100	79	
			LS Mean	0.603	5.522	-4.919
		SEM	1.671	1.852	2.491	
		95% CI	(-2.7, 3.9)	( 1.9, 9.2)	(-9.8,-0.0)	
		Pr >  t			0.0486	
		Week 32	n	84	72	
			LS Mean	0.187	0.850	-0.662
		SEM	1.790	1.925	2.626	
		95% CI	(-3.3, 3.7)	(-2.9, 4.6)	(-5.8, 4.5)	
		Pr >  t			0.8009	
		Week 40	n	73	62	
			LS Mean	0.263	4.101	-3.839
		SEM	1.895	2.043	2.783	
		95% CI	(-3.5, 4.0)	( 0.1, 8.1)	(-9.3, 1.6)	
Pr >  t			0.1681			
Week 48	n	67	51			
	LS Mean	1.552	5.571	-4.019		
SEM	1.961	2.211	2.952			
95% CI	(-2.3, 5.4)	( 1.2, 9.9)	(-9.8, 1.8)			
Pr >  t			0.1735			
Week 56	n	57	45			
	LS Mean	0.792	3.057	-2.266		
SEM	2.091	2.328	3.127			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-3.3, 4.9)	(-1.5, 7.6)	(-8.4, 3.9)
	Pr >  t			0.4689
	n	45	42	
	LS Mean	0.187	3.336	-3.149
	SEM	2.300	2.397	3.320
Week 72	95% CI	(-4.3, 4.7)	(-1.4, 8.0)	(-9.7, 3.4)
	Pr >  t			0.3431
	n	46	35	
	LS Mean	4.203	2.880	1.324
	SEM	2.282	2.586	3.446
Week 84	95% CI	(-0.3, 8.7)	(-2.2, 8.0)	(-5.4, 8.1)
	Pr >  t			0.7010
	n	40	33	
	LS Mean	2.127	3.323	-1.196
	SEM	2.416	2.651	3.585
Week 96	95% CI	(-2.6, 6.9)	(-1.9, 8.5)	(-8.2, 5.8)
	Pr >  t			0.7386
	n	34	24	
	LS Mean	-0.623	6.813	-7.436
	SEM	2.589	3.040	3.991
Week 108	95% CI	(-5.7, 4.5)	( 0.9,12.8)	(-15.3, 0.4)
	Pr >  t			0.0626
	n	26	21	
	LS Mean	-2.001	5.253	-7.254
	SEM	2.908	3.225	4.341
Week 120	95% CI	(-7.7, 3.7)	(-1.1,11.6)	(-15.8, 1.3)
	Pr >  t			0.0949
	n	27	16	
	LS Mean	2.666	1.237	1.430
	SEM	2.863	3.645	4.632
Week 132	95% CI	(-2.9, 8.3)	(-5.9, 8.4)	(-7.7,10.5)
	Pr >  t			0.7576
	n	20	8	
	LS Mean	3.266	13.865	-10.60
	SEM	3.266	5.024	5.991
Week 144	95% CI	(-3.1, 9.7)	( 4.0,23.7)	(-22.3, 1.2)
	Pr >  t			0.0770
	n	14	5	
	LS Mean	6.585	2.916	3.670
	SEM	3.844	6.297	7.375

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.0,14.1)	(-9.4,15.3)	(-10.8,18.1)
		Pr >  t			0.6189
	Week 156	n	10	3	
		LS Mean	-0.323	3.454	-3.778
		SEM	4.498	8.063	9.232
		95% CI	(-9.1, 8.5)	(-12.4,19.3)	(-21.9,14.3)
		Pr >  t			0.6824
	Week 168	n	4	2	
		LS Mean	5.219	3.486	1.732
		SEM	6.985	9.837	12.06
		95% CI	(-8.5,18.9)	(-15.8,22.8)	(-21.9,25.4)
		Pr >  t			0.8859
	Week 180	n	1	1	
		LS Mean	30.538	3.425	27.113
		SEM	13.84	13.84	19.57
		95% CI	( 3.4,57.7)	(-23.7,30.6)	(-11.3,65.5)
		Pr >  t			0.1661
	Week 192	n	1	1	
		LS Mean	30.538	3.425	27.113
		SEM	13.84	13.84	19.57
		95% CI	( 3.4,57.7)	(-23.7,30.6)	(-11.3,65.5)
		Pr >  t			0.1661
Prior use	Week 8	n	8	6	
		LS Mean	1.467	10.388	-8.921
		SEM	10.64	13.10	18.03
		95% CI	(-22.1,25.0)	(-18.6,39.4)	(-48.9,31.1)
		Pr >  t			0.6311
	Week 16	n	6	3	
		LS Mean	1.712	20.786	-19.07
		SEM	10.99	15.32	20.09
		95% CI	(-22.2,25.7)	(-11.5,53.1)	(-61.9,23.8)
		Pr >  t			0.3575
	Week 24	n	5	2	
		LS Mean	1.764	23.033	-21.27
		SEM	11.21	15.56	20.31
		95% CI	(-22.5,26.0)	(-9.6,55.6)	(-64.4,21.8)
		Pr >  t			0.3108
	Week 32	n	2	1	
		LS Mean	-14.49	16.737	-31.23
		SEM	12.84	17.72	22.96

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-41.3,12.3)	(-19.7,53.2)	(-78.8,16.3)
	Pr >  t			0.1871
Week 40	n	2		
	LS Mean	-14.49	NE	NE
	SEM	12.84	NE	NE
	95% CI	(-41.3,12.3)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	-14.49	NE	NE
	SEM	12.84	NE	NE
	95% CI	(-41.3,12.3)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	-14.49	NE	NE
	SEM	12.84	NE	NE
	95% CI	(-41.3,12.3)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	2.172	NE	NE
	SEM	12.84	NE	NE
	95% CI	(-24.6,28.9)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	2.172	NE	NE
	SEM	12.84	NE	NE
	95% CI	(-24.6,28.9)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	27.930	NE	NE
	SEM	14.82	NE	NE
	95% CI	(-2.5,58.4)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	-5.400	NE	NE
	SEM	14.82	NE	NE
	95% CI	(-35.8,25.0)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	-5.400	NE	NE
	SEM	14.82	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-35.8,25.0)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	1.736	3.298	-1.562		
			SEM	2.349	2.394	2.228		
					95% CI	(-2.9, 6.4)	(-1.4, 8.0)	(-5.9, 2.8)
					Pr >  t			0.4835
				Week 16	n	111	91	
					LS Mean	1.507	3.703	-2.196
					SEM	2.416	2.559	2.427
					95% CI	(-3.2, 6.3)	(-1.3, 8.7)	(-7.0, 2.6)
					Pr >  t			0.3659
				Week 24	n	96	70	
					LS Mean	1.331	7.105	-5.774
					SEM	2.486	2.711	2.638
					95% CI	(-3.6, 6.2)	( 1.8,12.4)	(-11.0,-0.6)
					Pr >  t			0.0289
				Week 32	n	77	61	
					LS Mean	-0.280	2.323	-2.603
					SEM	2.616	2.802	2.821
					95% CI	(-5.4, 4.9)	(-3.2, 7.8)	(-8.1, 2.9)
					Pr >  t			0.3563
				Week 40	n	69	52	
					LS Mean	0.372	5.474	-5.102
					SEM	2.675	2.916	2.977
					95% CI	(-4.9, 5.6)	(-0.3,11.2)	(-10.9, 0.7)
			Pr >  t			0.0869		
		Week 48	n	62	41			
			LS Mean	0.880	7.634	-6.755		
			SEM	2.733	3.086	3.195		
			95% CI	(-4.5, 6.2)	( 1.6,13.7)	(-13.0,-0.5)		
			Pr >  t			0.0347		
		Week 56	n	53	35			
			LS Mean	1.117	2.658	-1.541		
			SEM	2.826	3.216	3.402		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.4, 6.7)	(-3.7, 9.0)	(-8.2, 5.1)
		Pr >  t			0.6507
	Week 64	n	44	33	
		LS Mean	1.147	4.893	-3.746
		SEM	2.950	3.270	3.556
		95% CI	(-4.6, 6.9)	(-1.5, 11.3)	(-10.7, 3.2)
		Pr >  t			0.2923
	Week 72	n	45	28	
		LS Mean	4.475	3.824	0.651
		SEM	2.936	3.424	3.686
		95% CI	(-1.3, 10.2)	(-2.9, 10.5)	(-6.6, 7.9)
		Pr >  t			0.8600
	Week 84	n	39	27	
		LS Mean	2.487	1.692	0.795
		SEM	3.054	3.461	3.806
		95% CI	(-3.5, 8.5)	(-5.1, 8.5)	(-6.7, 8.3)
		Pr >  t			0.8346
	Week 96	n	34	19	
		LS Mean	0.618	8.093	-7.475
		SEM	3.163	3.862	4.260
		95% CI	(-5.6, 6.8)	(0.5, 15.7)	(-15.8, 0.9)
		Pr >  t			0.0795
	Week 108	n	26	17	
		LS Mean	-1.748	5.652	-7.400
		SEM	3.427	4.012	4.584
		95% CI	(-8.5, 5.0)	(-2.2, 13.5)	(-16.4, 1.6)
		Pr >  t			0.1067
	Week 120	n	27	11	
		LS Mean	2.115	3.263	-1.148
		SEM	3.382	4.702	5.173
		95% CI	(-4.5, 8.8)	(-6.0, 12.5)	(-11.3, 9.0)
		Pr >  t			0.8244
	Week 132	n	20	6	
		LS Mean	3.494	16.184	-12.69
		SEM	3.726	6.013	6.573
		95% CI	(-3.8, 10.8)	(4.4, 28.0)	(-25.6, 0.2)
		Pr >  t			0.0537
	Week 144	n	15	4	
		LS Mean	6.251	4.051	2.200
		SEM	4.109	7.190	7.864



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-1.8,14.3)	(-10.1,18.2)	(-13.2,17.6)
		Pr >  t			0.7798
	Week 156	n	10	2	
		LS Mean	-0.117	4.659	-4.776
		SEM	4.810	9.891	10.68
		95% CI	(-9.6, 9.3)	(-14.7,24.1)	(-25.7,16.2)
		Pr >  t			0.6550
	Week 168	n	4	2	
		LS Mean	5.459	4.659	0.799
		SEM	7.127	9.891	11.91
		95% CI	(-8.5,19.4)	(-14.7,24.1)	(-22.6,24.2)
		Pr >  t			0.9465
	Week 180	n	1	1	
		LS Mean	30.751	4.628	26.123
		SEM	13.75	13.77	19.28
		95% CI	( 3.8,57.7)	(-22.4,31.6)	(-11.7,63.9)
		Pr >  t			0.1757
	Week 192	n	1	1	
		LS Mean	30.751	4.628	26.123
		SEM	13.75	13.77	19.28
		95% CI	( 3.8,57.7)	(-22.4,31.6)	(-11.7,63.9)
		Pr >  t			0.1757
>= 75 Years	Week 8	n	17	19	
		LS Mean	3.185	-1.763	4.948
		SEM	3.990	3.722	5.412
		95% CI	(-4.7,11.1)	(-9.1, 5.6)	(-5.7,15.6)
		Pr >  t			0.3621
	Week 16	n	13	16	
		LS Mean	1.369	-3.042	4.411
		SEM	4.526	4.035	6.038
		95% CI	(-7.6,10.3)	(-11.0, 4.9)	(-7.5,16.3)
		Pr >  t			0.4662
	Week 24	n	9	11	
		LS Mean	-2.961	-0.083	-2.878
		SEM	5.397	4.849	7.238
		95% CI	(-13.6, 7.7)	(-9.7, 9.5)	(-17.2,11.4)
		Pr >  t			0.6914
	Week 32	n	9	12	
		LS Mean	4.141	-4.684	8.825
		SEM	5.397	4.661	7.109

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.5,14.8)	(-13.9, 4.5)	(-5.2,22.9)
		Pr >  t			0.2162
	Week 40	n	6	10	
		LS Mean	-1.487	-1.256	-0.231
		SEM	6.585	5.080	8.291
		95% CI	(-14.5,11.5)	(-11.3, 8.8)	(-16.6,16.1)
		Pr >  t			0.9778
	Week 48	n	7	10	
		LS Mean	6.347	-1.729	8.075
		SEM	6.103	5.092	7.920
		95% CI	(-5.7,18.4)	(-11.8, 8.3)	(-7.6,23.7)
		Pr >  t			0.3094
	Week 56	n	6	10	
		LS Mean	-3.449	5.046	-8.494
		SEM	6.562	5.101	8.278
		95% CI	(-16.4, 9.5)	(-5.0,15.1)	(-24.8, 7.8)
		Pr >  t			0.3063
	Week 64	n	3	9	
		LS Mean	-4.612	-1.483	-3.129
		SEM	9.189	5.360	10.62
		95% CI	(-22.7,13.5)	(-12.1, 9.1)	(-24.1,17.8)
		Pr >  t			0.7686
	Week 72	n	3	7	
		LS Mean	6.498	1.232	5.266
		SEM	9.189	6.052	10.98
		95% CI	(-11.6,24.6)	(-10.7,13.2)	(-16.4,26.9)
		Pr >  t			0.6321
	Week 84	n	1	6	
		LS Mean	-1.352	13.344	-14.70
		SEM	15.72	6.510	16.99
		95% CI	(-32.4,29.7)	( 0.5,26.2)	(-48.2,18.8)
		Pr >  t			0.3883
	Week 96	n	1	5	
		LS Mean	-1.352	3.836	-5.188
		SEM	15.72	7.101	17.23
		95% CI	(-32.4,29.7)	(-10.2,17.9)	(-39.2,28.8)
		Pr >  t			0.7637
	Week 108	n		4	
		LS Mean	NE	5.929	NE
		SEM	NE	7.916	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-9.7,21.6)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	20.017	-2.830
		SEM	15.77	7.101
		95% CI	(-11.1,51.2)	(-16.8,11.2)
		Pr >  t		0.1887
	Week 132	n		2
		LS Mean	NE	9.183
		SEM	NE	11.06
		95% CI	NE	(-12.6,31.0)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	0.047
		SEM	NE	15.55
		95% CI	NE	(-30.7,30.7)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	0.047
		SEM	NE	15.55
		95% CI	NE	(-30.7,30.7)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	3.993	-0.593	4.586		
			SEM	4.959	4.715	4.275		
			95% CI	(-5.9,13.8)	(-10.0, 8.8)	(-3.9,13.0)		
					Pr >  t			0.2848
		Week 16	n	30	30			
			LS Mean	-0.282	-0.215	-0.067		
			SEM	5.005	4.961	4.505		
			95% CI	(-10.2, 9.7)	(-10.1, 9.6)	(-9.0, 8.8)		
					Pr >  t			0.9881
		Week 24	n	21	26			
			LS Mean	2.700	3.526	-0.826		
			SEM	5.297	5.060	4.965		
			95% CI	(-7.8,13.2)	(-6.5,13.6)	(-10.6, 9.0)		
					Pr >  t			0.8680
		Week 32	n	19	24			
			LS Mean	-2.206	-2.113	-0.093		
			SEM	5.390	5.130	5.150		
			95% CI	(-12.9, 8.5)	(-12.3, 8.0)	(-10.2,10.1)		
					Pr >  t			0.9856
		Week 40	n	16	19			
			LS Mean	-2.442	5.167	-7.609		
			SEM	5.567	5.412	5.563		
			95% CI	(-13.5, 8.6)	(-5.5,15.9)	(-18.6, 3.3)		
			Pr >  t			0.1725		
Week 48	n	16	18					
	LS Mean	-0.359	4.890	-5.248				
	SEM	5.567	5.465	5.616				
	95% CI	(-11.4,10.7)	(-5.9,15.7)	(-16.3, 5.8)				
			Pr >  t			0.3508		
Week 56	n	12	14					
	LS Mean	1.432	-4.852	6.284				
	SEM	5.913	5.751	6.243				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.2,13.1)	(-16.2, 6.5)	(-6.0,18.6)
		Pr >  t			0.3149
	Week 64	n	12	11	
		LS Mean	4.210	4.187	0.023
		SEM	5.913	6.085	6.551
		95% CI	(-7.5,15.9)	(-7.8,16.2)	(-12.9,12.9)
		Pr >  t			0.9973
	Week 72	n	10	9	
		LS Mean	8.131	8.169	-0.038
		SEM	6.172	6.396	7.082
		95% CI	(-4.0,20.3)	(-4.4,20.8)	(-14.0,13.9)
		Pr >  t			0.9958
	Week 84	n	8	8	
		LS Mean	2.289	9.076	-6.787
		SEM	6.616	6.610	7.601
		95% CI	(-10.8,15.3)	(-3.9,22.1)	(-21.7, 8.2)
		Pr >  t			0.3725
	Week 96	n	6	6	
		LS Mean	-2.766	19.556	-22.32
		SEM	7.200	7.201	8.601
		95% CI	(-16.9,11.4)	( 5.4,33.7)	(-39.2,-5.4)
		Pr >  t			0.0098
	Week 108	n	4	5	
		LS Mean	-2.679	10.637	-13.32
		SEM	8.237	7.640	9.825
		95% CI	(-18.9,13.5)	(-4.4,25.7)	(-32.6, 6.0)
		Pr >  t			0.1761
	Week 120	n	4	4	
		LS Mean	5.654	2.008	3.645
		SEM	8.237	8.252	10.31
		95% CI	(-10.5,21.9)	(-14.2,18.2)	(-16.6,23.9)
		Pr >  t			0.7238
	Week 132	n	3	2	
		LS Mean	7.813	10.922	-3.109
		SEM	9.148	10.73	13.01
		95% CI	(-10.2,25.8)	(-10.2,32.0)	(-28.7,22.5)
		Pr >  t			0.8113
	Week 144	n	3	1	
		LS Mean	18.926	4.206	14.721
		SEM	9.148	14.49	16.25

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.9,36.9)	(-24.3,32.7)	(-17.2,46.7)
		Pr >  t			0.3656
	Week 156	n	2	1	
		LS Mean	-4.941	4.206	-9.147
		SEM	10.73	14.49	17.19
		95% CI	(-26.0,16.2)	(-24.3,32.7)	(-43.0,24.7)
		Pr >  t			0.5950
	Week 168	n	1		
		LS Mean	1.940	NE	NE
		SEM	14.46	NE	NE
		95% CI	(-26.5,30.4)	NE	NE
		Pr >  t			NE
Other	Week 8	n	16	17	
		LS Mean	-11.48	-12.33	0.842
		SEM	9.103	8.914	5.594
		95% CI	(-29.6, 6.6)	(-30.0, 5.4)	(-10.3,12.0)
		Pr >  t			0.8808
	Week 16	n	15	14	
		LS Mean	-15.55	-17.87	2.315
		SEM	9.156	8.312	6.032
		95% CI	(-33.8, 2.7)	(-34.4,-1.3)	( -9.7,14.3)
		Pr >  t			0.7021
	Week 24	n	12	11	
		LS Mean	-17.55	-9.152	-8.403
		SEM	9.348	9.238	6.619
		95% CI	(-36.2, 1.0)	(-27.5, 9.2)	(-21.5, 4.7)
		Pr >  t			0.2072
	Week 32	n	8	9	
		LS Mean	-14.86	-12.78	-2.076
		SEM	9.801	9.474	7.542
		95% CI	(-34.3, 4.6)	(-31.6, 6.0)	(-17.0,12.9)
		Pr >  t			0.7836
	Week 40	n	6	7	
		LS Mean	-19.19	-10.25	-8.946
		SEM	10.22	9.771	8.402
		95% CI	(-39.5, 1.1)	(-29.6, 9.1)	(-25.6, 7.7)
		Pr >  t			0.2889
	Week 48	n	4	6	
		LS Mean	-21.10	-9.446	-11.65
		SEM	10.96	10.00	9.531

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 56	95% CI	(-42.8, 0.6)	(-29.3,10.4)	(-30.5, 7.2)	
	Pr >  t			0.2236	
	n	4	6		
	LS Mean	-10.11	-15.55	5.437	
	SEM	10.96	10.01	9.529	
Week 64	95% CI	(-31.8,11.6)	(-35.4, 4.3)	(-13.4,24.3)	
	Pr >  t			0.5692	
	n	4	4		
	LS Mean	-12.25	-8.331	-3.917	
	SEM	10.98	10.76	10.31	
Week 72	95% CI	(-34.0, 9.5)	(-29.6,13.0)	(-24.3,16.5)	
	Pr >  t			0.7046	
	n	4	4		
	LS Mean	-20.58	-8.331	-12.25	
	SEM	10.98	10.76	10.31	
Week 84	95% CI	(-42.3, 1.2)	(-29.6,13.0)	(-32.6, 8.1)	
	Pr >  t			0.2369	
	n	4	4		
	LS Mean	-21.10	8.336	-29.43	
	SEM	10.96	10.76	10.32	
Week 96	95% CI	(-42.8, 0.6)	(-13.0,29.6)	(-49.8,-9.0)	
	Pr >  t			0.0050	
	n	3	2		
	LS Mean	-22.04	-10.81	-11.23	
	SEM	11.66	12.69	12.93	
Week 108	95% CI	(-45.1, 1.0)	(-35.9,14.3)	(-36.8,14.3)	
	Pr >  t			0.3866	
	n	3	3		
	LS Mean	-22.04	-11.54	-10.50	
	SEM	11.66	11.44	11.70	
Week 120	95% CI	(-45.1, 1.0)	(-34.2,11.1)	(-33.6,12.6)	
	Pr >  t			0.3709	
	n	2	1		
	LS Mean	-19.85	-10.96	-8.892	
	SEM	12.90	15.84	16.95	
Week 132	95% CI	(-45.4, 5.7)	(-42.3,20.4)	(-42.4,24.6)	
	Pr >  t			0.6008	
	n	2	1		
	LS Mean	12.860	-10.96	23.818	
	SEM	12.89	15.84	16.96	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.6,38.3)	(-42.3,20.4)	(-9.7,57.4)
		Pr >  t			0.1627
	Week 156	n	1		
		LS Mean	-14.54	NE	NE
		SEM	16.05	NE	NE
		95% CI	(-46.3,17.2)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-14.54	NE	NE
		SEM	16.05	NE	NE
		95% CI	(-46.3,17.2)	NE	NE
		Pr >  t			NE
White	Week 8	n	93	85	
		LS Mean	2.824	6.609	-3.785
		SEM	2.693	2.839	2.592
		95% CI	(-2.5, 8.1)	( 1.0,12.2)	(-8.9, 1.3)
		Pr >  t			0.1449
	Week 16	n	79	61	
		LS Mean	4.618	7.783	-3.165
		SEM	2.799	3.096	2.888
		95% CI	(-0.9,10.1)	( 1.7,13.9)	(-8.8, 2.5)
		Pr >  t			0.2737
	Week 24	n	71	43	
		LS Mean	3.090	9.632	-6.542
		SEM	2.863	3.322	3.185
		95% CI	(-2.5, 8.7)	( 3.1,16.2)	(-12.8,-0.3)
		Pr >  t			0.0404
	Week 32	n	59	39	
		LS Mean	3.438	4.187	-0.748
		SEM	3.005	3.417	3.350
		95% CI	(-2.5, 9.3)	(-2.5,10.9)	(-7.3, 5.8)
		Pr >  t			0.8233
	Week 40	n	52	35	
		LS Mean	4.349	7.366	-3.017
		SEM	3.080	3.502	3.503
		95% CI	(-1.7,10.4)	( 0.5,14.2)	(-9.9, 3.9)
		Pr >  t			0.3894
	Week 48	n	48	26	
		LS Mean	5.572	8.989	-3.416
		SEM	3.129	3.763	3.804



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-0.6,11.7)	(-10.9, 4.1)
		Pr >  t		0.3694
	Week 56	n	42	24
		LS Mean	2.315	12.842
		SEM	3.215	3.842
		95% CI	(-4.0, 8.6)	(-18.3,-2.8)
		Pr >  t		0.0079
	Week 64	n	30	26
		LS Mean	2.167	6.955
		SEM	3.473	3.765
		95% CI	(-4.7, 9.0)	(-12.8, 3.3)
		Pr >  t		0.2431
	Week 72	n	34	21
		LS Mean	7.288	4.671
		SEM	3.371	3.983
		95% CI	( 0.7,13.9)	(-3.2,12.5)
		Pr >  t		0.5350
	Week 84	n	28	20
		LS Mean	6.117	1.815
		SEM	3.544	4.036
		95% CI	(-0.8,13.1)	(-6.1, 9.7)
		Pr >  t		0.3284
	Week 96	n	26	15
		LS Mean	4.779	7.420
		SEM	3.604	4.396
		95% CI	(-2.3,11.9)	(-1.2,16.0)
		Pr >  t		0.5812
	Week 108	n	19	12
		LS Mean	1.779	6.129
		SEM	3.955	4.728
		95% CI	(-6.0, 9.5)	(-3.2,15.4)
		Pr >  t		0.4152
	Week 120	n	22	10
		LS Mean	5.389	2.704
		SEM	3.778	5.036
		95% CI	(-2.0,12.8)	(-7.2,12.6)
		Pr >  t		0.6253
	Week 132	n	15	4
		LS Mean	1.961	3.749
		SEM	4.258	7.228
				7.802

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.4,10.3)	(-10.4,17.9)	(-17.1,13.5)
		Pr >  t			0.8188
	Week 144	n	12	4	
		LS Mean	5.725	5.553	0.172
		SEM	4.580	7.232	7.995
		95% CI	(-3.3,14.7)	(-8.6,19.7)	(-15.5,15.9)
		Pr >  t			0.9828
	Week 156	n	7	2	
		LS Mean	3.797	6.034	-2.237
		SEM	5.632	9.838	10.91
		95% CI	(-7.3,14.8)	(-13.3,25.3)	(-23.6,19.2)
		Pr >  t			0.8376
	Week 168	n	2	2	
		LS Mean	12.385	6.034	6.351
		SEM	9.751	9.838	13.50
		95% CI	(-6.8,31.5)	(-13.3,25.3)	(-20.2,32.9)
		Pr >  t			0.6383
	Week 180	n	1	1	
		LS Mean	33.412	5.930	27.482
		SEM	13.57	13.61	18.97
		95% CI	( 6.8,60.0)	(-20.8,32.6)	(-9.7,64.7)
		Pr >  t			0.1477
	Week 192	n	1	1	
		LS Mean	33.412	5.930	27.482
		SEM	13.57	13.61	18.97
		95% CI	( 6.8,60.0)	(-20.8,32.6)	(-9.7,64.7)
		Pr >  t			0.1477

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	-1.343	-2.123	0.780		
			SEM	7.401	7.589	2.971		
			95% CI	(-16.0,13.3)	(-17.1,12.9)	(-5.1, 6.6)		
					Pr >  t			0.7930
		Week 16	n	69	55			
			LS Mean	-1.631	-1.599	-0.031		
			SEM	7.412	7.670	3.203		
			95% CI	(-16.3,13.0)	(-16.7,13.5)	(-6.3, 6.3)		
					Pr >  t			0.9922
		Week 24	n	54	46			
			LS Mean	-1.451	3.632	-5.084		
			SEM	7.448	7.723	3.472		
			95% CI	(-16.2,13.3)	(-11.6,18.9)	(-11.9, 1.7)		
					Pr >  t			0.1438
		Week 32	n	49	41			
			LS Mean	-0.063	-1.008	0.945		
			SEM	7.553	7.761	3.616		
			95% CI	(-15.0,14.8)	(-16.3,14.3)	(-6.2, 8.0)		
					Pr >  t			0.7938
		Week 40	n	40	33			
			LS Mean	-1.154	-1.248	0.093		
			SEM	7.618	7.842	3.916		
			95% CI	(-16.2,13.9)	(-16.7,14.2)	(-7.6, 7.8)		
			Pr >  t			0.9810		
Week 48	n	38	28					
	LS Mean	1.268	2.268	-1.000				
	SEM	7.636	7.913	4.092				
	95% CI	(-13.8,16.3)	(-13.3,17.9)	(-9.0, 7.0)				
			Pr >  t			0.8070		
Week 56	n	32	28					
	LS Mean	-2.501	-3.075	0.574				
	SEM	7.705	7.913	4.215				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-17.7,12.7)	(-18.7,12.5)	(-7.7, 8.8)
	Pr >  t			0.8916
	n	23	26	
	LS Mean	0.066	0.708	-0.642
	SEM	7.862	7.948	4.558
Week 72	95% CI	(-15.4,15.6)	(-15.0,16.4)	(-9.6, 8.3)
	Pr >  t			0.8879
	n	27	25	
	LS Mean	0.937	-1.769	2.706
	SEM	7.780	7.968	4.451
Week 84	95% CI	(-14.4,16.3)	(-17.5,13.9)	(-6.0,11.4)
	Pr >  t			0.5434
	n	23	22	
	LS Mean	1.100	1.816	-0.716
	SEM	7.862	8.036	4.709
Week 96	95% CI	(-14.4,16.6)	(-14.0,17.7)	(-10.0, 8.5)
	Pr >  t			0.8791
	n	20	16	
	LS Mean	-0.023	1.935	-1.957
	SEM	7.943	8.243	5.181
Week 108	95% CI	(-15.7,15.6)	(-14.3,18.2)	(-12.1, 8.2)
	Pr >  t			0.7057
	n	20	14	
	LS Mean	-4.915	1.413	-6.328
	SEM	7.944	8.348	5.350
Week 120	95% CI	(-20.6,10.7)	(-15.0,17.9)	(-16.8, 4.2)
	Pr >  t			0.2372
	n	17	11	
	LS Mean	0.978	-2.137	3.115
	SEM	8.051	8.571	5.844
Week 132	95% CI	(-14.9,16.8)	(-19.0,14.7)	(-8.4,14.6)
	Pr >  t			0.5942
	n	13	6	
	LS Mean	-0.422	12.984	-13.41
	SEM	8.268	9.387	7.233
Week 144	95% CI	(-16.7,15.9)	(-5.5,31.4)	(-27.6, 0.8)
	Pr >  t			0.0642
	n	10	5	
	LS Mean	4.892	-0.231	5.123
	SEM	8.532	9.729	7.957

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.9,21.7)	(-19.4,18.9)	(-10.5,20.7)
		Pr >  t			0.5198
	Week 156	n	7	3	
		LS Mean	-6.121	0.204	-6.324
		SEM	9.004	10.97	9.863
		95% CI	(-23.8,11.6)	(-21.3,21.8)	(-25.7,13.0)
		Pr >  t			0.5215
	Week 168	n	3	2	
		LS Mean	5.847	0.226	5.620
		SEM	10.85	12.35	12.89
		95% CI	(-15.5,27.2)	(-24.0,24.5)	(-19.7,30.9)
		Pr >  t			0.6629
	Week 180	n		1	
		LS Mean	NE	0.275	NE
		SEM	NE	15.76	NE
		95% CI	NE	(-30.7,31.2)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	0.275	NE
		SEM	NE	15.76	NE
		95% CI	NE	(-30.7,31.2)	NE
		Pr >  t			NE
Second Line	Week 8	n	66	67	
		LS Mean	1.463	3.822	-2.360
		SEM	2.541	2.552	2.859
		95% CI	(-3.5, 6.5)	(-1.2, 8.9)	(-8.0, 3.3)
		Pr >  t			0.4097
	Week 16	n	54	52	
		LS Mean	1.045	3.017	-1.971
		SEM	2.716	2.801	3.170
		95% CI	(-4.3, 6.4)	(-2.5, 8.5)	(-8.2, 4.3)
		Pr >  t			0.5343
	Week 24	n	49	35	
		LS Mean	-0.534	4.137	-4.671
		SEM	2.811	3.167	3.552
		95% CI	(-6.1, 5.0)	(-2.1,10.4)	(-11.7, 2.3)
		Pr >  t			0.1892
	Week 32	n	36	32	
		LS Mean	-3.867	-0.811	-3.056
		SEM	3.106	3.274	3.847

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-10.0, 2.2)	(-7.2, 5.6)	(-10.6, 4.5)
	Pr >  t			0.4274
	n	33	29	
	LS Mean	-1.436	6.803	-8.239
	SEM	3.188	3.401	4.005
Week 48	95% CI	(-7.7, 4.8)	(0.1, 13.5)	(-16.1, -0.4)
	Pr >  t			0.0401
	n	29	23	
	LS Mean	-1.777	6.034	-7.811
	SEM	3.317	3.662	4.329
Week 56	95% CI	(-8.3, 4.7)	(-1.2, 13.2)	(-16.3, 0.7)
	Pr >  t			0.0717
	n	25	17	
	LS Mean	0.132	8.294	-8.162
	SEM	3.476	4.063	4.797
Week 64	95% CI	(-6.7, 7.0)	(0.3, 16.3)	(-17.6, 1.3)
	Pr >  t			0.0893
	n	22	16	
	LS Mean	-1.153	2.677	-3.830
	SEM	3.626	4.155	4.984
Week 72	95% CI	(-8.3, 6.0)	(-5.5, 10.8)	(-13.6, 6.0)
	Pr >  t			0.4425
	n	20	10	
	LS Mean	5.728	6.631	-0.903
	SEM	3.745	4.973	5.765
Week 84	95% CI	(-1.6, 13.1)	(-3.1, 16.4)	(-12.2, 10.4)
	Pr >  t			0.8756
	n	16	11	
	LS Mean	0.045	0.118	-0.073
	SEM	4.082	4.789	5.821
Week 96	95% CI	(-8.0, 8.1)	(-9.3, 9.5)	(-11.5, 11.4)
	Pr >  t			0.9900
	n	15	8	
	LS Mean	-2.669	10.611	-13.28
	SEM	4.170	5.441	6.434
Week 108	95% CI	(-10.9, 5.5)	(-0.1, 21.3)	(-25.9, -0.6)
	Pr >  t			0.0394
	n	6	7	
	LS Mean	0.548	6.968	-6.420
	SEM	6.077	5.753	8.019

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-11.4,12.5)	(-4.3,18.3)	(-22.2, 9.3)
	Pr >  t			0.4237
	n	11	5	
	LS Mean	0.978	2.184	-1.206
	SEM	4.709	6.650	7.800
Week 132	95% CI	(-8.3,10.2)	(-10.9,15.2)	(-16.5,14.1)
	Pr >  t			0.8772
	n	7	2	
	LS Mean	5.636	7.511	-1.875
	SEM	5.686	10.11	11.35
Week 144	95% CI	(-5.5,16.8)	(-12.4,27.4)	(-24.2,20.4)
	Pr >  t			0.8689
	n	5		
	LS Mean	3.447	NE	NE
	SEM	6.563	NE	NE
Week 156	95% CI	(-9.4,16.3)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	7.542	NE	NE
	SEM	8.314	NE	NE
Week 168	95% CI	(-8.8,23.9)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-3.807	NE	NE
	SEM	14.05	NE	NE
Week 180	95% CI	(-31.4,23.8)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	29.523	NE	NE
	SEM	14.05	NE	NE
Week 192	95% CI	(-1.9,57.1)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	29.523	NE	NE
	SEM	14.05	NE	NE
	95% CI	(-1.9,57.1)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	-15.28	NE	NE	
			SEM	11.87	NE	NE	
			95% CI	( -166, 135)	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	1.389	NE	NE	
			SEM	11.87	NE	NE	
			95% CI	( -149, 152)	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	-6.944	NE	NE	
			SEM	18.05	NE	NE	
			95% CI	( -236, 222)	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	-6.944	NE	NE	
			SEM	18.05	NE	NE	
			95% CI	( -236, 222)	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	9.721	NE	NE	
			SEM	19.29	NE	NE	
			95% CI	( -235, 255)	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	9.721	NE	NE	
			SEM	19.29	NE	NE	
95% CI	( -235, 255)		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	-23.61	NE	NE			
	SEM	19.29	NE	NE			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive	Week 72	95% CI	(-269, 222)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-6.944	NE	NE
		SEM	18.05	NE	NE
	Week 84	95% CI	(-236, 222)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	26.386	NE	NE
		SEM	18.05	NE	NE
	Week 96	95% CI	(-203, 256)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-6.944	NE	NE
		SEM	18.05	NE	NE
	Week 8	95% CI	(-236, 222)	NE	NE
		Pr >  t			NE
		n	140	140	
		LS Mean	2.247	2.751	-0.504
		SEM	2.274	2.304	2.071
	Week 16	95% CI	(-2.2, 6.7)	(-1.8, 7.3)	(-4.6, 3.6)
		Pr >  t			0.8077
		n	122	107	
		LS Mean	1.559	2.790	-1.231
SEM		2.344	2.448	2.260	
Week 24	95% CI	(-3.0, 6.2)	(-2.0, 7.6)	(-5.7, 3.2)	
	Pr >  t			0.5860	
	n	104	81		
	LS Mean	1.189	6.250	-5.061	
	SEM	2.416	2.593	2.476	
Week 32	95% CI	(-3.6, 5.9)	(1.2, 11.3)	(-9.9, -0.2)	
	Pr >  t			0.0412	
	n	85	73		
	LS Mean	0.442	1.470	-1.028	
	SEM	2.534	2.660	2.627	
Week 40	95% CI	(-4.5, 5.4)	(-3.8, 6.7)	(-6.2, 4.1)	
	Pr >  t			0.6955	
	n	74	62		
		LS Mean	0.243	4.791	-4.547
		SEM	2.605	2.764	2.790

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-4.9, 5.4)	(-0.6, 10.2)	(-10.0, 0.9)
	Pr >  t			0.1034
	n	68	51	
	LS Mean	1.480	6.279	-4.800
	SEM	2.650	2.890	2.956
Week 56	95% CI	(-3.7, 6.7)	(0.6, 12.0)	(-10.6, 1.0)
	Pr >  t			0.1047
	n	58	45	
	LS Mean	1.243	3.765	-2.522
	SEM	2.742	2.980	3.129
Week 64	95% CI	(-4.1, 6.6)	(-2.1, 9.6)	(-8.7, 3.6)
	Pr >  t			0.4203
	n	47	42	
	LS Mean	0.965	4.044	-3.079
	SEM	2.879	3.034	3.302
Week 72	95% CI	(-4.7, 6.6)	(-1.9, 10.0)	(-9.6, 3.4)
	Pr >  t			0.3513
	n	47	35	
	LS Mean	4.968	3.592	1.375
	SEM	2.881	3.185	3.442
Week 84	95% CI	(-0.7, 10.6)	(-2.7, 9.8)	(-5.4, 8.1)
	Pr >  t			0.6896
	n	39	33	
	LS Mean	1.865	4.032	-2.167
	SEM	3.035	3.238	3.610
Week 96	95% CI	(-4.1, 7.8)	(-2.3, 10.4)	(-9.2, 4.9)
	Pr >  t			0.5484
	n	34	24	
	LS Mean	0.882	7.526	-6.644
	SEM	3.147	3.563	3.997
Week 108	95% CI	(-5.3, 7.1)	(0.5, 14.5)	(-14.5, 1.2)
	Pr >  t			0.0967
	n	26	21	
	LS Mean	-1.566	5.970	-7.536
	SEM	3.420	3.722	4.345
Week 120	95% CI	(-8.3, 5.1)	(-1.3, 13.3)	(-16.1, 1.0)
	Pr >  t			0.0830
	n	28	16	
	LS Mean	2.957	1.958	1.000
	SEM	3.336	4.090	4.608

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.6, 9.5)	(-6.1, 10.0)	(-8.0, 10.0)
		Pr >  t			0.8283
	Week 132	n	20	8	
		LS Mean	3.699	14.588	-10.89
		SEM	3.728	5.351	5.988
		95% CI	(-3.6, 11.0)	(4.1, 25.1)	(-22.6, 0.9)
		Pr >  t			0.0692
	Week 144	n	15	5	
		LS Mean	6.457	3.690	2.767
		SEM	4.121	6.556	7.307
		95% CI	(-1.6, 14.5)	(-9.2, 16.6)	(-11.6, 17.1)
		Pr >  t			0.7050
	Week 156	n	10	3	
		LS Mean	0.094	4.208	-4.114
		SEM	4.839	8.261	9.219
		95% CI	(-9.4, 9.6)	(-12.0, 20.4)	(-22.2, 14.0)
		Pr >  t			0.6555
	Week 168	n	4	2	
		LS Mean	5.683	4.239	1.444
		SEM	7.202	9.994	12.04
		95% CI	(-8.4, 19.8)	(-15.4, 23.8)	(-22.2, 25.1)
		Pr >  t			0.9046
	Week 180	n	1	1	
		LS Mean	31.009	4.182	26.827
		SEM	13.93	13.94	19.53
		95% CI	(3.7, 58.3)	(-23.2, 31.5)	(-11.5, 65.1)
		Pr >  t			0.1699
	Week 192	n	1	1	
		LS Mean	31.009	4.182	26.827
		SEM	13.93	13.94	19.53
		95% CI	(3.7, 58.3)	(-23.2, 31.5)	(-11.5, 65.1)
		Pr >  t			0.1699

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-24i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Dyspnoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95			
			LS Mean	3.677	4.597	-0.920		
			SEM	2.435	2.522	2.422		
			95% CI	(-1.1, 8.5)	(-0.4, 9.6)	(-5.7, 3.8)		
					Pr >  t			0.7041
		Week 16	n	90	75			
			LS Mean	3.642	5.157	-1.515		
			SEM	2.512	2.676	2.638		
			95% CI	(-1.3, 8.6)	(-0.1, 10.4)	(-6.7, 3.7)		
					Pr >  t			0.5661
		Week 24	n	79	62			
			LS Mean	1.171	8.484	-7.312		
			SEM	2.590	2.811	2.823		
			95% CI	(-3.9, 6.3)	( 3.0, 14.0)	(-12.9, -1.8)		
					Pr >  t			0.0098
		Week 32	n	70	56			
			LS Mean	2.066	2.810	-0.743		
			SEM	2.690	2.892	2.951		
			95% CI	(-3.2, 7.4)	(-2.9, 8.5)	(-6.5, 5.0)		
					Pr >  t			0.8012
		Week 40	n	61	46			
			LS Mean	2.291	5.720	-3.428		
			SEM	2.771	3.043	3.159		
			95% CI	(-3.2, 7.7)	(-0.3, 11.7)	(-9.6, 2.8)		
			Pr >  t			0.2782		
Week 48	n	56	38					
	LS Mean	3.214	8.585	-5.371				
	SEM	2.824	3.196	3.351				
	95% CI	(-2.3, 8.8)	( 2.3, 14.9)	(-11.9, 1.2)				
			Pr >  t			0.1093		
Week 56	n	49	33					
	LS Mean	2.281	5.951	-3.669				
		SEM	2.911	3.320	3.547			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.4, 8.0)	(-0.6, 12.5)	(-10.6, 3.3)
		Pr >  t			0.3011
	Week 64	n	37	29	
		LS Mean	2.444	6.494	-4.050
		SEM	3.122	3.449	3.840
		95% CI	(-3.7, 8.6)	(-0.3, 13.3)	(-11.6, 3.5)
		Pr >  t			0.2918
	Week 72	n	40	25	
		LS Mean	7.125	5.173	1.951
		SEM	3.061	3.603	3.931
		95% CI	( 1.1, 13.1)	(-1.9, 12.2)	(-5.8, 9.7)
		Pr >  t			0.6197
	Week 84	n	32	23	
		LS Mean	3.791	7.134	-3.343
		SEM	3.268	3.699	4.167
		95% CI	(-2.6, 10.2)	(-0.1, 14.4)	(-11.5, 4.8)
		Pr >  t			0.4226
	Week 96	n	29	17	
		LS Mean	2.637	6.243	-3.606
		SEM	3.356	4.087	4.586
		95% CI	(-4.0, 9.2)	(-1.8, 14.3)	(-12.6, 5.4)
		Pr >  t			0.4318
	Week 108	n	22	15	
		LS Mean	0.544	5.317	-4.773
		SEM	3.671	4.271	4.971
		95% CI	(-6.7, 7.7)	(-3.1, 13.7)	(-14.5, 5.0)
		Pr >  t			0.3371
	Week 120	n	23	13	
		LS Mean	5.426	4.525	0.900
		SEM	3.610	4.503	5.134
		95% CI	(-1.7, 12.5)	(-4.3, 13.4)	(-9.2, 11.0)
		Pr >  t			0.8609
	Week 132	n	17	5	
		LS Mean	6.631	20.369	-13.74
		SEM	4.006	6.634	7.282
		95% CI	(-1.2, 14.5)	( 7.4, 33.4)	(-28.0, 0.5)
		Pr >  t			0.0595
	Week 144	n	14	3	
		LS Mean	9.316	5.732	3.584
		SEM	4.286	8.357	9.016

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.9,17.7)	(-10.7,22.1)	(-14.1,21.3)
		Pr >  t			0.6911
	Week 156	n	9	2	
		LS Mean	2.845	6.038	-3.192
		SEM	5.111	10.09	10.99
		95% CI	( -7.2,12.9)	(-13.8,25.8)	(-24.8,18.4)
		Pr >  t			0.7715
	Week 168	n	4	1	
		LS Mean	7.524	6.063	1.461
		SEM	7.263	14.06	15.60
		95% CI	( -6.7,21.8)	(-21.5,33.7)	(-29.2,32.1)
		Pr >  t			0.9254
	Week 180	n	1	1	
		LS Mean	32.898	6.063	26.835
		SEM	14.02	14.06	19.68
		95% CI	( 5.4,60.4)	(-21.5,33.7)	(-11.8,65.4)
		Pr >  t			0.1729
	Week 192	n	1	1	
		LS Mean	32.898	6.063	26.835
		SEM	14.02	14.06	19.68
		95% CI	( 5.4,60.4)	(-21.5,33.7)	(-11.8,65.4)
		Pr >  t			0.1729
>= 3	Week 8	n	37	45	
		LS Mean	-1.958	-1.455	-0.503
		SEM	6.919	6.875	3.962
		95% CI	(-15.6,11.7)	(-15.0,12.1)	( -8.3, 7.3)
		Pr >  t			0.8992
	Week 16	n	34	32	
		LS Mean	-3.761	-2.921	-0.840
		SEM	7.128	7.206	4.336
		95% CI	(-17.8,10.3)	(-17.1,11.3)	( -9.4, 7.7)
		Pr >  t			0.8465
	Week 24	n	26	19	
		LS Mean	1.909	0.625	1.284
		SEM	7.283	7.530	5.099
		95% CI	(-12.5,16.3)	(-14.2,15.5)	( -8.8,11.3)
		Pr >  t			0.8014
	Week 32	n	16	17	
		LS Mean	-4.035	-1.014	-3.021
		SEM	7.644	7.629	5.733



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-19.1,11.0)	(-16.0,14.0)	(-14.3, 8.3)
	Pr >  t			0.5985
Week 40	n	14	16	
	LS Mean	-4.679	3.223	-7.901
	SEM	7.772	7.677	5.967
	95% CI	(-20.0,10.6)	(-11.9,18.4)	(-19.6, 3.8)
	Pr >  t			0.1864
Week 48	n	13	13	
	LS Mean	-2.271	0.783	-3.054
	SEM	7.838	7.871	6.300
	95% CI	(-17.7,13.2)	(-14.7,16.3)	(-15.4, 9.3)
	Pr >  t			0.6281
Week 56	n	10	12	
	LS Mean	-1.923	-1.371	-0.552
	SEM	8.148	7.960	6.760
	95% CI	(-18.0,14.1)	(-17.0,14.3)	(-13.8,12.7)
	Pr >  t			0.9350
Week 64	n	10	13	
	LS Mean	-2.670	-1.378	-1.292
	SEM	8.150	7.880	6.669
	95% CI	(-18.7,13.4)	(-16.9,14.1)	(-14.4,11.8)
	Pr >  t			0.8465
Week 72	n	8	10	
	LS Mean	-2.889	0.177	-3.066
	SEM	8.443	8.170	7.353
	95% CI	(-19.5,13.7)	(-15.9,16.3)	(-17.5,11.4)
	Pr >  t			0.6770
Week 84	n	8	10	
	LS Mean	-0.023	-2.854	2.831
	SEM	8.449	8.165	7.354
	95% CI	(-16.7,16.6)	(-18.9,13.2)	(-11.6,17.3)
	Pr >  t			0.7005
Week 96	n	6	7	
	LS Mean	-4.613	11.064	-15.68
	SEM	8.927	8.673	8.413
	95% CI	(-22.2,13.0)	(-6.0,28.1)	(-32.2, 0.9)
	Pr >  t			0.0632
Week 108	n	4	6	
	LS Mean	-8.538	7.868	-16.41
	SEM	9.787	8.924	9.570

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-27.8,10.7)	(-9.7,25.4)	(-35.2, 2.4)
		Pr >  t			0.0873
	Week 120	n	5	3	
		LS Mean	-5.008	-5.960	0.952
		SEM	9.275	10.58	10.68
		95% CI	(-23.3,13.2)	(-26.8,14.8)	(-20.1,22.0)
		Pr >  t			0.9291
	Week 132	n	3	3	
		LS Mean	-7.956	3.963	-11.92
		SEM	10.57	10.59	11.83
		95% CI	(-28.8,12.8)	(-16.9,24.8)	(-35.2,11.4)
		Pr >  t			0.3145
	Week 144	n	1	2	
		LS Mean	-13.95	-1.026	-12.93
		SEM	15.50	12.01	17.34
		95% CI	(-44.4,16.5)	(-24.6,22.6)	(-47.0,21.2)
		Pr >  t			0.4565
	Week 156	n	1	1	
		LS Mean	-13.95	0.608	-14.56
		SEM	15.50	15.52	19.92
		95% CI	(-44.4,16.5)	(-29.9,31.1)	(-53.8,24.6)
		Pr >  t			0.4654
	Week 168	n		1	
		LS Mean	NE	0.608	NE
		SEM	NE	15.52	NE
		95% CI	NE	(-29.9,31.1)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-45: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Schlaflosigkeit“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73	
			LS Mean	-3.536	-4.957	1.421
			SEM	4.396	4.420	4.029
			95% CI	(-12.2, 5.1)	(-13.7, 3.8)	(-6.5, 9.3)
			Pr >  t			0.7245
	Week 16	n	67	56		
		LS Mean	-2.717	0.898	-3.615	
		SEM	4.474	4.697	4.369	
		95% CI	(-11.5, 6.1)	(-8.3,10.1)	(-12.2, 5.0)	
		Pr >  t			0.4085	
	Week 24	n	61	46		
		LS Mean	1.521	-1.725	3.246	
		SEM	4.566	4.857	4.627	
		95% CI	(-7.5,10.5)	(-11.3, 7.8)	(-5.8,12.3)	
		Pr >  t			0.4833	
	Week 32	n	52	41		
		LS Mean	-3.875	-3.950	0.075	
		SEM	4.732	4.988	4.855	
		95% CI	(-13.2, 5.4)	(-13.8, 5.9)	(-9.5, 9.6)	
		Pr >  t			0.9877	
Week 40	n	45	36			
	LS Mean	-2.979	-4.765	1.785		
	SEM	4.849	5.142	5.100		
	95% CI	(-12.5, 6.6)	(-14.9, 5.3)	(-8.2,11.8)		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.7264
Week 48	n	42	30	
	LS Mean	-0.123	-3.387	3.263
	SEM	4.912	5.337	5.358
	95% CI	(-9.8, 9.5)	(-13.9, 7.1)	(-7.3, 13.8)
	Pr >  t			0.5427
Week 56	n	35	24	
	LS Mean	0.253	-2.227	2.480
	SEM	5.082	5.616	5.790
	95% CI	(-9.7, 10.2)	(-13.3, 8.8)	(-8.9, 13.8)
	Pr >  t			0.6685
Week 64	n	25	25	
	LS Mean	-8.727	-4.821	-3.906
	SEM	5.458	5.564	6.082
	95% CI	(-19.5, 2.0)	(-15.8, 6.1)	(-15.8, 8.0)
	Pr >  t			0.5209
Week 72	n	27	20	
	LS Mean	-2.670	-2.452	-0.218
	SEM	5.366	5.874	6.287
	95% CI	(-13.2, 7.9)	(-14.0, 9.1)	(-12.6, 12.1)
	Pr >  t			0.9723
Week 84	n	23	19	
	LS Mean	-4.498	-0.814	-3.684
	SEM	5.590	5.954	6.536
	95% CI	(-15.5, 6.5)	(-12.5, 10.9)	(-16.5, 9.1)
	Pr >  t			0.5731
Week 96	n	20	13	
	LS Mean	-6.174	2.395	-8.569
	SEM	5.791	6.628	7.314
	95% CI	(-17.5, 5.2)	(-10.6, 15.4)	(-22.9, 5.8)
	Pr >  t			0.2417
Week 108	n	17	13	
	LS Mean	-2.284	-0.136	-2.148
	SEM	6.051	6.629	7.519
	95% CI	(-14.2, 9.6)	(-13.2, 12.9)	(-16.9, 12.6)
	Pr >  t			0.7752
Week 120	n	17	12	
	LS Mean	-3.671	0.689	-4.359
	SEM	6.049	6.796	7.667
	95% CI	(-15.5, 8.2)	(-12.7, 14.0)	(-19.4, 10.7)

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.5698
	Week 132	n	13	6	
		LS Mean	0.872	-2.536	3.409
		SEM	6.545	8.648	9.677
		95% CI	(-12.0,13.7)	(-19.5,14.4)	(-15.6,22.4)
		Pr >  t			0.7247
	Week 144	n	11	4	
		LS Mean	5.749	-2.190	7.940
		SEM	6.903	10.18	11.28
		95% CI	(-7.8,19.3)	(-22.2,17.8)	(-14.2,30.1)
		Pr >  t			0.4816
	Week 156	n	7	2	
		LS Mean	2.093	1.854	0.239
		SEM	8.088	13.74	15.17
		95% CI	(-13.8,18.0)	(-25.1,28.8)	(-29.5,30.0)
		Pr >  t			0.9874
	Week 168	n	3	1	
		LS Mean	20.962	-26.88	47.837
		SEM	11.41	18.96	21.58
		95% CI	(-1.4,43.4)	(-64.1,10.3)	(-5.5,90.2)
		Pr >  t			0.0269
	Week 180	n	1	1	
		LS Mean	44.787	6.455	38.332
		SEM	18.92	18.96	26.33
		95% CI	(-7.7,81.9)	(-30.8,43.7)	(-13.4,90.0)
		Pr >  t			0.1459
	Week 192	n	1	1	
		LS Mean	44.787	-26.88	71.662
		SEM	18.92	18.96	26.33
		95% CI	(-7.7,81.9)	(-64.1,10.3)	(-20.0, 123)
		Pr >  t			0.0066
Present	Week 8	n	65	67	
		LS Mean	6.992	9.771	-2.779
		SEM	4.328	4.469	3.782
		95% CI	(-1.5,15.5)	(-1.0,18.6)	(-10.2, 4.7)
		Pr >  t			0.4631
	Week 16	n	57	51	
		LS Mean	2.109	11.022	-8.914
		SEM	4.502	4.684	4.096
		95% CI	(-6.8,11.0)	(-1.8,20.3)	(-17.0,-0.9)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.0302
	Week 24	n	44	35	
		LS Mean	5.176	11.695	-6.519
		SEM	4.665	5.037	4.620
		95% CI	(-4.0,14.4)	( 1.8,21.6)	(-15.6, 2.6)
		Pr >  t			0.1589
	Week 32	n	34	32	
		LS Mean	4.864	6.853	-1.989
		SEM	4.903	5.125	4.926
		95% CI	(-4.8,14.5)	(-3.2,16.9)	(-11.7, 7.7)
		Pr >  t			0.6866
	Week 40	n	30	26	
		LS Mean	5.736	4.427	1.309
		SEM	5.020	5.330	5.253
		95% CI	(-4.1,15.6)	(-6.1,14.9)	(-9.0,11.6)
		Pr >  t			0.8033
	Week 48	n	27	21	
		LS Mean	8.942	11.557	-2.616
		SEM	5.115	5.573	5.589
		95% CI	(-1.1,19.0)	( 0.6,22.5)	(-13.6, 8.4)
		Pr >  t			0.6399
	Week 56	n	24	21	
		LS Mean	3.574	12.789	-9.215
		SEM	5.239	5.571	5.705
		95% CI	(-6.7,13.9)	( 1.8,23.7)	(-20.4, 2.0)
		Pr >  t			0.1067
	Week 64	n	22	17	
		LS Mean	4.781	3.285	1.496
		SEM	5.336	5.848	6.065
		95% CI	(-5.7,15.3)	(-8.2,14.8)	(-10.4,13.4)
		Pr >  t			0.8053
	Week 72	n	21	15	
		LS Mean	3.459	12.159	-8.701
		SEM	5.394	6.028	6.289
		95% CI	(-7.1,14.1)	( 0.3,24.0)	(-21.0, 3.6)
		Pr >  t			0.1670
	Week 84	n	17	14	
		LS Mean	11.519	7.401	4.118
		SEM	5.682	6.132	6.619
		95% CI	( 0.4,22.7)	(-4.6,19.5)	(-8.9,17.1)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.5341
Week 96	n	15	11	
	LS Mean	5.573	10.496	-4.923
	SEM	5.841	6.551	7.162
	95% CI	(-5.9,17.1)	(-2.4,23.4)	(-19.0, 9.1)
	Pr >  t			0.4921
Week 108	n	9	8	
	LS Mean	11.879	7.964	3.916
	SEM	6.800	7.221	8.505
	95% CI	(-1.5,25.2)	(-6.2,22.1)	(-12.8,20.6)
	Pr >  t			0.6454
Week 120	n	11	4	
	LS Mean	12.986	-6.549	19.535
	SEM	6.380	9.261	10.04
	95% CI	( 0.5,25.5)	(-24.7,11.6)	(-0.2,39.2)
	Pr >  t			0.0521
Week 132	n	7	2	
	LS Mean	5.757	7.617	-1.860
	SEM	7.394	12.32	13.43
	95% CI	(-8.8,20.3)	(-16.6,31.8)	(-28.2,24.5)
	Pr >  t			0.8899
Week 144	n	4	1	
	LS Mean	-0.813	6.958	-7.771
	SEM	9.048	16.87	18.48
	95% CI	(-18.6,17.0)	(-26.2,40.1)	(-44.1,28.5)
	Pr >  t			0.6743
Week 156	n	3	1	
	LS Mean	-1.657	6.958	-8.615
	SEM	10.25	16.87	19.07
	95% CI	(-21.8,18.5)	(-26.2,40.1)	(-46.1,28.8)
	Pr >  t			0.6515
Week 168	n	1	1	
	LS Mean	2.509	6.958	-4.448
	SEM	16.81	16.87	23.26
	95% CI	(-30.5,35.5)	(-26.2,40.1)	(-50.1,41.2)
	Pr >  t			0.8484

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Presence of Lung Metastases (L)	No	Week 8	n	98	84	
			LS Mean	1.949	-0.006	1.954
			SEM	3.596	3.809	3.628
			95% CI	(-5.1, 9.0)	(-7.5, 7.5)	(-5.2, 9.1)
			Pr >  t			0.5903
		Week 16	n	86	68	
			LS Mean	-0.623	5.190	-5.813
			SEM	3.694	3.986	3.891
			95% CI	(-7.9, 6.6)	(-2.7, 13.0)	(-13.5, 1.8)
			Pr >  t			0.1358
		Week 24	n	73	48	
			LS Mean	4.263	4.268	-0.005
			SEM	3.814	4.320	4.327
			95% CI	(-3.2, 11.8)	(-4.2, 12.8)	(-8.5, 8.5)
			Pr >  t			0.9991
		Week 32	n	60	43	
			LS Mean	-0.013	0.020	-0.033
			SEM	4.009	4.450	4.569
			95% CI	(-7.9, 7.9)	(-8.7, 8.8)	(-9.0, 8.9)
			Pr >  t			0.9943
		Week 40	n	50	38	
			LS Mean	0.473	-1.510	1.982
			SEM	4.163	4.600	4.834
			95% CI	(-7.7, 8.7)	(-10.5, 7.5)	(-7.5, 11.5)
Pr >  t				0.6819		
Week 48	n	48	31			
	LS Mean	5.722	0.248	5.474		
	SEM	4.203	4.836	5.095		
	95% CI	(-2.5, 14.0)	(-9.2, 9.7)	(-4.5, 15.5)		
	Pr >  t			0.2829		
Week 56	n	41	25			
	LS Mean	3.323	3.954	-0.632		
	SEM	4.352	5.125	5.492		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-5.2,11.9)	(-6.1,14.0)	(-11.4,10.1)
	Pr >  t			0.9085
	n	30	24	
	LS Mean	-3.940	-1.229	-2.711
	SEM	4.699	5.186	5.833
Week 72	95% CI	(-13.2, 5.3)	(-11.4, 9.0)	(-14.2, 8.7)
	Pr >  t			0.6422
	n	32	19	
	LS Mean	1.129	1.055	0.074
	SEM	4.623	5.554	6.104
Week 84	95% CI	(-8.0,10.2)	(-9.8,12.0)	(-11.9,12.1)
	Pr >  t			0.9903
	n	26	19	
	LS Mean	-0.189	4.654	-4.843
	SEM	4.913	5.555	6.310
Week 96	95% CI	(-9.8, 9.5)	(-6.3,15.6)	(-17.2, 7.5)
	Pr >  t			0.4430
	n	23	14	
	LS Mean	-2.465	5.301	-7.766
	SEM	5.079	6.129	6.952
Week 108	95% CI	(-12.4, 7.5)	(-6.7,17.3)	(-21.4, 5.9)
	Pr >  t			0.2643
	n	19	13	
	LS Mean	1.611	3.492	-1.881
	SEM	5.401	6.284	7.311
Week 120	95% CI	(-9.0,12.2)	(-8.8,15.8)	(-16.2,12.5)
	Pr >  t			0.7970
	n	19	11	
	LS Mean	0.362	5.411	-5.049
	SEM	5.384	6.668	7.644
Week 132	95% CI	(-10.2,10.9)	(-7.7,18.5)	(-20.0,10.0)
	Pr >  t			0.5090
	n	15	5	
	LS Mean	1.364	2.231	-0.867
	SEM	5.836	9.085	10.07
Week 144	95% CI	(-10.1,12.8)	(-15.6,20.1)	(-20.6,18.9)
	Pr >  t			0.9314
	n	12	3	
Week 144	LS Mean	8.378	2.947	5.431
	SEM	6.298	11.37	12.41

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-4.0,20.7)	(-19.4,25.3)	(-18.9,29.8)
		Pr >  t			0.6618
	Week 156	n	7	2	
		LS Mean	5.768	6.115	-0.347
		SEM	7.786	13.68	15.25
		95% CI	(-9.5,21.0)	(-20.7,33.0)	(-30.3,29.6)
		Pr >  t			0.9818
	Week 168	n	3	1	
		LS Mean	24.633	-22.67	47.299
		SEM	11.25	18.99	21.73
		95% CI	( 2.6,46.7)	(-59.9,14.6)	( 4.7,89.9)
		Pr >  t			0.0298
	Week 180	n	1	1	
		LS Mean	48.641	10.664	37.977
		SEM	18.93	18.99	26.53
		95% CI	( 11.5,85.8)	(-26.6,47.9)	(-14.1,90.0)
		Pr >  t			0.1527
	Week 192	n	1	1	
		LS Mean	48.641	-22.67	71.307
		SEM	18.93	18.99	26.53
		95% CI	( 11.5,85.8)	(-59.9,14.6)	( 19.2, 123)
		Pr >  t			0.0073
Yes	Week 8	n	44	56	
		LS Mean	0.362	5.745	-5.383
		SEM	7.005	6.726	4.402
		95% CI	(-13.5,14.2)	(-7.5,19.0)	(-14.1, 3.3)
		Pr >  t			0.2229
	Week 16	n	38	39	
		LS Mean	-0.059	7.173	-7.232
		SEM	7.211	7.123	4.821
		95% CI	(-14.3,14.2)	(-6.9,21.2)	(-16.7, 2.3)
		Pr >  t			0.1349
	Week 24	n	32	33	
		LS Mean	1.753	5.740	-3.987
		SEM	7.323	7.203	5.101
		95% CI	(-12.7,16.2)	(-8.5,19.9)	(-14.0, 6.1)
		Pr >  t			0.4351
	Week 32	n	26	30	
		LS Mean	0.615	3.780	-3.165
		SEM	7.459	7.269	5.381

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.1,15.3)	(-10.5,18.1)	(-13.8, 7.4)
		Pr >  t			0.5568
	Week 40	n	25	24	
		LS Mean	2.295	2.464	-0.169
		SEM	7.490	7.423	5.627
		95% CI	(-12.5,17.1)	(-12.2,17.1)	(-11.2,10.9)
		Pr >  t			0.9761
	Week 48	n	21	20	
		LS Mean	0.223	9.238	-9.016
		SEM	7.616	7.571	5.979
		95% CI	(-14.8,15.2)	(-5.7,24.1)	(-20.8, 2.7)
		Pr >  t			0.1324
	Week 56	n	18	20	
		LS Mean	-0.552	7.124	-7.676
		SEM	7.746	7.569	6.147
		95% CI	(-15.8,14.7)	(-7.8,22.0)	(-19.8, 4.4)
		Pr >  t			0.2124
	Week 64	n	17	18	
		LS Mean	0.253	0.960	-0.707
		SEM	7.798	7.665	6.330
		95% CI	(-15.1,15.6)	(-14.1,16.0)	(-13.1,11.7)
		Pr >  t			0.9111
	Week 72	n	16	16	
		LS Mean	-1.338	9.519	-10.86
		SEM	7.861	7.775	6.538
		95% CI	(-16.8,14.1)	(-5.8,24.8)	(-23.7, 2.0)
		Pr >  t			0.0975
	Week 84	n	14	14	
		LS Mean	7.993	2.300	5.693
		SEM	7.992	7.912	6.862
		95% CI	(-7.7,23.7)	(-13.3,17.9)	(-7.8,19.2)
		Pr >  t			0.4071
	Week 96	n	12	10	
		LS Mean	2.706	8.670	-5.963
		SEM	8.176	8.343	7.553
		95% CI	(-13.4,18.8)	(-7.7,25.1)	(-20.8, 8.9)
		Pr >  t			0.4302
	Week 108	n	7	8	
		LS Mean	9.259	5.430	3.829
		SEM	9.017	8.707	8.809

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.5,27.0)	(-11.7,22.6)	(-13.5,21.1)
		Pr >  t			0.6640
	Week 120	n	9	5	
		LS Mean	10.576	-7.493	18.069
		SEM	8.600	9.699	9.403
		95% CI	(-6.3,27.5)	(-26.6,11.6)	(-0.4,36.5)
		Pr >  t			0.0552
	Week 132	n	5	3	
		LS Mean	10.275	3.311	6.964
		SEM	9.751	11.22	11.89
		95% CI	(-8.9,29.4)	(-18.7,25.4)	(-16.4,30.3)
		Pr >  t			0.5584
	Week 144	n	3	2	
		LS Mean	-4.729	2.506	-7.235
		SEM	11.26	12.89	14.60
		95% CI	(-26.9,17.4)	(-22.8,27.8)	(-35.9,21.5)
		Pr >  t			0.6205
	Week 156	n	3	1	
		LS Mean	-4.926	3.349	-8.275
		SEM	11.27	16.90	18.25
		95% CI	(-27.1,17.2)	(-29.8,36.5)	(-44.1,27.6)
		Pr >  t			0.6504
	Week 168	n	1	1	
		LS Mean	-0.550	3.349	-3.898
		SEM	16.96	16.90	22.22
		95% CI	(-33.9,32.8)	(-29.8,36.5)	(-47.6,39.8)
		Pr >  t			0.8608

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Presence of Liver Metastases (L)	No	Week 8	n	104	98	
			LS Mean	-2.189	-3.417	1.228
			SEM	3.892	3.860	3.312
			95% CI	(-9.8, 5.5)	(-11.0, 4.2)	(-5.3, 7.7)
		Pr >  t			0.7110	
		Week 16	n	92	77	
			LS Mean	-2.350	2.712	-5.063
			SEM	3.944	4.085	3.559
			95% CI	(-10.1, 5.4)	(-5.3, 10.7)	(-12.1, 1.9)
		Pr >  t			0.1555	
		Week 24	n	83	66	
			LS Mean	2.222	0.786	1.436
			SEM	4.016	4.177	3.738
			95% CI	(-5.7, 10.1)	(-7.4, 9.0)	(-5.9, 8.8)
		Pr >  t			0.7009	
		Week 32	n	72	60	
			LS Mean	-1.525	-2.367	0.843
			SEM	4.110	4.262	3.899
			95% CI	(-9.6, 6.6)	(-10.7, 6.0)	(-6.8, 8.5)
		Pr >  t			0.8289	
		Week 40	n	64	51	
			LS Mean	-0.600	-2.777	2.177
			SEM	4.181	4.397	4.103
			95% CI	(-8.8, 7.6)	(-11.4, 5.9)	(-5.9, 10.2)
		Pr >  t			0.5959	
		Week 48	n	58	45	
			LS Mean	0.731	-0.994	1.726
			SEM	4.243	4.497	4.275
95% CI	(-7.6, 9.1)		(-9.8, 7.8)	(-6.7, 10.1)		
Pr >  t			0.6865			
Week 56	n	49	38			
	LS Mean	0.269	-0.986	1.255		
	SEM	4.361	4.647	4.551		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.3, 8.8)	(-10.1, 8.1)	(-7.7,10.2)
	Pr >  t			0.7828
	n	39	37	
	LS Mean	-5.660	-4.298	-1.362
	SEM	4.545	4.674	4.760
Week 72	95% CI	(-14.6, 3.3)	(-13.5, 4.9)	(-10.7, 8.0)
	Pr >  t			0.7749
	n	41	32	
	LS Mean	-1.160	1.744	-2.904
	SEM	4.504	4.818	4.862
Week 84	95% CI	(-10.0, 7.7)	(-7.7,11.2)	(-12.4, 6.6)
	Pr >  t			0.5503
	n	33	29	
	LS Mean	-0.158	-0.499	0.340
	SEM	4.729	4.925	5.154
Week 96	95% CI	(-9.4, 9.1)	(-10.2, 9.2)	(-9.8,10.5)
	Pr >  t			0.9473
	n	31	21	
	LS Mean	-2.544	4.591	-7.135
	SEM	4.783	5.335	5.604
Week 108	95% CI	(-11.9, 6.9)	(-5.9,15.1)	(-18.1, 3.9)
	Pr >  t			0.2031
	n	23	18	
	LS Mean	1.843	2.145	-0.301
	SEM	5.152	5.567	6.122
Week 120	95% CI	(-8.3,12.0)	(-8.8,13.1)	(-12.3,11.7)
	Pr >  t			0.9607
	n	25	15	
	LS Mean	0.589	-1.225	1.814
	SEM	5.033	5.875	6.319
Week 132	95% CI	(-9.3,10.5)	(-12.8,10.3)	(-10.6,14.2)
	Pr >  t			0.7741
	n	17	8	
	LS Mean	4.617	-1.001	5.618
	SEM	5.598	7.262	8.003
Week 144	95% CI	(-6.4,15.6)	(-15.2,13.2)	(-10.1,21.3)
	Pr >  t			0.4828
	n	15	5	
	LS Mean	3.744	-0.961	4.705
	SEM	5.793	8.737	9.491

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.6,15.1)	(-18.1,16.2)	(-13.9,23.3)
		Pr >  t			0.6201
	Week 156	n	10	3	
		LS Mean	0.454	1.532	-1.078
		SEM	6.648	10.85	11.92
		95% CI	(-12.6,13.5)	(-19.8,22.8)	(-24.5,22.3)
		Pr >  t			0.9279
	Week 168	n	4	2	
		LS Mean	16.076	-13.77	29.844
		SEM	9.535	13.03	15.51
		95% CI	(-2.6,34.8)	(-39.3,11.8)	(-0.6,60.3)
		Pr >  t			0.0546
	Week 180	n	1	1	
		LS Mean	45.949	8.295	37.654
		SEM	18.01	18.02	25.08
		95% CI	( 10.6,81.3)	(-27.1,43.6)	(-11.6,86.9)
		Pr >  t			0.1336
	Week 192	n	1	1	
		LS Mean	45.949	-25.03	70.984
		SEM	18.01	18.02	25.08
		95% CI	( 10.6,81.3)	(-60.4,10.3)	( 21.8, 120)
		Pr >  t			0.0047
Yes	Week 8	n	38	42	
		LS Mean	7.920	12.428	-4.509
		SEM	5.132	5.549	5.196
		95% CI	(-2.2,18.1)	( 1.4,23.4)	(-14.8, 5.8)
		Pr >  t			0.3870
	Week 16	n	32	30	
		LS Mean	1.482	10.008	-8.525
		SEM	5.469	5.829	5.731
		95% CI	(-9.3,12.3)	(-1.5,21.5)	(-19.8, 2.8)
		Pr >  t			0.1387
	Week 24	n	22	15	
		LS Mean	2.534	10.867	-8.333
		SEM	5.847	6.874	7.068
		95% CI	(-9.0,14.1)	(-2.7,24.4)	(-22.3, 5.6)
		Pr >  t			0.2395
	Week 32	n	14	13	
		LS Mean	0.172	6.623	-6.451
		SEM	6.668	7.127	7.865



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-13.0,13.3)	(-7.4,20.7)	(-21.9, 9.0)
	Pr >  t			0.4128
	n	11	11	
	LS Mean	0.676	0.482	0.194
	SEM	7.130	7.436	8.518
Week 48	95% CI	(-13.4,14.7)	(-14.2,15.1)	(-16.6,17.0)
	Pr >  t			0.9819
	n	11	6	
	LS Mean	12.797	15.654	-2.857
	SEM	7.130	8.873	9.797
Week 56	95% CI	(-1.2,26.8)	(-1.8,33.1)	(-22.1,16.4)
	Pr >  t			0.7708
	n	10	7	
	LS Mean	3.526	22.803	-19.28
	SEM	7.324	8.446	9.562
Week 64	95% CI	(-10.9,17.9)	(-6.2,39.4)	(-38.1,-0.5)
	Pr >  t			0.0447
	n	8	5	
	LS Mean	5.497	4.216	1.282
	SEM	7.816	9.421	10.79
Week 72	95% CI	(-9.9,20.9)	(-14.3,22.8)	(-20.0,22.5)
	Pr >  t			0.9055
	n	7	3	
	LS Mean	-1.629	-1.748	0.120
	SEM	8.150	11.30	12.68
Week 84	95% CI	(-17.7,14.4)	(-24.0,20.5)	(-24.8,25.1)
	Pr >  t			0.9925
	n	7	4	
	LS Mean	7.894	9.101	-1.207
	SEM	8.150	10.17	11.68
Week 96	95% CI	(-8.1,23.9)	(-10.9,29.1)	(-24.2,21.8)
	Pr >  t			0.9177
	n	4	3	
	LS Mean	-1.659	-1.748	0.090
	SEM	9.884	11.30	13.85
Week 108	95% CI	(-21.1,17.8)	(-24.0,20.5)	(-27.2,27.4)
	Pr >  t			0.9948
	n	3	3	
	LS Mean	3.892	-0.274	4.166
	SEM	11.03	11.30	14.70

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.8,25.6)	(-22.5,22.0)	(-24.8,33.1)
		Pr >  t			0.7770
	Week 120	n	3	1	
		LS Mean	13.004	-6.254	19.258
		SEM	11.03	17.89	20.21
		95% CI	(-8.7,34.7)	(-41.5,29.0)	(-20.6,59.1)
		Pr >  t			0.3417
	Week 132	n	3		
		LS Mean	-11.55	NE	NE
		SEM	11.03	NE	NE
		95% CI	(-33.3,10.2)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	2.935	6.292	-3.358		
			SEM	3.533	3.528	3.128		
			95% CI	(-4.0, 9.9)	(-0.6, 13.2)	(-9.5, 2.8)		
					Pr >  t			0.2836
		Week 16	n	92	83			
			LS Mean	0.871	7.610	-6.739		
			SEM	3.634	3.742	3.381		
			95% CI	(-6.3, 8.0)	(0.3, 15.0)	(-13.4, -0.1)		
					Pr >  t			0.0467
		Week 24	n	77	59			
			LS Mean	4.697	6.733	-2.036		
			SEM	3.720	3.981	3.728		
			95% CI	(-2.6, 12.0)	(-1.1, 14.6)	(-9.4, 5.3)		
					Pr >  t			0.5850
		Week 32	n	57	53			
			LS Mean	2.212	2.413	-0.200		
			SEM	3.953	4.060	4.003		
			95% CI	(-5.6, 10.0)	(-5.6, 10.4)	(-8.1, 7.7)		
					Pr >  t			0.9601
		Week 40	n	50	44			
			LS Mean	1.200	-0.718	1.918		
			SEM	4.051	4.224	4.249		
			95% CI	(-6.8, 9.2)	(-9.0, 7.6)	(-6.4, 10.3)		
					Pr >  t			0.6519
		Week 48	n	47	37			
			LS Mean	6.490	7.081	-0.590		
			SEM	4.096	4.380	4.448		
95% CI	(-1.6, 14.5)		(-1.5, 15.7)	(-9.3, 8.1)				
			Pr >  t			0.8944		
Week 56	n	40	32					
	LS Mean	3.604	7.758	-4.154				
	SEM	4.230	4.524	4.710				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-4.7,11.9)	(-1.1,16.6)	(-13.4, 5.1)
	Pr >  t			0.3780
	n	32	27	
Week 72	LS Mean	-0.199	0.561	-0.760
	SEM	4.441	4.713	5.077
	95% CI	(-8.9, 8.5)	(-8.7, 9.8)	(-10.7, 9.2)
Week 84	Pr >  t			0.8810
	n	31	23	
	LS Mean	1.095	6.398	-5.303
Week 96	SEM	4.477	4.911	5.291
	95% CI	(-7.7, 9.9)	(-3.2,16.0)	(-15.7, 5.1)
	Pr >  t			0.3164
Week 108	n	27	21	
	LS Mean	3.643	2.996	0.647
	SEM	4.634	5.031	5.527
Week 120	95% CI	(-5.5,12.7)	(-6.9,12.9)	(-10.2,11.5)
	Pr >  t			0.9069
	n	23	16	
Week 132	LS Mean	1.339	9.509	-8.170
	SEM	4.821	5.443	6.062
	95% CI	(-8.1,10.8)	(-1.2,20.2)	(-20.1, 3.7)
Week 144	Pr >  t			0.1780
	n	15	14	
	LS Mean	6.710	8.211	-1.501
Week 120	SEM	5.474	5.674	6.779
	95% CI	(-4.0,17.5)	(-2.9,19.3)	(-14.8,11.8)
	Pr >  t			0.8247
Week 132	n	18	8	
	LS Mean	4.468	-7.577	12.045
	SEM	5.173	6.897	7.632
Week 144	95% CI	(-5.7,14.6)	(-21.1, 6.0)	(-2.9,27.0)
	Pr >  t			0.1148
	n	12	4	
Week 120	LS Mean	4.511	7.702	-3.192
	SEM	5.892	9.103	10.07
	95% CI	(-7.1,16.1)	(-10.2,25.6)	(-22.9,16.6)
Week 132	Pr >  t			0.7513
	n	8	3	
	LS Mean	6.260	1.150	5.109
Week 144	SEM	6.797	10.33	11.71

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-7.1,19.6)	(-19.1,21.4)	(-17.9,28.1)
		Pr >  t			0.6626
	Week 156	n	5	1	
		LS Mean	10.088	3.420	6.668
		SEM	8.229	17.17	18.61
		95% CI	(-6.1,26.2)	(-30.3,37.1)	(-29.9,43.2)
		Pr >  t			0.7202
	Week 168	n	2	1	
		LS Mean	25.938	3.420	22.518
		SEM	12.36	17.17	20.77
		95% CI	( 1.7,50.2)	(-30.3,37.1)	(-18.2,63.3)
		Pr >  t			0.2786
	Week 180	n	1		
		LS Mean	50.075	NE	NE
		SEM	17.12	NE	NE
		95% CI	( 16.5,83.7)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	50.075	NE	NE
		SEM	17.12	NE	NE
		95% CI	( 16.5,83.7)	NE	NE
		Pr >  t			NE
Yes	Week 8	n	38	30	
		LS Mean	-4.942	-13.96	9.016
		SEM	6.671	7.177	6.208
		95% CI	(-18.2, 8.3)	(-28.2, 0.3)	(-3.2,21.3)
		Pr >  t			0.1481
	Week 16	n	32	24	
		LS Mean	-5.996	-1.801	-4.195
		SEM	6.810	7.428	6.738
		95% CI	(-19.5, 7.5)	(-16.5,12.9)	(-17.5, 9.1)
		Pr >  t			0.5342
	Week 24	n	28	22	
		LS Mean	-1.570	-4.356	2.786
		SEM	7.054	7.533	7.019
		95% CI	(-15.5,12.4)	(-19.3,10.6)	(-11.0,16.6)
		Pr >  t			0.6918
	Week 32	n	29	20	
		LS Mean	-6.751	-5.256	-1.496
		SEM	7.021	7.772	7.124

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-20.7, 7.2)	(-20.6,10.1)	(-15.5,12.5)
	Pr >  t			0.8339
	n	25	18	
	LS Mean	-2.004	-2.849	0.846
Week 48	SEM	7.174	7.912	7.434
	95% CI	(-16.2,12.2)	(-18.5,12.8)	(-13.8,15.5)
	Pr >  t			0.9095
	n	22	14	
Week 56	LS Mean	-3.654	-9.441	5.787
	SEM	7.319	8.300	7.992
	95% CI	(-18.1,10.8)	(-25.8, 6.9)	( -9.9,21.5)
	Pr >  t			0.4696
Week 64	n	19	13	
	LS Mean	-3.423	-6.122	2.698
	SEM	7.501	8.438	8.313
	95% CI	(-18.3,11.4)	(-22.8,10.5)	(-13.7,19.0)
Week 72	Pr >  t			0.7457
	n	15	15	
	LS Mean	-9.631	-8.327	-1.304
	SEM	7.836	8.199	8.398
Week 84	95% CI	(-25.1, 5.8)	(-24.5, 7.9)	(-17.8,15.2)
	Pr >  t			0.8767
	n	17	12	
	LS Mean	-4.317	-4.765	0.448
Week 96	SEM	7.652	8.581	8.600
	95% CI	(-19.4,10.8)	(-21.7,12.2)	(-16.5,17.4)
	Pr >  t			0.9585
	n	13	12	
Week 108	LS Mean	-2.242	-1.895	-0.347
	SEM	8.147	8.584	8.999
	95% CI	(-18.3,13.8)	(-18.8,15.0)	(-18.0,17.3)
	Pr >  t			0.9693
Week 108	n	12	8	
	LS Mean	-7.730	-5.377	-2.353
	SEM	8.293	9.467	9.968
	95% CI	(-24.1, 8.6)	(-24.0,13.3)	(-21.9,17.2)
Week 108	Pr >  t			0.8135
	n	11	7	
	LS Mean	-4.236	-9.447	5.210
	SEM	8.466	9.813	10.43

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.9,12.5)	(-28.8, 9.9)	(-15.3,25.7)
		Pr >  t			0.6175
	Week 120	n	10	8	
		LS Mean	-1.223	3.092	-4.316
		SEM	8.660	9.465	10.26
		95% CI	(-18.3,15.8)	(-15.6,21.7)	(-24.5,15.9)
		Pr >  t			0.6744
	Week 132	n	8	4	
		LS Mean	-1.046	-9.800	8.754
		SEM	9.188	11.68	12.72
		95% CI	(-19.1,17.0)	(-32.8,13.2)	(-16.2,33.7)
		Pr >  t			0.4916
	Week 144	n	7	2	
		LS Mean	0.964	-1.817	2.781
		SEM	9.546	15.17	16.19
		95% CI	(-17.8,19.8)	(-31.6,28.0)	(-29.0,34.6)
		Pr >  t			0.8637
	Week 156	n	5	2	
		LS Mean	-9.489	-1.817	-7.672
		SEM	10.61	15.17	16.84
		95% CI	(-30.3,11.4)	(-31.6,28.0)	(-40.8,25.4)
		Pr >  t			0.6489
	Week 168	n	2	1	
		LS Mean	5.914	-30.79	36.709
		SEM	14.95	20.42	24.11
		95% CI	(-23.5,35.3)	(-70.9, 9.3)	(-10.7,84.1)
		Pr >  t			0.1286
	Week 180	n		1	
		LS Mean	NE	2.536	NE
		SEM	NE	20.42	NE
		95% CI	NE	(-37.6,42.7)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-30.79	NE
		SEM	NE	20.42	NE
		95% CI	NE	(-70.9, 9.3)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	-2.930	-2.003	-0.926		
			SEM	2.026	2.026	2.870		
			95% CI	(-6.9, 1.0)	(-6.0, 2.0)	(-6.6, 4.7)		
					Pr >  t			0.7470
		Week 16	n	118	104			
			LS Mean	-4.673	1.842	-6.515		
			SEM	2.125	2.244	3.094		
			95% CI	(-8.8,-0.5)	(-2.6, 6.2)	(-12.6,-0.4)		
					Pr >  t			0.0356
		Week 24	n	100	79			
			LS Mean	-0.310	0.925	-1.236		
			SEM	2.261	2.491	3.366		
			95% CI	(-4.7, 4.1)	(-4.0, 5.8)	(-7.8, 5.4)		
					Pr >  t			0.7136
		Week 32	n	84	72			
			LS Mean	-3.701	-2.818	-0.883		
			SEM	2.408	2.582	3.531		
			95% CI	(-8.4, 1.0)	(-7.9, 2.2)	(-7.8, 6.0)		
					Pr >  t			0.8027
		Week 40	n	73	62			
			LS Mean	-2.713	-4.187	1.475		
			SEM	2.536	2.727	3.725		
			95% CI	(-7.7, 2.3)	(-9.5, 1.2)	(-5.8, 8.8)		
					Pr >  t			0.6922
		Week 48	n	67	51			
			LS Mean	0.415	-0.454	0.869		
			SEM	2.616	2.934	3.932		
95% CI	(-4.7, 5.5)		(-6.2, 5.3)	(-6.8, 8.6)				
			Pr >  t			0.8251		
Week 56	n	57	45					
	LS Mean	-1.504	0.905	-2.409				
	SEM	2.777	3.078	4.147				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.0, 3.9)	(-5.1, 6.9)	(-10.5, 5.7)
	Pr >  t			0.5614
	n	45	42	
	LS Mean	-6.213	-4.684	-1.529
	SEM	3.036	3.164	4.387
Week 72	95% CI	(-12.2,-0.3)	(-10.9, 1.5)	(-10.1, 7.1)
	Pr >  t			0.7275
	n	46	35	
	LS Mean	-4.917	0.324	-5.242
	SEM	3.013	3.397	4.542
Week 84	95% CI	(-10.8, 1.0)	(-6.3, 7.0)	(-14.2, 3.7)
	Pr >  t			0.2487
	n	40	33	
	LS Mean	-1.318	-0.746	-0.572
	SEM	3.180	3.478	4.714
Week 96	95% CI	(-7.6, 4.9)	(-7.6, 6.1)	(-9.8, 8.7)
	Pr >  t			0.9035
	n	34	24	
	LS Mean	-4.663	2.281	-6.944
	SEM	3.394	3.963	5.219
Week 108	95% CI	(-11.3, 2.0)	(-5.5,10.1)	(-17.2, 3.3)
	Pr >  t			0.1836
	n	26	21	
	LS Mean	-0.229	0.055	-0.284
	SEM	3.791	4.195	5.654
Week 120	95% CI	(-7.7, 7.2)	(-8.2, 8.3)	(-11.4,10.8)
	Pr >  t			0.9600
	n	27	16	
	LS Mean	-0.151	-2.566	2.415
	SEM	3.734	4.722	6.020
Week 132	95% CI	(-7.5, 7.2)	(-11.8, 6.7)	(-9.4,14.2)
	Pr >  t			0.6883
	n	20	8	
	LS Mean	-0.224	-1.537	1.313
	SEM	4.239	6.461	7.727
Week 144	95% CI	(-8.5, 8.1)	(-14.2,11.1)	(-13.8,16.5)
	Pr >  t			0.8651
	n	14	5	
	LS Mean	2.508	-1.522	4.030
	SEM	4.965	8.074	9.477

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.2,12.2)	(-17.4,14.3)	(-14.6,22.6)
		Pr >  t			0.6707
	Week 156	n	10	3	
		LS Mean	-1.402	0.982	-2.384
		SEM	5.790	10.32	11.83
		95% CI	(-12.8,10.0)	(-19.3,21.2)	(-25.6,20.8)
		Pr >  t			0.8403
	Week 168	n	4	2	
		LS Mean	14.193	-14.36	28.549
		SEM	8.942	12.57	15.43
		95% CI	(-3.3,31.7)	(-39.0,10.3)	(-1.7,58.8)
		Pr >  t			0.0645
	Week 180	n	1	1	
		LS Mean	44.154	7.695	36.459
		SEM	17.66	17.67	24.99
		95% CI	( 9.5,78.8)	(-27.0,42.4)	(-12.6,85.5)
		Pr >  t			0.1447
	Week 192	n	1	1	
		LS Mean	44.154	-25.64	69.789
		SEM	17.66	17.67	24.99
		95% CI	( 9.5,78.8)	(-60.3, 9.0)	( 20.8, 119)
		Pr >  t			0.0053
Prior use	Week 8	n	8	6	
		LS Mean	17.240	16.140	1.101
		SEM	9.146	11.88	14.16
		95% CI	(-2.6,37.0)	(-9.5,41.8)	(-29.4,31.6)
		Pr >  t			0.9392
	Week 16	n	6	3	
		LS Mean	15.662	15.599	0.063
		SEM	9.804	14.39	16.96
		95% CI	(-5.1,36.5)	(-14.5,45.6)	(-35.3,35.5)
		Pr >  t			0.9971
	Week 24	n	5	2	
		LS Mean	12.185	0.713	11.473
		SEM	10.28	15.84	18.41
		95% CI	(-9.4,33.8)	(-31.9,33.3)	(-26.5,49.4)
		Pr >  t			0.5389
	Week 32	n	2	1	
		LS Mean	6.920	13.579	-6.659
		SEM	13.43	19.07	23.17

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.6,34.5)	(-54.1,40.8)
		Pr >  t		0.7760
	Week 40	n	2	
		LS Mean	6.920	NE
		SEM	13.43	NE
		95% CI	(-20.6,34.5)	NE
		Pr >  t		NE
	Week 48	n	2	
		LS Mean	6.920	NE
		SEM	13.43	NE
		95% CI	(-20.6,34.5)	NE
		Pr >  t		NE
	Week 56	n	2	
		LS Mean	6.920	NE
		SEM	13.43	NE
		95% CI	(-20.6,34.5)	NE
		Pr >  t		NE
	Week 64	n	2	
		LS Mean	6.920	NE
		SEM	13.43	NE
		95% CI	(-20.6,34.5)	NE
		Pr >  t		NE
	Week 72	n	2	
		LS Mean	40.250	NE
		SEM	13.43	NE
		95% CI	( 12.7,67.8)	NE
		Pr >  t		NE
	Week 96	n	1	
		LS Mean	8.216	NE
		SEM	16.94	NE
		95% CI	(-26.6,43.0)	NE
		Pr >  t		NE
	Week 120	n	1	
		LS Mean	8.216	NE
		SEM	16.94	NE
		95% CI	(-26.6,43.0)	NE
		Pr >  t		NE
	Week 144	n	1	
		LS Mean	8.216	NE
		SEM	16.94	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-26.6,43.0)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
PTEN Loss of Expression (L)	No	Week 8	n	137	130	
			LS Mean	1.489	2.513	-1.024
			SEM	3.177	3.249	2.903
			95% CI	(-4.8, 7.7)	(-3.9, 8.9)	(-6.7, 4.7)
			Pr >  t			0.7244
		Week 16	n	119	97	
			LS Mean	0.410	5.907	-5.497
			SEM	3.266	3.445	3.160
			95% CI	(-6.0, 6.8)	(-0.9, 12.7)	(-11.7, 0.7)
			Pr >  t			0.0823
		Week 24	n	100	75	
			LS Mean	3.389	5.147	-1.759
			SEM	3.359	3.619	3.425
			95% CI	(-3.2, 10.0)	(-2.0, 12.3)	(-8.5, 5.0)
			Pr >  t			0.6077
		Week 32	n	82	69	
			LS Mean	0.534	2.037	-1.502
			SEM	3.499	3.690	3.596
			95% CI	(-6.3, 7.4)	(-5.2, 9.3)	(-8.6, 5.6)
			Pr >  t			0.6761
		Week 40	n	73	58	
			LS Mean	1.843	0.704	1.139
			SEM	3.571	3.824	3.792
			95% CI	(-5.2, 8.9)	(-6.8, 8.2)	(-6.3, 8.6)
			Pr >  t			0.7639
		Week 48	n	66	48	
			LS Mean	4.955	3.190	1.765
			SEM	3.635	3.975	4.005
95% CI	(-2.2, 12.1)		(-4.6, 11.0)	(-6.1, 9.6)		
Pr >  t				0.6595		
Week 56	n	56	43			
	LS Mean	3.022	4.381	-1.359		
	SEM	3.750	4.074	4.209		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-4.3,10.4)	(-3.6,12.4)	(-9.6, 6.9)
		Pr >  t			0.7468
	Week 64	n	45	41	
		LS Mean	-1.630	-0.073	-1.557
		SEM	3.925	4.120	4.413
		95% CI	(-9.3, 6.1)	(-8.2, 8.0)	(-10.2, 7.1)
		Pr >  t			0.7242
	Week 72	n	46	34	
		LS Mean	1.114	5.178	-4.064
		SEM	3.909	4.307	4.573
		95% CI	(-6.6, 8.8)	(-3.3,13.6)	(-13.0, 4.9)
		Pr >  t			0.3743
	Week 84	n	37	32	
		LS Mean	4.566	4.099	0.467
		SEM	4.124	4.373	4.808
		95% CI	(-3.5,12.7)	(-4.5,12.7)	(-9.0, 9.9)
		Pr >  t			0.9227
	Week 96	n	33	23	
		LS Mean	0.174	5.981	-5.808
		SEM	4.239	4.787	5.286
		95% CI	(-8.1, 8.5)	(-3.4,15.4)	(-16.2, 4.6)
		Pr >  t			0.2721
	Week 108	n	24	20	
		LS Mean	5.889	3.536	2.353
		SEM	4.640	4.994	5.783
		95% CI	(-3.2,15.0)	(-6.3,13.3)	(-9.0,13.7)
		Pr >  t			0.6842
	Week 120	n	25	16	
		LS Mean	4.780	1.757	3.023
		SEM	4.578	5.366	6.067
		95% CI	(-4.2,13.8)	(-8.8,12.3)	(-8.9,14.9)
		Pr >  t			0.6184
	Week 132	n	19	8	
		LS Mean	6.333	2.768	3.565
		SEM	4.985	6.911	7.720
		95% CI	(-3.4,16.1)	(-10.8,16.3)	(-11.6,18.7)
		Pr >  t			0.6443
	Week 144	n	14	5	
		LS Mean	4.370	2.824	1.545
		SEM	5.515	8.405	9.391

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.4,15.2)	(-13.7,19.3)	(-16.9,20.0)
		Pr >  t			0.8693
	Week 156	n	10	3	
		LS Mean	3.313	5.270	-1.957
		SEM	6.263	10.53	11.71
		95% CI	(-9.0,15.6)	(-15.4,25.9)	(-24.9,21.0)
		Pr >  t			0.8673
	Week 168	n	4	2	
		LS Mean	18.916	-10.11	29.029
		SEM	9.195	12.70	15.26
		95% CI	( 0.9,37.0)	(-35.0,14.8)	(-0.9,59.0)
		Pr >  t			0.0573
	Week 180	n	1	1	
		LS Mean	48.568	12.002	36.566
		SEM	17.63	17.65	24.69
		95% CI	( 14.0,83.2)	(-22.6,46.6)	(-11.9,85.0)
		Pr >  t			0.1389
	Week 192	n	1	1	
		LS Mean	48.568	-21.33	69.896
		SEM	17.63	17.65	24.69
		95% CI	( 14.0,83.2)	(-56.0,13.3)	( 21.5, 118)
		Pr >  t			0.0047
Yes	Week 8	n	5	9	
		LS Mean	-11.78	-18.73	6.958
		SEM	10.15	7.417	12.56
		95% CI	(-32.3, 8.7)	(-33.7,-3.8)	(-18.4,32.3)
		Pr >  t			0.5824
	Week 16	n	5	9	
		LS Mean	-31.78	-8.435	-23.34
		SEM	10.15	7.365	12.60
		95% CI	(-52.3, -11)	(-23.3, 6.4)	(-48.7, 2.1)
		Pr >  t			0.0707
	Week 24	n	5	5	
		LS Mean	-5.112	-12.25	7.138
		SEM	10.15	10.07	14.32
		95% CI	(-25.6,15.4)	(-32.5, 8.0)	(-21.7,36.0)
		Pr >  t			0.6205
	Week 32	n	4	3	
		LS Mean	-14.12	-19.88	5.760
		SEM	11.29	13.17	17.38



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-36.9, 8.6)	(-46.3, 6.6)	(-29.2,40.7)
		Pr >  t			0.7418
	Week 40	n	2	3	
		LS Mean	-22.24	-23.15	0.912
		SEM	15.68	13.22	20.35
		95% CI	(-53.7, 9.3)	(-49.7, 3.4)	(-39.9,41.8)
		Pr >  t			0.9644
	Week 48	n	3	2	
		LS Mean	-18.67	-6.447	-12.22
		SEM	12.90	16.29	20.52
		95% CI	(-44.6, 7.3)	(-39.1,26.3)	(-53.4,29.0)
		Pr >  t			0.5541
	Week 56	n	3	1	
		LS Mean	-18.67	10.114	-28.78
		SEM	12.90	23.06	26.56
		95% CI	(-44.6, 7.3)	(-36.2,56.4)	(-82.1,24.5)
		Pr >  t			0.2836
	Week 64	n	2		
		LS Mean	-22.24	NE	NE
		SEM	15.68	NE	NE
		95% CI	(-53.7, 9.3)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	-20.16	NE	NE
		SEM	15.85	NE	NE
		95% CI	(-52.0,11.7)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	-29.78	NE	NE
		SEM	12.90	NE	NE
		95% CI	(-55.7,-3.8)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	-22.24	NE	NE
		SEM	15.68	NE	NE
		95% CI	(-53.7, 9.3)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	-30.28	NE	NE
		SEM	15.85	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-62.1, 1.5)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	-18.67	NE	NE
	SEM	12.90	NE	NE
	95% CI	(-44.6, 7.3)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-49.02	NE	NE
	SEM	22.27	NE	NE
	95% CI	(-93.8,-4.3)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	17.647	NE	NE
	SEM	22.27	NE	NE
	95% CI	(-27.1,62.4)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-2.877	-3.481	0.604		
			SEM	5.952	5.856	4.381		
			95% CI	(-14.6, 8.9)	(-15.0, 8.1)	(-8.0, 9.2)		
					Pr >  t			0.8905
		Week 16	n	60	51			
			LS Mean	-7.327	0.725	-8.052		
			SEM	6.050	6.133	4.662		
			95% CI	(-19.3, 4.6)	(-11.4, 12.8)	(-17.2, 1.1)		
					Pr >  t			0.0852
		Week 24	n	51	42			
			LS Mean	-0.449	1.575	-2.025		
			SEM	6.135	6.248	4.935		
			95% CI	(-12.5, 11.6)	(-10.7, 13.9)	(-11.7, 7.7)		
					Pr >  t			0.6819
		Week 32	n	46	36			
			LS Mean	-3.034	-1.653	-1.381		
			SEM	6.234	6.404	5.152		
			95% CI	(-15.3, 9.3)	(-14.3, 11.0)	(-11.5, 8.7)		
					Pr >  t			0.7887
		Week 40	n	40	33			
			LS Mean	-3.798	-4.389	0.591		
			SEM	6.325	6.473	5.344		
			95% CI	(-16.3, 8.7)	(-17.1, 8.4)	(-9.9, 11.1)		
			Pr >  t			0.9119		
Week 48	n	37	28					
	LS Mean	0.624	3.153	-2.529				
	SEM	6.374	6.608	5.563				
	95% CI	(-11.9, 13.2)	(-9.9, 16.2)	(-13.5, 8.4)				
			Pr >  t			0.6496		
Week 56	n	33	23					
	LS Mean	-1.221	0.487	-1.708				
	SEM	6.456	6.789	5.873				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	95% CI	(-13.9,11.5)	(-12.9,13.8)	(-13.2, 9.8)	
	Pr >  t			0.7713	
	n	26	20		
	LS Mean	-6.843	-3.376	-3.466	
	SEM	6.646	6.943	6.255	
Week 72	95% CI	(-19.9, 6.2)	(-17.0,10.3)	(-15.7, 8.8)	
	Pr >  t			0.5796	
	n	28	17		
	LS Mean	-4.737	2.060	-6.797	
	SEM	6.584	7.130	6.401	
Week 84	95% CI	(-17.7, 8.2)	(-12.0,16.1)	(-19.4, 5.8)	
	Pr >  t			0.2887	
	n	23	17		
	LS Mean	-4.454	-3.425	-1.029	
	SEM	6.758	7.134	6.584	
Week 96	95% CI	(-17.8, 8.8)	(-17.5,10.6)	(-14.0,11.9)	
	Pr >  t			0.8759	
	n	23	11		
	LS Mean	-8.386	6.580	-14.97	
	SEM	6.760	7.790	7.291	
Week 108	95% CI	(-21.7, 4.9)	(-8.7,21.9)	(-29.3,-0.7)	
	Pr >  t			0.0404	
	n	15	13		
	LS Mean	0.132	0.433	-0.301	
	SEM	7.264	7.515	7.479	
Week 120	95% CI	(-14.2,14.4)	(-14.3,15.2)	(-15.0,14.4)	
	Pr >  t			0.9679	
	n	16	9		
	LS Mean	-1.012	-5.820	4.807	
	SEM	7.183	8.176	8.068	
Week 132	95% CI	(-15.1,13.1)	(-21.9,10.2)	(-11.0,20.6)	
	Pr >  t			0.5514	
	n	14	5		
	LS Mean	3.543	-0.686	4.229	
	SEM	7.360	9.667	9.709	
Week 144	95% CI	(-10.9,18.0)	(-19.7,18.3)	(-14.8,23.3)	
	Pr >  t			0.6633	
	n	8	3		
	LS Mean	-5.429	0.908	-6.337	
	SEM	8.381	11.55	12.25	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-21.9,11.0)	(-21.8,23.6)	(-30.4,17.7)
		Pr >  t			0.6052
		n	7	2	
	Week 168	LS Mean	8.587	2.911	5.676
		SEM	8.689	13.53	14.32
		95% CI	(-8.5,25.7)	(-23.6,29.5)	(-22.4,33.8)
	Week 180	Pr >  t			0.6920
		n	4	2	
		LS Mean	13.971	-13.75	27.725
	Week 192	SEM	10.36	13.53	15.39
		95% CI	(-6.4,34.3)	(-40.3,12.8)	(-2.5,57.9)
		Pr >  t			0.0721
	Week 8	n	1	1	
		LS Mean	43.195	8.357	34.837
		SEM	18.16	18.19	24.64
	Week 16	95% CI	( 7.6,78.8)	(-27.3,44.1)	(-13.5,83.2)
		Pr >  t			0.1579
		n	1	1	
	Week 24	LS Mean	43.195	-24.97	68.167
		SEM	18.16	18.19	24.64
		95% CI	( 7.6,78.8)	(-60.7,10.7)	( 19.8, 117)
	Week 32	Pr >  t			0.0058
		n	18	17	
		LS Mean	-4.669	5.141	-9.810
Week 8	SEM	5.150	5.327	7.401	
	95% CI	(-14.8, 5.5)	(-5.4,15.7)	(-24.4, 4.8)	
	Pr >  t			0.1869	
Week 16	n	17	11		
	LS Mean	-4.854	10.580	-15.43	
	SEM	5.305	6.619	8.469	
Week 24	95% CI	(-15.3, 5.6)	(-2.5,23.6)	(-32.2, 1.3)	
	Pr >  t			0.0702	
	n	15	5		
Week 32	LS Mean	-5.464	-8.256	2.791	
	SEM	5.650	9.755	11.29	
	95% CI	(-16.6, 5.7)	(-27.5,11.0)	(-19.5,25.1)	
Week 8	Pr >  t			0.8051	
	n	13	5		
	LS Mean	-15.33	-1.590	-13.74	
		SEM	6.062	9.755	11.51

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI			
Week 40		Pr >  t	(-27.3,-3.4)	(-20.8,17.7)	(-36.5, 9.0)
		n	11	5	0.2344
		LS Mean	-3.599	-14.92	11.323
		SEM	6.571	9.755	11.78
		95% CI	(-16.6, 9.4)	(-34.2, 4.3)	(-11.9,34.6)
Week 48		Pr >  t			0.3377
		n	11	2	
		LS Mean	3.550	-2.036	5.586
		SEM	6.577	15.20	16.56
		95% CI	(-9.4,16.5)	(-32.0,28.0)	(-27.1,38.3)
Week 56		Pr >  t			0.7363
		n	8	2	
		LS Mean	-7.486	-2.036	-5.450
		SEM	7.656	15.20	17.02
		95% CI	(-22.6, 7.6)	(-32.0,28.0)	(-39.0,28.1)
Week 64		Pr >  t			0.7492
		n	7	3	
		LS Mean	-13.01	-22.03	9.019
		SEM	8.151	12.49	14.92
		95% CI	(-29.1, 3.1)	(-46.7, 2.6)	(-20.4,38.5)
Week 72		Pr >  t			0.5463
		n	7	3	
		LS Mean	-5.557	-10.92	5.359
		SEM	8.167	12.49	14.93
		95% CI	(-21.7,10.6)	(-35.6,13.7)	(-24.1,34.8)
Week 84		Pr >  t			0.7200
		n	7	2	
		LS Mean	3.967	-2.036	6.003
		SEM	8.167	15.20	17.25
		95% CI	(-12.2,20.1)	(-32.0,28.0)	(-28.1,40.1)
Week 96		Pr >  t			0.7283
		n	6	3	
		LS Mean	6.165	0.194	5.971
		SEM	8.788	12.49	15.27
		95% CI	(-11.2,23.5)	(-24.5,24.9)	(-24.2,36.1)
Week 108		Pr >  t			0.6963
		n	7	2	
		LS Mean	-0.794	9.750	-10.54
	SEM	8.167	15.20	17.25	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-16.9,15.3)	(-20.3,39.8)	(-44.6,23.5)
		Pr >  t			0.5418
		n	6	1	
	Week 132	LS Mean	11.718	4.654	7.064
		SEM	8.788	21.39	23.12
		95% CI	(-5.6,29.1)	(-37.6,46.9)	(-38.6,52.7)
	Week 144	Pr >  t			0.7603
		n	4		
		LS Mean	-5.605	NE	NE
	Week 156	SEM	10.69	NE	NE
		95% CI	(-26.7,15.5)	NE	NE
		Pr >  t			NE
	Week 8	n	5		
		LS Mean	7.009	NE	NE
		SEM	9.604	NE	NE
	Week 16	95% CI	(-11.9,26.0)	NE	NE
		Pr >  t			NE
		n	3		
	Week 24	LS Mean	-26.27	NE	NE
		SEM	12.30	NE	NE
		95% CI	(-50.5,-2.0)	NE	NE
	Week 32	Pr >  t			NE
		n	59	57	
		LS Mean	3.951	3.373	0.578
Week 8	SEM	3.970	4.143	4.233	
	95% CI	(-3.9,11.8)	(-4.8,11.6)	(-7.8, 8.9)	
	Pr >  t			0.8915	
Week 16	n	47	44		
	LS Mean	4.852	5.959	-1.107	
	SEM	4.163	4.391	4.631	
Week 24	95% CI	(-3.4,13.1)	(-2.7,14.6)	(-10.2, 8.0)	
	Pr >  t			0.8113	
	n	39	34		
Week 32	LS Mean	6.996	5.195	1.801	
	SEM	4.346	4.684	5.030	
	95% CI	(-1.6,15.6)	(-4.0,14.4)	(-8.1,11.7)	
Week 8	Pr >  t			0.7205	
	n	27	32		
	LS Mean	5.508	0.451	5.057	
Week 16	SEM	4.770	4.745	5.425	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-3.9,14.9)	(-8.9, 9.8)	(-5.6,15.7)	
	Pr >  t			0.3519	
	n	24	24		
	LS Mean	4.355	3.032	1.323	
	SEM	4.910	5.084	5.829	
Week 48	95% CI	(-5.3,14.0)	(-7.0,13.0)	(-10.1,12.8)	
	Pr >  t			0.8206	
	n	21	21		
	LS Mean	2.371	-0.173	2.544	
	SEM	5.080	5.255	6.129	
Week 56	95% CI	(-7.6,12.4)	(-10.5,10.2)	(-9.5,14.6)	
	Pr >  t			0.6783	
	n	18	20		
	LS Mean	4.772	6.389	-1.617	
	SEM	5.293	5.323	6.372	
Week 64	95% CI	(-5.6,15.2)	(-4.1,16.9)	(-14.1,10.9)	
	Pr >  t			0.7998	
	n	14	19		
	LS Mean	3.703	1.195	2.507	
	SEM	5.691	5.395	6.772	
Week 72	95% CI	(-7.5,14.9)	(-9.4,11.8)	(-10.8,15.8)	
	Pr >  t			0.7114	
	n	13	15		
	LS Mean	4.189	5.319	-1.130	
	SEM	5.824	5.752	7.170	
Week 84	95% CI	(-7.3,15.6)	(-6.0,16.6)	(-15.2,13.0)	
	Pr >  t			0.8748	
	n	10	14		
	LS Mean	6.665	7.355	-0.690	
	SEM	6.389	5.865	7.688	
Week 96	95% CI	(-5.9,19.2)	(-4.2,18.9)	(-15.8,14.4)	
	Pr >  t			0.9285	
	n	6	10		
	LS Mean	2.318	2.612	-0.294	
	SEM	7.673	6.506	9.253	
Week 108	95% CI	(-12.8,17.4)	(-10.2,15.4)	(-18.5,17.9)	
	Pr >  t			0.9746	
	n	4	6		
	LS Mean	0.613	1.082	-0.470	
	SEM	9.062	7.789	11.26	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-17.2,18.4)	(-14.2,16.4)	(-22.6,21.6)
	Pr >  t			0.9667
	n	6	6	
	LS Mean	-6.850	6.171	-13.02
	SEM	7.669	7.792	10.19
Week 132	95% CI	(-21.9, 8.2)	(-9.1,21.5)	(-33.0, 7.0)
	Pr >  t			0.2020
	n	2	3	
	LS Mean	-13.21	2.190	-15.40
	SEM	12.24	10.28	15.48
Week 144	95% CI	(-37.3,10.8)	(-18.0,22.4)	(-45.8,15.0)
	Pr >  t			0.3202
	n	2	2	
	LS Mean	19.398	0.354	19.044
	SEM	12.20	12.31	16.90
Week 156	95% CI	(-4.6,43.4)	(-23.8,24.5)	(-14.2,52.3)
	Pr >  t			0.2604
	n		1	
	LS Mean	NE	2.746	NE
	SEM	NE	16.90	NE
	95% CI	NE	(-30.5,35.9)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-0.873	-1.091	0.217		
			SEM	4.269	4.250	3.541		
			95% CI	(-9.3, 7.5)	(-9.5, 7.3)	(-6.7, 7.2)		
					Pr >  t			0.9511
		Week 16	n	79	68			
			LS Mean	-3.323	2.660	-5.983		
			SEM	4.321	4.506	3.859		
			95% CI	(-11.8, 5.2)	(-6.2, 11.5)	(-13.6, 1.6)		
					Pr >  t			0.1216
		Week 24	n	64	55			
			LS Mean	1.903	0.773	1.130		
			SEM	4.470	4.708	4.186		
			95% CI	(-6.9, 10.7)	(-8.5, 10.0)	(-7.1, 9.4)		
					Pr >  t			0.7873
		Week 32	n	49	53			
			LS Mean	-1.617	-3.826	2.210		
			SEM	4.715	4.740	4.431		
			95% CI	(-10.9, 7.7)	(-13.1, 5.5)	(-6.5, 10.9)		
					Pr >  t			0.6181
		Week 40	n	44	45			
			LS Mean	-1.734	-4.178	2.444		
			SEM	4.805	4.869	4.665		
			95% CI	(-11.2, 7.7)	(-13.7, 5.4)	(-6.7, 11.6)		
					Pr >  t			0.6005
		Week 48	n	41	36			
			LS Mean	2.703	-0.665	3.368		
			SEM	4.864	5.071	4.934		
95% CI	(-6.9, 12.3)		(-10.6, 9.3)	(-6.3, 13.1)				
			Pr >  t			0.4951		
Week 56	n	33	32					
	LS Mean	0.297	1.270	-0.973				
	SEM	5.069	5.192	5.263				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.7,10.3)	(-8.9,11.5)	(-11.3, 9.4)
		Pr >  t			0.8534
	Week 64	n	27	31	
		LS Mean	-4.191	-5.525	1.334
		SEM	5.289	5.228	5.516
		95% CI	(-14.6, 6.2)	(-15.8, 4.7)	(-9.5,12.2)
		Pr >  t			0.8090
	Week 72	n	26	26	
		LS Mean	-3.648	-0.049	-3.599
		SEM	5.335	5.432	5.751
		95% CI	(-14.1, 6.8)	(-10.7,10.6)	(-14.9, 7.7)
		Pr >  t			0.5315
	Week 84	n	22	23	
		LS Mean	3.883	-0.464	4.347
		SEM	5.579	5.587	6.099
		95% CI	(-7.1,14.8)	(-11.4,10.5)	(-7.6,16.3)
		Pr >  t			0.4762
	Week 96	n	18	18	
		LS Mean	-0.344	2.666	-3.010
		SEM	5.880	5.947	6.692
		95% CI	(-11.9,11.2)	(-9.0,14.3)	(-16.1,10.1)
		Pr >  t			0.6530
	Week 108	n	14	14	
		LS Mean	1.203	-0.626	1.829
		SEM	6.325	6.388	7.457
		95% CI	(-11.2,13.6)	(-13.2,11.9)	(-12.8,16.5)
		Pr >  t			0.8063
	Week 120	n	12	12	
		LS Mean	-1.813	-4.102	2.289
		SEM	6.629	6.697	7.974
		95% CI	(-14.8,11.2)	(-17.2, 9.0)	(-13.4,17.9)
		Pr >  t			0.7741
	Week 132	n	9	5	
		LS Mean	2.477	0.301	2.176
		SEM	7.296	9.159	10.58
		95% CI	(-11.8,16.8)	(-17.7,18.3)	(-18.6,22.9)
		Pr >  t			0.8371
	Week 144	n	7	4	
		LS Mean	-2.609	-3.953	1.344
		SEM	7.991	10.04	11.81

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.3,13.1)	(-23.7,15.7)	(-21.8,24.5)
		Pr >  t			0.9094
	Week 156	n	4	2	
		LS Mean	-5.077	-2.237	-2.841
		SEM	9.973	13.56	16.07
		95% CI	(-24.6,14.5)	(-28.9,24.4)	(-34.4,28.7)
		Pr >  t			0.8597
	Week 168	n	2	1	
		LS Mean	9.476	-2.534	12.010
		SEM	13.51	18.73	22.54
		95% CI	(-17.0,36.0)	(-39.3,34.2)	(-32.2,56.2)
		Pr >  t			0.5943
Yes	Week 8	n	53	48	
		LS Mean	5.187	6.652	-1.466
		SEM	4.817	5.010	4.729
		95% CI	(-4.3,14.7)	(-3.3,16.6)	(-10.8, 7.9)
		Pr >  t			0.7570
	Week 16	n	45	39	
		LS Mean	4.403	10.142	-5.738
		SEM	5.024	5.231	5.054
		95% CI	(-5.5,14.3)	(-0.2,20.5)	(-15.7, 4.2)
		Pr >  t			0.2573
	Week 24	n	41	26	
		LS Mean	6.341	10.052	-3.711
		SEM	5.088	5.605	5.551
		95% CI	(-3.7,16.4)	(-1.0,21.1)	(-14.6, 7.2)
		Pr >  t			0.5043
	Week 32	n	37	20	
		LS Mean	3.412	10.401	-6.989
		SEM	5.203	5.957	5.949
		95% CI	(-6.9,13.7)	(-1.3,22.1)	(-18.7, 4.7)
		Pr >  t			0.2409
	Week 40	n	31	17	
		LS Mean	5.877	6.030	-0.154
		SEM	5.353	6.229	6.310
		95% CI	(-4.7,16.4)	(-6.2,18.3)	(-12.6,12.3)
		Pr >  t			0.9806
	Week 48	n	28	15	
		LS Mean	6.606	10.286	-3.680
		SEM	5.443	6.418	6.574

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-4.1,17.3)	(-2.3,22.9)	(-16.6, 9.2)
	Pr >  t			0.5759
Week 56	n	26	13	
	LS Mean	5.673	10.274	-4.601
	SEM	5.513	6.646	6.862
	95% CI	(-5.2,16.5)	(-2.8,23.3)	(-18.1, 8.9)
	Pr >  t			0.5029
Week 64	n	20	11	
	LS Mean	0.958	7.924	-6.966
	SEM	5.798	6.946	7.382
	95% CI	(-10.5,12.4)	(-5.7,21.6)	(-21.5, 7.5)
	Pr >  t			0.3458
Week 72	n	22	9	
	LS Mean	6.261	11.321	-5.060
	SEM	5.693	7.347	7.680
	95% CI	(-5.0,17.5)	(-3.1,25.8)	(-20.1,10.0)
	Pr >  t			0.5103
Week 84	n	18	10	
	LS Mean	2.298	8.723	-6.425
	SEM	5.947	7.133	7.659
	95% CI	(-9.4,14.0)	(-5.3,22.7)	(-21.5, 8.6)
	Pr >  t			0.4019
Week 96	n	17	6	
	LS Mean	0.334	11.405	-11.07
	SEM	6.006	8.347	8.855
	95% CI	(-11.5,12.2)	(-5.0,27.8)	(-28.5, 6.3)
	Pr >  t			0.2117
Week 108	n	12	7	
	LS Mean	7.771	11.724	-3.953
	SEM	6.569	7.934	8.861
	95% CI	(-5.1,20.7)	(-3.9,27.3)	(-21.4,13.4)
	Pr >  t			0.6556
Week 120	n	16	4	
	LS Mean	9.735	12.046	-2.311
	SEM	6.099	9.647	10.14
	95% CI	(-2.3,21.7)	(-6.9,31.0)	(-22.2,17.6)
	Pr >  t			0.8198
Week 132	n	11	3	
	LS Mean	6.656	5.828	0.828
	SEM	6.727	10.78	11.57

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.6,19.9)	(-15.3,27.0)	(-21.9,23.6)
		Pr >  t			0.9430
	Week 144	n	8	1	
		LS Mean	14.993	18.680	-3.687
		SEM	7.366	17.37	18.13
		95% CI	( 0.5,29.5)	(-15.4,52.8)	(-39.3,31.9)
		Pr >  t			0.8390
	Week 156	n	6	1	
		LS Mean	9.928	18.680	-8.752
		SEM	8.141	17.37	18.45
		95% CI	( -6.1,25.9)	(-15.4,52.8)	(-45.0,27.5)
		Pr >  t			0.6355
	Week 168	n	2	1	
		LS Mean	28.084	-14.65	42.735
		SEM	12.60	17.37	20.81
		95% CI	( 3.3,52.8)	(-48.8,19.5)	( 1.9,83.6)
		Pr >  t			0.0405
	Week 180	n	1	1	
		LS Mean	52.090	18.680	33.411
		SEM	17.21	17.37	23.88
		95% CI	( 18.3,85.9)	(-15.4,52.8)	(-13.5,80.3)
		Pr >  t			0.1624
	Week 192	n	1	1	
		LS Mean	52.090	-14.65	66.741
		SEM	17.21	17.37	23.88
		95% CI	( 18.3,85.9)	(-48.8,19.5)	( 19.8, 114)
		Pr >  t			0.0054

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
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Final

**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35			
			LS Mean	2.750	5.036	-2.286		
			SEM	5.513	6.052	5.781		
			95% CI	(-8.2,13.7)	(-7.0,17.0)	(-13.7, 9.2)		
					Pr >  t			0.6931
		Week 16	n	35	22			
			LS Mean	2.651	6.853	-4.202		
			SEM	5.722	6.753	6.513		
			95% CI	(-8.7,14.0)	(-6.5,20.2)	(-17.1, 8.7)		
					Pr >  t			0.5196
		Week 24	n	28	16			
			LS Mean	11.648	5.978	5.671		
			SEM	5.926	7.209	7.203		
			95% CI	(-0.1,23.4)	(-8.3,20.2)	(-8.5,19.9)		
					Pr >  t			0.4320
		Week 32	n	22	16			
			LS Mean	3.348	4.407	-1.060		
			SEM	6.272	7.228	7.427		
			95% CI	(-9.0,15.7)	(-9.9,18.7)	(-15.7,13.6)		
					Pr >  t			0.8867
		Week 40	n	19	12			
			LS Mean	4.886	-3.346	8.233		
			SEM	6.460	7.694	8.039		
			95% CI	(-7.9,17.6)	(-18.5,11.8)	(-7.6,24.1)		
			Pr >  t			0.3067		
Week 48	n	16	10					
	LS Mean	16.955	-1.265	18.220				
	SEM	6.692	8.048	8.569				
	95% CI	( 3.8,30.2)	(-17.1,14.6)	( 1.4,35.1)				
			Pr >  t			0.0343		
Week 56	n	14	7					
	LS Mean	9.898	3.685	6.213				
	SEM	6.902	8.857	9.496				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-3.7,23.5)	(-13.8,21.1)	(-12.5,24.9)
		Pr >  t			0.5134
	Week 64	n	8	7	
		LS Mean	4.157	7.433	-3.276
		SEM	7.958	8.862	10.32
		95% CI	(-11.5,19.8)	(-10.0,24.9)	(-23.6,17.0)
		Pr >  t			0.7510
	Week 72	n	12	6	
		LS Mean	12.245	3.874	8.370
		SEM	7.157	9.276	10.08
		95% CI	(-1.9,26.4)	(-14.4,22.1)	(-11.4,28.2)
		Pr >  t			0.4067
	Week 84	n	8	5	
		LS Mean	5.543	3.172	2.371
		SEM	8.013	9.816	11.15
		95% CI	(-10.2,21.3)	(-16.1,22.5)	(-19.6,24.3)
		Pr >  t			0.8317
	Week 96	n	5	5	
		LS Mean	1.875	9.840	-7.965
		SEM	9.302	9.816	12.11
		95% CI	(-16.4,20.2)	(-9.5,29.2)	(-31.8,15.9)
		Pr >  t			0.5112
	Week 108	n	7	5	
		LS Mean	8.793	3.172	5.621
		SEM	8.346	9.816	11.39
		95% CI	(-7.6,25.2)	(-16.1,22.5)	(-16.8,28.0)
		Pr >  t			0.6220
	Week 120	n	5	3	
		LS Mean	16.450	-8.349	24.798
		SEM	9.314	11.69	13.68
		95% CI	(-1.9,34.8)	(-31.3,14.7)	(-2.1,51.7)
		Pr >  t			0.0707
	Week 132	n	2	2	
		LS Mean	1.667	1.250	0.417
		SEM	13.24	13.57	17.98
		95% CI	(-24.4,27.7)	(-25.4,27.9)	(-35.0,35.8)
		Pr >  t			0.9815
	Week 144	n	2		
		LS Mean	37.848	NE	NE
		SEM	13.24	NE	NE



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 11.8,63.9)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	6.183	NE	NE
		SEM	13.26	NE	NE
		95% CI	(-19.9,32.3)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	3.337	NE	NE
		SEM	17.99	NE	NE
		95% CI	(-32.1,38.7)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	98	104	
		LS Mean	1.223	1.138	0.085
		SEM	3.935	3.883	3.275
		95% CI	( -6.5, 9.0)	( -6.5, 8.8)	( -6.3, 6.5)
		Pr >  t			0.9793
	Week 16	n	87	84	
		LS Mean	-1.732	5.584	-7.316
		SEM	4.022	4.014	3.499
		95% CI	( -9.6, 6.2)	( -2.3,13.5)	(-14.2,-0.4)
		Pr >  t			0.0370
	Week 24	n	76	65	
		LS Mean	1.221	4.235	-3.014
		SEM	4.117	4.198	3.770
		95% CI	( -6.9, 9.3)	( -4.0,12.5)	(-10.4, 4.4)
		Pr >  t			0.4243
	Week 32	n	62	57	
		LS Mean	-0.938	0.410	-1.348
		SEM	4.260	4.309	4.009
		95% CI	( -9.3, 7.4)	( -8.1, 8.9)	( -9.2, 6.5)
		Pr >  t			0.7368
	Week 40	n	54	50	
		LS Mean	-0.249	0.587	-0.836
		SEM	4.355	4.426	4.216
		95% CI	( -8.8, 8.3)	( -8.1, 9.3)	( -9.1, 7.4)
		Pr >  t			0.8429
	Week 48	n	52	41	
		LS Mean	0.346	4.730	-4.385
		SEM	4.382	4.591	4.414

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-8.3, 9.0)	(-4.3,13.7)	(-13.0, 4.3)
	Pr >  t			0.3208
Week 56	n	44	38	
	LS Mean	-0.031	5.064	-5.095
	SEM	4.509	4.660	4.615
	95% CI	(-8.9, 8.8)	(-4.1,14.2)	(-14.2, 4.0)
	Pr >  t			0.2698
Week 64	n	39	35	
	LS Mean	-4.022	-2.383	-1.640
	SEM	4.612	4.741	4.798
	95% CI	(-13.1, 5.0)	(-11.7, 6.9)	(-11.1, 7.8)
	Pr >  t			0.7326
Week 72	n	36	29	
	LS Mean	-3.228	4.331	-7.559
	SEM	4.687	4.938	5.063
	95% CI	(-12.4, 6.0)	(-5.4,14.0)	(-17.5, 2.4)
	Pr >  t			0.1357
Week 84	n	32	28	
	LS Mean	2.015	3.171	-1.156
	SEM	4.814	4.978	5.208
	95% CI	(-7.4,11.5)	(-6.6,12.9)	(-11.4, 9.1)
	Pr >  t			0.8243
Week 96	n	30	19	
	LS Mean	-1.720	5.277	-6.997
	SEM	4.871	5.494	5.764
	95% CI	(-11.3, 7.8)	(-5.5,16.1)	(-18.3, 4.3)
	Pr >  t			0.2250
Week 108	n	18	16	
	LS Mean	4.337	4.366	-0.029
	SEM	5.554	5.774	6.585
	95% CI	(-6.6,15.2)	(-7.0,15.7)	(-12.9,12.9)
	Pr >  t			0.9965
Week 120	n	23	13	
	LS Mean	0.510	3.637	-3.127
	SEM	5.190	6.158	6.647
	95% CI	(-9.7,10.7)	(-8.4,15.7)	(-16.2, 9.9)
	Pr >  t			0.6381
Week 132	n	18	6	
	LS Mean	3.088	2.903	0.185
	SEM	5.555	8.131	8.727

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.8,14.0)	(-13.1,18.9)	(-16.9,17.3)
		Pr >  t			0.9830
	Week 144	n	13	5	
		LS Mean	0.502	2.468	-1.966
		SEM	6.105	8.755	9.664
		95% CI	(-11.5,12.5)	(-14.7,19.6)	(-20.9,17.0)
		Pr >  t			0.8388
	Week 156	n	8	3	
		LS Mean	1.665	4.941	-3.276
		SEM	7.249	10.87	12.25
		95% CI	(-12.6,15.9)	(-16.4,26.3)	(-27.3,20.8)
		Pr >  t			0.7891
	Week 168	n	3	2	
		LS Mean	23.213	-10.41	33.626
		SEM	10.83	13.05	16.34
		95% CI	( 2.0,44.5)	(-36.0,15.2)	( 1.6,65.7)
		Pr >  t			0.0398
	Week 180	n	1	1	
		LS Mean	46.921	11.735	35.186
		SEM	18.04	18.04	25.11
		95% CI	( 11.5,82.3)	(-23.7,47.1)	(-14.1,84.4)
		Pr >  t			0.1614
	Week 192	n	1	1	
		LS Mean	46.921	-21.59	68.516
		SEM	18.04	18.04	25.11
		95% CI	( 11.5,82.3)	(-57.0,13.8)	( 19.3, 118)
		Pr >  t			0.0065

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	1.696	1.022	0.674		
			SEM	3.938	3.875	3.290		
			95% CI	(-6.1, 9.4)	(-6.6, 8.6)	(-5.8, 7.1)		
					Pr >  t			0.8379
		Week 16	n	85	84			
			LS Mean	-1.306	5.469	-6.775		
			SEM	4.028	4.007	3.518		
			95% CI	(-9.2, 6.6)	(-2.4, 13.3)	(-13.7, 0.1)		
					Pr >  t			0.0546
		Week 24	n	75	65			
			LS Mean	1.562	4.123	-2.561		
			SEM	4.120	4.192	3.784		
			95% CI	(-6.5, 9.7)	(-4.1, 12.4)	(-10.0, 4.9)		
					Pr >  t			0.4989
		Week 32	n	61	57			
			LS Mean	-0.617	0.295	-0.912		
			SEM	4.269	4.304	4.028		
			95% CI	(-9.0, 7.8)	(-8.2, 8.8)	(-8.8, 7.0)		
					Pr >  t			0.8210
		Week 40	n	53	50			
			LS Mean	0.289	0.469	-0.180		
			SEM	4.368	4.422	4.239		
			95% CI	(-8.3, 8.9)	(-8.2, 9.2)	(-8.5, 8.1)		
					Pr >  t			0.9661
		Week 48	n	51	41			
			LS Mean	0.246	4.609	-4.363		
			SEM	4.396	4.588	4.440		
95% CI	(-8.4, 8.9)		(-4.4, 13.6)	(-13.1, 4.3)				
			Pr >  t			0.3260		
Week 56	n	43	38					
	LS Mean	0.577	4.945	-4.368				
	SEM	4.529	4.657	4.646				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.3, 9.5)	(-4.2, 14.1)	(-13.5, 4.7)
	Pr >  t			0.3474
	n	39	35	
	LS Mean	-3.698	-2.498	-1.200
	SEM	4.614	4.739	4.811
Week 72	95% CI	(-12.8, 5.4)	(-11.8, 6.8)	(-10.6, 8.2)
	Pr >  t			0.8030
	n	35	29	
	LS Mean	-2.940	4.210	-7.149
	SEM	4.715	4.937	5.101
Week 84	95% CI	(-12.2, 6.3)	(-5.5, 13.9)	(-17.2, 2.9)
	Pr >  t			0.1613
	n	31	28	
	LS Mean	2.471	3.055	-0.585
	SEM	4.850	4.978	5.253
Week 96	95% CI	(-7.1, 12.0)	(-6.7, 12.8)	(-10.9, 9.7)
	Pr >  t			0.9114
	n	29	19	
	LS Mean	-1.380	5.158	-6.537
	SEM	4.911	5.497	5.811
Week 108	95% CI	(-11.0, 8.3)	(-5.6, 15.9)	(-17.9, 4.9)
	Pr >  t			0.2608
	n	18	16	
	LS Mean	4.665	4.255	0.411
	SEM	5.561	5.779	6.605
Week 120	95% CI	(-6.3, 15.6)	(-7.1, 15.6)	(-12.5, 13.4)
	Pr >  t			0.9504
	n	23	13	
	LS Mean	0.829	3.523	-2.694
	SEM	5.194	6.164	6.666
Week 132	95% CI	(-9.4, 11.0)	(-8.6, 15.6)	(-15.8, 10.4)
	Pr >  t			0.6862
	n	18	6	
	LS Mean	3.418	2.790	0.628
	SEM	5.563	8.148	8.754
Week 144	95% CI	(-7.5, 14.3)	(-13.2, 18.8)	(-16.5, 17.8)
	Pr >  t			0.9428
	n	13	5	
	LS Mean	0.833	2.341	-1.508
	SEM	6.115	8.775	9.694

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	(-11.2,12.8)	(-14.9,19.6)	(-20.5,17.5)
		Pr >  t			0.8764
		n	8	3	
	Week 168	LS Mean	2.008	4.818	-2.810
		SEM	7.264	10.90	12.28
		95% CI	(-12.2,16.3)	(-16.6,26.2)	(-26.9,21.3)
	Week 180	Pr >  t			0.8191
		n	3	2	
		LS Mean	23.572	-10.55	34.118
	Week 192	SEM	10.86	13.09	16.39
		95% CI	( 2.3,44.9)	(-36.2,15.1)	( 2.0,66.3)
		Pr >  t			0.0376
	Week 8	n	1	1	
		LS Mean	47.327	11.595	35.732
		SEM	18.10	18.10	25.19
	Week 16	95% CI	( 11.8,82.8)	(-23.9,47.1)	(-13.7,85.2)
		Pr >  t			0.1563
		n	1	1	
	Week 24	LS Mean	47.327	-21.73	69.062
		SEM	18.10	18.10	25.19
		95% CI	( 11.8,82.8)	(-57.2,13.8)	( 19.6, 118)
	Week 32	Pr >  t			0.0062
		n	42	35	
		LS Mean	2.750	5.036	-2.286
Week 8	SEM	5.513	6.052	5.781	
	95% CI	( -8.2,13.7)	( -7.0,17.0)	(-13.7, 9.2)	
	Pr >  t			0.6931	
Week 16	n	35	22		
	LS Mean	2.651	6.853	-4.202	
	SEM	5.722	6.753	6.513	
Week 24	95% CI	( -8.7,14.0)	( -6.5,20.2)	(-17.1, 8.7)	
	Pr >  t			0.5196	
	n	28	16		
Week 32	LS Mean	11.648	5.978	5.671	
	SEM	5.926	7.209	7.203	
	95% CI	( -0.1,23.4)	( -8.3,20.2)	( -8.5,19.9)	
Week 8	Pr >  t			0.4320	
	n	22	16		
	LS Mean	3.348	4.407	-1.060	
Week 16	SEM	6.272	7.228	7.427	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-9.0,15.7)	(-9.9,18.7)	(-15.7,13.6)
	Pr >  t			0.8867
	n	19	12	
	LS Mean	4.886	-3.346	8.233
	SEM	6.460	7.694	8.039
Week 48	95% CI	(-7.9,17.6)	(-18.5,11.8)	(-7.6,24.1)
	Pr >  t			0.3067
	n	16	10	
	LS Mean	16.955	-1.265	18.220
	SEM	6.692	8.048	8.569
Week 56	95% CI	( 3.8,30.2)	(-17.1,14.6)	( 1.4,35.1)
	Pr >  t			0.0343
	n	14	7	
	LS Mean	9.898	3.685	6.213
	SEM	6.902	8.857	9.496
Week 64	95% CI	(-3.7,23.5)	(-13.8,21.1)	(-12.5,24.9)
	Pr >  t			0.5134
	n	8	7	
	LS Mean	4.157	7.433	-3.276
	SEM	7.958	8.862	10.32
Week 72	95% CI	(-11.5,19.8)	(-10.0,24.9)	(-23.6,17.0)
	Pr >  t			0.7510
	n	12	6	
	LS Mean	12.245	3.874	8.370
	SEM	7.157	9.276	10.08
Week 84	95% CI	(-1.9,26.4)	(-14.4,22.1)	(-11.4,28.2)
	Pr >  t			0.4067
	n	8	5	
	LS Mean	5.543	3.172	2.371
	SEM	8.013	9.816	11.15
Week 96	95% CI	(-10.2,21.3)	(-16.1,22.5)	(-19.6,24.3)
	Pr >  t			0.8317
	n	5	5	
	LS Mean	1.875	9.840	-7.965
	SEM	9.302	9.816	12.11
Week 108	95% CI	(-16.4,20.2)	(-9.5,29.2)	(-31.8,15.9)
	Pr >  t			0.5112
	n	7	5	
	LS Mean	8.793	3.172	5.621
	SEM	8.346	9.816	11.39

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-7.6,25.2)	(-16.1,22.5)	(-16.8,28.0)
	Pr >  t			0.6220
	n	5	3	
	LS Mean	16.450	-8.349	24.798
	SEM	9.314	11.69	13.68
Week 132	95% CI	(-1.9,34.8)	(-31.3,14.7)	(-2.1,51.7)
	Pr >  t			0.0707
	n	2	2	
	LS Mean	1.667	1.250	0.417
	SEM	13.24	13.57	17.98
Week 144	95% CI	(-24.4,27.7)	(-25.4,27.9)	(-35.0,35.8)
	Pr >  t			0.9815
	n	2		
	LS Mean	37.848	NE	NE
	SEM	13.24	NE	NE
Week 156	95% CI	(11.8,63.9)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	6.183	NE	NE
	SEM	13.26	NE	NE
Week 168	95% CI	(-19.9,32.3)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	3.337	NE	NE
	SEM	17.99	NE	NE
	95% CI	(-32.1,38.7)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-25i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Insomnia score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95			
			LS Mean	2.796	1.357	1.439		
			SEM	3.332	3.450	3.271		
			95% CI	(-3.8, 9.4)	(-5.4, 8.1)	(-5.0, 7.9)		
					Pr >  t			0.6600
		Week 16	n	90	75			
			LS Mean	0.579	5.535	-4.957		
			SEM	3.428	3.635	3.532		
			95% CI	(-6.2, 7.3)	(-1.6,12.7)	(-11.9, 2.0)		
					Pr >  t			0.1610
		Week 24	n	79	62			
			LS Mean	3.008	4.020	-1.012		
			SEM	3.522	3.798	3.758		
			95% CI	(-3.9, 9.9)	(-3.4,11.5)	(-8.4, 6.4)		
					Pr >  t			0.7879
		Week 32	n	70	56			
			LS Mean	0.571	1.352	-0.781		
			SEM	3.640	3.895	3.914		
			95% CI	(-6.6, 7.7)	(-6.3, 9.0)	(-8.5, 6.9)		
					Pr >  t			0.8418
		Week 40	n	61	46			
			LS Mean	2.268	-2.192	4.460		
			SEM	3.736	4.076	4.167		
			95% CI	(-5.1, 9.6)	(-10.2, 5.8)	(-3.7,12.6)		
					Pr >  t			0.2848
		Week 48	n	56	38			
			LS Mean	3.856	1.958	1.898		
			SEM	3.799	4.260	4.403		
95% CI	(-3.6,11.3)		(-6.4,10.3)	(-6.7,10.5)				
			Pr >  t			0.6665		
Week 56	n	49	33					
	LS Mean	2.572	4.816	-2.244				
		SEM	3.904	4.408	4.641			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-5.1,10.2)	(-3.8,13.5)	(-11.4, 6.9)
		Pr >  t			0.6288
	Week 64	n	37	29	
		LS Mean	-2.769	0.278	-3.047
		SEM	4.158	4.565	5.004
		95% CI	(-10.9, 5.4)	(-8.7, 9.2)	(-12.9, 6.8)
		Pr >  t			0.5427
	Week 72	n	40	25	
		LS Mean	-0.310	4.778	-5.088
		SEM	4.085	4.751	5.116
		95% CI	(-8.3, 7.7)	(-4.5,14.1)	(-15.1, 4.9)
		Pr >  t			0.3201
	Week 84	n	32	23	
		LS Mean	-0.095	5.012	-5.108
		SEM	4.333	4.867	5.406
		95% CI	(-8.6, 8.4)	(-4.5,14.6)	(-15.7, 5.5)
		Pr >  t			0.3450
	Week 96	n	29	17	
		LS Mean	-3.075	5.519	-8.594
		SEM	4.439	5.341	5.924
		95% CI	(-11.8, 5.6)	(-5.0,16.0)	(-20.2, 3.0)
		Pr >  t			0.1471
	Week 108	n	22	15	
		LS Mean	1.877	2.078	-0.201
		SEM	4.819	5.566	6.397
		95% CI	(-7.6,11.3)	(-8.8,13.0)	(-12.8,12.4)
		Pr >  t			0.9749
	Week 120	n	23	13	
		LS Mean	2.343	2.036	0.306
		SEM	4.746	5.850	6.600
		95% CI	(-7.0,11.7)	(-9.4,13.5)	(-12.6,13.3)
		Pr >  t			0.9630
	Week 132	n	17	5	
		LS Mean	3.851	2.758	1.093
		SEM	5.227	8.488	9.277
		95% CI	(-6.4,14.1)	(-13.9,19.4)	(-17.1,19.3)
		Pr >  t			0.9062
	Week 144	n	14	3	
		LS Mean	7.918	3.447	4.471
		SEM	5.571	10.64	11.45

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.0,18.8)	(-17.4,24.3)	(-18.0,26.9)
		Pr >  t			0.6963
	Week 156	n	9	2	
		LS Mean	1.779	6.579	-4.800
		SEM	6.587	12.81	13.93
		95% CI	(-11.1,14.7)	(-18.5,31.7)	(-32.1,22.5)
		Pr >  t			0.7305
	Week 168	n	4	1	
		LS Mean	18.100	-22.36	40.457
		SEM	9.264	17.80	19.74
		95% CI	(-0.1,36.3)	(-57.3,12.6)	( 1.7,79.2)
		Pr >  t			0.0406
	Week 180	n	1	1	
		LS Mean	48.325	10.973	37.352
		SEM	17.75	17.80	24.88
		95% CI	( 13.5,83.1)	(-24.0,45.9)	(-11.5,86.2)
		Pr >  t			0.1335
	Week 192	n	1	1	
		LS Mean	48.325	-22.36	70.682
		SEM	17.75	17.80	24.88
		95% CI	( 13.5,83.1)	(-57.3,12.6)	( 21.9, 119)
		Pr >  t			0.0046
>= 3	Week 8	n	37	45	
		LS Mean	-6.744	-1.201	-5.543
		SEM	9.756	9.699	5.574
		95% CI	(-26.0,12.5)	(-20.4,18.0)	(-16.6, 5.5)
		Pr >  t			0.3216
	Week 16	n	34	32	
		LS Mean	-7.757	1.426	-9.183
		SEM	10.01	10.10	6.043
		95% CI	(-27.5,12.0)	(-18.5,21.4)	(-21.1, 2.7)
		Pr >  t			0.1303
	Week 24	n	26	19	
		LS Mean	1.213	1.696	-0.483
		SEM	10.20	10.50	6.980
		95% CI	(-18.9,21.4)	(-19.0,22.4)	(-14.2,13.3)
		Pr >  t			0.9449
	Week 32	n	16	17	
		LS Mean	-4.119	-3.605	-0.514
		SEM	10.65	10.61	7.757

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-25.1,16.9)	(-24.5,17.3)	(-15.8,14.8)
		Pr >  t			0.9472
	Week 40	n	14	16	
		LS Mean	-6.421	0.981	-7.402
		SEM	10.80	10.68	8.045
		95% CI	(-27.7,14.9)	(-20.1,22.0)	(-23.2, 8.4)
		Pr >  t			0.3583
	Week 48	n	13	13	
		LS Mean	2.375	3.639	-1.263
		SEM	10.88	10.91	8.453
		95% CI	(-19.1,23.8)	(-17.9,25.2)	(-17.9,15.4)
		Pr >  t			0.8813
	Week 56	n	10	12	
		LS Mean	-2.176	0.852	-3.028
		SEM	11.24	11.01	9.022
		95% CI	(-24.3,20.0)	(-20.9,22.6)	(-20.8,14.7)
		Pr >  t			0.7374
	Week 64	n	10	13	
		LS Mean	-3.438	-7.025	3.587
		SEM	11.24	10.92	8.909
		95% CI	(-25.6,18.7)	(-28.6,14.5)	(-13.9,21.1)
		Pr >  t			0.6875
	Week 72	n	8	10	
		LS Mean	0.778	-0.760	1.538
		SEM	11.60	11.25	9.753
		95% CI	(-22.1,23.6)	(-22.9,21.4)	(-17.6,20.7)
		Pr >  t			0.8748
	Week 84	n	8	10	
		LS Mean	11.242	-4.831	16.073
		SEM	11.60	11.24	9.754
		95% CI	(-11.6,34.1)	(-27.0,17.3)	(-3.1,35.3)
		Pr >  t			0.1002
	Week 96	n	6	7	
		LS Mean	8.324	4.093	4.230
		SEM	12.18	11.85	11.07
		95% CI	(-15.7,32.3)	(-19.2,27.4)	(-17.5,26.0)
		Pr >  t			0.7026
	Week 108	n	4	6	
		LS Mean	11.816	4.772	7.044
		SEM	13.22	12.16	12.52

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.2,37.8)	(-17.6,31.7)
		Pr >  t		0.5740
	Week 120	n	5	3
		LS Mean	7.475	-5.903
		SEM	12.60	14.18
		95% CI	(-17.3,32.3)	(-33.8,22.0)
		Pr >  t		(-14.0,40.8)
	Week 132	n	3	3
		LS Mean	0.794	-2.253
		SEM	14.18	14.19
		95% CI	(-27.1,28.7)	(-30.2,25.7)
		Pr >  t		(-27.2,33.3)
	Week 144	n	1	2
		LS Mean	-27.77	-3.115
		SEM	20.31	15.94
		95% CI	(-67.7,12.2)	(-34.5,28.2)
		Pr >  t		(-68.6,19.3)
	Week 156	n	1	1
		LS Mean	5.569	-2.589
		SEM	20.31	20.31
		95% CI	(-34.4,45.5)	(-42.5,37.3)
		Pr >  t		(-42.3,58.6)
	Week 168	n		1
		LS Mean	NE	-2.589
		SEM	NE	20.31
		95% CI	NE	(-42.5,37.3)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-46: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Appetitverlust“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Stratum 3 - Lung and/or Liver metas (L)	Week 8	n	77	73	
		LS Mean	18.761	7.480	11.281
		SEM	4.109	4.135	3.740
		95% CI	( 10.7,26.9)	( -0.7,15.6)	( 3.9,18.6)
		Pr >  t			0.0028
	Week 16	n	67	56	
		LS Mean	17.636	4.533	13.103
		SEM	4.180	4.389	4.058
		95% CI	( 9.4,25.9)	( -4.1,13.2)	( 5.1,21.1)
		Pr >  t			0.0013
	Week 24	n	61	46	
		LS Mean	17.131	2.648	14.484
		SEM	4.263	4.534	4.291
		95% CI	( 8.7,25.5)	( -6.3,11.6)	( 6.1,22.9)
		Pr >  t			0.0008
	Week 32	n	52	41	
		LS Mean	12.370	4.796	7.575
		SEM	4.415	4.653	4.500
		95% CI	( 3.7,21.1)	( -4.4,14.0)	( -1.3,16.4)
		Pr >  t			0.0930
Week 40	n	45	36		
	LS Mean	10.341	4.843	5.499	
	SEM	4.520	4.792	4.722	
	95% CI	( 1.4,19.2)	( -4.6,14.3)	( -3.8,14.8)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.2447
Week 48	n	42	30	
	LS Mean	9.755	4.923	4.831
	SEM	4.577	4.968	4.955
	95% CI	( 0.7,18.8)	( -4.8,14.7)	( -4.9,14.6)
	Pr >  t			0.3299
Week 56	n	35	24	
	LS Mean	7.641	4.640	3.001
	SEM	4.731	5.222	5.349
	95% CI	( -1.7,16.9)	( -5.6,14.9)	( -7.5,13.5)
	Pr >  t			0.5749
Week 64	n	25	25	
	LS Mean	8.505	6.693	1.811
	SEM	5.072	5.175	5.615
	95% CI	( -1.5,18.5)	( -3.5,16.9)	( -9.2,12.8)
	Pr >  t			0.7471
Week 72	n	27	20	
	LS Mean	11.638	5.369	6.269
	SEM	4.987	5.456	5.801
	95% CI	( 1.8,21.4)	( -5.4,16.1)	( -5.1,17.7)
	Pr >  t			0.2802
Week 84	n	23	19	
	LS Mean	7.046	10.816	-3.770
	SEM	5.192	5.528	6.029
	95% CI	( -3.2,17.2)	( -0.0,21.7)	( -15.6, 8.1)
	Pr >  t			0.5319
Week 96	n	20	13	
	LS Mean	13.847	10.592	3.255
	SEM	5.374	6.142	6.741
	95% CI	( 3.3,24.4)	( -1.5,22.7)	( -10.0,16.5)
	Pr >  t			0.6293
Week 108	n	17	13	
	LS Mean	7.176	9.739	-2.562
	SEM	5.612	6.143	6.932
	95% CI	( -3.8,18.2)	( -2.3,21.8)	( -16.2,11.0)
	Pr >  t			0.7117
Week 120	n	17	12	
	LS Mean	8.274	7.700	0.574
	SEM	5.609	6.295	7.066
	95% CI	( -2.7,19.3)	( -4.7,20.1)	( -13.3,14.4)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.9353
	Week 132	n 13	6	
		LS Mean 4.245	12.275	-8.030
		SEM 6.061	7.985	8.907
		95% CI (-7.7,16.1)	(-3.4,27.9)	(-25.5, 9.5)
		Pr >  t		0.3675
	Week 144	n 11	4	
		LS Mean 16.979	3.070	13.909
		SEM 6.388	9.383	10.38
		95% CI ( 4.4,29.5)	(-15.3,21.5)	(-6.5,34.3)
		Pr >  t		0.1804
	Week 156	n 7	2	
		LS Mean 3.004	3.965	-0.961
		SEM 7.469	12.65	13.95
		95% CI (-11.7,17.7)	(-20.9,28.8)	(-28.3,26.4)
		Pr >  t		0.9451
	Week 168	n 3	1	
		LS Mean 2.120	1.905	0.215
		SEM 10.51	17.43	19.83
		95% CI (-18.5,22.7)	(-32.3,36.1)	(-38.7,39.1)
		Pr >  t		0.9914
	Week 180	n 1	1	
		LS Mean 9.136	1.905	7.231
		SEM 17.39	17.43	24.19
		95% CI (-25.0,43.3)	(-32.3,36.1)	(-40.3,54.7)
		Pr >  t		0.7651
	Week 192	n 1	1	
		LS Mean 42.476	1.905	40.571
		SEM 17.39	17.43	24.19
		95% CI ( 8.3,76.6)	(-32.3,36.1)	(-6.9,88.1)
		Pr >  t		0.0939
Present	Week 8	n 65	67	
		LS Mean 12.881	1.408	11.473
		SEM 5.340	5.470	4.559
		95% CI ( 2.3,23.4)	(-9.4,12.2)	( 2.5,20.5)
		Pr >  t		0.0126
	Week 16	n 57	51	
		LS Mean 13.085	0.247	12.837
		SEM 5.503	5.675	4.860
		95% CI ( 2.2,23.9)	(-10.9,11.4)	( 3.3,22.4)



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.0088
Week 24	n	44	35	
	LS Mean	4.561	5.687	-1.126
	SEM	5.652	6.003	5.363
	95% CI	(-6.6,15.7)	(-6.1,17.5)	(-11.7, 9.4)
	Pr >  t			0.8338
Week 32	n	34	32	
	LS Mean	5.686	-0.196	5.882
	SEM	5.866	6.085	5.653
	95% CI	(-5.9,17.2)	(-12.2,11.8)	(-5.2,17.0)
	Pr >  t			0.2987
Week 40	n	30	26	
	LS Mean	5.437	3.028	2.409
	SEM	5.971	6.271	5.962
	95% CI	(-6.3,17.2)	(-9.3,15.4)	(-9.3,14.1)
	Pr >  t			0.6863
Week 48	n	27	21	
	LS Mean	2.341	3.118	-0.777
	SEM	6.057	6.497	6.285
	95% CI	(-9.6,14.3)	(-9.7,15.9)	(-13.1,11.6)
	Pr >  t			0.9017
Week 56	n	24	21	
	LS Mean	1.265	1.273	-0.008
	SEM	6.170	6.496	6.396
	95% CI	(-10.9,13.4)	(-11.5,14.1)	(-12.6,12.6)
	Pr >  t			0.9990
Week 64	n	22	17	
	LS Mean	5.282	3.128	2.154
	SEM	6.260	6.751	6.738
	95% CI	(-7.0,17.6)	(-10.1,16.4)	(-11.1,15.4)
	Pr >  t			0.7494
Week 72	n	21	15	
	LS Mean	-0.750	0.710	-1.461
	SEM	6.314	6.920	6.955
	95% CI	(-13.2,11.7)	(-12.9,14.3)	(-15.1,12.2)
	Pr >  t			0.8337
Week 84	n	17	14	
	LS Mean	2.994	3.062	-0.068
	SEM	6.576	7.018	7.276
	95% CI	(-9.9,15.9)	(-10.7,16.9)	(-14.4,14.2)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.9925
	Week 96	n	15	11	
		LS Mean	0.589	0.550	0.040
		SEM	6.727	7.412	7.805
		95% CI	(-12.6,13.8)	(-14.0,15.1)	(-15.3,15.4)
		Pr >  t			0.9959
	Week 108	n	9	8	
		LS Mean	1.407	1.219	0.188
		SEM	7.627	8.050	9.136
		95% CI	(-13.6,16.4)	(-14.6,17.0)	(-17.8,18.1)
		Pr >  t			0.9836
	Week 120	n	11	4	
		LS Mean	6.528	-5.770	12.298
		SEM	7.234	10.04	10.67
		95% CI	(-7.7,20.7)	(-25.5,13.9)	(-8.7,33.3)
		Pr >  t			0.2497
	Week 132	n	7	2	
		LS Mean	0.814	1.663	-0.849
		SEM	8.195	13.08	14.10
		95% CI	(-15.3,16.9)	(-24.0,27.3)	(-28.5,26.8)
		Pr >  t			0.9520
	Week 144	n	4	1	
		LS Mean	24.879	1.480	23.399
		SEM	9.817	17.69	19.26
		95% CI	( 5.6,44.2)	(-33.3,36.2)	(-14.4,61.2)
		Pr >  t			0.2249
	Week 156	n	3	1	
		LS Mean	-0.360	1.480	-1.839
		SEM	11.00	17.69	19.86
		95% CI	(-22.0,21.2)	(-33.3,36.2)	(-40.8,37.2)
		Pr >  t			0.9262
	Week 168	n	1	1	
		LS Mean	-4.125	1.480	-5.605
		SEM	17.63	17.69	24.17
		95% CI	(-38.7,30.5)	(-33.3,36.2)	(-53.1,41.9)
		Pr >  t			0.8167

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	16.558	2.130	14.428		
			SEM	3.590	3.792	3.554		
			95% CI	( 9.5,23.6)	( -5.3, 9.6)	( 7.4,21.4)		
					Pr >  t			<.0001
		Week 16	n	86	68			
			LS Mean	16.590	2.288	14.302		
			SEM	3.677	3.957	3.806		
			95% CI	( 9.4,23.8)	( -5.5,10.1)	( 6.8,21.8)		
					Pr >  t			0.0002
		Week 24	n	73	48			
			LS Mean	14.073	-0.409	14.483		
			SEM	3.783	4.254	4.196		
			95% CI	( 6.6,21.5)	( -8.8, 8.0)	( 6.2,22.7)		
					Pr >  t			0.0006
		Week 32	n	60	43			
			LS Mean	9.400	0.898	8.502		
			SEM	3.956	4.368	4.416		
			95% CI	( 1.6,17.2)	( -7.7, 9.5)	( -0.2,17.2)		
					Pr >  t			0.0546
		Week 40	n	50	38			
			LS Mean	7.671	1.848	5.823		
			SEM	4.091	4.499	4.651		
			95% CI	( -0.4,15.7)	( -7.0,10.7)	( -3.3,15.0)		
			Pr >  t			0.2110		
Week 48	n	48	31					
	LS Mean	7.891	1.211	6.679				
	SEM	4.127	4.709	4.885				
	95% CI	( -0.2,16.0)	( -8.0,10.5)	( -2.9,16.3)				
			Pr >  t			0.1719		
Week 56	n	41	25					
	LS Mean	5.788	0.824	4.964				
	SEM	4.258	4.967	5.245				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-2.6,14.2)	(-8.9,10.6)	(-5.3,15.3)
	Pr >  t			0.3442
	n	30	24	
	LS Mean	7.469	3.098	4.371
	SEM	4.566	5.021	5.553
Week 72	95% CI	(-1.5,16.4)	(-6.8,13.0)	(-6.5,15.3)
	Pr >  t			0.4314
	n	32	19	
	LS Mean	7.952	-0.058	8.010
	SEM	4.497	5.351	5.797
Week 84	95% CI	(-0.9,16.8)	(-10.6,10.4)	(-3.4,19.4)
	Pr >  t			0.1674
	n	26	19	
	LS Mean	6.426	6.926	-0.500
	SEM	4.756	5.351	5.987
Week 96	95% CI	(-2.9,15.8)	(-3.6,17.4)	(-12.2,11.2)
	Pr >  t			0.9335
	n	23	14	
	LS Mean	9.843	6.293	3.550
	SEM	4.904	5.867	6.570
Week 108	95% CI	( 0.2,19.5)	(-5.2,17.8)	(-9.3,16.4)
	Pr >  t			0.5890
	n	19	13	
	LS Mean	4.195	5.826	-1.631
	SEM	5.193	6.008	6.903
Week 120	95% CI	(-6.0,14.4)	(-6.0,17.6)	(-15.2,11.9)
	Pr >  t			0.8133
	n	19	11	
	LS Mean	5.704	4.140	1.564
	SEM	5.178	6.355	7.205
Week 132	95% CI	(-4.5,15.9)	(-8.3,16.6)	(-12.6,15.7)
	Pr >  t			0.8282
	n	15	5	
	LS Mean	0.889	9.894	-9.005
	SEM	5.585	8.559	9.437
Week 144	95% CI	(-10.1,11.9)	(-6.9,26.7)	(-27.5, 9.5)
	Pr >  t			0.3402
	n	12	3	
Week 144	LS Mean	14.017	-1.633	15.650
	SEM	6.003	10.66	11.60

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 2.2,25.8)	(-22.6,19.3)	( -7.1,38.4)
		Pr >  t			0.1774
	Week 156	n	7	2	
		LS Mean	0.474	0.218	0.256
		SEM	7.356	12.78	14.22
		95% CI	(-14.0,14.9)	(-24.9,25.3)	(-27.6,28.2)
		Pr >  t			0.9856
	Week 168	n	3	1	
		LS Mean	-0.424	-1.802	1.377
		SEM	10.53	17.70	20.22
		95% CI	(-21.1,20.2)	(-36.5,32.9)	(-38.3,41.1)
		Pr >  t			0.9457
	Week 180	n	1	1	
		LS Mean	6.651	-1.802	8.453
		SEM	17.63	17.70	24.67
		95% CI	(-28.0,41.3)	(-36.5,32.9)	(-40.0,56.9)
		Pr >  t			0.7320
	Week 192	n	1	1	
		LS Mean	39.991	-1.802	41.793
		SEM	17.63	17.70	24.67
		95% CI	( 5.4,74.6)	(-36.5,32.9)	( -6.6,90.2)
		Pr >  t			0.0906
Yes	Week 8	n	44	56	
		LS Mean	18.216	11.331	6.885
		SEM	7.967	7.610	5.014
		95% CI	( 2.5,34.0)	( -3.7,26.4)	( -3.0,16.8)
		Pr >  t			0.1716
	Week 16	n	38	39	
		LS Mean	16.452	6.509	9.943
		SEM	8.163	7.992	5.418
		95% CI	( 0.3,32.6)	( -9.3,22.3)	( -0.7,20.6)
		Pr >  t			0.0680
	Week 24	n	32	33	
		LS Mean	9.127	13.419	-4.292
		SEM	8.266	8.079	5.700
		95% CI	( -7.2,25.4)	( -2.5,29.4)	(-15.5, 6.9)
		Pr >  t			0.4522
	Week 32	n	26	30	
		LS Mean	12.329	8.306	4.023
		SEM	8.397	8.144	5.974

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-4.2,28.9)	(-7.8,24.4)	(-7.7,15.8)
		Pr >  t			0.5013
		n	25	24	
		LS Mean	11.416	10.326	1.090
		SEM	8.427	8.293	6.215
Week 48		95% CI	(-5.2,28.0)	(-6.0,26.7)	(-11.1,13.3)
		Pr >  t			0.8609
		n	21	20	
		LS Mean	5.864	11.581	-5.717
		SEM	8.547	8.436	6.563
Week 56		95% CI	(-11.0,22.7)	(-5.0,28.2)	(-18.6, 7.2)
		Pr >  t			0.3843
		n	18	20	
		LS Mean	5.095	9.625	-4.530
		SEM	8.674	8.436	6.728
Week 64		95% CI	(-12.0,22.2)	(-7.0,26.3)	(-17.8, 8.7)
		Pr >  t			0.5012
		n	17	18	
		LS Mean	9.027	11.339	-2.312
		SEM	8.726	8.527	6.907
Week 72		95% CI	(-8.2,26.2)	(-5.5,28.1)	(-15.9,11.3)
		Pr >  t			0.7380
		n	16	16	
		LS Mean	5.350	11.243	-5.893
		SEM	8.787	8.637	7.115
Week 84		95% CI	(-12.0,22.7)	(-5.8,28.3)	(-19.9, 8.1)
		Pr >  t			0.4080
		n	14	14	
		LS Mean	5.470	11.699	-6.229
		SEM	8.916	8.772	7.437
Week 96		95% CI	(-12.1,23.0)	(-5.6,29.0)	(-20.8, 8.4)
		Pr >  t			0.4027
		n	12	10	
		LS Mean	7.207	9.252	-2.045
		SEM	9.094	9.195	8.130
Week 108		95% CI	(-10.7,25.1)	(-8.8,27.4)	(-18.0,13.9)
		Pr >  t			0.8015
		n	7	8	
	LS Mean	8.570	9.813	-1.243	
	SEM	9.913	9.549	9.397	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.9,28.1)	(-9.0,28.6)	(-19.7,17.2)
		Pr >  t			0.8948
	Week 120	n	9	5	
		LS Mean	13.298	4.114	9.183
		SEM	9.504	10.53	10.00
		95% CI	(-5.4,32.0)	(-16.6,24.8)	(-10.5,28.8)
		Pr >  t			0.3589
	Week 132	n	5	3	
		LS Mean	10.711	9.920	0.790
		SEM	10.64	12.05	12.54
		95% CI	(-10.2,31.6)	(-13.8,33.6)	(-23.8,25.4)
		Pr >  t			0.9498
	Week 144	n	3	2	
		LS Mean	37.105	9.775	27.330
		SEM	12.14	13.73	15.32
		95% CI	( 13.3,61.0)	(-17.2,36.7)	(-2.8,57.4)
		Pr >  t			0.0750
	Week 156	n	3	1	
		LS Mean	5.532	9.951	-4.419
		SEM	12.15	17.82	19.08
		95% CI	(-18.3,29.4)	(-25.0,45.0)	(-41.9,33.1)
		Pr >  t			0.8169
	Week 168	n	1	1	
		LS Mean	1.648	9.951	-8.303
		SEM	17.92	17.82	23.18
		95% CI	(-33.6,36.8)	(-25.0,45.0)	(-53.9,37.3)
		Pr >  t			0.7204

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Presence of Liver Metastases (L)	No	Week 8	n	104	98	
			LS Mean	17.962	6.144	11.818
			SEM	3.879	3.848	3.238
			95% CI	( 10.3,25.6)	( -1.4,13.7)	( 5.5,18.2)
		Pr >  t			0.0003	
		Week 16	n	92	77	
			LS Mean	15.526	2.166	13.360
			SEM	3.926	4.050	3.466
			95% CI	( 7.8,23.3)	( -5.8,10.1)	( 6.6,20.2)
		Pr >  t			0.0001	
		Week 24	n	83	66	
			LS Mean	11.289	4.883	6.406
			SEM	3.989	4.131	3.625
			95% CI	( 3.4,19.1)	( -3.2,13.0)	( -0.7,13.5)
		Pr >  t			0.0777	
		Week 32	n	72	60	
			LS Mean	11.299	3.135	8.163
			SEM	4.071	4.206	3.770
			95% CI	( 3.3,19.3)	( -5.1,11.4)	( 0.8,15.6)
		Pr >  t			0.0307	
		Week 40	n	64	51	
			LS Mean	9.114	3.895	5.218
			SEM	4.132	4.324	3.952
			95% CI	( 1.0,17.2)	( -4.6,12.4)	( -2.5,13.0)
		Pr >  t			0.1870	
		Week 48	n	58	45	
			LS Mean	8.378	2.736	5.642
			SEM	4.187	4.411	4.105
95% CI	( 0.1,16.6)		( -5.9,11.4)	( -2.4,13.7)		
Pr >  t			0.1697			
Week 56	n	49	38			
	LS Mean	6.283	3.260	3.023		
	SEM	4.290	4.543	4.352		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-2.2,14.7)	(-5.7,12.2)	(-5.5,11.6)
	Pr >  t			0.4875
	n	39	37	
	LS Mean	8.615	7.134	1.481
	SEM	4.451	4.566	4.539
Week 72	95% CI	(-0.1,17.4)	(-1.8,16.1)	(-7.4,10.4)
	Pr >  t			0.7444
	n	41	32	
	LS Mean	8.199	4.427	3.773
	SEM	4.414	4.693	4.631
Week 84	95% CI	(-0.5,16.9)	(-4.8,13.6)	(-5.3,12.9)
	Pr >  t			0.4154
	n	33	29	
	LS Mean	5.208	8.128	-2.920
	SEM	4.611	4.788	4.895
Week 96	95% CI	(-3.9,14.3)	(-1.3,17.5)	(-12.5, 6.7)
	Pr >  t			0.5510
	n	31	21	
	LS Mean	10.371	7.940	2.431
	SEM	4.659	5.151	5.302
Week 108	95% CI	( 1.2,19.5)	(-2.2,18.1)	(-8.0,12.8)
	Pr >  t			0.6467
	n	23	18	
	LS Mean	6.233	6.362	-0.129
	SEM	4.985	5.358	5.774
Week 120	95% CI	(-3.6,16.0)	(-4.2,16.9)	(-11.5,11.2)
	Pr >  t			0.9822
	n	25	15	
	LS Mean	8.937	5.195	3.742
	SEM	4.880	5.632	5.953
Week 132	95% CI	(-0.6,18.5)	(-5.9,16.3)	(-7.9,15.4)
	Pr >  t			0.5297
	n	17	8	
	LS Mean	4.656	9.401	-4.745
	SEM	5.382	6.881	7.492
Week 144	95% CI	(-5.9,15.2)	(-4.1,22.9)	(-19.4,10.0)
	Pr >  t			0.5266
	n	15	5	
	LS Mean	19.361	2.246	17.114
	SEM	5.557	8.221	8.857

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 8.5,30.3)	(-13.9,18.4)	( -0.3,34.5)
		Pr >  t			0.0535
	Week 156	n	10	3	
		LS Mean	2.488	3.222	-0.733
		SEM	6.324	10.16	11.09
		95% CI	( -9.9,14.9)	(-16.7,23.1)	(-22.5,21.0)
		Pr >  t			0.9473
	Week 168	n	4	2	
		LS Mean	0.712	2.517	-1.805
		SEM	8.947	12.15	14.41
		95% CI	(-16.8,18.3)	(-21.3,26.4)	(-30.1,26.5)
		Pr >  t			0.9003
	Week 180	n	1	1	
		LS Mean	7.760	0.563	7.196
		SEM	16.74	16.75	23.25
		95% CI	(-25.1,40.6)	(-32.3,33.4)	(-38.4,52.8)
		Pr >  t			0.7570
	Week 192	n	1	1	
		LS Mean	41.100	0.563	40.536
		SEM	16.74	16.75	23.25
		95% CI	( 8.3,73.9)	(-32.3,33.4)	( -5.1,86.2)
		Pr >  t			0.0815
Yes	Week 8	n	38	42	
		LS Mean	9.616	-0.591	10.207
		SEM	6.462	6.818	6.399
		95% CI	( -3.2,22.4)	(-14.1,12.9)	( -2.5,22.9)
		Pr >  t			0.1131
	Week 16	n	32	30	
		LS Mean	14.995	2.600	12.395
		SEM	6.830	7.139	6.980
		95% CI	( 1.5,28.5)	(-11.5,16.7)	( -1.4,26.2)
		Pr >  t			0.0777
	Week 24	n	22	15	
		LS Mean	13.397	-1.256	14.653
		SEM	7.231	8.263	8.452
		95% CI	( -0.9,27.7)	(-17.6,15.0)	( -2.0,31.3)
		Pr >  t			0.0843
	Week 32	n	14	13	
		LS Mean	0.695	-0.648	1.343
		SEM	8.089	8.527	9.316

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-15.3,16.6)	(-17.5,16.2)	(-17.0,19.7)
	Pr >  t			0.8855
	n	11	11	
	LS Mean	3.650	3.833	-0.183
	SEM	8.574	8.857	10.02
Week 48	95% CI	(-13.2,20.5)	(-13.6,21.3)	(-19.9,19.5)
	Pr >  t			0.9854
	n	11	6	
	LS Mean	-2.411	15.311	-17.72
	SEM	8.574	10.41	11.42
Week 56	95% CI	(-19.3,14.5)	(-5.2,35.8)	(-40.2, 4.8)
	Pr >  t			0.1219
	n	10	7	
	LS Mean	-2.021	2.697	-4.717
	SEM	8.784	9.955	11.18
Week 64	95% CI	(-19.3,15.3)	(-16.9,22.3)	(-26.7,17.3)
	Pr >  t			0.6733
	n	8	5	
	LS Mean	0.799	-9.206	10.005
	SEM	9.307	11.01	12.51
Week 72	95% CI	(-17.5,19.1)	(-30.9,12.5)	(-14.6,34.6)
	Pr >  t			0.4244
	n	7	3	
	LS Mean	-3.947	-6.172	2.225
	SEM	9.672	13.09	14.60
Week 84	95% CI	(-23.0,15.1)	(-31.9,19.6)	(-26.5,31.0)
	Pr >  t			0.8790
	n	7	4	
	LS Mean	5.578	3.123	2.455
	SEM	9.672	11.84	13.50
Week 96	95% CI	(-13.5,24.6)	(-20.2,26.4)	(-24.1,29.0)
	Pr >  t			0.8558
	n	4	3	
	LS Mean	-6.126	-6.172	0.046
	SEM	11.55	13.09	15.90
Week 108	95% CI	(-28.9,16.6)	(-31.9,19.6)	(-31.3,31.4)
	Pr >  t			0.9977
	n	3	3	
	LS Mean	-4.538	6.482	-11.02
	SEM	12.81	13.08	16.84

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-29.7,20.7)	(-19.3,32.2)	(-44.2,22.1)
		Pr >  t			0.5135
	Week 120	n	3	1	
		LS Mean	-2.309	-15.51	13.205
		SEM	12.80	20.41	23.00
		95% CI	(-27.5,22.9)	(-55.7,24.7)	(-32.1,58.5)
		Pr >  t			0.5664
	Week 132	n	3		
		LS Mean	-8.359	NE	NE
		SEM	12.81	NE	NE
		95% CI	(-33.6,16.9)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	14.117	2.122	11.995		
			SEM	3.892	3.875	3.386		
			95% CI	( 6.5,21.8)	( -5.5, 9.7)	( 5.3,18.7)		
					Pr >  t			0.0004
		Week 16	n	92	83			
			LS Mean	14.686	1.356	13.330		
			SEM	3.985	4.076	3.626		
			95% CI	( 6.8,22.5)	( -6.7, 9.4)	( 6.2,20.5)		
					Pr >  t			0.0003
		Week 24	n	77	59			
			LS Mean	10.807	2.233	8.574		
			SEM	4.064	4.297	3.950		
			95% CI	( 2.8,18.8)	( -6.2,10.7)	( 0.8,16.3)		
					Pr >  t			0.0304
		Week 32	n	57	53			
			LS Mean	6.582	0.838	5.744		
			SEM	4.274	4.368	4.207		
			95% CI	( -1.8,15.0)	( -7.7, 9.4)	( -2.5,14.0)		
					Pr >  t			0.1726
		Week 40	n	50	44			
			LS Mean	5.572	1.802	3.771		
			SEM	4.361	4.517	4.435		
			95% CI	( -3.0,14.1)	( -7.1,10.7)	( -4.9,12.5)		
			Pr >  t			0.3955		
Week 48	n	47	37					
	LS Mean	5.997	3.521	2.476				
	SEM	4.403	4.660	4.622				
	95% CI	( -2.7,14.7)	( -5.6,12.7)	( -6.6,11.5)				
			Pr >  t			0.5922		
Week 56	n	40	32					
	LS Mean	3.230	2.257	0.973				
	SEM	4.524	4.793	4.869				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	95% CI	(-5.7,12.1)	(-7.2,11.7)	(-8.6,10.5)	
	Pr >  t			0.8417	
	n	32	27		
	LS Mean	6.088	2.591	3.498	
	SEM	4.718	4.966	5.214	
Week 72	95% CI	(-3.2,15.4)	(-7.2,12.3)	(-6.7,13.7)	
	Pr >  t			0.5025	
	n	31	23		
	LS Mean	2.664	2.690	-0.025	
	SEM	4.750	5.149	5.416	
Week 84	95% CI	(-6.7,12.0)	(-7.4,12.8)	(-10.7,10.6)	
	Pr >  t			0.9963	
	n	27	21		
	LS Mean	3.425	7.753	-4.328	
	SEM	4.894	5.262	5.642	
Week 96	95% CI	(-6.2,13.0)	(-2.6,18.1)	(-15.4, 6.7)	
	Pr >  t			0.4432	
	n	23	16		
	LS Mean	6.531	3.367	3.165	
	SEM	5.067	5.645	6.152	
Week 108	95% CI	(-3.4,16.5)	(-7.7,14.4)	(-8.9,15.2)	
	Pr >  t			0.6071	
	n	15	14		
	LS Mean	3.691	4.001	-0.311	
	SEM	5.675	5.862	6.841	
Week 120	95% CI	(-7.4,14.8)	(-7.5,15.5)	(-13.7,13.1)	
	Pr >  t			0.9638	
	n	18	8		
	LS Mean	6.792	-1.451	8.242	
	SEM	5.395	7.021	7.664	
Week 132	95% CI	(-3.8,17.4)	(-15.2,12.3)	(-6.8,23.3)	
	Pr >  t			0.2824	
	n	12	4		
	LS Mean	-0.470	3.741	-4.210	
	SEM	6.067	9.138	10.03	
Week 144	95% CI	(-12.4,11.4)	(-14.2,21.7)	(-23.9,15.5)	
	Pr >  t			0.6747	
	n	8	3		
Week 144	LS Mean	18.670	-0.406	19.077	
	SEM	6.927	10.33	11.63	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 5.1,32.3)	(-20.7,19.9)	( -3.7,41.9)
		Pr >  t			0.1012
	Week 156	n	5	1	
		LS Mean	-0.421	2.299	-2.720
		SEM	8.295	17.01	18.39
		95% CI	(-16.7,15.9)	(-31.1,35.7)	(-38.8,33.4)
		Pr >  t			0.8825
	Week 168	n	2	1	
		LS Mean	1.349	2.299	-0.950
		SEM	12.30	17.01	20.51
		95% CI	(-22.8,25.5)	(-31.1,35.7)	(-41.2,39.3)
		Pr >  t			0.9631
	Week 180	n	1		
		LS Mean	4.923	NE	NE
		SEM	16.96	NE	NE
		95% CI	(-28.4,38.2)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	38.263	NE	NE
		SEM	16.96	NE	NE
		95% CI	( 5.0,71.5)	NE	NE
		Pr >  t			NE
Yes	Week 8	n	38	30	
		LS Mean	22.834	13.173	9.661
		SEM	6.185	6.637	5.692
		95% CI	( 10.5,35.1)	( -0.0,26.4)	( -1.6,20.9)
		Pr >  t			0.0915
	Week 16	n	32	24	
		LS Mean	19.063	7.165	11.898
		SEM	6.313	6.855	6.191
		95% CI	( 6.5,31.6)	( -6.4,20.8)	( -0.3,24.1)
		Pr >  t			0.0560
	Week 24	n	28	22	
		LS Mean	15.439	9.718	5.721
		SEM	6.540	6.956	6.448
		95% CI	( 2.5,28.4)	( -4.1,23.5)	( -7.0,18.4)
		Pr >  t			0.3759
	Week 32	n	29	20	
		LS Mean	17.441	8.764	8.676
		SEM	6.512	7.177	6.553



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 4.5,30.4)	( -5.5,23.0)	( -4.2,21.6)
		Pr >  t			0.1868
	Week 40	n	25	18	
		LS Mean	15.633	11.255	4.378
		SEM	6.655	7.309	6.839
		95% CI	( 2.4,28.8)	( -3.2,25.7)	( -9.1,17.8)
		Pr >  t			0.5227
	Week 48	n	22	14	
		LS Mean	9.691	7.111	2.580
		SEM	6.788	7.663	7.359
		95% CI	( -3.8,23.1)	( -8.0,22.3)	( -11.9,17.1)
		Pr >  t			0.7261
	Week 56	n	19	13	
		LS Mean	10.271	7.023	3.248
		SEM	6.957	7.792	7.645
		95% CI	( -3.5,24.0)	( -8.4,22.4)	( -11.8,18.3)
		Pr >  t			0.6713
	Week 64	n	15	15	
		LS Mean	11.588	12.612	-1.024
		SEM	7.264	7.571	7.724
		95% CI	( -2.8,25.9)	( -2.4,27.6)	( -16.2,14.2)
		Pr >  t			0.8946
	Week 72	n	17	12	
		LS Mean	15.246	7.279	7.967
		SEM	7.093	7.925	7.911
		95% CI	( 1.2,29.3)	( -8.4,22.9)	( -7.6,23.5)
		Pr >  t			0.3146
	Week 84	n	13	12	
		LS Mean	11.219	9.962	1.257
		SEM	7.549	7.927	8.277
		95% CI	( -3.7,26.1)	( -5.7,25.6)	( -15.0,17.5)
		Pr >  t			0.8794
	Week 96	n	12	8	
		LS Mean	13.620	14.271	-0.651
		SEM	7.684	8.743	9.172
		95% CI	( -1.5,28.8)	( -3.0,31.5)	( -18.7,17.4)
		Pr >  t			0.9434
	Week 108	n	11	7	
		LS Mean	9.135	13.444	-4.309
		SEM	7.846	9.071	9.611

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.3,24.6)	(-4.4,31.3)	(-23.2,14.6)
		Pr >  t			0.6541
	Week 120	n	10	8	
		LS Mean	10.696	12.756	-2.060
		SEM	8.021	8.746	9.460
		95% CI	(-5.1,26.5)	(-4.5,30.0)	(-20.7,16.5)
		Pr >  t			0.8277
	Week 132	n	8	4	
		LS Mean	10.014	17.995	-7.981
		SEM	8.511	10.80	11.73
		95% CI	(-6.8,26.8)	(-3.2,39.2)	(-31.0,15.1)
		Pr >  t			0.4967
	Week 144	n	7	2	
		LS Mean	20.827	8.028	12.799
		SEM	8.842	14.02	14.94
		95% CI	( 3.4,38.2)	(-19.5,35.6)	(-16.6,42.2)
		Pr >  t			0.3922
	Week 156	n	5	2	
		LS Mean	6.492	8.028	-1.536
		SEM	9.823	14.02	15.54
		95% CI	(-12.8,25.8)	(-19.5,35.6)	(-32.1,29.0)
		Pr >  t			0.9213
	Week 168	n	2	1	
		LS Mean	1.317	6.055	-4.737
		SEM	13.83	18.86	22.26
		95% CI	(-25.9,28.5)	(-31.0,43.1)	(-48.5,39.0)
		Pr >  t			0.8316
	Week 180	n		1	
		LS Mean	NE	6.055	NE
		SEM	NE	18.86	NE
		95% CI	NE	(-31.0,43.1)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	6.055	NE
		SEM	NE	18.86	NE
		95% CI	NE	(-31.0,43.1)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	15.500	2.678	12.823		
			SEM	2.061	2.071	2.923		
			95% CI	( 11.5,19.5)	( -1.4, 6.7)	( 7.1,18.6)		
					Pr >  t			<.0001
		Week 16	n	118	104			
			LS Mean	14.277	0.311	13.966		
			SEM	2.154	2.277	3.135		
			95% CI	( 10.0,18.5)	( -4.2, 4.8)	( 7.8,20.1)		
					Pr >  t			<.0001
		Week 24	n	100	79			
			LS Mean	9.930	1.460	8.470		
			SEM	2.279	2.504	3.386		
			95% CI	( 5.5,14.4)	( -3.5, 6.4)	( 1.8,15.1)		
					Pr >  t			0.0126
		Week 32	n	84	72			
			LS Mean	8.069	0.518	7.551		
			SEM	2.415	2.588	3.539		
			95% CI	( 3.3,12.8)	( -4.6, 5.6)	( 0.6,14.5)		
					Pr >  t			0.0332
		Week 40	n	73	62			
			LS Mean	7.106	1.808	5.298		
			SEM	2.534	2.721	3.716		
			95% CI	( 2.1,12.1)	( -3.5, 7.1)	( -2.0,12.6)		
					Pr >  t			0.1543
		Week 48	n	67	51			
			LS Mean	5.493	1.929	3.564		
			SEM	2.608	2.912	3.908		
95% CI	( 0.4,10.6)		( -3.8, 7.6)	( -4.1,11.2)				
			Pr >  t			0.3620		
Week 56	n	57	45					
	LS Mean	3.172	0.934	2.237				
	SEM	2.756	3.046	4.108				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-2.2, 8.6)	(-5.0, 6.9)	(-5.8,10.3)
	Pr >  t			0.5861
	n	45	42	
	LS Mean	5.597	2.954	2.642
	SEM	2.996	3.125	4.328
Week 72	95% CI	(-0.3,11.5)	(-3.2, 9.1)	(-5.8,11.1)
	Pr >  t			0.5417
	n	46	35	
	LS Mean	5.297	1.154	4.144
	SEM	2.974	3.342	4.473
Week 84	95% CI	(-0.5,11.1)	(-5.4, 7.7)	(-4.6,12.9)
	Pr >  t			0.3544
	n	40	33	
	LS Mean	4.013	5.320	-1.308
	SEM	3.129	3.417	4.634
Week 96	95% CI	(-2.1,10.2)	(-1.4,12.0)	(-10.4, 7.8)
	Pr >  t			0.7778
	n	34	24	
	LS Mean	6.796	3.960	2.836
	SEM	3.329	3.872	5.106
Week 108	95% CI	( 0.3,13.3)	(-3.6,11.6)	(-7.2,12.9)
	Pr >  t			0.5787
	n	26	21	
	LS Mean	3.280	4.078	-0.798
	SEM	3.701	4.090	5.516
Week 120	95% CI	(-4.0,10.5)	(-3.9,12.1)	(-11.6,10.0)
	Pr >  t			0.8849
	n	27	16	
	LS Mean	5.933	1.407	4.526
	SEM	3.649	4.586	5.859
Week 132	95% CI	(-1.2,13.1)	(-7.6,10.4)	(-7.0,16.0)
	Pr >  t			0.4400
	n	20	8	
	LS Mean	1.306	6.603	-5.298
	SEM	4.123	6.232	7.472
Week 144	95% CI	(-6.8, 9.4)	(-5.6,18.8)	(-20.0, 9.4)
	Pr >  t			0.4784
	n	14	5	
	LS Mean	17.453	-0.569	18.022
	SEM	4.808	7.766	9.133

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( - 8.0,26.9)	( -15.8,14.7)	( 0.1,35.9)
		Pr >  t			0.0486
	Week 156	n	10	3	
		LS Mean	-0.070	0.398	-0.468
		SEM	5.590	9.904	11.37
		95% CI	(-11.0,10.9)	(-19.0,19.8)	(-22.8,21.8)
		Pr >  t			0.9672
	Week 168	n	4	2	
		LS Mean	-1.874	-0.292	-1.582
		SEM	8.590	12.06	14.80
		95% CI	(-18.7,15.0)	(-23.9,23.4)	(-30.6,27.5)
		Pr >  t			0.9149
	Week 180	n	1	1	
		LS Mean	5.181	-2.267	7.447
		SEM	16.92	16.93	23.93
		95% CI	(-28.0,38.4)	(-35.5,30.9)	(-39.5,54.4)
		Pr >  t			0.7557
	Week 192	n	1	1	
		LS Mean	38.521	-2.267	40.787
		SEM	16.92	16.93	23.93
		95% CI	( 5.3,71.7)	(-35.5,30.9)	( -6.2,87.7)
		Pr >  t			0.0886
Prior use	Week 8	n	8	6	
		LS Mean	4.091	13.928	-9.837
		SEM	11.45	13.44	17.68
		95% CI	(-20.6,28.8)	(-14.8,42.6)	(-47.8,28.1)
		Pr >  t			0.5868
	Week 16	n	6	3	
		LS Mean	16.336	28.973	-12.64
		SEM	12.30	16.41	20.58
		95% CI	( -9.7,42.4)	( -5.1,63.0)	(-55.6,30.3)
		Pr >  t			0.5462
	Week 24	n	5	2	
		LS Mean	20.807	28.494	-7.687
		SEM	12.79	18.04	22.20
		95% CI	( -6.1,47.7)	( -8.6,65.5)	(-53.5,38.1)
		Pr >  t			0.7321
	Week 32	n	2	1	
		LS Mean	13.851	9.312	4.539
		SEM	16.23	22.34	27.71

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-19.5,47.2)	(-36.5,55.1)	(-52.2,61.3)
	Pr >  t			0.8710
Week 40	n	2		
	LS Mean	-2.814	NE	NE
	SEM	16.23	NE	NE
	95% CI	(-36.1,30.5)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	-2.814	NE	NE
	SEM	16.23	NE	NE
	95% CI	(-36.1,30.5)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	13.851	NE	NE
	SEM	16.23	NE	NE
	95% CI	(-19.5,47.2)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	13.851	NE	NE
	SEM	16.23	NE	NE
	95% CI	(-19.5,47.2)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	-2.814	NE	NE
	SEM	16.23	NE	NE
	95% CI	(-36.1,30.5)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	7.971	NE	NE
	SEM	20.08	NE	NE
	95% CI	(-33.2,49.1)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	7.971	NE	NE
	SEM	20.08	NE	NE
	95% CI	(-33.2,49.1)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	7.971	NE	NE
	SEM	20.08	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-33.2,49.1)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	17.370	9.443	7.927		
			SEM	3.767	3.932	3.806		
			95% CI	( 9.9,24.8)	( 1.7,17.2)	( 0.4,15.4)		
					Pr >  t			0.0381
		Week 16	n	70	52			
			LS Mean	19.191	7.470	11.721		
			SEM	3.864	4.273	4.145		
			95% CI	( 11.6,26.8)	( -0.9,15.9)	( 3.6,19.9)		
					Pr >  t			0.0049
		Week 24	n	61	37			
			LS Mean	18.450	10.272	8.178		
			SEM	3.975	4.639	4.568		
			95% CI	( 10.6,26.3)	( 1.1,19.4)	( -0.8,17.2)		
					Pr >  t			0.0740
		Week 32	n	48	33			
			LS Mean	11.294	2.914	8.379		
			SEM	4.200	4.763	4.858		
			95% CI	( 3.0,19.6)	( -6.5,12.3)	( -1.2,17.9)		
					Pr >  t			0.0851
		Week 40	n	42	31			
			LS Mean	10.909	4.893	6.015		
			SEM	4.314	4.834	5.030		
			95% CI	( 2.4,19.4)	( -4.6,14.4)	( -3.9,15.9)		
			Pr >  t			0.2322		
Week 48	n	40	25					
	LS Mean	7.331	6.243	1.088				
	SEM	4.359	5.086	5.310				
	95% CI	( -1.2,15.9)	( -3.8,16.2)	( -9.3,11.5)				
			Pr >  t			0.8377		
Week 56	n	35	20					
	LS Mean	7.810	6.295	1.515				
	SEM	4.484	5.398	5.713				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.0,16.6)	(-4.3,16.9)	(-9.7,12.7)
		Pr >  t			0.7909
	Week 64	n	29	18	
		LS Mean	9.154	4.803	4.351
		SEM	4.678	5.564	6.022
		95% CI	(-0.0,18.3)	(-6.1,15.7)	(-7.5,16.2)
		Pr >  t			0.4703
	Week 72	n	28	18	
		LS Mean	9.720	2.996	6.724
		SEM	4.720	5.559	6.052
		95% CI	( 0.4,19.0)	(-7.9,13.9)	(-5.2,18.6)
		Pr >  t			0.2669
	Week 84	n	27	17	
		LS Mean	5.238	12.755	-7.517
		SEM	4.790	5.653	6.171
		95% CI	(-4.2,14.7)	( 1.7,23.9)	(-19.6, 4.6)
		Pr >  t			0.2236
	Week 96	n	23	14	
		LS Mean	11.127	10.702	0.425
		SEM	4.981	5.988	6.633
		95% CI	( 1.3,20.9)	(-1.1,22.5)	(-12.6,13.4)
		Pr >  t			0.9489
	Week 108	n	19	12	
		LS Mean	7.403	7.986	-0.583
		SEM	5.274	6.289	7.108
		95% CI	(-3.0,17.8)	(-4.4,20.3)	(-14.5,13.4)
		Pr >  t			0.9346
	Week 120	n	18	8	
		LS Mean	9.989	5.463	4.525
		SEM	5.339	7.239	8.014
		95% CI	(-0.5,20.5)	(-8.7,19.7)	(-11.2,20.3)
		Pr >  t			0.5724
	Week 132	n	11	4	
		LS Mean	5.229	8.352	-3.123
		SEM	6.283	9.516	10.64
		95% CI	(-7.1,17.6)	(-10.3,27.0)	(-24.0,17.8)
		Pr >  t			0.7692
	Week 144	n	11	4	
		LS Mean	18.664	3.499	15.165
		SEM	6.264	9.522	10.65

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
>= 65 Years	Week 156	95% CI	( 6.4,31.0)	(-15.2,22.2)	( -5.7,36.1)
		Pr >  t			0.1547
		n	5	2	
	Week 168	LS Mean	-0.037	4.441	-4.479
		SEM	8.526	12.90	14.91
		95% CI	(-16.8,16.7)	(-20.9,29.8)	(-33.8,24.8)
	Week 180	Pr >  t			0.7640
		n	1	2	
		LS Mean	-13.55	4.441	-17.99
	Week 192	SEM	17.71	12.90	21.53
		95% CI	(-48.3,21.2)	(-20.9,29.8)	(-60.2,24.3)
		Pr >  t			0.4035
	Week 8	n		1	
		LS Mean	NE	2.489	NE
		SEM	NE	17.81	NE
	Week 16	95% CI	NE	(-32.5,37.5)	NE
		Pr >  t			NE
		n		1	
	Week 24	LS Mean	NE	2.489	NE
		SEM	NE	17.81	NE
		95% CI	NE	(-32.5,37.5)	NE
	Week 32	Pr >  t			NE
		n	63	71	
		LS Mean	12.096	-3.305	15.401
Week 8	SEM	6.347	6.326	4.441	
	95% CI	( -0.4,24.6)	(-15.8, 9.2)	( 6.6,24.2)	
	Pr >  t			0.0006	
Week 16	n	54	55		
	LS Mean	8.640	-4.978	13.618	
	SEM	6.479	6.420	4.729	
Week 24	95% CI	( -4.2,21.4)	(-17.7, 7.7)	( 4.3,22.9)	
	Pr >  t			0.0043	
	n	44	44		
Week 32	LS Mean	0.185	-5.503	5.688	
	SEM	6.584	6.519	5.031	
	95% CI	(-12.8,13.2)	(-18.4, 7.4)	( -4.2,15.6)	
Week 8	Pr >  t			0.2591	
	n	38	40		
	LS Mean	4.395	-1.751	6.146	
Week 16	SEM	6.704	6.609	5.212	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 40	95% CI	(-8.8,17.6)	(-14.8,11.3)	(-4.1,16.4)
	Pr >  t			0.2391
	n	33	31	
	LS Mean	1.850	-0.340	2.190
	SEM	6.794	6.798	5.522
Week 48	95% CI	(-11.6,15.3)	(-13.7,13.1)	(-8.7,13.0)
	Pr >  t			0.6918
	n	29	26	
	LS Mean	2.995	-1.317	4.312
	SEM	6.879	6.933	5.790
Week 56	95% CI	(-10.6,16.6)	(-15.0,12.3)	(-7.1,15.7)
	Pr >  t			0.4568
	n	24	25	
	LS Mean	-1.785	-3.229	1.444
	SEM	7.024	6.962	5.998
Week 64	95% CI	(-15.6,12.1)	(-17.0,10.5)	(-10.3,13.2)
	Pr >  t			0.8098
	n	18	24	
	LS Mean	2.370	1.458	0.912
	SEM	7.291	6.998	6.351
Week 72	95% CI	(-12.0,16.7)	(-12.3,15.2)	(-11.6,13.4)
	Pr >  t			0.8858
	n	20	17	
	LS Mean	-0.997	0.626	-1.622
	SEM	7.191	7.328	6.599
Week 84	95% CI	(-15.2,13.2)	(-13.8,15.1)	(-14.6,11.3)
	Pr >  t			0.8059
	n	13	16	
	LS Mean	4.902	-1.118	6.020
	SEM	7.672	7.395	7.193
Week 96	95% CI	(-10.2,20.0)	(-15.7,13.4)	(-8.1,20.1)
	Pr >  t			0.4029
	n	12	10	
	LS Mean	1.427	-2.252	3.679
	SEM	7.787	8.053	7.980
Week 108	95% CI	(-13.9,16.7)	(-18.1,13.6)	(-12.0,19.3)
	Pr >  t			0.6449
	n	7	9	
Week 108	LS Mean	-1.836	1.556	-3.392
	SEM	8.737	8.233	9.075

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.0,15.3)	(-14.6,17.7)	(-21.2,14.4)
		Pr >  t			0.7086
	Week 120	n	10	8	
		LS Mean	1.191	-1.544	2.735
		SEM	8.085	8.458	8.662
		95% CI	(-14.7,17.1)	(-18.2,15.1)	(-14.3,19.7)
		Pr >  t			0.7523
	Week 132	n	9	4	
		LS Mean	-3.528	5.933	-9.461
		SEM	8.246	10.21	10.51
		95% CI	(-19.7,12.7)	(-14.1,26.0)	(-30.1,11.2)
		Pr >  t			0.3684
	Week 144	n	4	1	
		LS Mean	16.990	-1.571	18.561
		SEM	10.22	17.35	18.53
		95% CI	(-3.1,37.1)	(-35.6,32.5)	(-17.8,54.9)
		Pr >  t			0.3169
	Week 156	n	5	1	
		LS Mean	-1.002	-1.571	0.569
		SEM	9.562	17.35	18.18
		95% CI	(-19.8,17.8)	(-35.6,32.5)	(-35.1,36.3)
		Pr >  t			0.9750
	Week 168	n	3		
		LS Mean	-1.008	NE	NE
		SEM	11.24	NE	NE
		95% CI	(-23.1,21.1)	NE	NE
		Pr >  t			NE
	Week 180	n	1		
		LS Mean	1.018	NE	NE
		SEM	17.34	NE	NE
		95% CI	(-33.0,35.1)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	34.358	NE	NE
		SEM	17.34	NE	NE
		95% CI	( 0.3,68.4)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	10.014	-2.183	12.197		
			SEM	5.856	5.555	5.088		
			95% CI	(-1.6,21.7)	(-13.2, 8.9)	( 2.1,22.3)		
					Pr >  t			0.0180
		Week 16	n	28	29			
			LS Mean	17.516	-1.913	19.429		
			SEM	5.911	5.817	5.359		
			95% CI	( 5.8,29.3)	(-13.5, 9.6)	( 8.8,30.0)		
					Pr >  t			0.0004
		Week 24	n	21	25			
			LS Mean	3.843	0.724	3.119		
			SEM	6.139	5.924	5.746		
			95% CI	(-8.3,16.0)	(-11.0,12.5)	(-8.2,14.5)		
					Pr >  t			0.5880
		Week 32	n	19	23			
			LS Mean	8.917	-3.247	12.164		
			SEM	6.228	6.000	5.933		
			95% CI	(-3.4,21.3)	(-15.2, 8.7)	( 0.5,23.9)		
					Pr >  t			0.0417
		Week 40	n	16	18			
			LS Mean	4.333	-0.668	5.001		
			SEM	6.397	6.292	6.352		
			95% CI	(-8.3,17.0)	(-13.1,11.8)	(-7.5,17.5)		
					Pr >  t			0.4320
		Week 48	n	16	17			
			LS Mean	2.250	-0.723	2.973		
			SEM	6.397	6.347	6.407		
95% CI	(-10.4,14.9)		(-13.3,11.8)	(-9.7,15.6)				
			Pr >  t			0.6430		
Week 56	n	12	14					
	LS Mean	3.415	-2.692	6.107				
	SEM	6.729	6.562	6.959				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.9,16.7)	(-15.7,10.3)	(-7.6,19.8)
	Pr >  t			0.3809
	n	12	11	
	LS Mean	8.971	-0.196	9.167
	SEM	6.729	6.882	7.259
Week 72	95% CI	(-4.3,22.3)	(-13.8,13.4)	(-5.1,23.5)
	Pr >  t			0.2077
	n	10	8	
	LS Mean	-3.434	0.117	-3.551
	SEM	6.985	7.396	7.983
Week 84	95% CI	(-17.2,10.4)	(-14.5,14.7)	(-19.3,12.2)
	Pr >  t			0.6567
	n	8	8	
	LS Mean	6.545	0.117	6.428
	SEM	7.414	7.396	8.310
Week 96	95% CI	(-8.1,21.2)	(-14.5,14.7)	(-9.9,22.8)
	Pr >  t			0.4398
	n	6	6	
	LS Mean	5.709	0.639	5.070
	SEM	7.991	7.981	9.329
Week 108	95% CI	(-10.0,21.5)	(-15.1,16.4)	(-13.3,23.4)
	Pr >  t			0.5872
	n	4	5	
	LS Mean	8.723	-5.092	13.815
	SEM	9.024	8.419	10.58
Week 120	95% CI	(-9.0,26.5)	(-21.7,11.5)	(-7.0,34.6)
	Pr >  t			0.1923
	n	4	4	
	LS Mean	17.056	3.640	13.416
	SEM	9.024	9.034	11.07
Week 132	95% CI	(-0.7,34.8)	(-14.1,21.4)	(-8.4,35.2)
	Pr >  t			0.2264
	n	3	2	
	LS Mean	22.209	-0.570	22.779
	SEM	9.940	11.54	13.84
Week 144	95% CI	( 2.7,41.8)	(-23.3,22.1)	(-4.4,50.0)
	Pr >  t			0.1007
	n	3	1	
	LS Mean	33.322	-1.177	34.500
	SEM	9.940	15.40	17.18



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Europe	Week 156	95% CI	( 13.8,52.9)	(-31.5,29.1)	( 0.7,68.3)
		Pr >  t			0.0454
		n	2	1	
	Week 168	LS Mean	2.766	-1.177	3.944
		SEM	11.54	15.40	18.16
		95% CI	(-19.9,25.5)	(-31.5,29.1)	(-31.8,39.7)
	Week 8	Pr >  t			0.8282
		n	1		
		LS Mean	8.642	NE	NE
	Week 16	SEM	15.37	NE	NE
		95% CI	(-21.6,38.9)	NE	NE
		Pr >  t			NE
	Week 8	n	66	68	
		LS Mean	21.934	9.475	12.459
		SEM	8.892	8.873	4.676
	Week 16	95% CI	( 4.3,39.5)	(-8.1,27.0)	( 3.2,21.7)
		Pr >  t			0.0082
		n	58	48	
	Week 24	LS Mean	19.197	6.445	12.752
		SEM	8.932	9.003	5.084
		95% CI	( 1.5,36.9)	(-11.4,24.3)	( 2.7,22.8)
	Week 32	Pr >  t			0.0127
		n	51	36	
		LS Mean	15.360	7.625	7.735
Week 40	SEM	8.981	9.136	5.448	
	95% CI	(-2.4,33.1)	(-10.4,25.7)	(-3.0,18.4)	
	Pr >  t			0.1565	
Week 48	n	43	30		
	LS Mean	11.168	7.639	3.529	
	SEM	9.117	9.320	5.759	
Week 8	95% CI	(-6.9,29.2)	(-10.8,26.1)	(-7.8,14.8)	
	Pr >  t			0.5404	
	n	37	25		
Week 16	LS Mean	10.207	4.994	5.213	
	SEM	9.188	9.447	6.067	
	95% CI	(-8.0,28.4)	(-13.7,23.6)	(-6.7,17.1)	
Week 24	Pr >  t			0.3906	
	n	33	21		
	LS Mean	10.937	11.560	-0.623	
Week 32	SEM	9.249	9.584	6.369	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-7.3,29.2)	(-7.4,30.5)	(-13.1,11.9)
	Pr >  t			0.9222
	n	29	20	
	LS Mean	5.539	6.172	-0.633
	SEM	9.323	9.627	6.542
Week 64	95% CI	(-12.9,24.0)	(-12.8,25.2)	(-13.5,12.2)
	Pr >  t			0.9229
	n	23	20	
	LS Mean	10.066	6.069	3.997
	SEM	9.479	9.629	6.764
Week 72	95% CI	(-8.6,28.8)	(-12.9,25.1)	(-9.3,17.3)
	Pr >  t			0.5548
	n	25	19	
	LS Mean	11.756	7.978	3.778
	SEM	9.420	9.673	6.744
Week 84	95% CI	(-6.8,30.4)	(-11.1,27.1)	(-9.5,17.0)
	Pr >  t			0.5755
	n	22	17	
	LS Mean	6.288	16.147	-9.859
	SEM	9.514	9.776	7.019
Week 96	95% CI	(-12.5,25.1)	(-3.1,35.4)	(-23.6, 3.9)
	Pr >  t			0.1606
	n	20	13	
	LS Mean	11.392	9.127	2.265
	SEM	9.591	10.07	7.523
Week 108	95% CI	(-7.5,30.3)	(-10.7,29.0)	(-12.5,17.0)
	Pr >  t			0.7635
	n	15	11	
	LS Mean	6.586	10.422	-3.836
	SEM	9.869	10.29	8.157
Week 120	95% CI	(-12.9,26.1)	(-9.9,30.7)	(-19.8,12.2)
	Pr >  t			0.6383
	n	16	8	
	LS Mean	7.006	3.684	3.322
	SEM	9.804	10.81	8.729
Week 132	95% CI	(-12.3,26.3)	(-17.6,25.0)	(-13.8,20.5)
	Pr >  t			0.7036
	n	12	3	
	LS Mean	-1.959	5.926	-7.885
	SEM	10.13	13.54	12.21

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-21.9,18.0)	(-20.7,32.5)	(-31.9,16.1)
		Pr >  t			0.5187
	Week 144	n	7	4	
		LS Mean	19.042	4.459	14.583
		SEM	11.02	12.53	11.90
		95% CI	(-2.7,40.7)	(-20.2,29.1)	(-8.8,37.9)
		Pr >  t			0.2208
	Week 156	n	5	2	
		LS Mean	2.528	5.230	-2.702
		SEM	11.81	15.36	15.45
		95% CI	(-20.7,25.8)	(-24.9,35.4)	(-33.0,27.6)
		Pr >  t			0.8613
	Week 168	n	2	2	
		LS Mean	-6.347	5.230	-11.58
		SEM	15.31	15.36	18.27
		95% CI	(-36.4,23.7)	(-24.9,35.4)	(-47.4,24.3)
		Pr >  t			0.5265
	Week 180	n		1	
		LS Mean	NE	3.127	NE
		SEM	NE	19.83	NE
		95% CI	NE	(-35.8,42.1)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	3.127	NE
		SEM	NE	19.83	NE
		95% CI	NE	(-35.8,42.1)	NE
		Pr >  t			NE
Latin America	Week 8	n	14	13	
		LS Mean	4.523	-8.189	12.712
		SEM	5.812	5.929	8.485
		95% CI	(-7.1,16.1)	(-20.0, 3.6)	(-4.2,29.6)
		Pr >  t			0.1384
	Week 16	n	13	12	
		LS Mean	-5.022	-2.716	-2.306
		SEM	5.976	6.190	8.780
		95% CI	(-16.9, 6.9)	(-15.0, 9.6)	(-19.8,15.2)
		Pr >  t			0.7935
	Week 24	n	12	10	
		LS Mean	3.290	2.334	0.956
		SEM	6.157	6.625	9.175

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-8.9,15.5)	(-10.8,15.5)	(-17.3,19.2)
	Pr >  t			0.9173
	n	9	10	
	LS Mean	6.788	-7.666	14.453
	SEM	6.910	6.625	9.678
Week 40	95% CI	(-6.9,20.5)	(-20.8, 5.5)	(-4.8,33.7)
	Pr >  t			0.1386
	n	7	10	
	LS Mean	16.011	-4.333	20.343
	SEM	7.683	6.625	10.27
Week 48	95% CI	( 0.8,31.2)	(-17.5, 8.8)	(-0.0,40.7)
	Pr >  t			0.0502
	n	7	7	
	LS Mean	-3.037	-11.17	8.138
	SEM	7.683	7.644	10.92
Week 56	95% CI	(-18.2,12.2)	(-26.3, 4.0)	(-13.5,29.8)
	Pr >  t			0.4577
	n	6	7	
	LS Mean	-3.696	-0.077	-3.620
	SEM	8.203	7.635	11.30
Week 64	95% CI	(-19.9,12.5)	(-15.2,15.0)	(-26.0,18.7)
	Pr >  t			0.7492
	n	4	7	
	LS Mean	-3.938	3.050	-6.988
	SEM	9.725	7.643	12.43
Week 72	95% CI	(-23.2,15.3)	(-12.1,18.2)	(-31.6,17.6)
	Pr >  t			0.5750
	n	4	4	
	LS Mean	4.395	-11.32	15.718
	SEM	9.725	9.665	13.75
Week 84	95% CI	(-14.8,23.6)	(-30.4, 7.8)	(-11.5,42.9)
	Pr >  t			0.2549
	n	4	5	
	LS Mean	2.806	-3.674	6.480
	SEM	9.713	8.791	13.17
Week 96	95% CI	(-16.4,22.0)	(-21.1,13.7)	(-19.5,32.5)
	Pr >  t			0.6234
	n	3	2	
	LS Mean	-2.819	-8.879	6.060
	SEM	11.04	13.22	17.27

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	(-24.6,19.0)	(-35.0,17.2)	(-28.1,40.2)
		Pr >  t			0.7262
		n	2	3	
	Week 120	LS Mean	-3.646	8.566	-12.21
		SEM	13.30	11.04	17.37
		95% CI	(-29.9,22.6)	(-13.2,30.4)	(-46.5,22.1)
	Week 120	Pr >  t			0.4830
		n	2	2	
		LS Mean	-4.235	-0.825	-3.410
	Week 132	SEM	13.25	13.25	18.75
		95% CI	(-30.4,22.0)	(-27.0,25.3)	(-40.5,33.6)
		Pr >  t			0.8560
	Week 132	n	1	2	
		LS Mean	-9.704	15.840	-25.54
		SEM	18.41	13.25	22.71
	Week 8	95% CI	(-46.1,26.7)	(-10.3,42.0)	(-70.4,19.3)
		Pr >  t			0.2624
		n	16	19	
	Week 16	LS Mean	15.070	10.344	4.726
		SEM	6.800	6.785	8.248
		95% CI	( 1.4,28.8)	( -3.3,24.0)	(-11.8,21.3)
	Week 16	Pr >  t			0.5693
		n	12	14	
		LS Mean	8.890	4.322	4.568
	Week 24	SEM	7.290	7.274	8.930
		95% CI	( -5.7,23.5)	(-10.2,18.9)	(-13.3,22.4)
		Pr >  t			0.6108
	Week 24	n	12	8	
LS Mean		6.133	-2.964	9.096	
SEM		7.293	8.349	9.777	
Week 32	95% CI	( -8.5,20.7)	(-19.6,13.6)	(-10.4,28.6)	
	Pr >  t			0.3550	
	n	9	7		
Week 32	LS Mean	12.475	10.399	2.076	
	SEM	7.782	8.597	10.34	
	95% CI	( -3.1,28.0)	( -6.7,27.5)	(-18.5,22.6)	
Week 40	Pr >  t			0.8413	
	n	9	7		
	LS Mean	3.931	19.923	-15.99	
		SEM	7.813	8.597	10.35

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-11.7,19.5)	( 2.8,37.0)	(-36.6, 4.6)
	Pr >  t			0.1259
	n	8	5	
	LS Mean	7.566	5.470	2.096
	SEM	8.023	9.336	11.13
Week 56	95% CI	( -8.4,23.6)	(-13.0,24.0)	(-20.0,24.2)
	Pr >  t			0.8510
	n	7	3	
	LS Mean	9.203	8.948	0.255
	SEM	8.275	10.88	12.62
Week 64	95% CI	( -7.3,25.7)	(-12.6,30.5)	(-24.7,25.2)
	Pr >  t			0.9839
	n	5	3	
	LS Mean	5.266	20.058	-14.79
	SEM	9.027	10.88	13.13
Week 72	95% CI	(-12.6,23.2)	( -1.5,41.6)	(-40.8,11.2)
	Pr >  t			0.2621
	n	5	3	
	LS Mean	7.333	9.234	-1.901
	SEM	8.999	10.85	13.08
Week 84	95% CI	(-10.5,25.2)	(-12.2,30.7)	(-27.8,24.0)
	Pr >  t			0.8847
	n	2	2	
	LS Mean	10.646	-5.709	16.355
	SEM	12.19	12.47	16.62
Week 96	95% CI	(-13.5,34.8)	(-30.4,18.9)	(-16.5,49.2)
	Pr >  t			0.3267
	n	3	2	
	LS Mean	7.446	27.626	-20.18
	SEM	10.49	12.47	15.45
Week 108	95% CI	(-13.3,28.2)	( 3.0,52.3)	(-50.7,10.4)
	Pr >  t			0.1937
	n	1	2	
	LS Mean	9.475	10.956	-1.481
	SEM	16.03	12.47	19.59
Week 120	95% CI	(-22.2,41.2)	(-13.7,35.6)	(-40.2,37.3)
	Pr >  t			0.9398
	n	3	2	
	LS Mean	7.446	10.956	-3.510
	SEM	10.49	12.47	15.45

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.3,28.2)	(-13.7,35.6)	(-34.1,27.0)
		Pr >  t			0.8207
	Week 132	n	1	1	
		LS Mean	5.329	14.700	-9.371
		SEM	16.02	16.24	22.21
		95% CI	(-26.3,37.0)	(-17.4,46.8)	(-53.3,34.6)
		Pr >  t			0.6737
	Week 144	n	2		
		LS Mean	6.432	NE	NE
		SEM	12.10	NE	NE
		95% CI	(-17.5,30.4)	NE	NE
		Pr >  t			NE
	Week 156	n	1		
		LS Mean	5.329	NE	NE
		SEM	16.02	NE	NE
		95% CI	(-26.3,37.0)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	5.329	NE	NE
		SEM	16.02	NE	NE
		95% CI	(-26.3,37.0)	NE	NE
		Pr >  t			NE
	Week 180	n	1		
		LS Mean	5.329	NE	NE
		SEM	16.02	NE	NE
		95% CI	(-26.3,37.0)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	38.669	NE	NE
		SEM	16.02	NE	NE
		95% CI	( 7.0,70.3)	NE	NE
		Pr >  t			NE
Other	Week 8	n	16	5	
		LS Mean	20.923	10.097	10.826
		SEM	7.644	11.75	13.12
		95% CI	( 5.2,36.6)	(-13.8,34.0)	(-15.9,37.5)
		Pr >  t			0.4152
	Week 16	n	13	4	
		LS Mean	28.618	4.036	24.583
		SEM	8.190	13.32	14.39

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	( 11.9,45.3)	(-22.8,30.9)	( -4.5,53.7)
	Pr >  t			0.0954
Week 24	n	9	2	
	LS Mean	33.542	-2.665	36.207
	SEM	9.170	16.99	18.20
	95% CI	( 15.1,52.0)	(-36.6,31.3)	( -0.2,72.6)
	Pr >  t			0.0510
Week 32	n	6	3	
	LS Mean	1.806	-3.536	5.342
	SEM	10.52	14.73	16.80
	95% CI	(-19.2,22.8)	(-33.1,26.0)	(-28.3,39.0)
	Pr >  t			0.7518
Week 40	n	6	2	
	LS Mean	6.941	-2.665	9.606
	SEM	10.66	16.99	18.87
	95% CI	(-14.4,28.2)	(-36.6,31.3)	(-28.1,47.3)
	Pr >  t			0.6123
Week 48	n	5	1	
	LS Mean	5.343	-5.276	10.619
	SEM	11.25	22.48	24.24
	95% CI	(-17.1,27.8)	(-50.0,39.5)	(-37.6,58.9)
	Pr >  t			0.6625
Week 56	n	5	1	
	LS Mean	12.009	-5.276	17.285
	SEM	11.25	22.48	24.24
	95% CI	(-10.4,34.5)	(-50.0,39.5)	(-31.0,65.5)
	Pr >  t			0.4779
Week 64	n	3	1	
	LS Mean	1.861	-5.276	7.137
	SEM	13.40	22.48	25.31
	95% CI	(-24.8,28.5)	(-50.0,39.5)	(-43.2,57.5)
	Pr >  t			0.7787
Week 72	n	4	1	
	LS Mean	3.874	-5.276	9.150
	SEM	12.14	22.48	24.67
	95% CI	(-20.3,28.1)	(-50.0,39.5)	(-40.0,58.3)
	Pr >  t			0.7117
Week 84	n	4	1	
	LS Mean	3.874	-5.276	9.150
	SEM	12.14	22.48	24.67



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-20.3,28.1)	(-50.0,39.5)	(-40.0,58.3)
	Pr >  t			0.7117
	n	3	1	
	LS Mean	12.971	-5.276	18.247
	SEM	13.40	22.48	25.31
Week 108	95% CI	(-13.7,39.6)	(-50.0,39.5)	(-32.1,68.6)
	Pr >  t			0.4731
	n	4		
	LS Mean	3.874	NE	NE
	SEM	12.14	NE	NE
Week 120	95% CI	(-20.3,28.1)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	12.971	NE	NE
	SEM	13.40	NE	NE
Week 132	95% CI	(-13.7,39.6)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	12.971	NE	NE
	SEM	13.40	NE	NE
Week 144	95% CI	(-13.7,39.6)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	14.997	NE	NE
	SEM	13.41	NE	NE
Week 156	95% CI	(-11.7,41.7)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	2.036	NE	NE
	SEM	15.55	NE	NE
	95% CI	(-28.9,33.0)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Endocrine Status (L) Primary resistant		Week 8	n	21	16			
			LS Mean	11.286	2.190	9.095		
			SEM	7.006	8.256	9.045		
			95% CI	(-2.9,25.5)	(-14.5,18.9)	(-9.0,27.2)		
					Pr >  t			0.3192
		Week 16	n	17	10			
			LS Mean	13.341	5.008	8.333		
			SEM	7.482	9.378	10.05		
			95% CI	(-1.7,28.4)	(-13.8,23.8)	(-11.7,28.4)		
					Pr >  t			0.4098
		Week 24	n	9	5			
			LS Mean	10.303	13.891	-3.588		
			SEM	8.629	11.38	12.92		
			95% CI	(-6.9,27.5)	(-8.7,36.5)	(-29.2,22.0)		
					Pr >  t			0.7818
		Week 32	n	8	4			
			LS Mean	4.103	6.697	-2.594		
			SEM	8.918	12.18	13.85		
			95% CI	(-13.7,21.9)	(-17.5,30.9)	(-30.1,24.9)		
					Pr >  t			0.8518
		Week 40	n	5	4			
			LS Mean	1.279	6.697	-5.418		
			SEM	10.19	12.18	14.81		
			95% CI	(-18.9,21.5)	(-17.5,30.9)	(-34.8,23.9)		
			Pr >  t			0.7152		
Week 48	n	5	3					
	LS Mean	7.947	-3.596	11.543				
	SEM	10.19	13.34	15.78				
	95% CI	(-12.3,28.2)	(-30.0,22.8)	(-19.7,42.8)				
			Pr >  t			0.4659		
Week 56	n	4	3					
	LS Mean	9.816	7.514	2.302				
	SEM	10.94	13.34	16.32				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-11.9,31.5)	(-18.9,34.0)	(-30.0,34.6)
		Pr >  t			0.8881
		n	4	3	
		LS Mean	9.816	7.514	2.302
		SEM	10.94	13.34	16.32
Week 72		95% CI	(-11.9,31.5)	(-18.9,34.0)	(-30.0,34.6)
		Pr >  t			0.8881
		n	4	3	
		LS Mean	1.484	7.514	-6.031
		SEM	10.94	13.34	16.32
Week 84		95% CI	(-20.2,23.2)	(-18.9,34.0)	(-38.4,26.3)
		Pr >  t			0.7124
		n	2	3	
		LS Mean	22.686	7.514	15.172
		SEM	14.37	13.34	18.65
Week 96		95% CI	(-5.8,51.2)	(-18.9,34.0)	(-21.8,52.1)
		Pr >  t			0.4176
		n	1	3	
		LS Mean	6.978	18.627	-11.65
		SEM	19.11	13.34	22.76
Week 108		95% CI	(-31.0,44.9)	(-7.8,45.1)	(-56.8,33.5)
		Pr >  t			0.6098
		n		2	
		LS Mean	NE	25.014	NE
		SEM	NE	15.26	NE
Week 120		95% CI	NE	(-5.2,55.2)	NE
		Pr >  t			NE
		n	1	1	
		LS Mean	6.978	14.483	-7.505
		SEM	19.11	19.89	27.14
Week 132		95% CI	(-31.0,44.9)	(-25.0,53.9)	(-61.4,46.4)
		Pr >  t			0.7828
		n		1	
		LS Mean	NE	14.483	NE
		SEM	NE	19.89	NE
Week 144		95% CI	NE	(-25.0,53.9)	NE
		Pr >  t			NE
		n	1		
		LS Mean	6.978	NE	NE
		SEM	19.11	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Secondary resistant	Week 8	95% CI	(-31.0,44.9)	NE	NE
		Pr >  t			NE
		n	98	106	
	Week 16	LS Mean	15.522	4.411	11.110
		SEM	3.993	3.983	3.362
		95% CI	( 7.7,23.4)	( -3.4,12.3)	( 4.5,17.7)
	Week 24	Pr >  t			0.0010
		n	83	81	
		LS Mean	14.940	2.426	12.514
	Week 32	SEM	4.097	4.173	3.651
		95% CI	( 6.9,23.0)	( -5.8,10.6)	( 5.3,19.7)
		Pr >  t			0.0007
	Week 40	n	75	62	
		LS Mean	12.035	2.723	9.312
		SEM	4.172	4.365	3.904
	Week 48	95% CI	( 3.8,20.2)	( -5.9,11.3)	( 1.6,17.0)
		Pr >  t			0.0174
		n	59	56	
	Week 56	LS Mean	9.896	2.095	7.802
		SEM	4.378	4.432	4.141
		95% CI	( 1.3,18.5)	( -6.6,10.8)	( -0.3,15.9)
	Week 64	Pr >  t			0.0600
		n	52	48	
		LS Mean	9.238	2.298	6.940
Week 8	SEM	4.465	4.562	4.351	
	95% CI	( 0.5,18.0)	( -6.7,11.3)	( -1.6,15.5)	
	Pr >  t			0.1111	
Week 16	n	47	37		
	LS Mean	7.005	3.995	3.010	
	SEM	4.539	4.778	4.650	
Week 24	95% CI	( -1.9,15.9)	( -5.4,13.4)	( -6.1,12.1)	
	Pr >  t			0.5175	
	n	41	31		
Week 32	LS Mean	3.765	3.751	0.014	
	SEM	4.647	4.951	4.932	
	95% CI	( -5.4,12.9)	( -6.0,13.5)	( -9.7, 9.7)	
Week 40	Pr >  t			0.9977	
	n	32	28		
	LS Mean	6.529	5.689	0.841	
Week 48	SEM	4.873	5.063	5.252	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 72	95% CI	(-3.0,16.1)	(-4.3,15.6)	(-9.5,11.1)	
	Pr >  t			0.8729	
	n	29	22		
	LS Mean	9.081	0.341	8.739	
	SEM	4.980	5.356	5.629	
Week 84	95% CI	(-0.7,18.9)	(-10.2,10.9)	(-2.3,19.8)	
	Pr >  t			0.1208	
	n	26	21		
	LS Mean	2.345	3.416	-1.071	
	SEM	5.098	5.418	5.793	
Week 96	95% CI	(-7.7,12.4)	(-7.2,14.1)	(-12.4,10.3)	
	Pr >  t			0.8534	
	n	23	14		
	LS Mean	4.491	6.128	-1.637	
	SEM	5.250	6.059	6.517	
Week 108	95% CI	(-5.8,14.8)	(-5.8,18.0)	(-14.4,11.2)	
	Pr >  t			0.8018	
	n	18	13		
	LS Mean	5.764	5.739	0.025	
	SEM	5.595	6.198	6.922	
Week 120	95% CI	(-5.2,16.7)	(-6.4,17.9)	(-13.6,13.6)	
	Pr >  t			0.9971	
	n	19	10		
	LS Mean	7.808	4.017	3.791	
	SEM	5.518	6.745	7.356	
Week 132	95% CI	(-3.0,18.6)	(-9.2,17.3)	(-10.6,18.2)	
	Pr >  t			0.6064	
	n	13	4		
	LS Mean	3.320	11.599	-8.279	
	SEM	6.146	9.545	10.35	
Week 144	95% CI	(-8.7,15.4)	(-7.1,30.3)	(-28.6,12.0)	
	Pr >  t			0.4238	
	n	8	1		
	LS Mean	19.041	-0.910	19.951	
	SEM	7.239	17.86	18.69	
Week 156	95% CI	( 4.8,33.2)	(-36.0,34.1)	(-16.7,56.6)	
	Pr >  t			0.2862	
	n	5	1		
	LS Mean	1.124	-0.910	2.034	
	SEM	8.671	17.86	19.29	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Sensitive	Week 168	95% CI	(-15.9,18.1)	(-36.0,34.1)	(-35.8,39.9)
		Pr >  t			0.9161
		n	3	1	
	Week 180	LS Mean	-3.391	-0.910	-2.481
		SEM	10.74	17.86	20.31
		95% CI	(-24.5,17.7)	(-36.0,34.1)	(-42.3,37.4)
	Week 180	Pr >  t			0.9028
		n	1	1	
		LS Mean	6.298	-0.910	7.209
	Week 192	SEM	17.78	17.86	24.76
		95% CI	(-28.6,41.2)	(-36.0,34.1)	(-41.4,55.8)
		Pr >  t			0.7710
	Week 192	n	1	1	
		LS Mean	39.638	-0.910	40.549
		SEM	17.78	17.86	24.76
	Week 8	95% CI	( 4.7,74.5)	(-36.0,34.1)	( -8.1,89.2)
		Pr >  t			0.1019
		n	17	16	
	Week 16	LS Mean	12.440	5.673	6.767
		SEM	6.076	6.336	8.602
		95% CI	( 0.3,24.6)	( -7.0,18.4)	(-10.5,24.0)
	Week 16	Pr >  t			0.4348
		n	18	14	
		LS Mean	7.748	-1.286	9.033
Week 24	SEM	5.988	6.566	8.741	
	95% CI	( -4.3,19.8)	(-14.4,11.9)	( -8.5,26.5)	
	Pr >  t			0.3057	
Week 24	n	16	13		
	LS Mean	6.369	-1.474	7.843	
	SEM	6.173	6.679	8.943	
Week 32	95% CI	( -6.0,18.7)	(-14.8,11.9)	(-10.0,25.7)	
	Pr >  t			0.3839	
	n	15	13		
Week 32	LS Mean	4.331	-1.453	5.784	
	SEM	6.255	6.694	9.020	
	95% CI	( -8.2,16.8)	(-14.8,11.9)	(-12.2,23.8)	
Week 40	Pr >  t			0.5237	
	n	14	10		
	LS Mean	1.771	6.157	-4.385	
		SEM	6.370	7.079	9.380

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48		95% CI	(-11.0,14.5)	(-7.9,20.3)	(-23.1,14.3)
		Pr >  t			0.6415
		n	14	11	
		LS Mean	1.772	2.629	-0.857
		SEM	6.370	6.938	9.272
Week 56		95% CI	(-11.0,14.5)	(-11.2,16.5)	(-19.3,17.6)
		Pr >  t			0.9266
		n	11	11	
		LS Mean	1.324	-3.431	4.756
		SEM	6.713	6.938	9.518
Week 64		95% CI	(-12.0,14.7)	(-17.3,10.4)	(-14.2,23.7)
		Pr >  t			0.6187
		n	8	11	
		LS Mean	3.610	-0.401	4.011
		SEM	7.252	6.938	9.916
Week 72		95% CI	(-10.8,18.0)	(-14.2,13.4)	(-15.7,23.7)
		Pr >  t			0.6868
		n	11	10	
		LS Mean	1.324	5.599	-4.274
		SEM	6.713	7.086	9.625
Week 84		95% CI	(-12.0,14.7)	(-8.5,19.7)	(-23.4,14.9)
		Pr >  t			0.6582
		n	9	9	
		LS Mean	3.360	13.897	-10.54
		SEM	7.038	7.260	9.991
Week 96		95% CI	(-10.6,17.3)	(-0.5,28.3)	(-30.4, 9.3)
		Pr >  t			0.2943
		n	8	7	
		LS Mean	8.621	-1.720	10.341
		SEM	7.256	7.727	10.49
Week 108		95% CI	(-5.8,23.0)	(-17.0,13.6)	(-10.4,31.1)
		Pr >  t			0.3262
		n	7	6	
		LS Mean	-1.235	-1.679	0.444
		SEM	7.522	8.067	10.92
Week 120		95% CI	(-16.1,13.7)	(-17.7,14.3)	(-21.2,22.1)
		Pr >  t			0.9676
		n	6	5	
		LS Mean	-0.541	-2.420	1.879
		SEM	7.867	8.526	11.49



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 132	95% CI	(-16.1,15.0)	(-19.3,14.4)	(-20.8,24.6)
	Pr >  t			0.8703
	n	5	3	
	LS Mean	-0.887	1.326	-2.214
	SEM	8.314	10.06	12.95
Week 144	95% CI	(-17.3,15.5)	(-18.5,21.2)	(-27.8,23.3)
	Pr >  t			0.8645
	n	5	4	
	LS Mean	12.447	-0.635	13.082
	SEM	8.314	9.127	12.24
Week 156	95% CI	(-4.0,28.9)	(-18.7,17.4)	(-11.1,37.2)
	Pr >  t			0.2867
	n	4	2	
	LS Mean	-0.915	1.264	-2.179
	SEM	8.938	11.72	14.65
Week 168	95% CI	(-18.6,16.7)	(-21.8,24.3)	(-31.1,26.7)
	Pr >  t			0.8819
	n	1	1	
	LS Mean	3.647	1.280	2.367
	SEM	15.55	15.66	22.02
	95% CI	(-27.0,34.2)	(-29.6,32.1)	(-41.0,45.7)
	Pr >  t			0.9145

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	2.989	-5.993	8.982		
			SEM	10.98	11.26	4.132		
			95% CI	(-18.7,24.7)	(-28.3,16.3)	( 0.8,17.1)		
					Pr >  t			0.0306
		Week 16	n	69	55			
			LS Mean	3.491	-9.079	12.570		
			SEM	10.99	11.34	4.398		
			95% CI	(-18.2,25.2)	(-31.5,13.3)	( 3.9,21.2)		
					Pr >  t			0.0046
		Week 24	n	54	46			
			LS Mean	-0.271	-7.280	7.008		
			SEM	11.03	11.40	4.695		
			95% CI	(-22.1,21.5)	(-29.8,15.2)	( -2.2,16.2)		
					Pr >  t			0.1364
		Week 32	n	49	41			
			LS Mean	-1.382	-10.09	8.709		
			SEM	11.14	11.43	4.855		
			95% CI	(-23.4,20.6)	(-32.7,12.5)	( -0.8,18.3)		
					Pr >  t			0.0735
		Week 40	n	40	33			
			LS Mean	-2.327	-7.932	5.605		
			SEM	11.20	11.52	5.181		
			95% CI	(-24.5,19.8)	(-30.7,14.8)	( -4.6,15.8)		
					Pr >  t			0.2799
		Week 48	n	38	28			
			LS Mean	-1.757	-9.555	7.798		
			SEM	11.22	11.59	5.378		
95% CI	(-23.9,20.4)		(-32.4,13.3)	( -2.8,18.4)				
			Pr >  t			0.1476		
Week 56	n	32	28					
	LS Mean	-6.015	-9.328	3.312				
	SEM	11.29	11.59	5.515				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-28.3,16.3)	(-32.2,13.6)	(-7.5,14.1)
	Pr >  t			0.5484
	n	23	26	
	LS Mean	-1.071	-8.949	7.878
	SEM	11.44	11.62	5.897
Week 72	95% CI	(-23.7,21.5)	(-31.9,14.0)	(-3.7,19.5)
	Pr >  t			0.1821
	n	27	25	
	LS Mean	-4.526	-7.795	3.269
	SEM	11.36	11.64	5.778
Week 84	95% CI	(-27.0,17.9)	(-30.8,15.2)	(-8.1,14.6)
	Pr >  t			0.5717
	n	23	22	
	LS Mean	-6.899	-5.928	-0.971
	SEM	11.44	11.71	6.068
Week 96	95% CI	(-29.5,15.7)	(-29.0,17.2)	(-12.9,10.9)
	Pr >  t			0.8729
	n	20	16	
	LS Mean	-3.080	-9.262	6.182
	SEM	11.52	11.92	6.602
Week 108	95% CI	(-25.8,19.7)	(-32.8,14.3)	(-6.8,19.1)
	Pr >  t			0.3494
	n	20	14	
	LS Mean	-8.102	-9.051	0.950
	SEM	11.52	12.02	6.795
Week 120	95% CI	(-30.9,14.6)	(-32.8,14.7)	(-12.4,14.3)
	Pr >  t			0.8889
	n	17	11	
	LS Mean	-4.222	-5.571	1.349
	SEM	11.63	12.25	7.362
Week 132	95% CI	(-27.2,18.7)	(-29.7,18.6)	(-13.1,15.8)
	Pr >  t			0.8547
	n	13	6	
	LS Mean	-11.48	-4.254	-7.226
	SEM	11.85	13.08	8.970
Week 144	95% CI	(-34.9,11.9)	(-30.0,21.5)	(-24.8,10.4)
	Pr >  t			0.4207
	n	10	5	
	LS Mean	9.974	-10.90	20.874
	SEM	12.12	13.44	9.816

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.9,33.9)	(-37.4,15.6)	(-1.6,40.1)
		Pr >  t			0.0337
	Week 156	n	7	3	
		LS Mean	-10.31	-10.01	-0.299
		SEM	12.60	14.76	12.06
		95% CI	(-35.1,14.5)	(-39.0,19.0)	(-24.0,23.4)
		Pr >  t			0.9802
	Week 168	n	3	2	
		LS Mean	-14.28	-10.78	-3.503
		SEM	14.55	16.26	15.65
		95% CI	(-42.9,14.3)	(-42.7,21.2)	(-34.2,27.2)
		Pr >  t			0.8230
	Week 180	n		1	
		LS Mean	NE	-12.65	NE
		SEM	NE	20.08	NE
		95% CI	NE	(-52.1,26.8)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-12.65	NE
		SEM	NE	20.08	NE
		95% CI	NE	(-52.1,26.8)	NE
		Pr >  t			NE
Second Line	Week 8	n	66	67	
		LS Mean	18.301	4.059	14.242
		SEM	3.756	3.760	4.107
		95% CI	(10.9,25.7)	(-3.4,11.5)	(6.2,22.3)
		Pr >  t			0.0006
	Week 16	n	54	52	
		LS Mean	17.578	3.048	14.530
		SEM	3.960	4.057	4.482
		95% CI	(9.8,25.4)	(-4.9,11.0)	(5.7,23.3)
		Pr >  t			0.0013
	Week 24	n	49	35	
		LS Mean	13.744	3.348	10.396
		SEM	4.067	4.473	4.924
		95% CI	(5.7,21.8)	(-5.5,12.1)	(0.7,20.1)
		Pr >  t			0.0354
	Week 32	n	36	32	
		LS Mean	9.539	4.019	5.520
		SEM	4.392	4.591	5.265

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	( 0.9,18.2)	( -5.0,13.0)	( -4.8,15.9)
	Pr >  t			0.2950
Week 40	n	33	29	
	LS Mean	8.359	4.531	3.828
	SEM	4.483	4.732	5.446
	95% CI	( -0.5,17.2)	( -4.8,13.8)	( -6.9,14.5)
	Pr >  t			0.4824
Week 48	n	29	23	
	LS Mean	3.703	6.731	-3.029
	SEM	4.628	5.025	5.820
	95% CI	( -5.4,12.8)	( -3.1,16.6)	( -14.5, 8.4)
	Pr >  t			0.6030
Week 56	n	25	17	
	LS Mean	3.945	4.563	-0.618
	SEM	4.802	5.482	6.360
	95% CI	( -5.5,13.4)	( -6.2,15.3)	( -13.1,11.9)
	Pr >  t			0.9226
Week 64	n	22	16	
	LS Mean	5.309	9.155	-3.846
	SEM	4.970	5.587	6.577
	95% CI	( -4.5,15.1)	( -1.8,20.1)	( -16.8, 9.1)
	Pr >  t			0.5589
Week 72	n	20	10	
	LS Mean	6.090	1.835	4.255
	SEM	5.107	6.536	7.495
	95% CI	( -3.9,16.1)	( -11.0,14.7)	( -10.5,19.0)
	Pr >  t			0.5704
Week 84	n	16	11	
	LS Mean	7.172	11.022	-3.850
	SEM	5.484	6.321	7.562
	95% CI	( -3.6,17.9)	( -1.4,23.4)	( -18.7,11.0)
	Pr >  t			0.6108
Week 96	n	15	8	
	LS Mean	8.688	13.658	-4.970
	SEM	5.589	7.085	8.289
	95% CI	( -2.3,19.7)	( -0.3,27.6)	( -21.2,11.3)
	Pr >  t			0.5489
Week 108	n	6	7	
	LS Mean	10.319	13.397	-3.078
	SEM	7.822	7.454	10.19

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-5.0,25.7)	(-1.2,28.0)	(-23.1,16.9)
	Pr >  t			0.7628
	n	11	5	
	LS Mean	8.131	-1.987	10.117
	SEM	6.216	8.522	9.928
Week 132	95% CI	(-4.1,20.3)	(-18.7,14.7)	(-9.4,29.6)
	Pr >  t			0.3085
	n	7	2	
	LS Mean	8.498	11.969	-3.471
	SEM	7.355	12.72	14.25
Week 144	95% CI	(-5.9,22.9)	(-13.0,36.9)	(-31.4,24.5)
	Pr >  t			0.8076
	n	5		
	LS Mean	12.296	NE	NE
	SEM	8.407	NE	NE
Week 156	95% CI	(-4.2,28.8)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	2.154	NE	NE
	SEM	10.51	NE	NE
Week 168	95% CI	(-18.5,22.8)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	6.961	NE	NE
	SEM	17.53	NE	NE
Week 180	95% CI	(-27.5,41.4)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	6.961	NE	NE
	SEM	17.53	NE	NE
Week 192	95% CI	(-27.5,41.4)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	40.301	NE	NE
	SEM	17.53	NE	NE
	95% CI	( 5.9,74.7)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	25.022	10.710	14.312		
			SEM	5.639	5.495	4.204		
			95% CI	( 13.9,36.1)	( -0.1,21.5)	( 6.0,22.6)		
					Pr >  t			0.0008
		Week 16	n	60	51			
			LS Mean	20.199	9.508	10.691		
			SEM	5.731	5.750	4.447		
			95% CI	( 8.9,31.5)	( -1.8,20.8)	( 1.9,19.4)		
					Pr >  t			0.0168
		Week 24	n	51	42			
			LS Mean	16.535	9.553	6.982		
			SEM	5.807	5.860	4.708		
			95% CI	( 5.1,28.0)	( -2.0,21.1)	( -2.3,16.2)		
					Pr >  t			0.1390
		Week 32	n	46	36			
			LS Mean	17.963	8.676	9.287		
			SEM	5.897	6.003	4.907		
			95% CI	( 6.3,29.6)	( -3.1,20.5)	( -0.4,18.9)		
					Pr >  t			0.0592
		Week 40	n	40	33			
			LS Mean	15.204	9.357	5.847		
			SEM	5.982	6.066	5.079		
			95% CI	( 3.4,27.0)	( -2.6,21.3)	( -4.1,15.8)		
			Pr >  t			0.2503		
Week 48	n	37	28					
	LS Mean	12.503	9.545	2.957				
	SEM	6.028	6.192	5.284				
	95% CI	( 0.6,24.4)	( -2.6,21.7)	( -7.4,13.3)				
			Pr >  t			0.5760		
Week 56	n	33	23					
	LS Mean	12.231	9.405	2.825				
	SEM	6.106	6.364	5.572				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 64	95% CI	( 0.2,24.3)	( -3.1,21.9)	( -8.1,13.8)
	Pr >  t			0.6124
	n	26	20	
	LS Mean	12.379	9.305	3.074
	SEM	6.284	6.505	5.922
Week 72	95% CI	( 0.0,24.7)	( -3.5,22.1)	( -8.6,14.7)
	Pr >  t			0.6039
	n	28	17	
	LS Mean	13.859	9.450	4.409
	SEM	6.226	6.685	6.056
Week 84	95% CI	( 1.6,26.1)	( -3.7,22.6)	( -7.5,16.3)
	Pr >  t			0.4669
	n	23	17	
	LS Mean	14.750	9.391	5.360
	SEM	6.389	6.688	6.228
Week 96	95% CI	( 2.2,27.3)	( -3.8,22.5)	( -6.9,17.6)
	Pr >  t			0.3898
	n	23	11	
	LS Mean	13.296	8.693	4.603
	SEM	6.390	7.302	6.883
Week 108	95% CI	( 0.7,25.9)	( -5.7,23.0)	( -8.9,18.1)
	Pr >  t			0.5038
	n	15	13	
	LS Mean	10.776	9.789	0.987
	SEM	6.858	7.042	7.060
Week 120	95% CI	( -2.7,24.3)	( -4.1,23.6)	( -12.9,14.8)
	Pr >  t			0.8888
	n	16	9	
	LS Mean	16.097	6.767	9.330
	SEM	6.779	7.661	7.603
Week 132	95% CI	( 2.8,29.4)	( -8.3,21.8)	( -5.6,24.3)
	Pr >  t			0.2202
	n	14	5	
	LS Mean	7.605	11.612	-4.007
	SEM	6.946	9.057	9.136
Week 144	95% CI	( -6.1,21.3)	( -6.2,29.4)	( -21.9,13.9)
	Pr >  t			0.6611
	n	8	3	
	LS Mean	12.896	7.557	5.339
	SEM	7.894	10.82	11.51

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-2.6,28.4)	(-13.7,28.8)	(-17.3,27.9)
		Pr >  t			0.6429
		n	7	2	
	Week 168	LS Mean	7.461	6.753	0.708
		SEM	8.183	12.67	13.45
		95% CI	(-8.6,23.5)	(-18.1,31.6)	(-25.7,27.1)
	Week 180	Pr >  t			0.9580
		n	4	2	
		LS Mean	5.521	6.753	-1.232
	Week 192	SEM	9.742	12.67	14.45
		95% CI	(-13.6,24.6)	(-18.1,31.6)	(-29.6,27.1)
		Pr >  t			0.9321
	Week 8	n	1	1	
		LS Mean	12.224	4.849	7.375
		SEM	17.04	17.05	23.11
	Week 16	95% CI	(-21.2,45.7)	(-28.6,38.3)	(-38.0,52.7)
		Pr >  t			0.7497
		n	1	1	
	Week 24	LS Mean	45.564	4.849	40.715
		SEM	17.04	17.05	23.11
		95% CI	(12.1,79.0)	(-28.6,38.3)	(-4.7,86.1)
	Week 32	Pr >  t			0.0785
		n	18	17	
		LS Mean	14.143	6.288	7.855
Week 8	SEM	5.443	5.741	7.896	
	95% CI	(3.3,24.9)	(-5.1,17.7)	(-7.8,23.5)	
	Pr >  t			0.3223	
Week 16	n	17	11		
	LS Mean	20.539	2.856	17.683	
	SEM	5.580	6.959	8.922	
Week 24	95% CI	(9.5,31.6)	(-10.9,16.6)	(0.0,35.4)	
	Pr >  t			0.0499	
	n	15	5		
Week 32	LS Mean	13.588	6.509	7.079	
	SEM	5.883	9.785	11.41	
	95% CI	(1.9,25.2)	(-12.8,25.8)	(-15.5,29.6)	
Week 8	Pr >  t			0.5360	
	n	13	5		
	LS Mean	4.543	-0.157	4.699	
Week 16	SEM	6.252	9.785	11.62	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-7.8,16.9)	(-19.5,19.2)	(-18.3,27.7)	
	Pr >  t			0.6865	
	n	11	5		
	LS Mean	16.830	6.509	10.321	
	SEM	6.690	9.785	11.86	
Week 48	95% CI	( 3.6,30.1)	(-12.8,25.8)	(-13.1,33.8)	
	Pr >  t			0.3856	
	n	11	2		
	LS Mean	16.820	-1.015	17.835	
	SEM	6.694	14.54	16.01	
Week 56	95% CI	( 3.6,30.1)	(-29.7,27.7)	(-13.8,49.4)	
	Pr >  t			0.2669	
	n	8	2		
	LS Mean	5.102	-1.015	6.118	
	SEM	7.605	14.54	16.41	
Week 64	95% CI	(-9.9,20.1)	(-29.7,27.7)	(-26.3,38.5)	
	Pr >  t			0.7098	
	n	7	3		
	LS Mean	11.597	-0.969	12.566	
	SEM	8.025	12.19	14.59	
Week 72	95% CI	(-4.2,27.4)	(-25.0,23.1)	(-16.2,41.4)	
	Pr >  t			0.3904	
	n	7	3		
	LS Mean	3.920	-0.969	4.889	
	SEM	8.044	12.19	14.60	
Week 84	95% CI	(-12.0,19.8)	(-25.0,23.1)	(-23.9,33.7)	
	Pr >  t			0.7382	
	n	7	2		
	LS Mean	-0.842	15.650	-16.49	
	SEM	8.044	14.54	16.62	
Week 96	95% CI	(-16.7,15.0)	(-13.1,44.4)	(-49.3,16.3)	
	Pr >  t			0.3225	
	n	6	3		
	LS Mean	8.511	-0.969	9.480	
	SEM	8.572	12.19	14.90	
Week 108	95% CI	(-8.4,25.4)	(-25.0,23.1)	(-19.9,38.9)	
	Pr >  t			0.5255	
	n	7	2		
	LS Mean	3.919	15.166	-11.25	
	SEM	8.044	14.52	16.60	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-12.0,19.8)	(-13.5,43.8)	(-44.0,21.5)
		Pr >  t			0.4989
		n	6	1	
	Week 132	LS Mean	2.956	-0.876	3.833
		SEM	8.572	20.01	21.77
		95% CI	(-14.0,19.9)	(-40.4,38.6)	(-39.1,46.8)
	Week 144	Pr >  t			0.8604
		n	4		
		LS Mean	16.283	NE	NE
	Week 156	SEM	10.20	NE	NE
		95% CI	(-3.8,36.4)	NE	NE
		Pr >  t			NE
	Week 8	n	5		
		LS Mean	41.633	NE	NE
		SEM	9.260	NE	NE
	Week 16	95% CI	(23.4,59.9)	NE	NE
		Pr >  t			NE
		n	3		
	Week 24	LS Mean	3.043	NE	NE
		SEM	11.60	NE	NE
		95% CI	(-19.9,25.9)	NE	NE
	Week 32	Pr >  t			NE
		n	59	57	
		LS Mean	9.329	-0.516	9.845
Week 8	SEM	4.449	4.664	4.675	
	95% CI	(0.5,18.1)	(-9.7, 8.7)	(0.6,19.1)	
	Pr >  t			0.0365	
Week 16	n	47	44		
	LS Mean	12.006	-2.483	14.489	
	SEM	4.643	4.910	5.095	
Week 24	95% CI	(2.8,21.2)	(-12.2, 7.2)	(4.5,24.5)	
	Pr >  t			0.0048	
	n	39	34		
Week 32	LS Mean	9.022	-0.463	9.485	
	SEM	4.828	5.200	5.498	
	95% CI	(-0.5,18.5)	(-10.7, 9.8)	(-1.3,20.3)	
Week 8	Pr >  t			0.0855	
	n	27	32		
	LS Mean	4.236	-1.559	5.796	
Week 16	SEM	5.244	5.260	5.893	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-6.1,14.6)	(-11.9, 8.8)	(-5.8,17.4)
	Pr >  t			0.3260
	n	24	24	
	LS Mean	-1.396	-0.085	-1.311
	SEM	5.382	5.592	6.295
Week 48	95% CI	(-12.0, 9.2)	(-11.1,10.9)	(-13.7,11.1)
	Pr >  t			0.8352
	n	21	21	
	LS Mean	-2.294	0.976	-3.270
	SEM	5.553	5.761	6.595
Week 56	95% CI	(-13.2, 8.6)	(-10.4,12.3)	(-16.2, 9.7)
	Pr >  t			0.6203
	n	18	20	
	LS Mean	-1.297	-1.157	-0.140
	SEM	5.761	5.828	6.838
Week 64	95% CI	(-12.6,10.0)	(-12.6,10.3)	(-13.6,13.3)
	Pr >  t			0.9837
	n	14	19	
	LS Mean	3.161	3.521	-0.360
	SEM	6.156	5.899	7.239
Week 72	95% CI	(-8.9,15.3)	(-8.1,15.1)	(-14.6,13.9)
	Pr >  t			0.9604
	n	13	15	
	LS Mean	0.728	-0.361	1.089
	SEM	6.287	6.253	7.640
Week 84	95% CI	(-11.6,13.1)	(-12.7,11.9)	(-13.9,16.1)
	Pr >  t			0.8867
	n	10	14	
	LS Mean	-0.987	6.802	-7.789
	SEM	6.852	6.364	8.165
Week 96	95% CI	(-14.5,12.5)	(-5.7,19.3)	(-23.8, 8.2)
	Pr >  t			0.3405
	n	6	10	
	LS Mean	9.571	7.492	2.079
	SEM	8.148	7.003	9.756
Week 108	95% CI	(-6.4,25.6)	(-6.3,21.3)	(-17.1,21.2)
	Pr >  t			0.8313
	n	4	6	
	LS Mean	4.740	3.035	1.705
	SEM	9.564	8.293	11.81

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-14.0,23.5)	(-13.3,19.3)	(-21.5,24.9)
	Pr >  t			0.8853
	n	6	6	
	LS Mean	1.812	3.739	-1.927
	SEM	8.149	8.296	10.72
Week 132	95% CI	(-14.2,17.8)	(-12.6,20.0)	(-23.0,19.1)
	Pr >  t			0.8574
	n	2	3	
	LS Mean	-16.50	9.608	-26.11
	SEM	12.82	10.83	16.15
Week 144	95% CI	(-41.7, 8.7)	(-11.7,30.9)	(-57.8, 5.6)
	Pr >  t			0.1066
	n	2	2	
	LS Mean	4.649	-2.943	7.592
	SEM	12.78	12.90	17.62
Week 156	95% CI	(-20.5,29.8)	(-28.3,22.4)	(-27.0,42.2)
	Pr >  t			0.6668
	n		1	
	LS Mean	NE	0.960	NE
	SEM	NE	17.62	NE
	95% CI	NE	(-33.7,35.6)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Endocrine Status and Line of First Line Endocrine Resistant Therapy (L)	Week 8	n	57	57	
		LS Mean	3.388	-6.259	9.647
		SEM	10.89	11.25	4.760
		95% CI	(-18.2,25.0)	(-28.6,16.1)	( 0.3,19.0)
		Pr >  t			0.0440
	Week 16	n	51	41	
		LS Mean	5.659	-7.992	13.651
		SEM	10.92	11.39	5.169
		95% CI	(-16.0,27.3)	(-30.6,14.6)	( 3.5,23.8)
		Pr >  t			0.0088
	Week 24	n	38	33	
		LS Mean	1.069	-5.575	6.644
		SEM	10.99	11.49	5.635
		95% CI	(-20.7,22.9)	(-28.3,17.2)	( -4.4,17.7)
		Pr >  t			0.2393
	Week 32	n	34	28	
		LS Mean	0.352	-9.539	9.892
		SEM	11.17	11.57	5.907
		95% CI	(-21.8,22.5)	(-32.5,13.4)	( -1.7,21.5)
		Pr >  t			0.0949
	Week 40	n	26	23	
		LS Mean	0.311	-9.746	10.057
		SEM	11.32	11.69	6.396
		95% CI	(-22.1,22.7)	(-32.9,13.4)	( -2.5,22.6)
		Pr >  t			0.1166
	Week 48	n	24	17	
		LS Mean	1.426	-11.09	12.518
		SEM	11.37	11.91	6.879
95% CI		(-21.1,23.9)	(-34.7,12.5)	( -1.0,26.0)	
	Pr >  t			0.0694	
Week 56	n	21	17		
	LS Mean	-5.080	-6.762	1.682	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	11.46	11.91	7.027
	95% CI	(-27.8,17.6)	(-30.3,16.8)	(-12.1,15.5)
	Pr >  t			0.8109
Week 64	n	15	15	
	LS Mean	1.266	-7.993	9.259
	SEM	11.73	12.02	7.637
	95% CI	(-21.9,24.5)	(-31.8,15.8)	(-5.7,24.3)
	Pr >  t			0.2259
Week 72	n	16	15	
	LS Mean	-2.746	-10.11	7.367
	SEM	11.67	12.02	7.552
	95% CI	(-25.8,20.3)	(-33.9,13.7)	(-7.5,22.2)
	Pr >  t			0.3298
Week 84	n	14	13	
	LS Mean	-7.907	-12.79	4.885
	SEM	11.79	12.16	7.956
	95% CI	(-31.2,15.4)	(-36.8,11.3)	(-10.7,20.5)
	Pr >  t			0.5394
Week 96	n	12	9	
	LS Mean	-5.187	-7.081	1.894
	SEM	11.96	12.61	8.854
	95% CI	(-28.8,18.5)	(-32.0,17.8)	(-15.5,19.3)
	Pr >  t			0.8307
Week 108	n	13	8	
	LS Mean	-7.046	-6.811	-0.235
	SEM	11.87	12.78	8.995
	95% CI	(-30.5,16.4)	(-32.1,18.4)	(-17.9,17.4)
	Pr >  t			0.9792
Week 120	n	11	6	
	LS Mean	-1.430	0.469	-1.900
	SEM	12.06	13.30	9.943
	95% CI	(-25.3,22.4)	(-25.8,26.7)	(-21.4,17.6)
	Pr >  t			0.8485
Week 132	n	8	3	
	LS Mean	-12.85	0.574	-13.42
	SEM	12.51	15.17	12.78
	95% CI	(-37.5,11.8)	(-29.3,30.4)	(-38.5,11.7)
	Pr >  t			0.2941
Week 144	n	5	1	
	LS Mean	15.375	-12.34	27.710



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
First Line Endocrine Sensitive	Week 156	SEM	13.43	21.08	20.03
		95% CI	(-11.1,41.8)	(-53.7,29.1)	(-11.6,67.1)
		Pr >  t			0.1671
	Week 168	n	3	1	
		LS Mean	-13.15	-12.34	-0.815
		SEM	14.94	21.08	21.07
	Week 180	95% CI	(-42.5,16.2)	(-53.7,29.1)	(-42.2,40.6)
		Pr >  t			0.9691
		n	2	1	
	Week 192	LS Mean	-18.87	-12.34	-6.534
		SEM	16.62	21.08	22.29
		95% CI	(-51.5,13.8)	(-53.7,29.1)	(-50.3,37.3)
	Week 8	Pr >  t			0.7695
		n		1	
		LS Mean	NE	-12.34	NE
	Week 16	SEM	NE	21.08	NE
		95% CI	NE	(-53.7,29.1)	NE
		Pr >  t			NE
	Week 24	n		1	
		LS Mean	NE	-12.34	NE
		SEM	NE	21.08	NE
	Week 32	95% CI	NE	(-53.7,29.1)	NE
		Pr >  t			NE
		n	17	16	
	Week 8	LS Mean	12.440	5.673	6.767
		SEM	6.076	6.336	8.602
		95% CI	( 0.3,24.6)	( -7.0,18.4)	(-10.5,24.0)
	Week 16	Pr >  t			0.4348
		n	18	14	
		LS Mean	7.748	-1.286	9.033
Week 24	SEM	5.988	6.566	8.741	
	95% CI	( -4.3,19.8)	(-14.4,11.9)	( -8.5,26.5)	
	Pr >  t			0.3057	
Week 32	n	16	13		
	LS Mean	6.369	-1.474	7.843	
	SEM	6.173	6.679	8.943	
Week 8	95% CI	( -6.0,18.7)	(-14.8,11.9)	(-10.0,25.7)	
	Pr >  t			0.3839	
	n	15	13		
Week 16	LS Mean	4.331	-1.453	5.784	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	SEM	6.255	6.694	9.020	
	95% CI	(-8.2,16.8)	(-14.8,11.9)	(-12.2,23.8)	
	Pr >  t			0.5237	
	n	14	10		
	LS Mean	1.771	6.157	-4.385	
Week 48	SEM	6.370	7.079	9.380	
	95% CI	(-11.0,14.5)	(-7.9,20.3)	(-23.1,14.3)	
	Pr >  t			0.6415	
	n	14	11		
	LS Mean	1.772	2.629	-0.857	
Week 56	SEM	6.370	6.938	9.272	
	95% CI	(-11.0,14.5)	(-11.2,16.5)	(-19.3,17.6)	
	Pr >  t			0.9266	
	n	11	11		
	LS Mean	1.324	-3.431	4.756	
Week 64	SEM	6.713	6.938	9.518	
	95% CI	(-12.0,14.7)	(-17.3,10.4)	(-14.2,23.7)	
	Pr >  t			0.6187	
	n	8	11		
	LS Mean	3.610	-0.401	4.011	
Week 72	SEM	7.252	6.938	9.916	
	95% CI	(-10.8,18.0)	(-14.2,13.4)	(-15.7,23.7)	
	Pr >  t			0.6868	
	n	11	10		
	LS Mean	1.324	5.599	-4.274	
Week 84	SEM	6.713	7.086	9.625	
	95% CI	(-12.0,14.7)	(-8.5,19.7)	(-23.4,14.9)	
	Pr >  t			0.6582	
	n	9	9		
	LS Mean	3.360	13.897	-10.54	
Week 96	SEM	7.038	7.260	9.991	
	95% CI	(-10.6,17.3)	(-0.5,28.3)	(-30.4, 9.3)	
	Pr >  t			0.2943	
	n	8	7		
	LS Mean	8.621	-1.720	10.341	
Week 108	SEM	7.256	7.727	10.49	
	95% CI	(-5.8,23.0)	(-17.0,13.6)	(-10.4,31.1)	
	Pr >  t			0.3262	
	n	7	6		
	LS Mean	-1.235	-1.679	0.444	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	7.522	8.067	10.92
		95% CI	(-16.1,13.7)	(-17.7,14.3)	(-21.2,22.1)
		Pr >  t			0.9676
	Week 120	n	6	5	
		LS Mean	-0.541	-2.420	1.879
		SEM	7.867	8.526	11.49
		95% CI	(-16.1,15.0)	(-19.3,14.4)	(-20.8,24.6)
		Pr >  t			0.8703
	Week 132	n	5	3	
		LS Mean	-0.887	1.326	-2.214
		SEM	8.314	10.06	12.95
		95% CI	(-17.3,15.5)	(-18.5,21.2)	(-27.8,23.3)
		Pr >  t			0.8645
	Week 144	n	5	4	
		LS Mean	12.447	-0.635	13.082
		SEM	8.314	9.127	12.24
		95% CI	(-4.0,28.9)	(-18.7,17.4)	(-11.1,37.2)
		Pr >  t			0.2867
	Week 156	n	4	2	
		LS Mean	-0.915	1.264	-2.179
		SEM	8.938	11.72	14.65
		95% CI	(-18.6,16.7)	(-21.8,24.3)	(-31.1,26.7)
		Pr >  t			0.8819
	Week 168	n	1	1	
		LS Mean	3.647	1.280	2.367
		SEM	15.55	15.66	22.02
		95% CI	(-27.0,34.2)	(-29.6,32.1)	(-41.0,45.7)
		Pr >  t			0.9145
Second Line (progression following (neo)adjuvant/metastatic treatment)	Week 8	n	17	19	
		LS Mean	21.998	6.281	15.717
		SEM	8.346	7.587	9.305
		95% CI	( 5.2,38.8)	( -9.0,21.6)	( -3.0,34.4)
		Pr >  t			0.0975
	Week 16	n	15	17	
		LS Mean	28.962	6.335	22.626
		SEM	8.616	7.814	9.508
		95% CI	( 11.6,46.3)	( -9.4,22.0)	( 3.6,41.7)
		Pr >  t			0.0210
	Week 24	n	14	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	LS Mean	20.969	1.953	19.017
	SEM	8.692	8.305	10.03
	95% CI	( 3.5,38.4)	(-14.7,18.6)	(-1.0,39.1)
	Pr >  t			0.0626
	n	12	9	
Week 40	LS Mean	3.517	-0.144	3.661
	SEM	8.912	8.659	10.46
	95% CI	(-14.4,21.4)	(-17.4,17.1)	(-17.2,24.5)
	Pr >  t			0.7272
	n	11	7	
Week 48	LS Mean	9.228	-0.835	10.063
	SEM	9.040	9.202	10.94
	95% CI	(-8.9,27.3)	(-19.1,17.5)	(-11.7,31.8)
	Pr >  t			0.3604
	n	8	6	
Week 56	LS Mean	7.973	4.454	3.519
	SEM	9.481	9.519	11.58
	95% CI	(-10.9,26.9)	(-14.4,23.4)	(-19.4,26.5)
	Pr >  t			0.7617
	n	7	5	
Week 64	LS Mean	4.726	1.195	3.531
	SEM	9.703	9.905	12.09
	95% CI	(-14.6,24.1)	(-18.4,20.8)	(-20.4,27.5)
	Pr >  t			0.7709
	n	5	3	
Week 72	LS Mean	-2.024	1.069	-3.093
	SEM	10.35	11.36	13.78
	95% CI	(-22.6,18.5)	(-21.4,23.5)	(-30.3,24.1)
	Pr >  t			0.8227
	n	5	2	
Week 84	LS Mean	6.848	0.398	6.450
	SEM	10.38	12.95	15.14
	95% CI	(-13.8,27.5)	(-25.2,26.0)	(-23.4,36.3)
	Pr >  t			0.6706
	n	4	2	
Week 96	LS Mean	3.535	0.398	3.137
	SEM	10.87	12.95	15.49
	95% CI	(-18.0,25.1)	(-25.2,26.0)	(-27.5,33.7)
	Pr >  t			0.8398
	n	4	2	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	LS Mean	12.921	0.398	12.523
	SEM	10.88	12.95	15.49
	95% CI	(-8.7,34.5)	(-25.2,26.0)	(-18.1,43.1)
	Pr >  t			0.4201
Week 108	n	1	2	
	LS Mean	-8.139	1.761	-9.900
	SEM	16.84	12.90	20.11
	95% CI	(-41.4,25.1)	(-23.7,27.2)	(-49.6,29.8)
	Pr >  t			0.6231
Week 120	n	5	1	
	LS Mean	13.514	2.114	11.401
	SEM	10.38	16.66	18.42
	95% CI	(-7.1,34.1)	(-30.8,35.0)	(-25.0,47.8)
	Pr >  t			0.5367
Week 132	n	3	1	
	LS Mean	3.377	2.114	1.263
	SEM	11.71	16.66	19.20
	95% CI	(-19.8,26.6)	(-30.8,35.0)	(-36.6,39.2)
	Pr >  t			0.9476
Week 144	n	3		
	LS Mean	14.487	NE	NE
	SEM	11.71	NE	NE
	95% CI	(-8.7,37.7)	NE	NE
	Pr >  t			NE
Week 156	n	3		
	LS Mean	3.377	NE	NE
	SEM	11.71	NE	NE
	95% CI	(-19.8,26.6)	NE	NE
	Pr >  t			NE
Week 168	n	1		
	LS Mean	8.294	NE	NE
	SEM	16.81	NE	NE
	95% CI	(-24.9,41.5)	NE	NE
	Pr >  t			NE
Week 180	n	1		
	LS Mean	8.294	NE	NE
	SEM	16.81	NE	NE
	95% CI	(-24.9,41.5)	NE	NE
	Pr >  t			NE
Week 192	n	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Second Line (progression following metastatic treatment only)	Week 8	LS Mean	41.634	NE	NE
		SEM	16.81	NE	NE
		95% CI	( 8.5,74.8)	NE	NE
		Pr >  t			NE
		n	37	39	
	Week 16	LS Mean	22.081	4.194	17.887
		SEM	4.865	4.867	5.349
		95% CI	( 12.4,31.7)	( -5.4,13.8)	( 7.3,28.4)
		Pr >  t			0.0010
		n	30	29	
	Week 24	LS Mean	17.219	3.791	13.428
		SEM	5.067	5.360	5.961
		95% CI	( 7.2,27.2)	( -6.8,14.4)	( 1.7,25.2)
		Pr >  t			0.0254
		n	26	20	
	Week 32	LS Mean	15.595	6.559	9.036
		SEM	5.310	6.016	6.654
		95% CI	( 5.1,26.1)	( -5.3,18.4)	( -4.1,22.1)
		Pr >  t			0.1757
n		18	20		
Week 40	LS Mean	15.731	6.558	9.172	
	SEM	5.915	6.016	7.128	
	95% CI	( 4.1,27.4)	( -5.3,18.4)	( -4.9,23.2)	
	Pr >  t			0.1992	
	n	18	19		
Week 48	LS Mean	7.631	8.777	-1.146	
	SEM	5.913	6.099	7.197	
	95% CI	( -4.0,19.3)	( -3.2,20.8)	( -15.3,13.0)	
	Pr >  t			0.8736	
	n	16	14		
Week 56	LS Mean	3.699	10.510	-6.811	
	SEM	6.110	6.625	7.812	
	95% CI	( -8.3,15.7)	( -2.5,23.6)	( -22.2, 8.6)	
	Pr >  t			0.3839	
	n	14	10		
	LS Mean	5.830	8.697	-2.868	
	SEM	6.350	7.352	8.631	
	95% CI	( -6.7,18.3)	( -5.8,23.2)	( -19.8,14.1)	
	Pr >  t			0.7399	
	n				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	n		13	11	
	LS Mean		8.031	11.646	-3.615
	SEM		6.497	7.131	8.560
	95% CI		(-4.8,20.8)	(-2.4,25.7)	(-20.5,13.2)
	Pr >  t				0.6731
Week 72	n		10	6	
	LS Mean		4.613	-1.064	5.677
	SEM		7.061	8.797	10.38
	95% CI		(-9.3,18.5)	(-18.4,16.2)	(-14.7,26.1)
	Pr >  t				0.5846
Week 84	n		8	7	
	LS Mean		12.543	9.193	3.351
	SEM		7.716	8.311	10.39
	95% CI		(-2.6,27.7)	(-7.2,25.5)	(-17.1,23.8)
	Pr >  t				0.7473
Week 96	n		6	5	
	LS Mean		16.695	21.590	-4.896
	SEM		8.555	9.416	11.92
	95% CI		(-0.1,33.5)	( 3.1,40.1)	(-28.3,18.5)
	Pr >  t				0.6814
Week 108	n		2	4	
	LS Mean		29.470	14.205	15.265
	SEM		13.66	10.29	16.48
	95% CI		( 2.6,56.3)	(-6.0,34.4)	(-17.1,47.7)
	Pr >  t				0.3549
Week 120	n		4	4	
	LS Mean		5.248	-2.460	7.708
	SEM		10.05	10.29	13.69
	95% CI		(-14.5,25.0)	(-22.7,17.8)	(-19.2,34.6)
	Pr >  t				0.5738
Week 132	n		3	1	
	LS Mean		8.653	18.995	-10.34
	SEM		11.42	18.95	21.64
	95% CI		(-13.8,31.1)	(-18.3,56.3)	(-52.9,32.2)
	Pr >  t				0.6331
Week 144	n		2		
	LS Mean		13.089	NE	NE
	SEM		13.58	NE	NE
	95% CI		(-13.6,39.8)	NE	NE
	Pr >  t				NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35			
			LS Mean	21.838	9.583	12.255		
			SEM	5.961	6.438	6.252		
			95% CI	( 10.0,33.7)	( -3.2,22.4)	( -0.1,24.6)		
					Pr >  t			0.0522
		Week 16	n	35	22			
			LS Mean	21.318	6.629	14.689		
			SEM	6.205	7.258	7.071		
			95% CI	( 9.0,33.6)	( -7.7,21.0)	( 0.7,28.6)		
					Pr >  t			0.0393
		Week 24	n	28	16			
			LS Mean	18.135	12.772	5.363		
			SEM	6.435	7.765	7.828		
			95% CI	( 5.4,30.9)	( -2.6,28.1)	(-10.1,20.8)		
					Pr >  t			0.4940
		Week 32	n	22	16			
			LS Mean	10.635	7.869	2.766		
			SEM	6.824	7.786	8.082		
			95% CI	( -2.9,24.1)	( -7.5,23.2)	(-13.2,18.7)		
					Pr >  t			0.7325
		Week 40	n	19	12			
			LS Mean	13.808	3.787	10.021		
			SEM	7.024	8.310	8.753		
			95% CI	( -0.1,27.7)	(-12.6,20.2)	( -7.2,27.3)		
					Pr >  t			0.2533
		Week 48	n	16	10			
			LS Mean	20.429	6.908	13.520		
			SEM	7.285	8.705	9.338		
95% CI	( 6.1,34.8)		(-10.3,24.1)	( -4.9,31.9)				
			Pr >  t			0.1487		
Week 56	n	14	7					
	LS Mean	15.382	10.087	5.296				
		SEM	7.515	9.615	10.37			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 0.6,30.2)	( -8.8,29.0)	(-15.1,25.7)
	Pr >  t			0.6099
	n	8	7	
	LS Mean	8.524	22.676	-14.15
	SEM	8.698	9.615	11.28
Week 72	95% CI	( -8.6,25.6)	( 3.7,41.6)	(-36.3, 8.0)
	Pr >  t			0.2106
	n	12	6	
	LS Mean	13.139	16.916	-3.778
	SEM	7.798	10.08	11.01
Week 84	95% CI	( -2.2,28.5)	( -2.9,36.8)	(-25.4,17.9)
	Pr >  t			0.7317
	n	8	5	
	LS Mean	10.856	12.413	-1.557
	SEM	8.760	10.68	12.21
Week 96	95% CI	( -6.4,28.1)	( -8.6,33.4)	(-25.6,22.5)
	Pr >  t			0.8986
	n	5	5	
	LS Mean	3.791	5.747	-1.956
	SEM	10.19	10.68	13.28
Week 108	95% CI	(-16.3,23.8)	(-15.3,26.8)	(-28.1,24.2)
	Pr >  t			0.8830
	n	7	5	
	LS Mean	2.610	12.413	-9.803
	SEM	9.130	10.68	12.48
Week 120	95% CI	(-15.4,20.6)	( -8.6,33.4)	(-34.4,14.7)
	Pr >  t			0.4328
	n	5	3	
	LS Mean	6.057	15.941	-9.884
	SEM	10.20	12.78	15.02
Week 132	95% CI	(-14.0,26.1)	( -9.2,41.1)	(-39.4,19.7)
	Pr >  t			0.5111
	n	2	2	
	LS Mean	4.428	23.694	-19.27
	SEM	14.55	14.87	19.78
Week 144	95% CI	(-24.2,33.1)	( -5.6,52.9)	(-58.2,19.7)
	Pr >  t			0.3308
	n	2		
	LS Mean	61.397	NE	NE
	SEM	14.57	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 32.7,90.1)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	9.816	NE	NE
		SEM	14.58	NE	NE
		95% CI	(-18.9,38.5)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	2.848	NE	NE
		SEM	19.80	NE	NE
		95% CI	(-36.1,41.8)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	98	104	
		LS Mean	11.980	1.050	10.931
		SEM	4.067	4.011	3.290
		95% CI	( 4.0,20.0)	( -6.8, 8.9)	( 4.5,17.4)
		Pr >  t			0.0010
	Week 16	n	87	84	
		LS Mean	11.639	-0.640	12.279
		SEM	4.141	4.125	3.491
		95% CI	( 3.5,19.8)	( -8.8, 7.5)	( 5.4,19.1)
		Pr >  t			0.0005
	Week 24	n	76	65	
		LS Mean	7.267	-0.790	8.057
		SEM	4.222	4.283	3.731
		95% CI	( -1.0,15.6)	( -9.2, 7.6)	( 0.7,15.4)
		Pr >  t			0.0312
	Week 32	n	62	57	
		LS Mean	7.053	-1.224	8.276
		SEM	4.342	4.375	3.939
		95% CI	( -1.5,15.6)	( -9.8, 7.4)	( 0.5,16.0)
		Pr >  t			0.0360
	Week 40	n	54	50	
		LS Mean	4.071	1.578	2.492
		SEM	4.422	4.472	4.117
		95% CI	( -4.6,12.8)	( -7.2,10.4)	( -5.6,10.6)
		Pr >  t			0.5451
	Week 48	n	52	41	
		LS Mean	-0.004	1.025	-1.029
		SEM	4.445	4.610	4.290

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.7, 8.7)	(-8.0, 10.1)	(-9.5, 7.4)
		Pr >  t			0.8105
	Week 56	n	44	38	
		LS Mean	-0.829	-0.870	0.041
		SEM	4.550	4.668	4.465
		95% CI	(-9.8, 8.1)	(-10.0, 8.3)	(-8.7, 8.8)
		Pr >  t			0.9926
	Week 64	n	39	35	
		LS Mean	3.863	-0.983	4.846
		SEM	4.637	4.736	4.623
		95% CI	(-5.3, 13.0)	(-10.3, 8.3)	(-4.2, 13.9)
		Pr >  t			0.2948
	Week 72	n	36	29	
		LS Mean	1.722	-2.026	3.748
		SEM	4.700	4.903	4.855
		95% CI	(-7.5, 11.0)	(-11.7, 7.6)	(-5.8, 13.3)
		Pr >  t			0.4403
	Week 84	n	32	28	
		LS Mean	1.191	3.886	-2.696
		SEM	4.805	4.937	4.983
		95% CI	(-8.3, 10.6)	(-5.8, 13.6)	(-12.5, 7.1)
		Pr >  t			0.5887
	Week 96	n	30	19	
		LS Mean	5.499	4.106	1.394
		SEM	4.854	5.378	5.472
		95% CI	(-4.0, 15.0)	(-6.5, 14.7)	(-9.3, 12.1)
		Pr >  t			0.7990
	Week 108	n	18	16	
		LS Mean	1.546	2.463	-0.917
		SEM	5.436	5.619	6.205
		95% CI	(-9.1, 12.2)	(-8.6, 13.5)	(-13.1, 11.3)
		Pr >  t			0.8826
	Week 120	n	23	13	
		LS Mean	4.415	-1.617	6.032
		SEM	5.126	5.951	6.259
		95% CI	(-5.7, 14.5)	(-13.3, 10.1)	(-6.2, 18.3)
		Pr >  t			0.3354
	Week 132	n	18	6	
		LS Mean	-1.291	2.114	-3.404
		SEM	5.437	7.689	8.127

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-12.0, 9.4)	(-13.0,17.2)	(-19.3,12.5)
	Pr >  t			0.6754
Week 144	n	13	5	
	LS Mean	8.207	-2.380	10.587
	SEM	5.914	8.245	8.974
	95% CI	(-3.4,19.8)	(-18.6,13.8)	(-7.0,28.2)
	Pr >  t			0.2384
Week 156	n	8	3	
	LS Mean	-3.818	-1.394	-2.424
	SEM	6.913	10.14	11.32
	95% CI	(-17.4, 9.7)	(-21.3,18.5)	(-24.6,19.8)
	Pr >  t			0.8304
Week 168	n	3	2	
	LS Mean	-4.896	-2.060	-2.837
	SEM	10.11	12.11	15.04
	95% CI	(-24.7,14.9)	(-25.8,21.7)	(-32.4,26.7)
	Pr >  t			0.8504
Week 180	n	1	1	
	LS Mean	1.925	-4.037	5.962
	SEM	16.65	16.65	23.06
	95% CI	(-30.7,34.6)	(-36.7,28.6)	(-39.3,51.2)
	Pr >  t			0.7960
Week 192	n	1	1	
	LS Mean	35.265	-4.037	39.302
	SEM	16.65	16.65	23.06
	95% CI	(-2.6,67.9)	(-36.7,28.6)	(-5.9,84.5)
	Pr >  t			0.0886

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	12.240	0.946	11.293		
			SEM	4.089	4.023	3.317		
			95% CI	( 4.2,20.3)	( -7.0, 8.9)	( 4.8,17.8)		
					Pr >  t			0.0007
		Week 16	n	85	84			
			LS Mean	11.912	-0.750	12.662		
			SEM	4.166	4.138	3.521		
			95% CI	( 3.7,20.1)	( -8.9, 7.4)	( 5.7,19.6)		
					Pr >  t			0.0004
		Week 24	n	75	65			
			LS Mean	7.388	-0.897	8.285		
			SEM	4.245	4.296	3.758		
			95% CI	( -1.0,15.7)	( -9.3, 7.6)	( 0.9,15.7)		
					Pr >  t			0.0279
		Week 32	n	61	57			
			LS Mean	7.169	-1.331	8.500		
			SEM	4.369	4.389	3.969		
			95% CI	( -1.4,15.8)	( -10.0, 7.3)	( 0.7,16.3)		
					Pr >  t			0.0326
		Week 40	n	53	50			
			LS Mean	4.152	1.469	2.683		
			SEM	4.452	4.486	4.151		
			95% CI	( -4.6,12.9)	( -7.4,10.3)	( -5.5,10.8)		
					Pr >  t			0.5182
		Week 48	n	51	41			
			LS Mean	-0.004	0.917	-0.921		
			SEM	4.476	4.625	4.325		
95% CI	( -8.8, 8.8)		( -8.2,10.0)	( -9.4, 7.6)				
			Pr >  t			0.8315		
Week 56	n	43	38					
	LS Mean	-0.866	-0.980	0.114				
	SEM	4.586	4.684	4.505				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.9, 8.2)	(-10.2, 8.2)	(-8.7, 9.0)
	Pr >  t			0.9799
	n	39	35	
	LS Mean	3.930	-1.092	5.021
	SEM	4.657	4.752	4.647
Week 72	95% CI	(-5.2, 13.1)	(-10.4, 8.2)	(-4.1, 14.1)
	Pr >  t			0.2802
	n	35	29	
	LS Mean	1.684	-2.136	3.820
	SEM	4.743	4.920	4.902
Week 84	95% CI	(-7.6, 11.0)	(-11.8, 7.5)	(-5.8, 13.4)
	Pr >  t			0.4361
	n	31	28	
	LS Mean	1.122	3.777	-2.656
	SEM	4.855	4.954	5.036
Week 96	95% CI	(-8.4, 10.7)	(-6.0, 13.5)	(-12.5, 7.2)
	Pr >  t			0.5981
	n	29	19	
	LS Mean	5.572	3.996	1.576
	SEM	4.907	5.397	5.528
Week 108	95% CI	(-4.1, 15.2)	(-6.6, 14.6)	(-9.3, 12.4)
	Pr >  t			0.7756
	n	18	16	
	LS Mean	1.611	2.356	-0.744
	SEM	5.461	5.640	6.235
Week 120	95% CI	(-9.1, 12.3)	(-8.7, 13.4)	(-13.0, 11.5)
	Pr >  t			0.9050
	n	23	13	
	LS Mean	4.480	-1.721	6.201
	SEM	5.149	5.973	6.289
Week 132	95% CI	(-5.6, 14.6)	(-13.4, 10.0)	(-6.1, 18.5)
	Pr >  t			0.3243
	n	18	6	
	LS Mean	-1.224	2.009	-3.234
	SEM	5.461	7.719	8.165
Week 144	95% CI	(-11.9, 9.5)	(-13.1, 17.2)	(-19.3, 12.8)
	Pr >  t			0.6921
	n	13	5	
	LS Mean	8.276	-2.487	10.762
	SEM	5.940	8.278	9.015

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	(-3.4,19.9)	(-18.7,13.8)	(-6.9,28.5)
		Pr >  t			0.2328
		n	8	3	
	Week 168	LS Mean	-3.748	-1.504	-2.244
		SEM	6.943	10.19	11.37
		95% CI	(-17.4, 9.9)	(-21.5,18.5)	(-24.5,20.1)
	Week 180	Pr >  t			0.8435
		n	3	2	
		LS Mean	-4.821	-2.171	-2.649
	Week 192	SEM	10.16	12.16	15.11
		95% CI	(-24.7,15.1)	(-26.0,21.7)	(-32.3,27.0)
		Pr >  t			0.8608
	Week 8	n	1	1	
		LS Mean	2.012	-4.142	6.154
		SEM	16.72	16.72	23.16
	Week 16	95% CI	(-30.8,34.8)	(-36.9,28.7)	(-39.3,51.6)
		Pr >  t			0.7905
		n	1	1	
	Week 24	LS Mean	35.352	-4.142	39.494
		SEM	16.72	16.72	23.16
		95% CI	( 2.5,68.2)	(-36.9,28.7)	(-5.9,84.9)
	Week 32	Pr >  t			0.0884
		n	42	35	
		LS Mean	21.838	9.583	12.255
Week 8	SEM	5.961	6.438	6.252	
	95% CI	( 10.0,33.7)	(-3.2,22.4)	(-0.1,24.6)	
	Pr >  t			0.0522	
Week 16	n	35	22		
	LS Mean	21.318	6.629	14.689	
	SEM	6.205	7.258	7.071	
Week 24	95% CI	( 9.0,33.6)	(-7.7,21.0)	( 0.7,28.6)	
	Pr >  t			0.0393	
	n	28	16		
Week 32	LS Mean	18.135	12.772	5.363	
	SEM	6.435	7.765	7.828	
	95% CI	( 5.4,30.9)	(-2.6,28.1)	(-10.1,20.8)	
Week 8	Pr >  t			0.4940	
	n	22	16		
	LS Mean	10.635	7.869	2.766	
Week 16	SEM	6.824	7.786	8.082	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-2.9,24.1)	(-7.5,23.2)	(-13.2,18.7)
	Pr >  t			0.7325
	n	19	12	
	LS Mean	13.808	3.787	10.021
	SEM	7.024	8.310	8.753
Week 48	95% CI	(-0.1,27.7)	(-12.6,20.2)	(-7.2,27.3)
	Pr >  t			0.2533
	n	16	10	
	LS Mean	20.429	6.908	13.520
	SEM	7.285	8.705	9.338
Week 56	95% CI	( 6.1,34.8)	(-10.3,24.1)	(-4.9,31.9)
	Pr >  t			0.1487
	n	14	7	
	LS Mean	15.382	10.087	5.296
	SEM	7.515	9.615	10.37
Week 64	95% CI	( 0.6,30.2)	(-8.8,29.0)	(-15.1,25.7)
	Pr >  t			0.6099
	n	8	7	
	LS Mean	8.524	22.676	-14.15
	SEM	8.698	9.615	11.28
Week 72	95% CI	(-8.6,25.6)	( 3.7,41.6)	(-36.3, 8.0)
	Pr >  t			0.2106
	n	12	6	
	LS Mean	13.139	16.916	-3.778
	SEM	7.798	10.08	11.01
Week 84	95% CI	(-2.2,28.5)	(-2.9,36.8)	(-25.4,17.9)
	Pr >  t			0.7317
	n	8	5	
	LS Mean	10.856	12.413	-1.557
	SEM	8.760	10.68	12.21
Week 96	95% CI	(-6.4,28.1)	(-8.6,33.4)	(-25.6,22.5)
	Pr >  t			0.8986
	n	5	5	
	LS Mean	3.791	5.747	-1.956
	SEM	10.19	10.68	13.28
Week 108	95% CI	(-16.3,23.8)	(-15.3,26.8)	(-28.1,24.2)
	Pr >  t			0.8830
	n	7	5	
	LS Mean	2.610	12.413	-9.803
	SEM	9.130	10.68	12.48

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-15.4,20.6)	(-8.6,33.4)	(-34.4,14.7)
	Pr >  t			0.4328
	n	5	3	
	LS Mean	6.057	15.941	-9.884
	SEM	10.20	12.78	15.02
Week 132	95% CI	(-14.0,26.1)	(-9.2,41.1)	(-39.4,19.7)
	Pr >  t			0.5111
	n	2	2	
	LS Mean	4.428	23.694	-19.27
	SEM	14.55	14.87	19.78
Week 144	95% CI	(-24.2,33.1)	(-5.6,52.9)	(-58.2,19.7)
	Pr >  t			0.3308
	n	2		
	LS Mean	61.397	NE	NE
	SEM	14.57	NE	NE
Week 156	95% CI	(32.7,90.1)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	9.816	NE	NE
	SEM	14.58	NE	NE
Week 168	95% CI	(-18.9,38.5)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	2.848	NE	NE
	SEM	19.80	NE	NE
	95% CI	(-36.1,41.8)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-26i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Appetite loss score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	9.151	-4.682	13.833		
			SEM	8.087	8.353	3.875		
			95% CI	(-6.9,25.2)	(-21.3,11.9)	( 6.2,21.5)		
					Pr >  t		0.0004	
		Week 16	n	59	49			
			LS Mean	7.145	-6.616	13.761		
			SEM	8.130	8.438	4.176		
			95% CI	(-9.0,23.3)	(-23.4,10.1)	( 5.6,22.0)		
					Pr >  t		0.0011	
		Week 24	n	54	41			
			LS Mean	4.502	-8.418	12.920		
			SEM	8.153	8.523	4.406		
			95% CI	(-11.7,20.7)	(-25.3, 8.5)	( 4.3,21.6)		
					Pr >  t		0.0035	
		Week 32	n	48	37			
			LS Mean	1.161	-6.068	7.230		
			SEM	8.190	8.571	4.588		
			95% CI	(-15.1,17.4)	(-23.1,10.9)	( -1.8,16.2)		
					Pr >  t		0.1157	
		Week 40	n	43	33			
			LS Mean	-1.203	-6.215	5.012		
			SEM	8.228	8.630	4.776		
			95% CI	(-17.5,15.1)	(-23.3,10.9)	( -4.4,14.4)		
					Pr >  t		0.2945	
		Week 48	n	41	28			
			LS Mean	-0.169	-6.134	5.965		
			SEM	8.247	8.725	4.985		
95% CI	(-16.5,16.2)		(-23.4,11.1)	( -3.8,15.8)				
			Pr >  t		0.2319			
Week 56	n	35	22					
	LS Mean	-2.823	-6.468	3.645				
	SEM	8.312	8.894	5.393				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.3,13.7)	(-24.1,11.1)	(-6.9,14.2)
		Pr >  t			0.4994
	Week 64	n	26	23	
		LS Mean	-2.088	-4.218	2.129
		SEM	8.469	8.861	5.607
		95% CI	(-18.9,14.7)	(-21.8,13.3)	(-8.9,13.1)
		Pr >  t			0.7042
	Week 72	n	28	18	
		LS Mean	0.975	-7.480	8.456
		SEM	8.425	9.060	5.847
		95% CI	(-15.7,17.7)	(-25.4,10.4)	(-3.0,19.9)
		Pr >  t			0.1486
	Week 84	n	22	18	
		LS Mean	-3.602	-0.103	-3.498
		SEM	8.636	9.060	6.085
		95% CI	(-20.7,13.5)	(-18.0,17.8)	(-15.4, 8.4)
		Pr >  t			0.5655
	Week 96	n	21	13	
		LS Mean	3.022	-0.634	3.656
		SEM	8.610	9.397	6.627
		95% CI	(-14.0,20.1)	(-19.2,17.9)	(-9.4,16.7)
		Pr >  t			0.5814
	Week 108	n	17	12	
		LS Mean	-3.596	-1.143	-2.453
		SEM	8.858	9.496	6.998
		95% CI	(-21.1,13.9)	(-19.9,17.6)	(-16.2,11.3)
		Pr >  t			0.7261
	Week 120	n	18	11	
		LS Mean	-2.201	-3.328	1.127
		SEM	8.730	9.611	7.090
		95% CI	(-19.5,15.1)	(-22.3,15.6)	(-12.8,15.0)
		Pr >  t			0.8738
	Week 132	n	13	5	
		LS Mean	-6.571	2.521	-9.092
		SEM	9.140	11.11	9.354
		95% CI	(-24.6,11.5)	(-19.4,24.4)	(-27.5, 9.3)
		Pr >  t			0.3313
	Week 144	n	12	3	
		LS Mean	5.814	-9.124	14.938
		SEM	9.140	12.72	11.30

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.2,23.9)	(-34.1,15.9)	( -7.2,37.1)
		Pr >  t			0.1864
	Week 156	n	7	2	
		LS Mean	-7.821	-7.290	-0.531
		SEM	10.11	14.45	13.84
		95% CI	(-27.7,12.1)	(-35.7,21.1)	(-27.7,26.6)
		Pr >  t			0.9694
	Week 168	n	3	1	
		LS Mean	-8.574	-9.279	0.705
		SEM	12.49	18.73	19.68
		95% CI	(-33.1,16.0)	(-46.0,27.5)	(-37.9,39.3)
		Pr >  t			0.9714
	Week 180	n	1	1	
		LS Mean	-1.264	-9.279	8.015
		SEM	18.58	18.73	24.01
		95% CI	(-37.7,35.2)	(-46.0,27.5)	(-39.1,55.2)
		Pr >  t			0.7386
	Week 192	n	1	1	
		LS Mean	32.076	-9.279	41.355
		SEM	18.58	18.73	24.01
		95% CI	( -4.4,68.5)	(-46.0,27.5)	( -5.8,88.5)
		Pr >  t			0.0854
Yes	Week 8	n	73	80	
		LS Mean	19.906	10.170	9.736
		SEM	5.730	5.773	4.297
		95% CI	( 8.6,31.2)	( -1.2,21.6)	( 1.3,18.2)
		Pr >  t			0.0243
	Week 16	n	65	58	
		LS Mean	20.801	8.429	12.373
		SEM	5.859	5.995	4.602
		95% CI	( 9.2,32.4)	( -3.4,20.2)	( 3.3,21.4)
		Pr >  t			0.0076
	Week 24	n	51	40	
		LS Mean	15.534	12.927	2.607
		SEM	5.967	6.267	5.057
		95% CI	( 3.8,27.3)	( 0.6,25.3)	( -7.3,12.6)
		Pr >  t			0.6065
	Week 32	n	38	36	
		LS Mean	14.575	7.794	6.781
		SEM	6.209	6.351	5.371

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	( 2.3,26.8)	( -4.7,20.3)	( -3.8,17.3)
		Pr >  t			0.2074
		n	32	29	
		LS Mean	14.918	10.824	4.093
		SEM	6.349	6.522	5.715
Week 48		95% CI	( 2.4,27.4)	( -2.0,23.7)	( -7.1,15.3)
		Pr >  t			0.4742
		n	28	23	
		LS Mean	9.652	10.954	-1.302
		SEM	6.454	6.741	6.071
Week 56		95% CI	( -3.1,22.4)	( -2.3,24.2)	( -13.2,10.6)
		Pr >  t			0.8302
		n	24	23	
		LS Mean	9.404	9.258	0.147
		SEM	6.601	6.740	6.221
Week 64		95% CI	( -3.6,22.4)	( -4.0,22.5)	( -12.1,12.4)
		Pr >  t			0.9812
		n	21	19	
		LS Mean	13.784	10.925	2.858
		SEM	6.740	6.942	6.579
Week 72		95% CI	( 0.5,27.0)	( -2.7,24.6)	( -10.1,15.8)
		Pr >  t			0.6641
		n	20	17	
		LS Mean	7.459	10.767	-3.308
		SEM	6.798	7.074	6.774
Week 84		95% CI	( -5.9,20.8)	( -3.1,24.7)	( -16.6,10.0)
		Pr >  t			0.6254
		n	18	15	
		LS Mean	11.214	11.174	0.040
		SEM	6.904	7.239	7.055
Week 96		95% CI	( -2.4,24.8)	( -3.1,25.4)	( -13.8,13.9)
		Pr >  t			0.9955
		n	14	11	
		LS Mean	8.780	8.832	-0.052
		SEM	7.242	7.719	7.847
Week 108		95% CI	( -5.5,23.0)	( -6.3,24.0)	( -15.5,15.4)
		Pr >  t			0.9947
		n	9	9	
		LS Mean	10.052	9.420	0.632
		SEM	7.994	8.088	8.888

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.7,25.8)	(-6.5,25.3)	(-16.8,18.1)
		Pr >  t			0.9433
	Week 120	n	10	5	
		LS Mean	15.190	3.847	11.343
		SEM	7.816	9.552	10.10
		95% CI	(-0.2,30.5)	(-14.9,22.6)	(-8.5,31.2)
		Pr >  t			0.2617
	Week 132	n	7	3	
		LS Mean	9.479	9.614	-0.135
		SEM	8.546	11.36	12.33
		95% CI	(-7.3,26.3)	(-12.7,31.9)	(-24.3,24.1)
		Pr >  t			0.9913
	Week 144	n	3	2	
		LS Mean	39.996	9.393	30.603
		SEM	11.28	13.30	15.95
		95% CI	( 17.8,62.1)	(-16.7,35.5)	(-0.7,61.9)
		Pr >  t			0.0554
	Week 156	n	3	1	
		LS Mean	8.389	9.697	-1.308
		SEM	11.30	17.89	19.93
		95% CI	(-13.8,30.6)	(-25.4,44.8)	(-40.5,37.8)
		Pr >  t			0.9477
	Week 168	n	1	1	
		LS Mean	4.437	9.697	-5.260
		SEM	17.88	17.89	24.28
		95% CI	(-30.7,39.6)	(-25.4,44.8)	(-52.9,42.4)
		Pr >  t			0.8286

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-47: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Obstipation“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73	
			LS Mean	-6.060	-0.940	-5.121
		SEM	3.316	3.344	3.091	
		95% CI	(-12.6, 0.5)	(-7.5, 5.6)	(-11.2, 1.0)	
		Pr >  t			0.0983	
		Week 16	n	67	56	
			LS Mean	-10.42	-2.811	-7.606
			SEM	3.383	3.573	3.373
			95% CI	(-17.1,-3.8)	(-9.8, 4.2)	(-14.2,-1.0)
			Pr >  t			0.0246
		Week 24	n	61	46	
			LS Mean	-7.826	-2.501	-5.325
			SEM	3.460	3.710	3.587
			95% CI	(-14.6,-1.0)	(-9.8, 4.8)	(-12.4, 1.7)
			Pr >  t			0.1382
		Week 32	n	52	41	
			LS Mean	-7.484	-0.439	-7.045
			SEM	3.605	3.823	3.779
			95% CI	(-14.6,-0.4)	(-8.0, 7.1)	(-14.5, 0.4)
			Pr >  t			0.0628
Week 40	n	45	36			
	LS Mean	-9.213	-4.124	-5.090		
	SEM	3.704	3.954	3.984		
	95% CI	(-16.5,-1.9)	(-11.9, 3.6)	(-12.9, 2.7)		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.2018
Week 48	n	42	30	
	LS Mean	-7.703	-0.452	-7.250
	SEM	3.759	4.120	4.197
	95% CI	(-15.1,-0.3)	(-8.5, 7.6)	(-15.5, 1.0)
	Pr >  t			0.0845
Week 56	n	35	24	
	LS Mean	-10.91	-4.647	-6.266
	SEM	3.903	4.356	4.557
	95% CI	(-18.6,-3.2)	(-13.2, 3.9)	(-15.2, 2.7)
	Pr >  t			0.1696
Week 64	n	25	25	
	LS Mean	-8.960	-3.423	-5.536
	SEM	4.222	4.312	4.800
	95% CI	(-17.3,-0.7)	(-11.9, 5.0)	(-15.0, 3.9)
	Pr >  t			0.2491
Week 72	n	27	20	
	LS Mean	-12.38	3.924	-16.30
	SEM	4.145	4.575	4.970
	95% CI	(-20.5,-4.2)	(-5.1,12.9)	(-26.1,-6.5)
	Pr >  t			0.0011
Week 84	n	23	19	
	LS Mean	-9.731	-8.914	-0.818
	SEM	4.337	4.642	5.177
	95% CI	(-18.2,-1.2)	(-18.0, 0.2)	(-11.0, 9.3)
	Pr >  t			0.8745
Week 96	n	20	13	
	LS Mean	-6.470	-0.850	-5.621
	SEM	4.506	5.208	5.822
	95% CI	(-15.3, 2.4)	(-11.1, 9.4)	(-17.0, 5.8)
	Pr >  t			0.3346
Week 108	n	17	13	
	LS Mean	-9.133	-5.346	-3.787
	SEM	4.727	5.210	5.994
	95% CI	(-18.4, 0.1)	(-15.6, 4.9)	(-15.6, 8.0)
	Pr >  t			0.5277
Week 120	n	17	12	
	LS Mean	-6.083	-8.299	2.216
	SEM	4.726	5.350	6.116
	95% CI	(-15.4, 3.2)	(-18.8, 2.2)	(-9.8,14.2)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.7171
	Week 132	n 13	6	
		LS Mean -9.274	-4.136	-5.138
		SEM 5.142	6.892	7.771
		95% CI (-19.4, 0.8)	(-17.7, 9.4)	(-20.4,10.1)
		Pr >  t		0.5087
	Week 144	n 11	4	
		LS Mean 7.745	-5.790	13.535
		SEM 5.443	8.150	9.083
		95% CI (-2.9,18.4)	(-21.8,10.2)	(-4.3,31.4)
		Pr >  t		0.1366
	Week 156	n 7	2	
		LS Mean -11.36	-6.321	-5.041
		SEM 6.428	11.07	12.26
		95% CI (-24.0, 1.3)	(-28.1,15.4)	(-29.1,19.0)
		Pr >  t		0.6812
	Week 168	n 3	1	
		LS Mean -12.52	-8.596	-3.926
		SEM 9.168	15.33	17.48
		95% CI (-30.5, 5.5)	(-38.7,21.5)	(-38.2,30.4)
		Pr >  t		0.8224
	Week 180	n 1	1	
		LS Mean -14.28	-8.596	-5.687
		SEM 15.30	15.33	21.35
		95% CI (-44.3,15.8)	(-38.7,21.5)	(-47.6,36.2)
		Pr >  t		0.7900
	Week 192	n 1	1	
		LS Mean -14.28	-8.596	-5.687
		SEM 15.30	15.33	21.35
		95% CI (-44.3,15.8)	(-38.7,21.5)	(-47.6,36.2)
		Pr >  t		0.7900
Present	Week 8	n 65	67	
		LS Mean -5.042	-0.568	-4.473
		SEM 3.466	3.568	3.044
		95% CI (-11.9, 1.8)	(-7.6, 6.5)	(-10.5, 1.5)
		Pr >  t		0.1427
	Week 16	n 57	51	
		LS Mean -7.707	-4.317	-3.390
		SEM 3.614	3.757	3.314
		95% CI (-14.8,-0.6)	(-11.7, 3.1)	(-9.9, 3.1)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.3071
Week 24	n	44	35	
	LS Mean	-5.038	-3.625	-1.412
	SEM	3.755	4.063	3.770
	95% CI	(-12.4, 2.4)	(-11.6, 4.4)	(-8.8, 6.0)
	Pr >  t			0.7081
Week 32	n	34	32	
	LS Mean	-7.092	-7.071	-0.021
	SEM	3.962	4.139	4.029
	95% CI	(-14.9, 0.7)	(-15.2, 1.1)	(-7.9, 7.9)
	Pr >  t			0.9958
Week 40	n	30	26	
	LS Mean	-7.086	0.087	-7.173
	SEM	4.063	4.316	4.311
	95% CI	(-15.1, 0.9)	(-8.4, 8.6)	(-15.6, 1.3)
	Pr >  t			0.0967
Week 48	n	27	21	
	LS Mean	-6.158	-8.340	2.182
	SEM	4.146	4.527	4.599
	95% CI	(-14.3, 2.0)	(-17.2, 0.6)	(-6.8, 11.2)
	Pr >  t			0.6353
Week 56	n	24	21	
	LS Mean	-8.112	-4.333	-3.778
	SEM	4.253	4.527	4.699
	95% CI	(-16.5, 0.3)	(-13.2, 4.6)	(-13.0, 5.4)
	Pr >  t			0.4217
Week 64	n	22	17	
	LS Mean	-3.714	-7.157	3.443
	SEM	4.338	4.766	5.007
	95% CI	(-12.2, 4.8)	(-16.5, 2.2)	(-6.4, 13.3)
	Pr >  t			0.4919
Week 72	n	21	15	
	LS Mean	-7.169	-4.412	-2.756
	SEM	4.387	4.926	5.199
	95% CI	(-15.8, 1.5)	(-14.1, 5.3)	(-13.0, 7.5)
	Pr >  t			0.5962
Week 84	n	17	14	
	LS Mean	-6.727	0.341	-7.068
	SEM	4.638	5.017	5.482
	95% CI	(-15.8, 2.4)	(-9.5, 10.2)	(-17.8, 3.7)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Pr >  t			0.1977
Week 96	n	15	11	
	LS Mean	-4.511	-0.952	-3.559
	SEM	4.774	5.377	5.944
	95% CI	(-13.9, 4.9)	(-11.5, 9.6)	(-15.2, 8.1)
	Pr >  t			0.5496
Week 108	n	9	8	
	LS Mean	-2.825	-8.180	5.355
	SEM	5.601	5.949	7.082
	95% CI	(-13.8, 8.2)	(-19.9, 3.5)	(-8.6,19.3)
	Pr >  t			0.4498
Week 120	n	11	4	
	LS Mean	-8.111	-12.43	4.319
	SEM	5.237	7.690	8.381
	95% CI	(-18.4, 2.2)	(-27.5, 2.7)	(-12.1,20.8)
	Pr >  t			0.6065
Week 132	n	7	2	
	LS Mean	-11.60	-7.910	-3.687
	SEM	6.108	10.28	11.24
	95% CI	(-23.6, 0.4)	(-28.1,12.3)	(-25.8,18.4)
	Pr >  t			0.7431
Week 144	n	4	1	
	LS Mean	-9.337	-7.206	-2.131
	SEM	7.516	14.13	15.50
	95% CI	(-24.1, 5.4)	(-34.9,20.5)	(-32.6,28.3)
	Pr >  t			0.8907
Week 156	n	3	1	
	LS Mean	-10.34	-7.206	-3.133
	SEM	8.538	14.13	16.00
	95% CI	(-27.1, 6.4)	(-34.9,20.5)	(-34.6,28.3)
	Pr >  t			0.8448
Week 168	n	1	1	
	LS Mean	-7.106	-7.206	0.100
	SEM	14.08	14.13	19.52
	95% CI	(-34.8,20.6)	(-34.9,20.5)	(-38.2,38.4)
	Pr >  t			0.9959

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	-5.144	-0.303	-4.842		
			SEM	2.686	2.846	2.738		
			95% CI	(-10.4, 0.1)	(-5.9, 5.3)	(-10.2, 0.5)		
					Pr >  t			0.0776
		Week 16	n	86	68			
			LS Mean	-9.370	-1.775	-7.595		
			SEM	2.763	2.992	2.952		
			95% CI	(-14.8,-3.9)	(-7.7, 4.1)	(-13.4,-1.8)		
					Pr >  t			0.0103
		Week 24	n	73	48			
			LS Mean	-5.975	-1.902	-4.073		
			SEM	2.860	3.262	3.302		
			95% CI	(-11.6,-0.3)	(-8.3, 4.5)	(-10.6, 2.4)		
					Pr >  t			0.2178
		Week 32	n	60	43			
			LS Mean	-6.882	-0.715	-6.166		
			SEM	3.022	3.369	3.498		
			95% CI	(-12.8,-0.9)	(-7.3, 5.9)	(-13.0, 0.7)		
					Pr >  t			0.0783
		Week 40	n	50	38			
			LS Mean	-8.347	-2.912	-5.435		
			SEM	3.148	3.491	3.711		
			95% CI	(-14.5,-2.2)	(-9.8, 3.9)	(-12.7, 1.8)		
					Pr >  t			0.1434
		Week 48	n	48	31			
			LS Mean	-5.249	-2.310	-2.939		
			SEM	3.180	3.684	3.920		
95% CI	(-11.5, 1.0)		(-9.5, 4.9)	(-10.6, 4.8)				
			Pr >  t			0.4536		
Week 56	n	41	25					
	LS Mean	-10.13	-6.890	-3.244				
	SEM	3.302	3.921	4.241				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-16.6,-3.6)	(-14.6, 0.8)	(-11.6, 5.1)
	Pr >  t			0.4446
	n	30	24	
	LS Mean	-7.581	-4.191	-3.390
	SEM	3.586	3.970	4.515
Week 72	95% CI	(-14.6,-0.5)	(-12.0, 3.6)	(-12.2, 5.5)
	Pr >  t			0.4529
	n	32	19	
	LS Mean	-11.53	5.109	-16.64
	SEM	3.523	4.269	4.733
Week 84	95% CI	(-18.4,-4.6)	(-3.3,13.5)	(-25.9,-7.4)
	Pr >  t			0.0005
	n	26	19	
	LS Mean	-8.280	-9.217	0.936
	SEM	3.761	4.270	4.898
Week 96	95% CI	(-15.7,-0.9)	(-17.6,-0.8)	(-8.7,10.5)
	Pr >  t			0.8485
	n	23	14	
	LS Mean	-6.777	-1.513	-5.264
	SEM	3.896	4.734	5.412
Week 108	95% CI	(-14.4, 0.9)	(-10.8, 7.8)	(-15.9, 5.4)
	Pr >  t			0.3310
	n	19	13	
	LS Mean	-7.249	-6.949	-0.300
	SEM	4.158	4.861	5.703
Week 120	95% CI	(-15.4, 0.9)	(-16.5, 2.6)	(-11.5,10.9)
	Pr >  t			0.9581
	n	19	11	
	LS Mean	-6.246	-8.790	2.544
	SEM	4.145	5.170	5.969
Week 132	95% CI	(-14.4, 1.9)	(-18.9, 1.4)	(-9.2,14.3)
	Pr >  t			0.6700
	n	15	5	
	LS Mean	-9.868	-4.264	-5.603
	SEM	4.511	7.109	7.907
Week 144	95% CI	(-18.7,-1.0)	(-18.2, 9.7)	(-21.1, 9.9)
	Pr >  t			0.4787
	n	12	3	
	LS Mean	7.346	-6.604	13.949
	SEM	4.883	8.931	9.767

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-2.2,16.9)	(-24.1,10.9)	(-5.2,33.1)
		Pr >  t			0.1536
	Week 156	n	7	2	
		LS Mean	-10.49	-6.567	-3.923
		SEM	6.078	10.76	12.02
		95% CI	(-22.4, 1.4)	(-27.7,14.6)	(-27.5,19.7)
		Pr >  t			0.7441
	Week 168	n	3	1	
		LS Mean	-11.68	-8.876	-2.799
		SEM	8.840	14.98	17.15
		95% CI	(-29.0, 5.7)	(-38.3,20.5)	(-36.5,30.9)
		Pr >  t			0.8704
	Week 180	n	1	1	
		LS Mean	-13.51	-8.876	-4.638
		SEM	14.93	14.98	20.95
		95% CI	(-42.8,15.8)	(-38.3,20.5)	(-45.8,36.5)
		Pr >  t			0.8249
	Week 192	n	1	1	
		LS Mean	-13.51	-8.876	-4.638
		SEM	14.93	14.98	20.95
		95% CI	(-42.8,15.8)	(-38.3,20.5)	(-45.8,36.5)
		Pr >  t			0.8249
Yes	Week 8	n	44	56	
		LS Mean	-11.01	-6.130	-4.884
		SEM	5.793	5.518	3.637
		95% CI	(-22.4, 0.4)	(-17.0, 4.7)	(-12.0, 2.3)
		Pr >  t			0.1806
	Week 16	n	38	39	
		LS Mean	-13.35	-11.28	-2.069
		SEM	5.994	5.885	4.038
		95% CI	(-25.2,-1.5)	(-22.9, 0.3)	(-10.0, 5.9)
		Pr >  t			0.6088
	Week 24	n	32	33	
		LS Mean	-12.65	-9.566	-3.087
		SEM	6.096	5.972	4.310
		95% CI	(-24.7,-0.6)	(-21.3, 2.2)	(-11.6, 5.4)
		Pr >  t			0.4743
	Week 32	n	26	30	
		LS Mean	-12.52	-12.00	-0.523
		SEM	6.219	6.036	4.566



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-24.8,-0.3)	(-23.9,-0.1)	(-9.5, 8.5)
	Pr >  t			0.9089
	n	25	24	
	LS Mean	-12.83	-6.195	-6.640
	SEM	6.250	6.183	4.794
Week 48	95% CI	(-25.1,-0.5)	(-18.4, 6.0)	(-16.1, 2.8)
	Pr >  t			0.1668
	n	21	20	
	LS Mean	-15.65	-10.57	-5.076
	SEM	6.369	6.325	5.124
Week 56	95% CI	(-28.2,-3.1)	(-23.0, 1.9)	(-15.1, 5.0)
	Pr >  t			0.3224
	n	18	20	
	LS Mean	-13.35	-6.376	-6.973
	SEM	6.496	6.324	5.282
Week 64	95% CI	(-26.1,-0.6)	(-18.8, 6.1)	(-17.4, 3.4)
	Pr >  t			0.1874
	n	17	18	
	LS Mean	-9.494	-10.88	1.390
	SEM	6.549	6.414	5.452
Week 72	95% CI	(-22.4, 3.4)	(-23.5, 1.7)	(-9.3,12.1)
	Pr >  t			0.7989
	n	16	16	
	LS Mean	-11.83	-10.21	-1.616
	SEM	6.605	6.522	5.646
Week 84	95% CI	(-24.8, 1.2)	(-23.0, 2.6)	(-12.7, 9.5)
	Pr >  t			0.7749
	n	14	14	
	LS Mean	-13.49	-4.032	-9.459
	SEM	6.732	6.655	5.948
Week 96	95% CI	(-26.7,-0.2)	(-17.1, 9.1)	(-21.1, 2.2)
	Pr >  t			0.1124
	n	12	10	
	LS Mean	-7.923	-4.632	-3.291
	SEM	6.908	7.067	6.589
Week 108	95% CI	(-21.5, 5.7)	(-18.5, 9.3)	(-16.2, 9.7)
	Pr >  t			0.6176
	n	7	8	
Week 108	LS Mean	-9.945	-10.24	0.290
	SEM	7.701	7.408	7.741

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.1, 5.2)	(-24.8, 4.3)	(-14.9,15.5)
		Pr >  t			0.9701
	Week 120	n	9	5	
		LS Mean	-12.37	-15.49	3.123
		SEM	7.305	8.341	8.282
		95% CI	(-26.7, 2.0)	(-31.9, 0.9)	(-13.1,19.4)
		Pr >  t			0.7063
	Week 132	n	5	3	
		LS Mean	-14.67	-11.65	-3.019
		SEM	8.390	9.755	10.55
		95% CI	(-31.2, 1.8)	(-30.8, 7.5)	(-23.7,17.7)
		Pr >  t			0.7748
	Week 144	n	3	2	
		LS Mean	-16.09	-10.96	-5.128
		SEM	9.797	11.29	13.01
		95% CI	(-35.3, 3.2)	(-33.1,11.2)	(-30.7,20.4)
		Pr >  t			0.6936
	Week 156	n	3	1	
		LS Mean	-16.00	-11.70	-4.302
		SEM	9.807	14.96	16.30
		95% CI	(-35.3, 3.3)	(-41.1,17.7)	(-36.3,27.7)
		Pr >  t			0.7919
	Week 168	n	1	1	
		LS Mean	-12.51	-11.70	-0.817
		SEM	15.02	14.96	19.87
		95% CI	(-42.0,17.0)	(-41.1,17.7)	(-39.9,38.2)
		Pr >  t			0.9672

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	-5.857	-0.706	-5.151		
			SEM	3.057	3.036	2.630		
			95% CI	(-11.9, 0.2)	(-6.7, 5.3)	(-10.3, 0.0)		
					Pr >  t			0.0507
		Week 16	n	92	77			
			LS Mean	-10.29	-4.626	-5.660		
			SEM	3.104	3.223	2.840		
			95% CI	(-16.4,-4.2)	(-11.0, 1.7)	(-11.2,-0.1)		
					Pr >  t			0.0467
		Week 24	n	83	66			
			LS Mean	-8.025	-3.846	-4.179		
			SEM	3.166	3.302	2.989		
			95% CI	(-14.3,-1.8)	(-10.3, 2.6)	(-10.0, 1.7)		
					Pr >  t			0.1625
		Week 32	n	72	60			
			LS Mean	-7.949	-2.783	-5.166		
			SEM	3.245	3.374	3.124		
			95% CI	(-14.3,-1.6)	(-9.4, 3.9)	(-11.3, 1.0)		
					Pr >  t			0.0987
		Week 40	n	64	51			
			LS Mean	-9.819	-3.004	-6.814		
			SEM	3.305	3.490	3.296		
			95% CI	(-16.3,-3.3)	(-9.9, 3.9)	(-13.3,-0.3)		
					Pr >  t			0.0390
		Week 48	n	58	45			
			LS Mean	-8.925	-3.412	-5.512		
			SEM	3.359	3.575	3.440		
95% CI	(-15.5,-2.3)		(-10.4, 3.6)	(-12.3, 1.2)				
			Pr >  t			0.1094		
Week 56	n	49	38					
	LS Mean	-9.952	-4.518	-5.433				
	SEM	3.459	3.702	3.671				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-16.7,-3.2)	(-11.8, 2.8)	(-12.6, 1.8)
	Pr >  t			0.1392
	n	39	37	
	LS Mean	-6.779	-4.705	-2.074
	SEM	3.615	3.724	3.845
Week 72	95% CI	(-13.9, 0.3)	(-12.0, 2.6)	(-9.6, 5.5)
	Pr >  t			0.5898
	n	41	32	
	LS Mean	-10.66	0.848	-11.51
	SEM	3.580	3.847	3.930
Week 84	95% CI	(-17.7,-3.6)	(-6.7, 8.4)	(-19.2,-3.8)
	Pr >  t			0.0035
	n	33	29	
	LS Mean	-9.639	-6.053	-3.587
	SEM	3.772	3.938	4.175
Week 96	95% CI	(-17.0,-2.2)	(-13.8, 1.7)	(-11.8, 4.6)
	Pr >  t			0.3905
	n	31	21	
	LS Mean	-5.310	-1.777	-3.532
	SEM	3.817	4.283	4.550
Week 108	95% CI	(-12.8, 2.2)	(-10.2, 6.6)	(-12.5, 5.4)
	Pr >  t			0.4377
	n	23	18	
	LS Mean	-8.116	-5.739	-2.377
	SEM	4.131	4.480	4.983
Week 120	95% CI	(-16.2,-0.0)	(-14.5, 3.1)	(-12.2, 7.4)
	Pr >  t			0.6333
	n	25	15	
	LS Mean	-6.682	-9.860	3.178
	SEM	4.030	4.738	5.146
Week 132	95% CI	(-14.6, 1.2)	(-19.2,-0.6)	(-6.9,13.3)
	Pr >  t			0.5370
	n	17	8	
	LS Mean	-9.655	-5.609	-4.046
	SEM	4.507	5.900	6.544
Week 144	95% CI	(-18.5,-0.8)	(-17.2, 6.0)	(-16.9, 8.8)
	Pr >  t			0.5365
	n	15	5	
Week 144	LS Mean	2.846	-6.595	9.441
	SEM	4.671	7.126	7.777

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.3,12.0)	(-20.6, 7.4)	(-5.8,24.7)
		Pr >  t			0.2250
	Week 156	n	10	3	
		LS Mean	-11.54	-6.921	-4.621
		SEM	5.388	8.882	9.780
		95% CI	(-22.1,-1.0)	(-24.3,10.5)	(-23.8,14.6)
		Pr >  t			0.6367
	Week 168	n	4	2	
		LS Mean	-11.73	-7.953	-3.780
		SEM	7.790	10.68	12.75
		95% CI	(-27.0, 3.5)	(-28.9,13.0)	(-28.8,21.2)
		Pr >  t			0.7669
	Week 180	n	1	1	
		LS Mean	-14.44	-9.229	-5.213
		SEM	14.79	14.80	20.63
		95% CI	(-43.5,14.6)	(-38.3,19.8)	(-45.7,35.3)
		Pr >  t			0.8006
	Week 192	n	1	1	
		LS Mean	-14.44	-9.229	-5.213
		SEM	14.79	14.80	20.63
		95% CI	(-43.5,14.6)	(-38.3,19.8)	(-45.7,35.3)
		Pr >  t			0.8006
Yes	Week 8	n	38	42	
		LS Mean	-5.587	-1.242	-4.345
		SEM	3.736	3.974	3.789
		95% CI	(-13.0, 1.8)	(-9.1, 6.6)	(-11.8, 3.1)
		Pr >  t			0.2530
	Week 16	n	32	30	
		LS Mean	-6.785	-0.881	-5.904
		SEM	4.030	4.234	4.234
		95% CI	(-14.7, 1.2)	(-9.2, 7.5)	(-14.3, 2.4)
		Pr >  t			0.1647
	Week 24	n	22	15	
		LS Mean	-2.953	-0.452	-2.501
		SEM	4.369	5.168	5.428
		95% CI	(-11.6, 5.7)	(-10.6, 9.7)	(-13.2, 8.2)
		Pr >  t			0.6453
	Week 32	n	14	13	
		LS Mean	-6.645	-7.095	0.451
		SEM	5.129	5.390	6.135

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 40	95% CI	(-16.7, 3.5)	(-17.7, 3.5)	(-11.6,12.5)	
	Pr >  t			0.9415	
	n	11	11		
	LS Mean	-2.986	-0.770	-2.216	
	SEM	5.535	5.672	6.714	
Week 48	95% CI	(-13.9, 7.9)	(-11.9,10.4)	(-15.4,11.0)	
	Pr >  t			0.7416	
	n	11	6		
	LS Mean	0.045	-8.393	8.439	
	SEM	5.535	6.956	7.834	
Week 56	95% CI	(-10.9,10.9)	(-22.1, 5.3)	(-7.0,23.9)	
	Pr >  t			0.2823	
	n	10	7		
	LS Mean	-11.09	-5.409	-5.677	
	SEM	5.707	6.583	7.631	
Week 64	95% CI	(-22.3, 0.2)	(-18.4, 7.6)	(-20.7, 9.3)	
	Pr >  t			0.4576	
	n	8	5		
	LS Mean	-8.177	-8.946	0.769	
	SEM	6.145	7.444	8.688	
Week 72	95% CI	(-20.3, 3.9)	(-23.6, 5.7)	(-16.3,17.9)	
	Pr >  t			0.9295	
	n	7	3		
	LS Mean	-10.16	-7.914	-2.243	
	SEM	6.445	9.114	10.33	
Week 84	95% CI	(-22.8, 2.5)	(-25.9,10.0)	(-22.6,18.1)	
	Pr >  t			0.8284	
	n	7	4		
	LS Mean	-5.395	0.469	-5.865	
	SEM	6.445	8.121	9.468	
Week 96	95% CI	(-18.1, 7.3)	(-15.5,16.5)	(-24.5,12.8)	
	Pr >  t			0.5362	
	n	4	3		
	LS Mean	-13.07	3.196	-16.27	
	SEM	7.963	9.114	11.34	
Week 108	95% CI	(-28.7, 2.6)	(-14.7,21.1)	(-38.6, 6.1)	
	Pr >  t			0.1528	
	n	3	3		
Week 108	LS Mean	-1.215	-12.99	11.772	
	SEM	8.960	9.105	12.06	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.9,16.4)	(-30.9, 4.9)	(-12.0,35.5)
		Pr >  t			0.3300
	Week 120	n	3	1	
		LS Mean	-12.77	-9.592	-3.178
		SEM	8.962	14.77	16.75
		95% CI	(-30.4, 4.9)	(-38.7,19.5)	(-36.2,29.8)
		Pr >  t			0.8498
	Week 132	n	3		
		LS Mean	-14.98	NE	NE
		SEM	8.958	NE	NE
		95% CI	(-32.6, 2.7)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	-4.526	-0.042	-4.484		
			SEM	2.805	2.798	2.480		
			95% CI	(-10.0, 1.0)	(-5.5, 5.5)	(-9.4, 0.4)		
					Pr >  t			0.0712
		Week 16	n	92	83			
			LS Mean	-7.710	-2.774	-4.936		
			SEM	2.886	2.973	2.688		
			95% CI	(-13.4,-2.0)	(-8.6, 3.1)	(-10.2, 0.3)		
					Pr >  t			0.0668
		Week 24	n	77	59			
			LS Mean	-6.437	-1.262	-5.175		
			SEM	2.956	3.166	2.969		
			95% CI	(-12.3,-0.6)	(-7.5, 5.0)	(-11.0, 0.7)		
					Pr >  t			0.0818
		Week 32	n	57	53			
			LS Mean	-7.358	-3.610	-3.748		
			SEM	3.145	3.229	3.191		
			95% CI	(-13.5,-1.2)	(-10.0, 2.7)	(-10.0, 2.5)		
					Pr >  t			0.2404
		Week 40	n	50	44			
			LS Mean	-7.200	-1.014	-6.186		
			SEM	3.223	3.362	3.389		
			95% CI	(-13.5,-0.9)	(-7.6, 5.6)	(-12.8, 0.5)		
					Pr >  t			0.0683
		Week 48	n	47	37			
			LS Mean	-5.498	-1.662	-3.836		
			SEM	3.260	3.487	3.548		
95% CI	(-11.9, 0.9)		(-8.5, 5.2)	(-10.8, 3.1)				
			Pr >  t			0.2799		
Week 56	n	40	32					
	LS Mean	-8.332	-1.186	-7.145				
	SEM	3.368	3.604	3.759				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-14.9,-1.7)	(-8.3, 5.9)	(-14.5, 0.2)
	Pr >  t			0.0576
	n	32	27	
	LS Mean	-5.758	-3.966	-1.791
Week 72	SEM	3.538	3.756	4.054
	95% CI	(-12.7, 1.2)	(-11.3, 3.4)	(-9.7, 6.2)
	Pr >  t			0.6587
	n	31	23	
Week 84	LS Mean	-8.833	0.841	-9.674
	SEM	3.567	3.916	4.226
	95% CI	(-15.8,-1.8)	(-6.8, 8.5)	(-18.0,-1.4)
	Pr >  t			0.0223
Week 96	n	27	21	
	LS Mean	-9.176	-1.123	-8.054
	SEM	3.693	4.013	4.417
	95% CI	(-16.4,-1.9)	(-9.0, 6.8)	(-16.7, 0.6)
Week 108	Pr >  t			0.0685
	n	23	16	
	LS Mean	-5.041	-0.052	-4.989
	SEM	3.844	4.344	4.846
Week 120	95% CI	(-12.6, 2.5)	(-8.6, 8.5)	(-14.5, 4.5)
	Pr >  t			0.3034
	n	15	14	
	LS Mean	-5.767	-2.220	-3.547
Week 132	SEM	4.370	4.530	5.422
	95% CI	(-14.3, 2.8)	(-11.1, 6.7)	(-14.2, 7.1)
	Pr >  t			0.5131
	n	18	8	
Week 144	LS Mean	-11.11	-6.826	-4.281
	SEM	4.127	5.513	6.106
	95% CI	(-19.2,-3.0)	(-17.6, 4.0)	(-16.3, 7.7)
	Pr >  t			0.4834
Week 132	n	12	4	
	LS Mean	-13.86	3.865	-17.72
	SEM	4.706	7.283	8.061
	95% CI	(-23.1,-4.6)	(-10.4,18.2)	(-33.5,-1.9)
Week 144	Pr >  t			0.0281
	n	8	3	
	LS Mean	-9.476	-3.922	-5.554
	SEM	5.433	8.270	9.377

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.1, 1.2)	(-20.1,12.3)	(-24.0,12.8)
		Pr >  t			0.5538
	Week 156	n	5	1	
		LS Mean	-11.36	-4.049	-7.307
		SEM	6.584	13.76	14.91
		95% CI	(-24.3, 1.6)	(-31.0,22.9)	(-36.6,22.0)
		Pr >  t			0.6242
	Week 168	n	2	1	
		LS Mean	-11.49	-4.049	-7.442
		SEM	9.901	13.76	16.64
		95% CI	(-30.9, 7.9)	(-31.0,22.9)	(-40.1,25.2)
		Pr >  t			0.6549
	Week 180	n	1		
		LS Mean	-14.72	NE	NE
		SEM	13.72	NE	NE
		95% CI	(-41.6,12.2)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	-14.72	NE	NE
		SEM	13.72	NE	NE
		95% CI	(-41.6,12.2)	NE	NE
		Pr >  t			NE
Yes	Week 8	n	38	30	
		LS Mean	-6.847	-1.901	-4.947
		SEM	4.525	4.894	4.505
		95% CI	(-15.8, 2.1)	(-11.6, 7.8)	(-13.8, 3.9)
		Pr >  t			0.2731
	Week 16	n	32	24	
		LS Mean	-11.75	-3.531	-8.223
		SEM	4.657	5.121	4.943
		95% CI	(-21.0,-2.6)	(-13.6, 6.6)	(-17.9, 1.5)
		Pr >  t			0.0971
	Week 24	n	28	22	
		LS Mean	-5.528	-5.868	0.340
		SEM	4.881	5.230	5.189
		95% CI	(-15.2, 4.1)	(-16.2, 4.5)	(-9.9,10.5)
		Pr >  t			0.9478
	Week 32	n	29	20	
		LS Mean	-5.995	-0.984	-5.011
		SEM	4.849	5.461	5.287

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-15.6, 3.6)	(-11.8, 9.8)	(-15.4, 5.4)
		Pr >  t			0.3439
		n	25	18	
		LS Mean	-9.342	-3.888	-5.454
		SEM	5.000	5.598	5.569
Week 48		95% CI	(-19.2, 0.5)	(-14.9, 7.1)	(-16.4, 5.5)
		Pr >  t			0.3280
		n	22	14	
		LS Mean	-8.958	-6.657	-2.301
		SEM	5.145	5.974	6.073
Week 56		95% CI	(-19.1, 1.2)	(-18.4, 5.1)	(-14.2, 9.6)
		Pr >  t			0.7050
		n	19	13	
		LS Mean	-11.18	-9.872	-1.310
		SEM	5.318	6.101	6.359
Week 64		95% CI	(-21.7,-0.7)	(-21.9, 2.1)	(-13.8,11.2)
		Pr >  t			0.8368
		n	15	15	
		LS Mean	-6.969	-5.117	-1.852
		SEM	5.644	5.868	6.435
Week 72		95% CI	(-18.1, 4.1)	(-16.7, 6.4)	(-14.5,10.8)
		Pr >  t			0.7736
		n	17	12	
		LS Mean	-11.18	1.661	-12.84
		SEM	5.466	6.241	6.619
Week 84		95% CI	(-22.0,-0.4)	(-10.6,13.9)	(-25.9, 0.2)
		Pr >  t			0.0530
		n	13	12	
		LS Mean	-5.480	-9.916	4.436
		SEM	5.950	6.243	6.971
Week 96		95% CI	(-17.2, 6.2)	(-22.2, 2.4)	( -9.3,18.1)
		Pr >  t			0.5249
		n	12	8	
		LS Mean	-5.398	-0.559	-4.839
		SEM	6.087	7.066	7.832
Week 108		95% CI	(-17.4, 6.6)	(-14.5,13.3)	(-20.2,10.6)
		Pr >  t			0.5370
		n	11	7	
		LS Mean	-7.080	-12.76	5.676
		SEM	6.250	7.396	8.252

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120		95% CI	(-19.4, 5.2)	(-27.3, 1.8)	(-10.5,21.9)
		Pr >  t			0.4919
		n	10	8	
		LS Mean	2.089	-11.92	14.009
		SEM	6.437	7.070	8.109
Week 132		95% CI	(-10.6,14.8)	(-25.8, 2.0)	( -1.9,29.9)
		Pr >  t			0.0847
		n	8	4	
		LS Mean	-3.047	-13.92	10.876
		SEM	6.929	9.105	10.25
Week 144		95% CI	(-16.7,10.6)	(-31.8, 4.0)	( -9.3,31.0)
		Pr >  t			0.2893
		n	7	2	
		LS Mean	19.227	-9.220	28.447
		SEM	7.261	12.17	13.23
Week 156		95% CI	( 5.0,33.5)	(-33.1,14.7)	( 2.4,54.5)
		Pr >  t			0.0321
		n	5	2	
		LS Mean	-9.077	-9.220	0.143
		SEM	8.223	12.17	13.79
Week 168		95% CI	(-25.2, 7.1)	(-33.1,14.7)	(-26.9,27.2)
		Pr >  t			0.9917
		n	2	1	
		LS Mean	-8.555	-11.37	2.811
		SEM	12.06	16.68	19.95
Week 180		95% CI	(-32.2,15.1)	(-44.1,21.4)	(-36.4,42.0)
		Pr >  t			0.8880
		n		1	
		LS Mean	NE	-11.37	NE
		SEM	NE	16.68	NE
Week 192		95% CI	NE	(-44.1,21.4)	NE
		Pr >  t			NE
		n		1	
		LS Mean	NE	-11.37	NE
		SEM	NE	16.68	NE
		95% CI	NE	(-44.1,21.4)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	-3.356	1.580	-4.936		
			SEM	1.585	1.583	2.239		
			95% CI	(-6.5,-0.2)	(-1.5, 4.7)	(-9.3,-0.5)		
					Pr >  t			0.0278
		Week 16	n	118	104			
			LS Mean	-6.902	-1.689	-5.213		
			SEM	1.667	1.766	2.428		
			95% CI	(-10.2,-3.6)	(-5.2, 1.8)	(-10.0,-0.4)		
					Pr >  t			0.0321
		Week 24	n	100	79			
			LS Mean	-4.186	-1.447	-2.739		
			SEM	1.782	1.973	2.657		
			95% CI	(-7.7,-0.7)	(-5.3, 2.4)	(-8.0, 2.5)		
					Pr >  t			0.3028
		Week 32	n	84	72			
			LS Mean	-4.839	-1.750	-3.089		
			SEM	1.907	2.049	2.797		
			95% CI	(-8.6,-1.1)	(-5.8, 2.3)	(-8.6, 2.4)		
					Pr >  t			0.2696
		Week 40	n	73	62			
			LS Mean	-5.908	-0.457	-5.451		
			SEM	2.015	2.171	2.960		
			95% CI	(-9.9,-2.0)	(-4.7, 3.8)	(-11.3, 0.4)		
					Pr >  t			0.0658
		Week 48	n	67	51			
			LS Mean	-4.570	-1.790	-2.779		
			SEM	2.082	2.345	3.134		
95% CI	(-8.7,-0.5)		(-6.4, 2.8)	(-8.9, 3.4)				
			Pr >  t			0.3753		
Week 56	n	57	45					
	LS Mean	-7.346	-2.503	-4.843				
	SEM	2.218	2.467	3.316				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-11.7,-3.0)	(-7.3, 2.3)	(-11.3, 1.7)
	Pr >  t			0.1444
	n	45	42	
	LS Mean	-4.067	-3.039	-1.029
	SEM	2.436	2.538	3.516
Week 72	95% CI	(-8.8, 0.7)	(-8.0, 1.9)	(-7.9, 5.9)
	Pr >  t			0.7699
	n	46	35	
	LS Mean	-7.735	2.311	-10.05
	SEM	2.416	2.734	3.647
Week 84	95% CI	(-12.5,-3.0)	(-3.1, 7.7)	(-17.2,-2.9)
	Pr >  t			0.0060
	n	40	33	
	LS Mean	-6.080	-3.066	-3.014
	SEM	2.556	2.802	3.791
Week 96	95% CI	(-11.1,-1.1)	(-8.6, 2.4)	(-10.5, 4.4)
	Pr >  t			0.4267
	n	34	24	
	LS Mean	-3.186	1.083	-4.269
	SEM	2.735	3.207	4.214
Week 108	95% CI	(-8.6, 2.2)	(-5.2, 7.4)	(-12.5, 4.0)
	Pr >  t			0.3112
	n	26	21	
	LS Mean	-4.388	-4.538	0.149
	SEM	3.067	3.400	4.577
Week 120	95% CI	(-10.4, 1.6)	(-11.2, 2.1)	(-8.8, 9.1)
	Pr >  t			0.9740
	n	27	16	
	LS Mean	-4.384	-7.635	3.251
	SEM	3.020	3.837	4.881
Week 132	95% CI	(-10.3, 1.5)	(-15.2,-0.1)	(-6.3,12.8)
	Pr >  t			0.5055
	n	20	8	
	LS Mean	-7.551	-3.409	-4.143
	SEM	3.440	5.277	6.298
Week 144	95% CI	(-14.3,-0.8)	(-13.8, 6.9)	(-16.5, 8.2)
	Pr >  t			0.5107
	n	14	5	
	LS Mean	6.678	-4.436	11.114
	SEM	4.043	6.608	7.745

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.3,14.6)	(-17.4, 8.5)	(-4.1,26.3)
		Pr >  t			0.1515
	Week 156	n	10	3	
		LS Mean	-8.427	-4.740	-3.687
		SEM	4.726	8.456	9.686
		95% CI	(-17.7, 0.8)	(-21.3,11.8)	(-22.7,15.3)
		Pr >  t			0.7035
	Week 168	n	4	2	
		LS Mean	-8.644	-5.756	-2.888
		SEM	7.326	10.31	12.65
		95% CI	(-23.0, 5.7)	(-26.0,14.5)	(-27.7,21.9)
		Pr >  t			0.8195
	Week 180	n	1	1	
		LS Mean	-11.36	-7.013	-4.352
		SEM	14.50	14.50	20.51
		95% CI	(-39.8,17.1)	(-35.5,21.4)	(-44.6,35.9)
		Pr >  t			0.8320
	Week 192	n	1	1	
		LS Mean	-11.36	-7.013	-4.352
		SEM	14.50	14.50	20.51
		95% CI	(-39.8,17.1)	(-35.5,21.4)	(-44.6,35.9)
		Pr >  t			0.8320
Prior use	Week 8	n	8	6	
		LS Mean	-11.47	-9.339	-2.127
		SEM	4.881	5.636	7.438
		95% CI	(-21.7,-1.2)	(-21.1, 2.4)	(-17.7,13.4)
		Pr >  t			0.7780
	Week 16	n	6	3	
		LS Mean	-16.69	8.326	-25.01
		SEM	5.626	7.794	9.612
		95% CI	(-28.3,-5.0)	(-7.7,24.4)	(-44.8,-5.2)
		Pr >  t			0.0155
	Week 24	n	5	2	
		LS Mean	-16.81	22.435	-39.24
		SEM	6.017	9.329	11.11
		95% CI	(-29.2,-4.4)	( 3.3,41.5)	(-62.0, -16)
		Pr >  t			0.0015
	Week 32	n	2	1	
		LS Mean	-18.90	34.173	-53.08
		SEM	8.776	12.48	15.27



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-36.9,-0.9)	( 8.5,59.8)	(-84.4, -22)
	Pr >  t			0.0017
Week 40	n	2		
	LS Mean	-18.90	NE	NE
	SEM	8.776	NE	NE
	95% CI	(-36.9,-0.9)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	-18.90	NE	NE
	SEM	8.776	NE	NE
	95% CI	(-36.9,-0.9)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	-18.90	NE	NE
	SEM	8.776	NE	NE
	95% CI	(-36.9,-0.9)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	-18.90	NE	NE
	SEM	8.776	NE	NE
	95% CI	(-36.9,-0.9)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	-18.90	NE	NE
	SEM	8.776	NE	NE
	95% CI	(-36.9,-0.9)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	-17.38	NE	NE
	SEM	11.64	NE	NE
	95% CI	(-41.3, 6.6)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	-17.38	NE	NE
	SEM	11.64	NE	NE
	95% CI	(-41.3, 6.6)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	-17.38	NE	NE
	SEM	11.64	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-41.3, 6.6)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-5.883	-0.652	-5.232		
			SEM	2.387	2.440	2.216		
			95% CI	(-10.6,-1.2)	(-5.4, 4.1)	(-9.6,-0.9)		
					Pr >  t			0.0185
		Week 16	n	119	97			
			LS Mean	-8.828	-3.739	-5.090		
			SEM	2.463	2.608	2.433		
			95% CI	(-13.7,-4.0)	(-8.9, 1.4)	(-9.9,-0.3)		
					Pr >  t			0.0367
		Week 24	n	100	75			
			LS Mean	-6.099	-2.862	-3.237		
			SEM	2.544	2.758	2.658		
			95% CI	(-11.1,-1.1)	(-8.3, 2.6)	(-8.5, 2.0)		
					Pr >  t			0.2236
		Week 32	n	82	69			
			LS Mean	-7.089	-3.382	-3.708		
			SEM	2.668	2.820	2.805		
			95% CI	(-12.3,-1.9)	(-8.9, 2.2)	(-9.2, 1.8)		
					Pr >  t			0.1865
		Week 40	n	73	58			
			LS Mean	-7.927	-1.958	-5.969		
			SEM	2.730	2.937	2.972		
			95% CI	(-13.3,-2.6)	(-7.7, 3.8)	(-11.8,-0.1)		
					Pr >  t			0.0448
		Week 48	n	66	48			
			LS Mean	-6.457	-3.732	-2.725		
			SEM	2.786	3.069	3.153		
95% CI	(-11.9,-1.0)		(-9.8, 2.3)	(-8.9, 3.5)				
			Pr >  t			0.3876		
Week 56	n	56	43					
	LS Mean	-9.240	-5.643	-3.597				
	SEM	2.887	3.154	3.327				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.9,-3.6)	(-11.8, 0.5)	(-10.1, 2.9)
		Pr >  t			0.2798
	Week 64	n	45	41	
		LS Mean	-6.073	-5.048	-1.025
		SEM	3.039	3.194	3.499
		95% CI	(-12.0,-0.1)	(-11.3, 1.2)	(-7.9, 5.8)
		Pr >  t			0.7697
	Week 72	n	46	34	
		LS Mean	-9.437	0.453	-9.890
		SEM	3.024	3.356	3.635
		95% CI	(-15.4,-3.5)	(-6.1, 7.0)	(-17.0,-2.8)
		Pr >  t			0.0066
	Week 84	n	37	32	
		LS Mean	-6.928	-5.085	-1.844
		SEM	3.212	3.414	3.834
		95% CI	(-13.2,-0.6)	(-11.8, 1.6)	(-9.4, 5.7)
		Pr >  t			0.6307
	Week 96	n	33	23	
		LS Mean	-4.977	-0.760	-4.217
		SEM	3.311	3.770	4.237
		95% CI	(-11.5, 1.5)	(-8.2, 6.6)	(-12.5, 4.1)
		Pr >  t			0.3197
	Week 108	n	24	20	
		LS Mean	-5.900	-6.654	0.754
		SEM	3.656	3.947	4.654
		95% CI	(-13.1, 1.3)	(-14.4, 1.1)	(-8.4, 9.9)
		Pr >  t			0.8714
	Week 120	n	25	16	
		LS Mean	-4.488	-9.632	5.144
		SEM	3.603	4.263	4.892
		95% CI	(-11.6, 2.6)	(-18.0,-1.3)	(-4.5,14.7)
		Pr >  t			0.2932
	Week 132	n	19	8	
		LS Mean	-7.854	-5.429	-2.425
		SEM	3.951	5.566	6.270
		95% CI	(-15.6,-0.1)	(-16.3, 5.5)	(-14.7, 9.9)
		Pr >  t			0.6990
	Week 144	n	14	5	
		LS Mean	4.716	-6.415	11.132
		SEM	4.400	6.813	7.656

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.9,13.3)	(-19.8, 6.9)	(-3.9,26.1)
		Pr >  t			0.1462
	Week 156	n	10	3	
		LS Mean	-10.14	-6.717	-3.427
		SEM	5.032	8.578	9.572
		95% CI	(-20.0,-0.3)	(-23.5,10.1)	(-22.2,15.4)
		Pr >  t			0.7204
	Week 168	n	4	2	
		LS Mean	-10.35	-7.729	-2.626
		SEM	7.477	10.37	12.50
		95% CI	(-25.0, 4.3)	(-28.1,12.6)	(-27.1,21.9)
		Pr >  t			0.8336
	Week 180	n	1	1	
		LS Mean	-13.10	-9.005	-4.097
		SEM	14.45	14.46	20.26
		95% CI	(-41.4,15.2)	(-37.4,19.4)	(-43.8,35.7)
		Pr >  t			0.8398
	Week 192	n	1	1	
		LS Mean	-13.10	-9.005	-4.097
		SEM	14.45	14.46	20.26
		95% CI	(-41.4,15.2)	(-37.4,19.4)	(-43.8,35.7)
		Pr >  t			0.8398
Yes	Week 8	n	5	9	
		LS Mean	3.469	-6.454	9.923
		SEM	10.15	7.412	12.67
		95% CI	(-17.3,24.2)	(-21.5, 8.6)	(-15.9,35.8)
		Pr >  t			0.4397
	Week 16	n	5	9	
		LS Mean	-16.53	-5.849	-10.68
		SEM	10.15	7.565	12.82
		95% CI	(-37.3, 4.2)	(-21.2, 9.5)	(-36.9,15.5)
		Pr >  t			0.4112
	Week 24	n	5	5	
		LS Mean	-16.53	-9.323	-7.208
		SEM	10.15	9.518	14.07
		95% CI	(-37.3, 4.2)	(-28.5, 9.9)	(-35.8,21.3)
		Pr >  t			0.6116
	Week 32	n	4	3	
		LS Mean	-9.274	-5.186	-4.088
		SEM	11.00	11.64	16.19

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-31.6,13.1)	(-28.6,18.2)	(-36.7,28.6)
		Pr >  t			0.8019
	Week 40	n	2	3	
		LS Mean	-15.04	-14.60	-0.438
		SEM	14.18	11.89	18.56
		95% CI	(-43.6,13.5)	(-38.5, 9.3)	(-37.7,36.9)
		Pr >  t			0.9813
	Week 48	n	3	2	
		LS Mean	-17.57	-11.26	-6.314
		SEM	12.24	14.21	18.76
		95% CI	(-42.3, 7.2)	(-39.8,17.3)	(-44.0,31.4)
		Pr >  t			0.7379
	Week 56	n	3	1	
		LS Mean	-17.57	45.381	-62.95
		SEM	12.24	19.18	23.02
		95% CI	(-42.3, 7.2)	( 6.8,83.9)	( -109, -17)
		Pr >  t			0.0086
	Week 64	n	2		
		LS Mean	-15.04	NE	NE
		SEM	14.18	NE	NE
		95% CI	(-43.6,13.5)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	-19.71	NE	NE
		SEM	14.21	NE	NE
		95% CI	(-48.3, 8.9)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	-28.68	NE	NE
		SEM	12.24	NE	NE
		95% CI	(-53.4,-4.0)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	-15.04	NE	NE
		SEM	14.18	NE	NE
		95% CI	(-43.6,13.5)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	-17.96	NE	NE
		SEM	14.32	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-46.7,10.8)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	-28.68	NE	NE
	SEM	12.24	NE	NE
	95% CI	(-53.4,-4.0)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-46.62	NE	NE
	SEM	19.00	NE	NE
	95% CI	(-84.8,-8.5)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-13.29	NE	NE
	SEM	19.00	NE	NE
	95% CI	(-51.4,24.9)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-5.545	-0.795	-4.750		
			SEM	2.473	2.521	2.356		
			95% CI	(-10.4,-0.7)	(-5.7, 4.2)	(-9.4,-0.1)		
					Pr >  t			0.0442
		Week 16	n	111	91			
			LS Mean	-9.195	-3.788	-5.407		
			SEM	2.546	2.699	2.571		
			95% CI	(-14.2,-4.2)	(-9.1, 1.5)	(-10.5,-0.4)		
					Pr >  t			0.0358
		Week 24	n	96	70			
			LS Mean	-6.800	-3.930	-2.871		
			SEM	2.621	2.863	2.798		
			95% CI	(-12.0,-1.7)	(-9.6, 1.7)	(-8.4, 2.6)		
					Pr >  t			0.3052
		Week 32	n	77	61			
			LS Mean	-8.374	-4.166	-4.207		
			SEM	2.763	2.963	2.995		
			95% CI	(-13.8,-2.9)	(-10.0, 1.7)	(-10.1, 1.7)		
					Pr >  t			0.1604
		Week 40	n	69	52			
			LS Mean	-8.785	-2.463	-6.323		
			SEM	2.826	3.086	3.164		
			95% CI	(-14.3,-3.2)	(-8.5, 3.6)	(-12.5,-0.1)		
			Pr >  t			0.0459		
Week 48	n	62	41					
	LS Mean	-6.718	-4.176	-2.542				
	SEM	2.890	3.271	3.400				
	95% CI	(-12.4,-1.0)	(-10.6, 2.2)	(-9.2, 4.1)				
			Pr >  t			0.4547		
Week 56	n	53	35					
	LS Mean	-10.91	-7.744	-3.169				
	SEM	2.991	3.412	3.623				



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.8,-5.0)	(-14.4,-1.0)	(-10.3, 3.9)
		Pr >  t			0.3819
	Week 64	n	44	33	
		LS Mean	-7.636	-5.051	-2.585
		SEM	3.126	3.470	3.790
		95% CI	(-13.8,-1.5)	(-11.9, 1.8)	(-10.0, 4.9)
		Pr >  t			0.4954
	Week 72	n	45	28	
		LS Mean	-10.61	0.573	-11.18
		SEM	3.110	3.637	3.931
		95% CI	(-16.7,-4.5)	( -6.6, 7.7)	(-18.9,-3.5)
		Pr >  t			0.0045
	Week 84	n	39	27	
		LS Mean	-8.413	-6.160	-2.253
		SEM	3.239	3.677	4.060
		95% CI	(-14.8,-2.1)	(-13.4, 1.1)	(-10.2, 5.7)
		Pr >  t			0.5790
	Week 96	n	34	19	
		LS Mean	-5.408	-1.086	-4.322
		SEM	3.356	4.111	4.549
		95% CI	(-12.0, 1.2)	( -9.2, 7.0)	(-13.2, 4.6)
		Pr >  t			0.3423
	Week 108	n	26	17	
		LS Mean	-7.109	-8.212	1.104
		SEM	3.643	4.273	4.898
		95% CI	(-14.3, 0.0)	(-16.6, 0.2)	( -8.5,10.7)
		Pr >  t			0.8218
	Week 120	n	27	11	
		LS Mean	-6.809	-10.43	3.619
		SEM	3.594	5.017	5.532
		95% CI	(-13.9, 0.2)	(-20.3,-0.6)	( -7.2,14.5)
		Pr >  t			0.5131
	Week 132	n	20	6	
		LS Mean	-10.28	-5.793	-4.490
		SEM	3.966	6.430	7.038
		95% CI	(-18.1,-2.5)	(-18.4, 6.8)	(-18.3, 9.3)
		Pr >  t			0.5236
	Week 144	n	15	4	
		LS Mean	3.215	-7.587	10.803
		SEM	4.380	7.696	8.425

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-5.4,11.8)	(-22.7, 7.5)	(-5.7,27.3)
		Pr >  t			0.2000
	Week 156	n	10	2	
		LS Mean	-11.17	-8.508	-2.661
		SEM	5.136	10.60	11.45
		95% CI	(-21.2,-1.1)	(-29.3,12.3)	(-25.1,19.8)
		Pr >  t			0.8163
	Week 168	n	4	2	
		LS Mean	-11.40	-8.508	-2.888
		SEM	7.629	10.60	12.77
		95% CI	(-26.4, 3.6)	(-29.3,12.3)	(-27.9,22.2)
		Pr >  t			0.8211
	Week 180	n	1	1	
		LS Mean	-14.13	-9.787	-4.348
		SEM	14.74	14.76	20.68
		95% CI	(-43.1,14.8)	(-38.8,19.2)	(-44.9,36.2)
		Pr >  t			0.8335
	Week 192	n	1	1	
		LS Mean	-14.13	-9.787	-4.348
		SEM	14.74	14.76	20.68
		95% CI	(-43.1,14.8)	(-38.8,19.2)	(-44.9,36.2)
		Pr >  t			0.8335
>= 75 Years	Week 8	n	17	19	
		LS Mean	-3.789	0.784	-4.573
		SEM	4.312	3.909	5.818
		95% CI	(-12.4, 4.8)	(-7.0, 8.5)	(-16.1, 7.0)
		Pr >  t			0.4341
	Week 16	n	13	16	
		LS Mean	-6.920	-0.204	-6.716
		SEM	4.790	4.192	6.319
		95% CI	(-16.4, 2.6)	(-8.5, 8.1)	(-19.3, 5.8)
		Pr >  t			0.2906
	Week 24	n	9	11	
		LS Mean	-3.147	4.605	-7.752
		SEM	5.502	4.869	7.312
		95% CI	(-14.0, 7.7)	(-5.0,14.2)	(-22.2, 6.7)
		Pr >  t			0.2911
	Week 32	n	9	12	
		LS Mean	4.461	3.232	1.229
		SEM	5.502	4.735	7.221

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.4,15.4)	(-6.1,12.6)	(-13.1,15.5)
		Pr >  t			0.8652
	Week 40	n	6	10	
		LS Mean	-1.758	0.255	-2.013
		SEM	6.416	5.045	8.125
		95% CI	(-14.4,10.9)	(-9.7,10.2)	(-18.1,14.0)
		Pr >  t			0.8047
	Week 48	n	7	10	
		LS Mean	-7.586	1.048	-8.634
		SEM	6.054	5.065	7.856
		95% CI	(-19.6, 4.4)	(-9.0,11.1)	(-24.2, 6.9)
		Pr >  t			0.2737
	Week 56	n	6	10	
		LS Mean	2.844	10.430	-7.587
		SEM	6.405	5.069	8.120
		95% CI	(-9.8,15.5)	( 0.4,20.5)	(-23.6, 8.5)
		Pr >  t			0.3517
	Week 64	n	3	9	
		LS Mean	8.559	-1.369	9.928
		SEM	8.475	5.273	9.944
		95% CI	(-8.2,25.3)	(-11.8, 9.1)	(-9.7,29.6)
		Pr >  t			0.3195
	Week 72	n	3	7	
		LS Mean	-2.551	2.817	-5.368
		SEM	8.475	5.808	10.23
		95% CI	(-19.3,14.2)	(-8.7,14.3)	(-25.6,14.8)
		Pr >  t			0.6006
	Week 84	n	1	6	
		LS Mean	-20.40	3.028	-23.43
		SEM	13.88	6.165	15.15
		95% CI	(-47.8, 7.0)	(-9.1,15.2)	(-53.3, 6.5)
		Pr >  t			0.1239
	Week 96	n	1	5	
		LS Mean	-20.40	3.285	-23.69
		SEM	13.88	6.637	15.35
		95% CI	(-47.8, 7.0)	(-9.8,16.4)	(-54.0, 6.6)
		Pr >  t			0.1247
	Week 108	n		4	
		LS Mean	NE	3.818	NE
		SEM	NE	7.284	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-10.6,18.2)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	-9.212	-3.381
		SEM	13.92	6.637
		95% CI	(-36.7,18.3)	(-16.5, 9.7)
		Pr >  t		(-36.2,24.6)
	Week 132	n		2
		LS Mean	NE	-0.349
		SEM	NE	9.830
		95% CI	NE	(-19.8,19.1)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	1.168
		SEM	NE	13.57
		95% CI	NE	(-25.6,28.0)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	1.168
		SEM	NE	13.57
		95% CI	NE	(-25.6,28.0)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	-3.453	1.398	-4.852		
			SEM	3.249	3.257	2.717		
			95% CI	(-9.8, 2.9)	(-5.0, 7.8)	(-10.2, 0.5)		
					Pr >  t			0.0747
		Week 16	n	79	68			
			LS Mean	-7.275	-2.026	-5.249		
			SEM	3.291	3.473	2.986		
			95% CI	(-13.7,-0.8)	(-8.9, 4.8)	(-11.1, 0.6)		
					Pr >  t			0.0793
		Week 24	n	64	55			
			LS Mean	-4.980	-3.479	-1.501		
			SEM	3.419	3.639	3.262		
			95% CI	(-11.7, 1.7)	(-10.6, 3.7)	(-7.9, 4.9)		
					Pr >  t			0.6456
		Week 32	n	49	53			
			LS Mean	-4.620	-2.805	-1.816		
			SEM	3.629	3.664	3.464		
			95% CI	(-11.8, 2.5)	(-10.0, 4.4)	(-8.6, 5.0)		
					Pr >  t			0.6003
		Week 40	n	44	45			
			LS Mean	-6.020	-4.731	-1.289		
			SEM	3.704	3.773	3.658		
			95% CI	(-13.3, 1.3)	(-12.1, 2.7)	(-8.5, 5.9)		
					Pr >  t			0.7246
		Week 48	n	41	36			
			LS Mean	-9.392	-4.627	-4.765		
			SEM	3.755	3.941	3.882		
95% CI	(-16.8,-2.0)		(-12.4, 3.1)	(-12.4, 2.9)				
			Pr >  t			0.2200		
Week 56	n	33	32					
	LS Mean	-6.675	-2.674	-4.002				
	SEM	3.928	4.043	4.154				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.4, 1.0)	(-10.6, 5.3)	(-12.2, 4.2)
		Pr >  t			0.3356
	Week 64	n	27	31	
		LS Mean	-5.077	-5.209	0.131
		SEM	4.112	4.074	4.362
		95% CI	(-13.2, 3.0)	(-13.2, 2.8)	(-8.4, 8.7)
		Pr >  t			0.9760
	Week 72	n	26	26	
		LS Mean	-6.420	0.425	-6.845
		SEM	4.151	4.245	4.556
		95% CI	(-14.6, 1.7)	(-7.9, 8.8)	(-15.8, 2.1)
		Pr >  t			0.1334
	Week 84	n	22	23	
		LS Mean	-7.161	-4.004	-3.157
		SEM	4.355	4.375	4.844
		95% CI	(-15.7, 1.4)	(-12.6, 4.6)	(-12.7, 6.3)
		Pr >  t			0.5148
	Week 96	n	18	18	
		LS Mean	-5.319	1.650	-6.969
		SEM	4.607	4.675	5.333
		95% CI	(-14.4, 3.7)	(-7.5, 10.8)	(-17.4, 3.5)
		Pr >  t			0.1916
	Week 108	n	14	14	
		LS Mean	-0.291	-3.931	3.640
		SEM	4.980	5.041	5.959
		95% CI	(-10.1, 9.5)	(-13.8, 6.0)	(-8.1, 15.3)
		Pr >  t			0.5414
	Week 120	n	12	12	
		LS Mean	-2.226	-8.839	6.613
		SEM	5.233	5.297	6.384
		95% CI	(-12.5, 8.0)	(-19.2, 1.6)	(-5.9, 19.1)
		Pr >  t			0.3005
	Week 132	n	9	5	
		LS Mean	-12.12	-1.031	-11.09
		SEM	5.784	7.319	8.508
		95% CI	(-23.5, -0.8)	(-15.4, 13.3)	(-27.8, 5.6)
		Pr >  t			0.1929
	Week 144	n	7	4	
		LS Mean	11.040	-4.726	15.766
		SEM	6.357	8.042	9.510

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-1.4,23.5)	(-20.5,11.1)	(-2.9,34.4)
		Pr >  t			0.0977
	Week 156	n	4	2	
		LS Mean	-10.61	-4.407	-6.204
		SEM	7.983	10.91	12.97
		95% CI	(-26.3, 5.1)	(-25.8,17.0)	(-31.7,19.3)
		Pr >  t			0.6325
	Week 168	n	2	1	
		LS Mean	-8.918	-5.279	-3.638
		SEM	10.86	15.10	18.21
		95% CI	(-30.2,12.4)	(-34.9,24.4)	(-39.4,32.1)
		Pr >  t			0.8417
Yes	Week 8	n	53	48	
		LS Mean	-7.832	-3.734	-4.099
		SEM	3.684	3.830	3.671
		95% CI	(-15.1,-0.5)	(-11.3, 3.8)	(-11.3, 3.1)
		Pr >  t			0.2655
	Week 16	n	45	39	
		LS Mean	-11.17	-4.435	-6.735
		SEM	3.867	4.025	3.943
		95% CI	(-18.8,-3.5)	(-12.4, 3.5)	(-14.5, 1.0)
		Pr >  t			0.0889
	Week 24	n	41	26	
		LS Mean	-8.173	0.243	-8.417
		SEM	3.924	4.352	4.365
		95% CI	(-15.9,-0.4)	(-8.3, 8.8)	(-17.0, 0.2)
		Pr >  t			0.0547
	Week 32	n	37	20	
		LS Mean	-10.12	-2.110	-8.014
		SEM	4.021	4.655	4.702
		95% CI	(-18.1,-2.2)	(-11.3, 7.1)	(-17.3, 1.2)
		Pr >  t			0.0891
	Week 40	n	31	17	
		LS Mean	-10.79	6.760	-17.55
		SEM	4.151	4.886	5.006
		95% CI	(-19.0,-2.6)	(-2.9,16.4)	(-27.4,-7.7)
		Pr >  t			0.0005
	Week 48	n	28	15	
		LS Mean	-2.583	1.292	-3.876
		SEM	4.233	5.045	5.228

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.9, 5.8)	(-8.6, 11.2)	(-14.2, 6.4)
		Pr >  t			0.4589
	Week 56	n	26	13	
		LS Mean	-12.88	-5.946	-6.932
		SEM	4.295	5.240	5.472
		95% CI	(-21.3, -4.4)	(-16.3, 4.4)	(-17.7, 3.8)
		Pr >  t			0.2058
	Week 64	n	20	11	
		LS Mean	-7.889	-1.325	-6.564
		SEM	4.540	5.496	5.909
		95% CI	(-16.8, 1.1)	(-12.1, 9.5)	(-18.2, 5.0)
		Pr >  t			0.2671
	Week 72	n	22	9	
		LS Mean	-14.02	3.370	-17.39
		SEM	4.451	5.837	6.159
		95% CI	(-22.8, -5.3)	(-8.1, 14.8)	(-29.5, -5.3)
		Pr >  t			0.0049
	Week 84	n	18	10	
		LS Mean	-9.392	-4.536	-4.856
		SEM	4.670	5.655	6.141
		95% CI	(-18.6, -0.2)	(-15.7, 6.6)	(-16.9, 7.2)
		Pr >  t			0.4294
	Week 96	n	17	6	
		LS Mean	-5.796	-5.013	-0.783
		SEM	4.717	6.677	7.141
		95% CI	(-15.1, 3.5)	(-18.1, 8.1)	(-14.8, 13.2)
		Pr >  t			0.9128
	Week 108	n	12	7	
		LS Mean	-13.87	-8.841	-5.028
		SEM	5.201	6.333	7.146
		95% CI	(-24.1, -3.6)	(-21.3, 3.6)	(-19.1, 9.0)
		Pr >  t			0.4820
	Week 120	n	16	4	
		LS Mean	-10.42	-8.355	-2.066
		SEM	4.799	7.768	8.212
		95% CI	(-19.9, -1.0)	(-23.6, 6.9)	(-18.2, 14.1)
		Pr >  t			0.8014
	Week 132	n	11	3	
		LS Mean	-8.536	-10.04	1.500
		SEM	5.333	8.719	9.400



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.0, 1.9)	(-27.2, 7.1)	(-17.0,20.0)
		Pr >  t			0.8733
	Week 144	n	8	1	
		LS Mean	-3.235	-9.021	5.786
		SEM	5.872	14.17	14.81
		95% CI	(-14.8, 8.3)	(-36.8,18.8)	(-23.3,34.9)
		Pr >  t			0.6963
	Week 156	n	6	1	
		LS Mean	-11.61	-9.021	-2.585
		SEM	6.526	14.17	15.08
		95% CI	(-24.4, 1.2)	(-36.8,18.8)	(-32.2,27.0)
		Pr >  t			0.8639
	Week 168	n	2	1	
		LS Mean	-13.13	-9.021	-4.105
		SEM	10.24	14.17	17.01
		95% CI	(-33.2, 7.0)	(-36.8,18.8)	(-37.5,29.3)
		Pr >  t			0.8094
	Week 180	n	1	1	
		LS Mean	-15.73	-9.021	-6.706
		SEM	14.05	14.17	19.54
		95% CI	(-43.3,11.9)	(-36.8,18.8)	(-45.1,31.7)
		Pr >  t			0.7317
	Week 192	n	1	1	
		LS Mean	-15.73	-9.021	-6.706
		SEM	14.05	14.17	19.54
		95% CI	(-43.3,11.9)	(-36.8,18.8)	(-45.1,31.7)
		Pr >  t			0.7317

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
95% CI	NE		NE	NE	NE		
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	NE	NE	NE	NE		
	SEM	NE	NE	NE	NE		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	NE
		Pr >  t		NE
	Week 72	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
	Week 84	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
	Week 96	n	1	
		LS Mean	NE	NE
		SEM	NE	NE
		95% CI	NE	NE
		Pr >  t		NE
Positive	Week 8	n	140	140
		LS Mean	-5.658	-0.927
		SEM	2.404	2.436
		95% CI	(-10.4,-0.9)	(-5.7, 3.9)
		Pr >  t		(-9.0,-0.4) 0.0307
	Week 16	n	122	107
		LS Mean	-9.290	-3.672
		SEM	2.478	2.586
		95% CI	(-14.2,-4.4)	(-8.8, 1.4)
		Pr >  t		(-10.3,-0.9) 0.0187
	Week 24	n	104	81
		LS Mean	-6.705	-3.150
		SEM	2.553	2.738
		95% CI	(-11.7,-1.7)	(-8.5, 2.2)
		Pr >  t		(-8.7, 1.6) 0.1735
	Week 32	n	85	73
		LS Mean	-7.323	-3.485
		SEM	2.676	2.809
		95% CI	(-12.6,-2.1)	(-9.0, 2.0)
		Pr >  t		(-9.3, 1.6) 0.1658
	Week 40	n	74	62
		LS Mean	-8.385	-2.521
		SEM	2.750	2.917
				-5.864 2.940

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.8,-3.0)	(-8.2, 3.2)	(-11.6,-0.1)
		Pr >  t			0.0463
	Week 48	n	68	51	
		LS Mean	-7.071	-3.855	-3.217
		SEM	2.797	3.049	3.114
		95% CI	(-12.6,-1.6)	(-9.8, 2.1)	(-9.3, 2.9)
		Pr >  t			0.3017
	Week 56	n	58	45	
		LS Mean	-9.819	-4.568	-5.251
		SEM	2.893	3.143	3.294
		95% CI	(-15.5,-4.1)	(-10.7, 1.6)	(-11.7, 1.2)
		Pr >  t			0.1112
	Week 64	n	47	42	
		LS Mean	-6.661	-5.107	-1.554
		SEM	3.037	3.199	3.476
		95% CI	(-12.6,-0.7)	(-11.4, 1.2)	(-8.4, 5.3)
		Pr >  t			0.6549
	Week 72	n	47	35	
		LS Mean	-10.22	0.241	-10.46
		SEM	3.039	3.357	3.623
		95% CI	(-16.2,-4.3)	(-6.3, 6.8)	(-17.6,-3.4)
		Pr >  t			0.0040
	Week 84	n	39	33	
		LS Mean	-8.557	-5.137	-3.420
		SEM	3.200	3.413	3.799
		95% CI	(-14.8,-2.3)	(-11.8, 1.6)	(-10.9, 4.0)
		Pr >  t			0.3681
	Week 96	n	34	24	
		LS Mean	-5.609	-0.991	-4.618
		SEM	3.317	3.753	4.205
		95% CI	(-12.1, 0.9)	(-8.4, 6.4)	(-12.9, 3.6)
		Pr >  t			0.2722
	Week 108	n	26	21	
		LS Mean	-6.862	-6.604	-0.258
		SEM	3.603	3.919	4.569
		95% CI	(-13.9, 0.2)	(-14.3, 1.1)	(-9.2, 8.7)
		Pr >  t			0.9550
	Week 120	n	28	16	
		LS Mean	-6.849	-9.699	2.850
		SEM	3.515	4.304	4.845

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-13.7, 0.0)	(-18.1,-1.3)	(-6.7,12.4)
	Pr >  t			0.5564
Week 132	n	20	8	
	LS Mean	-10.04	-5.462	-4.573
	SEM	3.925	5.626	6.292
	95% CI	(-17.7,-2.3)	(-16.5, 5.6)	(-16.9, 7.8)
	Pr >  t			0.4675
Week 144	n	15	5	
	LS Mean	3.457	-6.511	9.968
	SEM	4.336	6.891	7.677
	95% CI	(-5.0,12.0)	(-20.0, 7.0)	(-5.1,25.0)
	Pr >  t			0.1943
Week 156	n	10	3	
	LS Mean	-10.92	-6.820	-4.104
	SEM	5.089	8.680	9.684
	95% CI	(-20.9,-0.9)	(-23.8,10.2)	(-23.1,14.9)
	Pr >  t			0.6718
Week 168	n	4	2	
	LS Mean	-11.13	-7.835	-3.293
	SEM	7.567	10.50	12.65
	95% CI	(-26.0, 3.7)	(-28.4,12.8)	(-28.1,21.5)
	Pr >  t			0.7947
Week 180	n	1	1	
	LS Mean	-13.87	-9.091	-4.781
	SEM	14.63	14.64	20.51
	95% CI	(-42.6,14.8)	(-37.8,19.6)	(-45.0,35.5)
	Pr >  t			0.8157
Week 192	n	1	1	
	LS Mean	-13.87	-9.091	-4.781
	SEM	14.63	14.64	20.51
	95% CI	(-42.6,14.8)	(-37.8,19.6)	(-45.0,35.5)
	Pr >  t			0.8157

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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Final



**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	-7.968	-5.124	-2.844
			SEM	4.155	4.492	4.438
			95% CI	(-16.2, 0.3)	(-14.0, 3.8)	(-11.6, 5.9)
		Pr >  t			0.5225	
		Week 16	n	35	22	
			LS Mean	-15.32	-8.596	-6.726
			SEM	4.353	5.170	5.107
			95% CI	(-23.9,-6.7)	(-18.8, 1.6)	(-16.8, 3.3)
		Pr >  t			0.1893	
		Week 24	n	28	16	
			LS Mean	-12.04	0.605	-12.64
			SEM	4.541	5.597	5.720
			95% CI	(-21.0,-3.1)	(-10.4,11.6)	(-23.9,-1.4)
		Pr >  t			0.0280	
		Week 32	n	22	16	
			LS Mean	-11.17	-7.619	-3.549
			SEM	4.874	5.612	5.929
			95% CI	(-20.8,-1.6)	(-18.7, 3.4)	(-15.2, 8.1)
		Pr >  t			0.5500	
		Week 40	n	19	12	
			LS Mean	-10.74	-13.72	2.985
			SEM	5.055	6.058	6.491
			95% CI	(-20.7,-0.8)	(-25.7,-1.8)	(-9.8,15.8)
		Pr >  t			0.6459	
		Week 48	n	16	10	
			LS Mean	-9.381	-6.843	-2.538
			SEM	5.279	6.391	6.975
95% CI	(-19.8, 1.0)		(-19.4, 5.7)	(-16.3,11.2)		
Pr >  t			0.7162			
Week 56	n	14	7			
	LS Mean	-9.992	-8.792	-1.199		
SEM	5.479	7.151	7.826			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-20.8, 0.8)	(-22.9, 5.3)	(-16.6,14.2)
	Pr >  t			0.8783
	n	8	7	
	LS Mean	-13.78	-14.32	0.544
	SEM	6.467	7.151	8.569
Week 72	95% CI	(-26.5,-1.1)	(-28.4,-0.2)	(-16.3,17.4)
	Pr >  t			0.9494
	n	12	6	
	LS Mean	-14.44	-14.46	0.025
	SEM	5.720	7.538	8.350
Week 84	95% CI	(-25.7,-3.2)	(-29.3, 0.4)	(-16.4,16.4)
	Pr >  t			0.9976
	n	8	5	
	LS Mean	-10.05	-4.630	-5.416
	SEM	6.529	8.037	9.326
Week 96	95% CI	(-22.9, 2.8)	(-20.4,11.2)	(-23.8,12.9)
	Pr >  t			0.5618
	n	5	5	
	LS Mean	-6.608	-4.630	-1.978
	SEM	7.708	8.037	10.19
Week 108	95% CI	(-21.8, 8.6)	(-20.4,11.2)	(-22.0,18.1)
	Pr >  t			0.8462
	n	7	5	
	LS Mean	-13.35	-11.30	-2.054
	SEM	6.839	8.037	9.544
Week 120	95% CI	(-26.8, 0.1)	(-27.1, 4.5)	(-20.8,16.7)
	Pr >  t			0.8298
	n	5	3	
	LS Mean	-13.65	-21.39	7.742
	SEM	7.729	9.753	11.59
Week 132	95% CI	(-28.9, 1.6)	(-40.6,-2.2)	(-15.1,30.6)
	Pr >  t			0.5047
	n	2	2	
	LS Mean	3.493	-20.03	23.525
	SEM	11.25	11.46	15.42
Week 144	95% CI	(-18.6,25.6)	(-42.6, 2.5)	( -6.8,53.9)
	Pr >  t			0.1280
	n	2		
	LS Mean	19.178	NE	NE
	SEM	11.27	NE	NE



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			
		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive	Week 156	95% CI	(-3.0,41.3)	NE	NE
		Pr >  t			NE
		n	2		
		LS Mean	-12.08	NE	NE
		SEM	11.28	NE	NE
	Week 168	95% CI	(-34.3,10.1)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-11.09	NE	NE
		SEM	15.46	NE	NE
	Week 8	95% CI	(-41.5,19.3)	NE	NE
		Pr >  t			NE
		n	98	104	
		LS Mean	-3.176	2.028	-5.204
		SEM	2.988	2.947	2.516
	Week 16	95% CI	(-9.1, 2.7)	(-3.8, 7.8)	(-10.1,-0.3)
		Pr >  t			0.0391
		n	87	84	
		LS Mean	-5.022	-0.775	-4.246
		SEM	3.057	3.058	2.699
	Week 24	95% CI	(-11.0, 1.0)	(-6.8, 5.2)	(-9.5, 1.1)
		Pr >  t			0.1162
		n	76	65	
		LS Mean	-2.846	-2.200	-0.646
SEM		3.138	3.211	2.927	
Week 32	95% CI	(-9.0, 3.3)	(-8.5, 4.1)	(-6.4, 5.1)	
	Pr >  t			0.8254	
	n	62	57		
	LS Mean	-3.921	-0.590	-3.331	
	SEM	3.260	3.305	3.126	
Week 40	95% CI	(-10.3, 2.5)	(-7.1, 5.9)	(-9.5, 2.8)	
	Pr >  t			0.2869	
	n	54	50		
	LS Mean	-5.566	2.086	-7.651	
	SEM	3.340	3.405	3.298	
Week 48	95% CI	(-12.1, 1.0)	(-4.6, 8.8)	(-14.1,-1.2)	
	Pr >  t			0.0205	
	n	52	41		
	LS Mean	-4.307	-1.241	-3.065	
		SEM	3.363	3.543	3.463

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-10.9, 2.3)	(-8.2, 5.7)	(-9.9, 3.7)
	Pr >  t			0.3762
	n	44	38	
	LS Mean	-7.716	-1.591	-6.125
	SEM	3.470	3.602	3.629
Week 64	95% CI	(-14.5,-0.9)	(-8.7, 5.5)	(-13.2, 1.0)
	Pr >  t			0.0918
	n	39	35	
	LS Mean	-2.921	-1.144	-1.777
	SEM	3.557	3.671	3.780
Week 72	95% CI	(-9.9, 4.1)	(-8.4, 6.1)	(-9.2, 5.6)
	Pr >  t			0.6384
	n	36	29	
	LS Mean	-6.838	5.374	-12.21
	SEM	3.620	3.837	3.999
Week 84	95% CI	(-13.9, 0.3)	(-2.2,12.9)	(-20.1,-4.4)
	Pr >  t			0.0023
	n	32	28	
	LS Mean	-6.032	-2.984	-3.048
	SEM	3.728	3.871	4.120
Week 96	95% CI	(-13.4, 1.3)	(-10.6, 4.6)	(-11.1, 5.0)
	Pr >  t			0.4595
	n	30	19	
	LS Mean	-3.174	1.800	-4.974
	SEM	3.775	4.303	4.577
Week 108	95% CI	(-10.6, 4.2)	(-6.6,10.2)	(-14.0, 4.0)
	Pr >  t			0.2773
	n	18	16	
	LS Mean	-4.077	-3.559	-0.518
	SEM	4.350	4.536	5.252
Week 120	95% CI	(-12.6, 4.5)	(-12.5, 5.3)	(-10.8, 9.8)
	Pr >  t			0.9214
	n	23	13	
	LS Mean	-3.135	-4.996	1.862
	SEM	4.043	4.854	5.302
Week 132	95% CI	(-11.1, 4.8)	(-14.5, 4.5)	(-8.5,12.3)
	Pr >  t			0.7256
	n	18	6	
	LS Mean	-8.992	0.874	-9.866
	SEM	4.350	6.480	7.001

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-17.5,-0.5)	(-11.8,13.6)	(-23.6, 3.9)
	Pr >  t			0.1590
Week 144	n	13	5	
	LS Mean	3.469	-3.100	6.569
	SEM	4.807	6.992	7.764
	95% CI	(-6.0,12.9)	(-16.8,10.6)	(-8.7,21.8)
	Pr >  t			0.3977
Week 156	n	8	3	
	LS Mean	-8.423	-3.414	-5.009
	SEM	5.754	8.722	9.862
	95% CI	(-19.7, 2.9)	(-20.5,13.7)	(-24.4,14.3)
	Pr >  t			0.6116
Week 168	n	3	2	
	LS Mean	-9.294	-4.459	-4.835
	SEM	8.689	10.49	13.18
	95% CI	(-26.3, 7.8)	(-25.0,16.1)	(-30.7,21.0)
	Pr >  t			0.7138
Week 180	n	1	1	
	LS Mean	-11.04	-5.707	-5.328
	SEM	14.55	14.55	20.28
	95% CI	(-39.6,17.5)	(-34.3,22.8)	(-45.1,34.5)
	Pr >  t			0.7928
Week 192	n	1	1	
	LS Mean	-11.04	-5.707	-5.328
	SEM	14.55	14.55	20.28
	95% CI	(-39.6,17.5)	(-34.3,22.8)	(-45.1,34.5)
	Pr >  t			0.7928

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	-3.186	1.946	-5.132		
			SEM	3.012	2.962	2.542		
			95% CI	(-9.1, 2.7)	(-3.9, 7.8)	(-10.1,-0.1)		
					Pr >  t			0.0439
		Week 16	n	85	84			
			LS Mean	-5.069	-0.858	-4.211		
			SEM	3.084	3.074	2.728		
			95% CI	(-11.1, 1.0)	(-6.9, 5.2)	(-9.6, 1.1)		
					Pr >  t			0.1232
		Week 24	n	75	65			
			LS Mean	-2.869	-2.281	-0.588		
			SEM	3.162	3.227	2.952		
			95% CI	(-9.1, 3.3)	(-8.6, 4.1)	(-6.4, 5.2)		
					Pr >  t			0.8421
		Week 32	n	61	57			
			LS Mean	-3.956	-0.671	-3.285		
			SEM	3.288	3.322	3.155		
			95% CI	(-10.4, 2.5)	(-7.2, 5.9)	(-9.5, 2.9)		
					Pr >  t			0.2980
		Week 40	n	53	50			
			LS Mean	-5.618	2.005	-7.623		
			SEM	3.371	3.422	3.330		
			95% CI	(-12.2, 1.0)	(-4.7, 8.7)	(-14.2,-1.1)		
					Pr >  t			0.0223
		Week 48	n	51	41			
			LS Mean	-4.335	-1.322	-3.013		
			SEM	3.395	3.561	3.496		
95% CI	(-11.0, 2.3)		(-8.3, 5.7)	(-9.9, 3.8)				
			Pr >  t			0.3890		
Week 56	n	43	38					
	LS Mean	-7.821	-1.673	-6.148				
	SEM	3.507	3.621	3.667				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-14.7,-0.9)	(-8.8, 5.4)	(-13.3, 1.0)
	Pr >  t			0.0939
	n	39	35	
	LS Mean	-2.975	-1.225	-1.750
	SEM	3.578	3.689	3.803
Week 72	95% CI	(-10.0, 4.1)	(-8.5, 6.0)	(-9.2, 5.7)
	Pr >  t			0.6455
	n	35	29	
	LS Mean	-6.951	5.293	-12.24
	SEM	3.664	3.856	4.043
Week 84	95% CI	(-14.1, 0.2)	(-2.3,12.9)	(-20.2,-4.3)
	Pr >  t			0.0025
	n	31	28	
	LS Mean	-6.125	-3.065	-3.060
	SEM	3.778	3.890	4.169
Week 96	95% CI	(-13.5, 1.3)	(-10.7, 4.6)	(-11.2, 5.1)
	Pr >  t			0.4631
	n	29	19	
	LS Mean	-3.170	1.719	-4.889
	SEM	3.828	4.325	4.629
Week 108	95% CI	(-10.7, 4.3)	(-6.8,10.2)	(-14.0, 4.2)
	Pr >  t			0.2911
	n	18	16	
	LS Mean	-4.131	-3.639	-0.491
	SEM	4.374	4.558	5.280
Week 120	95% CI	(-12.7, 4.5)	(-12.6, 5.3)	(-10.9, 9.9)
	Pr >  t			0.9259
	n	23	13	
	LS Mean	-3.189	-5.077	1.888
	SEM	4.066	4.878	5.331
Week 132	95% CI	(-11.2, 4.8)	(-14.6, 4.5)	(-8.6,12.3)
	Pr >  t			0.7233
	n	18	6	
	LS Mean	-9.045	0.794	-9.838
	SEM	4.374	6.511	7.036
Week 144	95% CI	(-17.6,-0.5)	(-12.0,13.6)	(-23.6, 4.0)
	Pr >  t			0.1623
	n	13	5	
	LS Mean	3.417	-3.180	6.597
	SEM	4.833	7.026	7.803

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive Negative	Week 156	95% CI	(-6.1,12.9)	(-17.0,10.6)	(-8.7,21.9)
		Pr >  t			0.3981
		n	8	3	
	Week 168	LS Mean	-8.475	-3.494	-4.981
		SEM	5.784	8.763	9.910
		95% CI	(-19.8, 2.9)	(-20.7,13.7)	(-24.4,14.5)
	Week 180	Pr >  t			0.6153
		n	3	2	
		LS Mean	-9.346	-4.541	-4.805
	Week 192	SEM	8.732	10.54	13.24
		95% CI	(-26.5, 7.8)	(-25.2,16.1)	(-30.8,21.2)
		Pr >  t			0.7168
	Week 8	n	1	1	
		LS Mean	-11.09	-5.787	-5.299
		SEM	14.61	14.62	20.37
	Week 16	95% CI	(-39.8,17.6)	(-34.5,22.9)	(-45.3,34.7)
		Pr >  t			0.7948
		n	1	1	
	Week 24	LS Mean	-11.09	-5.787	-5.299
		SEM	14.61	14.62	20.37
		95% CI	(-39.8,17.6)	(-34.5,22.9)	(-45.3,34.7)
	Week 32	Pr >  t			0.7948
		n	42	35	
		LS Mean	-7.968	-5.124	-2.844
Week 8	SEM	4.155	4.492	4.438	
	95% CI	(-16.2, 0.3)	(-14.0, 3.8)	(-11.6, 5.9)	
	Pr >  t			0.5225	
Week 16	n	35	22		
	LS Mean	-15.32	-8.596	-6.726	
	SEM	4.353	5.170	5.107	
Week 24	95% CI	(-23.9,-6.7)	(-18.8, 1.6)	(-16.8, 3.3)	
	Pr >  t			0.1893	
	n	28	16		
Week 32	LS Mean	-12.04	0.605	-12.64	
	SEM	4.541	5.597	5.720	
	95% CI	(-21.0,-3.1)	(-10.4,11.6)	(-23.9,-1.4)	
Week 8	Pr >  t			0.0280	
	n	22	16		
	LS Mean	-11.17	-7.619	-3.549	
Week 16	SEM	4.874	5.612	5.929	
	95% CI				
	Pr >  t				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-20.8,-1.6)	(-18.7, 3.4)	(-15.2, 8.1)
		Pr >  t			0.5500
		n	19	12	
		LS Mean	-10.74	-13.72	2.985
		SEM	5.055	6.058	6.491
Week 48		95% CI	(-20.7,-0.8)	(-25.7,-1.8)	(-9.8,15.8)
		Pr >  t			0.6459
		n	16	10	
		LS Mean	-9.381	-6.843	-2.538
		SEM	5.279	6.391	6.975
Week 56		95% CI	(-19.8, 1.0)	(-19.4, 5.7)	(-16.3,11.2)
		Pr >  t			0.7162
		n	14	7	
		LS Mean	-9.992	-8.792	-1.199
		SEM	5.479	7.151	7.826
Week 64		95% CI	(-20.8, 0.8)	(-22.9, 5.3)	(-16.6,14.2)
		Pr >  t			0.8783
		n	8	7	
		LS Mean	-13.78	-14.32	0.544
		SEM	6.467	7.151	8.569
Week 72		95% CI	(-26.5,-1.1)	(-28.4,-0.2)	(-16.3,17.4)
		Pr >  t			0.9494
		n	12	6	
		LS Mean	-14.44	-14.46	0.025
		SEM	5.720	7.538	8.350
Week 84		95% CI	(-25.7,-3.2)	(-29.3, 0.4)	(-16.4,16.4)
		Pr >  t			0.9976
		n	8	5	
		LS Mean	-10.05	-4.630	-5.416
		SEM	6.529	8.037	9.326
Week 96		95% CI	(-22.9, 2.8)	(-20.4,11.2)	(-23.8,12.9)
		Pr >  t			0.5618
		n	5	5	
		LS Mean	-6.608	-4.630	-1.978
		SEM	7.708	8.037	10.19
Week 108		95% CI	(-21.8, 8.6)	(-20.4,11.2)	(-22.0,18.1)
		Pr >  t			0.8462
		n	7	5	
		LS Mean	-13.35	-11.30	-2.054
		SEM	6.839	8.037	9.544

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-26.8, 0.1)	(-27.1, 4.5)	(-20.8,16.7)
	Pr >  t			0.8298
	n	5	3	
	LS Mean	-13.65	-21.39	7.742
	SEM	7.729	9.753	11.59
Week 132	95% CI	(-28.9, 1.6)	(-40.6,-2.2)	(-15.1,30.6)
	Pr >  t			0.5047
	n	2	2	
	LS Mean	3.493	-20.03	23.525
	SEM	11.25	11.46	15.42
Week 144	95% CI	(-18.6,25.6)	(-42.6, 2.5)	( -6.8,53.9)
	Pr >  t			0.1280
	n	2		
	LS Mean	19.178	NE	NE
	SEM	11.27	NE	NE
Week 156	95% CI	( -3.0,41.3)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	-12.08	NE	NE
	SEM	11.28	NE	NE
Week 168	95% CI	(-34.3,10.1)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-11.09	NE	NE
	SEM	15.46	NE	NE
	95% CI	(-41.5,19.3)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-5.353	0.423	-5.776
			SEM	2.659	2.751	2.627
			95% CI	(-10.6,-0.1)	(-5.0, 5.8)	(-10.9,-0.6)
		Pr >  t			0.0283	
		Week 16	n	90	75	
			LS Mean	-8.811	-2.278	-6.533
			SEM	2.740	2.914	2.855
			95% CI	(-14.2,-3.4)	(-8.0, 3.4)	(-12.1,-0.9)
		Pr >  t			0.0225	
		Week 24	n	79	62	
			LS Mean	-5.327	-1.693	-3.635
			SEM	2.821	3.056	3.051
			95% CI	(-10.9, 0.2)	(-7.7, 4.3)	(-9.6, 2.4)
		Pr >  t			0.2339	
		Week 32	n	70	56	
			LS Mean	-6.806	-0.933	-5.873
			SEM	2.926	3.141	3.186
			95% CI	(-12.6,-1.1)	(-7.1, 5.2)	(-12.1, 0.4)
		Pr >  t			0.0656	
		Week 40	n	61	46	
			LS Mean	-7.007	-3.066	-3.940
			SEM	3.010	3.299	3.405
			95% CI	(-12.9,-1.1)	(-9.5, 3.4)	(-10.6, 2.7)
		Pr >  t			0.2475	
		Week 48	n	56	38	
			LS Mean	-6.097	-3.189	-2.908
			SEM	3.065	3.459	3.608
95% CI	(-12.1,-0.1)		(-10.0, 3.6)	(-10.0, 4.2)		
Pr >  t			0.4204			
Week 56	n	49	33			
	LS Mean	-7.898	-2.585	-5.313		
	SEM	3.157	3.589	3.814		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-14.1,-1.7)	(-9.6, 4.5)	(-12.8, 2.2)
	Pr >  t			0.1639
	n	37	29	
	LS Mean	-6.245	-3.123	-3.122
	SEM	3.378	3.725	4.123
Week 72	95% CI	(-12.9, 0.4)	(-10.4, 4.2)	(-11.2, 5.0)
	Pr >  t			0.4491
	n	40	25	
	LS Mean	-10.43	2.671	-13.10
	SEM	3.313	3.886	4.219
Week 84	95% CI	(-16.9,-3.9)	(-5.0,10.3)	(-21.4,-4.8)
	Pr >  t			0.0019
	n	32	23	
	LS Mean	-7.060	-6.230	-0.829
	SEM	3.531	3.987	4.469
Week 96	95% CI	(-14.0,-0.1)	(-14.1, 1.6)	(-9.6, 7.9)
	Pr >  t			0.8528
	n	29	17	
	LS Mean	-5.941	0.286	-6.227
	SEM	3.623	4.396	4.911
Week 108	95% CI	(-13.1, 1.2)	(-8.3, 8.9)	(-15.9, 3.4)
	Pr >  t			0.2051
	n	22	15	
	LS Mean	-6.756	-5.649	-1.106
	SEM	3.954	4.590	5.319
Week 120	95% CI	(-14.5, 1.0)	(-14.7, 3.4)	(-11.5, 9.3)
	Pr >  t			0.8353
	n	23	13	
	LS Mean	-5.197	-9.090	3.894
	SEM	3.890	4.835	5.492
Week 132	95% CI	(-12.8, 2.4)	(-18.6, 0.4)	(-6.9,14.7)
	Pr >  t			0.4785
	n	17	5	
	LS Mean	-8.928	-3.666	-5.262
	SEM	4.306	7.090	7.770
Week 144	95% CI	(-17.4,-0.5)	(-17.6,10.2)	(-20.5,10.0)
	Pr >  t			0.4984
	n	14	3	
Week 144	LS Mean	5.733	-5.980	11.713
	SEM	4.602	8.917	9.611

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.3,14.8)	(-23.5,11.5)	(-7.1,30.6)
		Pr >  t			0.2232
	Week 156	n	9	2	
		LS Mean	-9.500	-5.907	-3.593
		SEM	5.473	10.75	11.71
		95% CI	(-20.2, 1.2)	(-27.0,15.2)	(-26.6,19.4)
		Pr >  t			0.7590
	Week 168	n	4	1	
		LS Mean	-10.21	-8.132	-2.078
		SEM	7.754	14.98	16.61
		95% CI	(-25.4, 5.0)	(-37.5,21.3)	(-34.7,30.5)
		Pr >  t			0.9005
	Week 180	n	1	1	
		LS Mean	-12.93	-8.132	-4.794
		SEM	14.93	14.98	20.95
		95% CI	(-42.2,16.4)	(-37.5,21.3)	(-45.9,36.3)
		Pr >  t			0.8190
	Week 192	n	1	1	
		LS Mean	-12.93	-8.132	-4.794
		SEM	14.93	14.98	20.95
		95% CI	(-42.2,16.4)	(-37.5,21.3)	(-45.9,36.3)
		Pr >  t			0.8190
>= 3	Week 8	n	37	45	
		LS Mean	-9.575	-6.944	-2.631
		SEM	6.785	6.735	3.905
		95% CI	(-23.0, 3.8)	(-20.3, 6.4)	(-10.3, 5.1)
		Pr >  t			0.5014
	Week 16	n	34	32	
		LS Mean	-13.77	-9.880	-3.893
		SEM	6.992	7.048	4.275
		95% CI	(-27.6, 0.0)	(-23.8, 4.0)	(-12.3, 4.5)
		Pr >  t			0.3636
	Week 24	n	26	19	
		LS Mean	-13.91	-9.734	-4.175
		SEM	7.142	7.370	5.016
		95% CI	(-28.0, 0.2)	(-24.3, 4.8)	(-14.1, 5.7)
		Pr >  t			0.4059
	Week 32	n	16	17	
		LS Mean	-11.63	-13.57	1.939
		SEM	7.493	7.465	5.632

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-26.4, 3.1)	(-28.3, 1.2)	(-9.1,13.0)
	Pr >  t			0.7308
	n	14	16	
Week 48	LS Mean	-16.27	-3.306	-12.97
	SEM	7.618	7.513	5.857
	95% CI	(-31.3,-1.3)	(-18.1,11.5)	(-24.5,-1.4)
Week 56	Pr >  t			0.0275
	n	13	13	
	LS Mean	-13.24	-8.125	-5.113
Week 64	SEM	7.683	7.703	6.178
	95% CI	(-28.4, 1.9)	(-23.3, 7.1)	(-17.3, 7.0)
	Pr >  t			0.4085
Week 72	n	10	12	
	LS Mean	-20.49	-12.44	-8.046
	SEM	7.977	7.790	6.628
Week 84	95% CI	(-36.2,-4.8)	(-27.8, 2.9)	(-21.1, 5.0)
	Pr >  t			0.2256
	n	10	13	
Week 96	LS Mean	-10.55	-12.54	1.987
	SEM	7.981	7.711	6.540
	95% CI	(-26.3, 5.2)	(-27.7, 2.7)	(-10.9,14.8)
Week 108	Pr >  t			0.7614
	n	8	10	
	LS Mean	-10.09	-8.404	-1.690
Week 108	SEM	8.264	7.990	7.202
	95% CI	(-26.4, 6.2)	(-24.1, 7.3)	(-15.9,12.5)
	Pr >  t			0.8146
Week 108	n	8	10	
	LS Mean	-16.48	-5.402	-11.07
	SEM	8.270	7.984	7.203
Week 108	95% CI	(-32.8,-0.2)	(-21.1,10.3)	(-25.2, 3.1)
	Pr >  t			0.1250
	n	6	7	
Week 108	LS Mean	-5.758	-6.788	1.029
	SEM	8.737	8.477	8.231
	95% CI	(-23.0,11.4)	(-23.5, 9.9)	(-15.2,17.2)
Week 108	Pr >  t			0.9006
	n	4	6	
	LS Mean	-8.048	-11.57	3.522
Week 108	SEM	9.570	8.725	9.355

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-26.9,10.8)	(-28.7, 5.6)	(-14.9,21.9)
		Pr >  t			0.7068
	Week 120	n	5	3	
		LS Mean	-15.76	-12.70	-3.062
		SEM	9.076	10.34	10.44
		95% CI	(-33.6, 2.1)	(-33.0, 7.6)	(-23.6,17.5)
		Pr >  t			0.7694
	Week 132	n	3	3	
		LS Mean	-16.89	-11.88	-5.011
		SEM	10.33	10.34	11.55
		95% CI	(-37.2, 3.4)	(-32.2, 8.5)	(-27.7,17.7)
		Pr >  t			0.6648
	Week 144	n	1	2	
		LS Mean	-22.00	-11.19	-10.81
		SEM	15.13	11.72	16.92
		95% CI	(-51.8, 7.8)	(-34.2,11.9)	(-44.1,22.5)
		Pr >  t			0.5233
	Week 156	n	1	1	
		LS Mean	-22.00	-12.03	-9.973
		SEM	15.13	15.14	19.43
		95% CI	(-51.8, 7.8)	(-41.8,17.7)	(-48.2,28.3)
		Pr >  t			0.6082
	Week 168	n		1	
		LS Mean	NE	-12.03	NE
		SEM	NE	15.14	NE
		95% CI	NE	(-41.8,17.7)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	-5.541	-1.485	-4.056		
			SEM	7.004	7.240	3.375		
			95% CI	(-19.4, 8.4)	(-15.9,12.9)	(-10.7, 2.6)		
					Pr >  t			0.2304
		Week 16	n	59	49			
			LS Mean	-10.73	-3.009	-7.721		
			SEM	7.037	7.312	3.636		
			95% CI	(-24.7, 3.2)	(-17.5,11.5)	(-14.9,-0.6)		
					Pr >  t			0.0343
		Week 24	n	54	41			
			LS Mean	-7.822	-2.783	-5.039		
			SEM	7.058	7.384	3.841		
			95% CI	(-21.8, 6.2)	(-17.4,11.9)	(-12.6, 2.5)		
					Pr >  t			0.1903
		Week 32	n	48	37			
			LS Mean	-8.316	0.321	-8.637		
			SEM	7.090	7.428	4.001		
			95% CI	(-22.4, 5.8)	(-14.4,15.1)	(-16.5,-0.8)		
					Pr >  t			0.0314
		Week 40	n	43	33			
			LS Mean	-10.29	-3.451	-6.837		
			SEM	7.125	7.481	4.170		
			95% CI	(-24.4, 3.8)	(-18.3,11.4)	(-15.0, 1.4)		
			Pr >  t			0.1017		
Week 48	n	41	28					
	LS Mean	-7.505	-1.985	-5.520				
	SEM	7.139	7.565	4.354				
	95% CI	(-21.7, 6.7)	(-17.0,13.0)	(-14.1, 3.0)				
			Pr >  t			0.2054		
Week 56	n	35	22					
	LS Mean	-11.05	-5.425	-5.627				
	SEM	7.200	7.717	4.717				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-25.3, 3.2)	(-20.7, 9.9)	(-14.9, 3.6)
		Pr >  t			0.2333
	Week 64	n	26	23	
		LS Mean	-9.104	-4.052	-5.052
		SEM	7.339	7.688	4.904
		95% CI	(-23.6, 5.4)	(-19.3, 11.2)	(-14.7, 4.6)
		Pr >  t			0.3033
	Week 72	n	28	18	
		LS Mean	-12.38	5.850	-18.23
		SEM	7.300	7.864	5.118
		95% CI	(-26.8, 2.1)	(-9.7, 21.4)	(-28.3, -8.2)
		Pr >  t			0.0004
	Week 84	n	22	18	
		LS Mean	-9.924	-9.270	-0.654
		SEM	7.485	7.864	5.327
		95% CI	(-24.7, 4.9)	(-24.8, 6.3)	(-11.1, 9.8)
		Pr >  t			0.9024
	Week 96	n	21	13	
		LS Mean	-6.739	-0.953	-5.787
		SEM	7.465	8.167	5.807
		95% CI	(-21.5, 8.0)	(-17.1, 15.2)	(-17.2, 5.6)
		Pr >  t			0.3193
	Week 108	n	17	12	
		LS Mean	-9.354	-5.560	-3.794
		SEM	7.684	8.253	6.134
		95% CI	(-24.5, 5.8)	(-21.9, 10.7)	(-15.8, 8.2)
		Pr >  t			0.5365
	Week 120	n	18	11	
		LS Mean	-6.346	-8.805	2.459
		SEM	7.571	8.356	6.216
		95% CI	(-21.3, 8.6)	(-25.3, 7.7)	(-9.7, 14.7)
		Pr >  t			0.6925
	Week 132	n	13	5	
		LS Mean	-9.526	-4.346	-5.180
		SEM	7.936	9.686	8.213
		95% CI	(-25.2, 6.2)	(-23.4, 14.7)	(-21.3, 10.9)
		Pr >  t			0.5284
	Week 144	n	12	3	
		LS Mean	6.246	-6.531	12.777
		SEM	7.936	11.12	9.926

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.4,21.9)	(-28.4,15.3)	(-6.7,32.3)
		Pr >  t			0.1984
	Week 156	n	7	2	
		LS Mean	-11.62	-6.534	-5.089
		SEM	8.804	12.65	12.17
		95% CI	(-29.0, 5.7)	(-31.4,18.3)	(-29.0,18.8)
		Pr >  t			0.6759
	Week 168	n	3	1	
		LS Mean	-12.82	-8.891	-3.927
		SEM	10.92	16.43	17.31
		95% CI	(-34.3, 8.6)	(-41.1,23.4)	(-37.9,30.1)
		Pr >  t			0.8206
	Week 180	n	1	1	
		LS Mean	-14.61	-8.891	-5.718
		SEM	16.30	16.43	21.12
		95% CI	(-46.6,17.4)	(-41.1,23.4)	(-47.2,35.8)
		Pr >  t			0.7867
	Week 192	n	1	1	
		LS Mean	-14.61	-8.891	-5.718
		SEM	16.30	16.43	21.12
		95% CI	(-46.6,17.4)	(-41.1,23.4)	(-47.2,35.8)
		Pr >  t			0.7867
Yes	Week 8	n	73	80	
		LS Mean	-4.887	0.491	-5.378
		SEM	3.640	3.681	2.840
		95% CI	(-12.1, 2.3)	(-6.8, 7.7)	(-11.0, 0.2)
		Pr >  t			0.0590
	Week 16	n	65	58	
		LS Mean	-6.965	-3.159	-3.806
		SEM	3.764	3.891	3.120
		95% CI	(-14.4, 0.4)	(-10.8, 4.5)	(-9.9, 2.3)
		Pr >  t			0.2232
	Week 24	n	51	40	
		LS Mean	-4.639	-2.387	-2.251
		SEM	3.871	4.160	3.548
		95% CI	(-12.3, 3.0)	(-10.6, 5.8)	(-9.2, 4.7)
		Pr >  t			0.5260
	Week 32	n	38	36	
		LS Mean	-5.323	-6.292	0.969
		SEM	4.125	4.242	3.838



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.4, 2.8)	(-14.6, 2.0)	(-6.6, 8.5)
		Pr >  t			0.8007
	Week 40	n	32	29	
		LS Mean	-5.070	-0.291	-4.779
		SEM	4.265	4.412	4.159
		95% CI	(-13.5, 3.3)	(-9.0, 8.4)	(-12.9, 3.4)
		Pr >  t			0.2510
	Week 48	n	28	23	
		LS Mean	-5.831	-4.962	-0.869
		SEM	4.373	4.628	4.487
		95% CI	(-14.4, 2.8)	(-14.1, 4.1)	(-9.7, 7.9)
		Pr >  t			0.8465
	Week 56	n	24	23	
		LS Mean	-7.294	-2.728	-4.566
		SEM	4.519	4.628	4.624
		95% CI	(-16.2, 1.6)	(-11.8, 6.4)	(-13.6, 4.5)
		Pr >  t			0.3238
	Week 64	n	21	19	
		LS Mean	-2.721	-5.188	2.467
		SEM	4.658	4.828	4.953
		95% CI	(-11.9, 6.4)	(-14.7, 4.3)	(-7.3, 12.2)
		Pr >  t			0.6186
	Week 72	n	20	17	
		LS Mean	-6.307	-4.682	-1.625
		SEM	4.714	4.958	5.129
		95% CI	(-15.6, 3.0)	(-14.4, 5.1)	(-11.7, 8.4)
		Pr >  t			0.7515
	Week 84	n	18	15	
		LS Mean	-5.903	1.059	-6.962
		SEM	4.819	5.121	5.383
		95% CI	(-15.4, 3.6)	(-9.0, 11.1)	(-17.5, 3.6)
		Pr >  t			0.1963
	Week 96	n	14	11	
		LS Mean	-3.499	0.197	-3.696
		SEM	5.148	5.580	6.088
		95% CI	(-13.6, 6.6)	(-10.8, 11.2)	(-15.6, 8.3)
		Pr >  t			0.5440
	Week 108	n	9	9	
		LS Mean	-2.002	-6.746	4.745
		SEM	5.863	5.925	7.000

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.5, 9.5)	(-18.4, 4.9)	(-9.0,18.5)
		Pr >  t			0.4981
	Week 120	n	10	5	
		LS Mean	-7.417	-9.936	2.519
		SEM	5.691	7.266	8.044
		95% CI	(-18.6, 3.8)	(-24.2, 4.3)	(-13.3,18.3)
		Pr >  t			0.7543
	Week 132	n	7	3	
		LS Mean	-10.81	-6.072	-4.737
		SEM	6.376	8.880	9.961
		95% CI	(-23.3, 1.7)	(-23.5,11.4)	(-24.3,14.8)
		Pr >  t			0.6346
	Week 144	n	3	2	
		LS Mean	-9.572	-5.346	-4.226
		SEM	8.832	10.57	13.02
		95% CI	(-26.9, 7.8)	(-26.1,15.4)	(-29.8,21.3)
		Pr >  t			0.7456
	Week 156	n	3	1	
		LS Mean	-9.586	-5.998	-3.589
		SEM	8.843	14.50	16.37
		95% CI	(-26.9, 7.8)	(-34.5,22.5)	(-35.7,28.6)
		Pr >  t			0.8265
	Week 168	n	1	1	
		LS Mean	-6.211	-5.998	-0.213
		SEM	14.50	14.50	20.00
		95% CI	(-34.7,22.3)	(-34.5,22.5)	(-39.5,39.1)
		Pr >  t			0.9915

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	-6.040	-4.425	-1.615
			SEM	7.649	8.430	7.205
			95% CI	(-21.5, 9.4)	(-21.5,12.7)	(-16.1,12.8)
			Pr >  t			0.8235
		Week 16	n	14	17	
			LS Mean	-18.31	-4.727	-13.58
			SEM	7.738	8.711	7.732
			95% CI	(-33.9,-2.7)	(-22.3,12.9)	(-29.0, 1.9)
			Pr >  t			0.0837
		Week 24	n	14	11	
			LS Mean	-15.93	1.544	-17.47
			SEM	7.738	9.129	8.193
			95% CI	(-31.5,-0.3)	(-16.8,19.9)	(-33.8,-1.2)
			Pr >  t			0.0361
		Week 32	n	10	10	
			LS Mean	-14.03	1.994	-16.02
			SEM	8.360	9.243	8.630
			95% CI	(-30.8, 2.7)	(-16.6,20.6)	(-33.2, 1.1)
			Pr >  t			0.0666
		Week 40	n	8	10	
			LS Mean	-8.984	-1.497	-7.487
			SEM	8.647	9.243	8.896
			95% CI	(-26.3, 8.3)	(-20.1,17.1)	(-25.1,10.2)
			Pr >  t			0.4020
		Week 48	n	7	11	
			LS Mean	-22.91	-4.568	-18.35
			SEM	8.838	9.150	9.027
95% CI	(-40.5,-5.3)		(-23.0,13.8)	(-36.2,-0.5)		
	Pr >  t			0.0446		
Week 56	n	6	9			
	LS Mean	-16.33	2.530	-18.86		
	SEM	9.080	9.361	9.475		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-34.4, 1.7)	(-16.3,21.3)	(-37.6,-0.1)
		Pr >  t			0.0487
	Week 64	n	5	8	
		LS Mean	-8.804	-4.668	-4.136
		SEM	9.403	9.502	9.908
		95% CI	(-27.5, 9.9)	(-23.7,14.4)	(-23.7,15.5)
		Pr >  t			0.6770
	Week 72	n	7	7	
		LS Mean	-16.06	5.090	-21.15
		SEM	8.829	9.681	9.553
		95% CI	(-33.7, 1.6)	(-14.3,24.5)	(-40.1,-2.2)
		Pr >  t			0.0287
	Week 84	n	7	7	
		LS Mean	-16.06	-4.434	-11.63
		SEM	8.829	9.681	9.553
		95% CI	(-33.7, 1.6)	(-23.8,14.9)	(-30.5, 7.3)
		Pr >  t			0.2259
	Week 96	n	5	6	
		LS Mean	-15.47	6.263	-21.74
		SEM	9.400	9.906	10.29
		95% CI	(-34.2, 3.2)	(-13.5,26.1)	(-42.1,-1.4)
		Pr >  t			0.0363
	Week 108	n	4	6	
		LS Mean	-16.01	6.263	-22.28
		SEM	9.878	9.906	10.74
		95% CI	(-35.6, 3.6)	(-13.5,26.1)	(-43.5,-1.1)
		Pr >  t			0.0396
	Week 120	n	4	4	
		LS Mean	-13.04	-6.970	-6.073
		SEM	9.883	10.65	11.44
		95% CI	(-32.6, 6.6)	(-28.2,14.2)	(-28.6,16.5)
		Pr >  t			0.5961
	Week 132	n	3	1	
		LS Mean	0.603	28.923	-28.32
		SEM	10.61	15.71	16.69
		95% CI	(-20.4,21.6)	(-2.1,59.9)	(-61.2, 4.6)
		Pr >  t			0.0912
	Week 144	n	1	1	
		LS Mean	51.032	-3.452	54.484
		SEM	15.22	15.79	20.00

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	( 21.0,81.0)	(-34.6,27.7)	( 15.0,93.9)
		Pr >  t			0.0070
		n	35	37	
	Week 16	LS Mean	-5.410	-1.079	-4.331
		SEM	8.592	9.031	3.978
		95% CI	(-22.4,11.5)	(-18.9,16.7)	(-12.2, 3.5)
	Week 24	Pr >  t			0.2775
		n	34	30	
		LS Mean	-6.639	0.406	-7.045
	Week 32	SEM	8.896	9.117	4.163
		95% CI	(-24.2,10.9)	(-17.6,18.4)	(-15.2, 1.2)
		Pr >  t			0.0920
	Week 40	n	32	23	
		LS Mean	-3.620	3.319	-6.940
		SEM	8.915	9.239	4.478
	Week 48	95% CI	(-21.2,14.0)	(-14.9,21.5)	(-15.8, 1.9)
		Pr >  t			0.1224
		n	21	22	
	Week 56	LS Mean	-2.873	-3.277	0.404
		SEM	9.104	9.265	4.901
		95% CI	(-20.8,15.1)	(-21.5,15.0)	( -9.2,10.0)
	Week 64	Pr >  t			0.9344
		n	20	20	
		LS Mean	-3.040	2.237	-5.277
	Week 8	SEM	9.133	9.316	5.048
		95% CI	(-21.0,15.0)	(-16.1,20.6)	(-15.2, 4.7)
		Pr >  t			0.2967
	Week 16	n	19	12	
LS Mean		-3.645	0.810	-4.455	
SEM		9.159	9.657	5.714	
Week 24	95% CI	(-21.7,14.4)	(-18.2,19.8)	(-15.7, 6.8)	
	Pr >  t			0.4360	
	n	16	8		
Week 32	LS Mean	-8.359	-4.504	-3.856	
	SEM	9.270	10.08	6.542	
	95% CI	(-26.6, 9.9)	(-24.4,15.3)	(-16.7, 9.0)	
Week 40	Pr >  t			0.5560	
	n	12	11		
	LS Mean	-6.196	-1.374	-4.822	
Week 48	SEM	9.485	9.747	6.339	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72	95% CI	(-24.9,12.5)	(-20.6,17.8)	(-17.3, 7.6)
	Pr >  t			0.4474
	n	13	7	
Week 84	LS Mean	-9.454	-9.702	0.248
	SEM	9.426	10.25	7.011
	95% CI	(-28.0, 9.1)	(-29.9,10.5)	(-13.5,14.0)
Week 96	Pr >  t			0.9718
	n	12	6	
	LS Mean	-5.022	-2.422	-2.601
Week 108	SEM	9.483	10.48	7.408
	95% CI	(-23.7,13.7)	(-23.1,18.2)	(-17.2,12.0)
	Pr >  t			0.7258
Week 120	n	7	6	
	LS Mean	-8.344	3.699	-12.04
	SEM	10.06	10.48	8.138
Week 132	95% CI	(-28.1,11.5)	(-16.9,24.3)	(-28.0, 4.0)
	Pr >  t			0.1397
	n	5	3	
Week 144	LS Mean	-3.336	-3.331	-0.005
	SEM	10.58	11.89	10.43
	95% CI	(-24.1,17.5)	(-26.7,20.1)	(-20.5,20.5)
Week 156	Pr >  t			0.9996
	n	8	3	
	LS Mean	-6.714	-3.331	-3.383
Week 172	SEM	9.909	11.89	9.737
	95% CI	(-26.2,12.8)	(-26.7,20.1)	(-22.5,15.8)
	Pr >  t			0.7284
Week 188	n	2	1	
	LS Mean	-14.78	-5.971	-8.808
	SEM	12.97	16.32	17.02
Week 204	95% CI	(-40.3,10.7)	(-38.1,26.1)	(-42.3,24.7)
	Pr >  t			0.6051
	n	2		
Week 220	LS Mean	-8.396	NE	NE
	SEM	12.98	NE	NE
	95% CI	(-33.9,17.1)	NE	NE
Week 236	Pr >  t			NE
	n	2		
	LS Mean	-8.396	NE	NE
Week 252	SEM	12.98	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
H1047X	Week 8	95% CI	(-33.9,17.1)	NE	NE	
		Pr >  t			NE	
		n	81	64		
		LS Mean	-7.711	-2.819	-4.893	
		SEM	2.908	3.054	2.964	
		95% CI	(-13.4,-2.0)	(-8.8, 3.2)	(-10.7, 0.9)	
		Pr >  t			0.0996	
		Week 16	n	70	52	
		LS Mean	-10.10	-6.748	-3.348	
		SEM	3.005	3.256	3.204	
		95% CI	(-16.0,-4.2)	(-13.2,-0.3)	(-9.6, 2.9)	
		Pr >  t			0.2966	
		Week 24	n	54	40	
		LS Mean	-7.437	-7.360	-0.077	
		SEM	3.176	3.497	3.569	
		95% CI	(-13.7,-1.2)	(-14.2,-0.5)	(-7.1, 6.9)	
		Pr >  t			0.9829	
		Week 32	n	50	36	
		LS Mean	-8.708	-5.764	-2.944	
		SEM	3.248	3.586	3.706	
		95% CI	(-15.1,-2.3)	(-12.8, 1.3)	(-10.2, 4.3)	
		Pr >  t			0.4272	
		Week 40	n	42	28	
		LS Mean	-12.28	-6.231	-6.051	
		SEM	3.374	3.846	4.048	
		95% CI	(-18.9,-5.6)	(-13.8, 1.3)	(-14.0, 1.9)	
		Pr >  t			0.1354	
		Week 48	n	38	24	
	LS Mean	-7.167	-6.478	-0.689		
	SEM	3.451	4.011	4.269		
	95% CI	(-14.0,-0.4)	(-14.4, 1.4)	(-9.1, 7.7)		
	Pr >  t			0.8718		
	Week 56	n	33	24		
	LS Mean	-10.48	-8.832	-1.650		
	SEM	3.570	4.013	4.373		
	95% CI	(-17.5,-3.5)	(-16.7,-0.9)	(-10.2, 6.9)		
	Pr >  t			0.7061		
	Week 64	n	27	19		
	LS Mean	-7.305	-11.96	4.652		
	SEM	3.757	4.297	4.786		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72	95% CI	(-14.7, 0.1)	(-20.4,-3.5)	(-4.7,14.0)
	Pr >  t			0.3314
	n	26	17	
	LS Mean	-10.33	-5.772	-4.559
	SEM	3.797	4.444	4.949
Week 84	95% CI	(-17.8,-2.9)	(-14.5, 3.0)	(-14.3, 5.2)
	Pr >  t			0.3572
	n	18	16	
	LS Mean	-7.843	-7.994	0.151
	SEM	4.263	4.532	5.370
Week 96	95% CI	(-16.2, 0.5)	(-16.9, 0.9)	(-10.4,10.7)
	Pr >  t			0.9776
	n	20	10	
	LS Mean	-5.217	-9.441	4.224
	SEM	4.114	5.322	5.958
Week 108	95% CI	(-13.3, 2.9)	(-19.9, 1.0)	(-7.5,15.9)
	Pr >  t			0.4786
	n	14	10	
	LS Mean	-6.892	-14.77	7.875
	SEM	4.636	5.322	6.320
Week 120	95% CI	(-16.0, 2.2)	(-25.2,-4.3)	(-4.5,20.3)
	Pr >  t			0.2131
	n	14	7	
	LS Mean	-3.728	-13.34	9.615
	SEM	4.615	6.097	6.983
Week 132	95% CI	(-12.8, 5.3)	(-25.3,-1.4)	(-4.1,23.3)
	Pr >  t			0.1689
	n	12	5	
	LS Mean	-11.52	-13.74	2.225
	SEM	4.890	6.993	7.933
Week 144	95% CI	(-21.1,-1.9)	(-27.5,-0.0)	(-13.3,17.8)
	Pr >  t			0.7792
	n	11	4	
	LS Mean	1.136	-10.90	12.035
	SEM	5.024	7.690	8.645
Week 156	95% CI	(-8.7,11.0)	(-26.0, 4.2)	(-4.9,29.0)
	Pr >  t			0.1643
	n	8	3	
	LS Mean	-12.06	-11.43	-0.634
	SEM	5.692	8.724	9.932



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168	95% CI	(-23.2,-0.9)	(-28.6, 5.7)	(-20.1,18.9)
	Pr >  t			0.9491
	n	4	2	
	LS Mean	-11.92	-12.42	0.499
	SEM	7.607	10.49	12.57
Week 180	95% CI	(-26.9, 3.0)	(-33.0, 8.2)	(-24.2,25.2)
	Pr >  t			0.9684
	n	1	1	
	LS Mean	-14.93	-13.63	-1.305
	SEM	14.51	14.54	20.30
Week 192	95% CI	(-43.4,13.5)	(-42.2,14.9)	(-41.2,38.5)
	Pr >  t			0.9487
	n	1	1	
	LS Mean	-14.93	-13.63	-1.305
	SEM	14.51	14.54	20.30
	95% CI	(-43.4,13.5)	(-42.2,14.9)	(-41.2,38.5)
	Pr >  t			0.9487

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-27i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Constipation score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	-7.711	-2.819	-4.893		
			SEM	2.908	3.054	2.964		
			95% CI	(-13.4,-2.0)	(-8.8, 3.2)	(-10.7, 0.9)		
					Pr >  t			0.0996
		Week 16	n	70	52			
			LS Mean	-10.10	-6.748	-3.348		
			SEM	3.005	3.256	3.204		
			95% CI	(-16.0,-4.2)	(-13.2,-0.3)	(-9.6, 2.9)		
					Pr >  t			0.2966
		Week 24	n	54	40			
			LS Mean	-7.437	-7.360	-0.077		
			SEM	3.176	3.497	3.569		
			95% CI	(-13.7,-1.2)	(-14.2,-0.5)	(-7.1, 6.9)		
					Pr >  t			0.9829
		Week 32	n	50	36			
			LS Mean	-8.708	-5.764	-2.944		
			SEM	3.248	3.586	3.706		
			95% CI	(-15.1,-2.3)	(-12.8, 1.3)	(-10.2, 4.3)		
					Pr >  t			0.4272
		Week 40	n	42	28			
			LS Mean	-12.28	-6.231	-6.051		
			SEM	3.374	3.846	4.048		
			95% CI	(-18.9,-5.6)	(-13.8, 1.3)	(-14.0, 1.9)		
			Pr >  t			0.1354		
Week 48	n	38	24					
	LS Mean	-7.167	-6.478	-0.689				
	SEM	3.451	4.011	4.269				
	95% CI	(-14.0,-0.4)	(-14.4, 1.4)	(-9.1, 7.7)				
			Pr >  t			0.8718		
Week 56	n	33	24					
	LS Mean	-10.48	-8.832	-1.650				
	SEM	3.570	4.013	4.373				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-17.5,-3.5)	(-16.7,-0.9)	(-10.2, 6.9)
		Pr >  t			0.7061
	Week 64	n	27	19	
		LS Mean	-7.305	-11.96	4.652
		SEM	3.757	4.297	4.786
		95% CI	(-14.7, 0.1)	(-20.4,-3.5)	( -4.7,14.0)
		Pr >  t			0.3314
	Week 72	n	26	17	
		LS Mean	-10.33	-5.772	-4.559
		SEM	3.797	4.444	4.949
		95% CI	(-17.8,-2.9)	(-14.5, 3.0)	(-14.3, 5.2)
		Pr >  t			0.3572
	Week 84	n	18	16	
		LS Mean	-7.843	-7.994	0.151
		SEM	4.263	4.532	5.370
		95% CI	(-16.2, 0.5)	(-16.9, 0.9)	(-10.4,10.7)
		Pr >  t			0.9776
	Week 96	n	20	10	
		LS Mean	-5.217	-9.441	4.224
		SEM	4.114	5.322	5.958
		95% CI	(-13.3, 2.9)	(-19.9, 1.0)	( -7.5,15.9)
		Pr >  t			0.4786
	Week 108	n	14	10	
		LS Mean	-6.892	-14.77	7.875
		SEM	4.636	5.322	6.320
		95% CI	(-16.0, 2.2)	(-25.2,-4.3)	( -4.5,20.3)
		Pr >  t			0.2131
	Week 120	n	14	7	
		LS Mean	-3.728	-13.34	9.615
		SEM	4.615	6.097	6.983
		95% CI	(-12.8, 5.3)	(-25.3,-1.4)	( -4.1,23.3)
		Pr >  t			0.1689
	Week 132	n	12	5	
		LS Mean	-11.52	-13.74	2.225
		SEM	4.890	6.993	7.933
		95% CI	(-21.1,-1.9)	(-27.5,-0.0)	(-13.3,17.8)
		Pr >  t			0.7792
	Week 144	n	11	4	
		LS Mean	1.136	-10.90	12.035
		SEM	5.024	7.690	8.645

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	(-8.7,11.0)	(-26.0, 4.2)	(-4.9,29.0)
		Pr >  t			0.1643
		n	8	3	
	Week 168	LS Mean	-12.06	-11.43	-0.634
		SEM	5.692	8.724	9.932
		95% CI	(-23.2,-0.9)	(-28.6, 5.7)	(-20.1,18.9)
	Week 180	Pr >  t			0.9491
		n	4	2	
		LS Mean	-11.92	-12.42	0.499
	Week 192	SEM	7.607	10.49	12.57
		95% CI	(-26.9, 3.0)	(-33.0, 8.2)	(-24.2,25.2)
		Pr >  t			0.9684
	Week 8	n	1	1	
		LS Mean	-14.93	-13.63	-1.305
		SEM	14.51	14.54	20.30
	Week 16	95% CI	(-43.4,13.5)	(-42.2,14.9)	(-41.2,38.5)
		Pr >  t			0.9487
		n	1	1	
	Week 24	LS Mean	-14.93	-13.63	-1.305
		SEM	14.51	14.54	20.30
		95% CI	(-43.4,13.5)	(-42.2,14.9)	(-41.2,38.5)
	Week 32	Pr >  t			0.9487
		n	53	64	
		LS Mean	-6.750	-3.684	-3.065
Week 8	SEM	4.917	5.267	3.457	
	95% CI	(-16.5, 3.0)	(-14.1, 6.7)	(-9.9, 3.7)	
	Pr >  t			0.3760	
Week 16	n	48	48		
	LS Mean	-12.00	-3.933	-8.066	
	SEM	5.036	5.401	3.721	
Week 24	95% CI	(-21.9,-2.1)	(-14.6, 6.7)	(-15.4,-0.7)	
	Pr >  t			0.0309	
	n	46	36		
Week 32	LS Mean	-9.236	-1.178	-8.058	
	SEM	5.054	5.551	3.971	
	95% CI	(-19.2, 0.7)	(-12.1, 9.8)	(-15.9,-0.2)	
Week 8	Pr >  t			0.0432	
	n	31	33		
	LS Mean	-8.112	-4.444	-3.668	
Week 16	SEM	5.380	5.606	4.324	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-18.7, 2.5)	(-15.5, 6.6)	(-12.2, 4.8)
	Pr >  t			0.3967
	n	28	30	
	LS Mean	-6.614	-1.878	-4.736
	SEM	5.450	5.665	4.484
Week 48	95% CI	(-17.4, 4.1)	(-13.1, 9.3)	(-13.5, 4.1)
	Pr >  t			0.2914
	n	26	23	
	LS Mean	-10.83	-4.469	-6.366
	SEM	5.501	5.852	4.781
Week 56	95% CI	(-21.7, 0.0)	(-16.0, 7.1)	(-15.8, 3.0)
	Pr >  t			0.1836
	n	22	17	
	LS Mean	-12.56	-3.397	-9.167
	SEM	5.628	6.121	5.243
Week 64	95% CI	(-23.6,-1.5)	(-15.5, 8.7)	(-19.5, 1.1)
	Pr >  t			0.0809
	n	17	19	
	LS Mean	-8.810	-5.483	-3.328
	SEM	5.862	6.017	5.377
Week 72	95% CI	(-20.3, 2.7)	(-17.3, 6.4)	(-13.9, 7.2)
	Pr >  t			0.5362
	n	20	14	
	LS Mean	-13.14	-4.848	-8.293
	SEM	5.715	6.331	5.573
Week 84	95% CI	(-24.4,-1.9)	(-17.3, 7.6)	(-19.2, 2.7)
	Pr >  t			0.1373
	n	19	13	
	LS Mean	-10.32	-6.184	-4.137
	SEM	5.755	6.418	5.716
Week 96	95% CI	(-21.7, 1.0)	(-18.8, 6.4)	(-15.4, 7.1)
	Pr >  t			0.4695
	n	12	12	
	LS Mean	-12.19	2.476	-14.67
	SEM	6.265	6.519	6.332
Week 108	95% CI	(-24.5, 0.1)	(-10.4,15.3)	(-27.1,-2.2)
	Pr >  t			0.0209
	n	9	9	
Week 108	LS Mean	-9.834	0.526	-10.36
	SEM	6.690	6.932	7.155

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-23.0, 3.3)	(-13.1,14.2)	(-24.4, 3.7)
		Pr >  t			0.1481
	Week 120	n	12	7	
		LS Mean	-10.59	-7.774	-2.817
		SEM	6.279	7.376	7.221
		95% CI	(-22.9, 1.8)	(-22.3, 6.7)	(-17.0,11.4)
		Pr >  t			0.6966
	Week 132	n	5	2	
		LS Mean	-5.042	9.988	-15.03
		SEM	7.887	11.15	12.04
		95% CI	(-20.5,10.4)	(-11.9,31.9)	(-38.7, 8.6)
		Pr >  t			0.2123
	Week 144	n	3	1	
		LS Mean	10.298	-6.603	16.902
		SEM	9.414	14.96	16.46
		95% CI	( -8.2,28.8)	(-36.0,22.8)	(-15.4,49.2)
		Pr >  t			0.3049
	Week 156	n	2		
		LS Mean	-10.49	NE	NE
		SEM	11.03	NE	NE
		95% CI	(-32.2,11.2)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-48: Ergebnisse für den Endpunkt „Krankheitssymptomatik (EORTC QLQ-C30): Diarrhoe“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73			
			LS Mean	17.649	6.025	11.624		
			SEM	3.560	3.592	3.360		
			95% CI	( 10.6,24.7)	( -1.0,13.1)	( 5.0,18.2)		
					Pr >  t			0.0006
		Week 16	n	67	56			
			LS Mean	16.554	7.245	9.309		
			SEM	3.636	3.855	3.680		
			95% CI	( 9.4,23.7)	( -0.3,14.8)	( 2.1,16.5)		
					Pr >  t			0.0117
		Week 24	n	61	46			
			LS Mean	18.768	4.430	14.338		
			SEM	3.725	4.011	3.923		
			95% CI	( 11.4,26.1)	( -3.5,12.3)	( 6.6,22.0)		
					Pr >  t			0.0003
		Week 32	n	52	41			
			LS Mean	17.662	2.037	15.625		
			SEM	3.892	4.141	4.143		
			95% CI	( 10.0,25.3)	( -6.1,10.2)	( 7.5,23.8)		
					Pr >  t			0.0002
		Week 40	n	45	36			
			LS Mean	18.088	5.384	12.704		
			SEM	4.007	4.293	4.375		
			95% CI	( 10.2,26.0)	( -3.1,13.8)	( 4.1,21.3)		
			Pr >  t			0.0038		
Week 48	n	42	30					
	LS Mean	17.704	3.633	14.071				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	SEM	4.068	4.483	4.616
	95% CI	( 9.7,25.7)	( -5.2,12.4)	( 5.0,23.1)
	Pr >  t			0.0024
	n	35	24	
	LS Mean	16.078	4.494	11.584
Week 64	SEM	4.235	4.754	5.025
	95% CI	( 7.8,24.4)	( -4.8,13.8)	( 1.7,21.4)
	Pr >  t			0.0214
	n	25	25	
	LS Mean	14.562	5.138	9.425
Week 72	SEM	4.604	4.704	5.299
	95% CI	( 5.5,23.6)	( -4.1,14.4)	( -1.0,19.8)
	Pr >  t			0.0756
	n	27	20	
	LS Mean	15.450	7.007	8.442
Week 84	SEM	4.513	5.004	5.492
	95% CI	( 6.6,24.3)	( -2.8,16.8)	( -2.3,19.2)
	Pr >  t			0.1246
	n	23	19	
	LS Mean	19.049	8.036	11.013
Week 96	SEM	4.734	5.081	5.726
	95% CI	( 9.8,28.3)	( -1.9,18.0)	( -0.2,22.3)
	Pr >  t			0.0548
	n	20	13	
	LS Mean	20.129	-1.258	21.387
Week 108	SEM	4.930	5.728	6.455
	95% CI	( 10.4,29.8)	( -12.5,10.0)	( 8.7,34.1)
	Pr >  t			0.0010
	n	17	13	
	LS Mean	13.461	3.178	10.283
Week 120	SEM	5.182	5.729	6.650
	95% CI	( 3.3,23.6)	( -8.1,14.4)	( -2.8,23.3)
	Pr >  t			0.1223
	n	17	12	
	LS Mean	16.138	6.076	10.063
Week 132	SEM	5.181	5.888	6.787
	95% CI	( 6.0,26.3)	( -5.5,17.6)	( -3.3,23.4)
	Pr >  t			0.1385
	n	13	6	
	LS Mean	16.017	4.116	11.900



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 144	SEM	5.656	7.637	8.653
		95% CI	( 4.9,27.1)	(-10.9,19.1)	( -5.1,28.9)
		Pr >  t			0.1694
		n	11	4	
		LS Mean	18.014	2.635	15.379
		SEM	5.998	9.060	10.13
	Week 156	95% CI	( 6.2,29.8)	(-15.1,20.4)	( -4.5,35.3)
		Pr >  t			0.1293
		n	7	2	
		LS Mean	16.195	4.236	11.959
		SEM	7.117	12.35	13.70
		95% CI	( 2.2,30.2)	(-20.0,28.5)	(-14.9,38.9)
	Week 168	Pr >  t			0.3830
		n	3	1	
		LS Mean	29.614	4.156	25.459
		SEM	10.21	17.14	19.56
		95% CI	( 9.6,49.6)	(-29.5,37.8)	(-12.9,63.8)
		Pr >  t			0.1933
	Week 180	n	1	1	
		LS Mean	54.991	4.156	50.835
		SEM	17.10	17.14	23.89
		95% CI	( 21.4,88.6)	(-29.5,37.8)	( 3.9,97.7)
		Pr >  t			0.0336
		n	1	1	
Week 192	LS Mean	88.321	4.156	84.165	
	SEM	17.10	17.14	23.89	
	95% CI	( 54.8, 122)	(-29.5,37.8)	( 37.3, 131)	
	Pr >  t			0.0004	
	n	65	67		
	LS Mean	9.985	-1.763	11.748	
Week 8	SEM	3.781	3.889	3.332	
	95% CI	( 2.5,17.4)	( -9.4, 5.9)	( 5.2,18.3)	
	Pr >  t			0.0005	
	n	57	51		
	LS Mean	10.874	-1.208	12.082	
	SEM	3.954	4.094	3.636	
Week 16	95% CI	( 3.1,18.7)	( -9.3, 6.9)	( 4.9,19.2)	
	Pr >  t			0.0010	
	n	44	35		
	LS Mean	10.877	-2.467	13.345	
	SEM				
	95% CI				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	SEM	4.112	4.442	4.145
	95% CI	( 2.8,19.0)	(-11.2, 6.3)	( 5.2,21.5)
	Pr >  t			0.0014
	n	34	32	
	LS Mean	9.371	-2.555	11.927
	SEM	4.345	4.529	4.439
Week 40	95% CI	( 0.8,17.9)	(-11.5, 6.4)	( 3.2,20.6)
	Pr >  t			0.0074
	n	30	26	
	LS Mean	10.822	-2.953	13.775
	SEM	4.454	4.730	4.753
	95% CI	( 2.1,19.6)	(-12.3, 6.3)	( 4.4,23.1)
Week 48	Pr >  t			0.0039
	n	27	21	
	LS Mean	6.342	0.630	5.712
	SEM	4.549	4.970	5.078
	95% CI	( -2.6,15.3)	( -9.1,10.4)	( -4.3,15.7)
	Pr >  t			0.2611
Week 56	n	24	21	
	LS Mean	13.083	-4.373	17.456
	SEM	4.670	4.969	5.190
	95% CI	( 3.9,22.3)	(-14.1, 5.4)	( 7.3,27.6)
	Pr >  t			0.0008
	n	22	17	
Week 64	LS Mean	11.849	-6.458	18.307
	SEM	4.765	5.238	5.534
	95% CI	( 2.5,21.2)	(-16.8, 3.8)	( 7.4,29.2)
	Pr >  t			0.0010
	n	21	15	
	LS Mean	5.926	-3.152	9.078
Week 72	SEM	4.821	5.417	5.750
	95% CI	( -3.6,15.4)	(-13.8, 7.5)	( -2.2,20.4)
	Pr >  t			0.1149
	n	17	14	
	LS Mean	11.936	-6.190	18.126
	SEM	5.105	5.520	6.067
Week 84	95% CI	( 1.9,22.0)	(-17.0, 4.7)	( 6.2,30.0)
	Pr >  t			0.0029
	n	15	11	
	LS Mean	16.286	-5.949	22.236

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	5.258	5.927	6.585
	95% CI	( 6.0,26.6)	(-17.6, 5.7)	( 9.3,35.2)
	Pr >  t			0.0008
Week 108	n	9	8	
	LS Mean	5.644	-6.426	12.070
	SEM	6.191	6.572	7.862
	95% CI	( -6.5,17.8)	(-19.3, 6.5)	( -3.4,27.5)
	Pr >  t			0.1252
Week 120	n	11	4	
	LS Mean	2.808	-8.451	11.259
	SEM	5.779	8.527	9.314
	95% CI	( -8.5,14.2)	(-25.2, 8.3)	( -7.0,29.5)
	Pr >  t			0.2272
Week 132	n	7	2	
	LS Mean	-2.941	-5.004	2.064
	SEM	6.760	11.42	12.51
	95% CI	(-16.2,10.3)	(-27.4,17.4)	(-22.5,26.6)
	Pr >  t			0.8691
Week 144	n	4	1	
	LS Mean	-0.642	-3.771	3.128
	SEM	8.336	15.72	17.27
	95% CI	(-17.0,15.7)	(-34.6,27.1)	(-30.8,37.0)
	Pr >  t			0.8563
Week 156	n	3	1	
	LS Mean	18.693	-3.771	22.464
	SEM	9.483	15.72	17.82
	95% CI	( 0.1,37.3)	(-34.6,27.1)	(-12.5,57.5)
	Pr >  t			0.2079
Week 168	n	1	1	
	LS Mean	-1.145	-3.771	2.626
	SEM	15.68	15.72	21.75
	95% CI	(-31.9,29.6)	(-34.6,27.1)	(-40.1,45.4)
	Pr >  t			0.9040

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Bone Lesions Only (L)	No	Week 8	n	104	110			
			LS Mean	13.959	2.326	11.633		
			SEM	2.915	2.908	2.610		
			95% CI	( 8.2,19.7)	( -3.4, 8.0)	( 6.5,16.8)		
					Pr >  t			<.0001
		Week 16	n	92	83			
			LS Mean	13.269	1.982	11.287		
			SEM	3.008	3.105	2.845		
			95% CI	( 7.4,19.2)	( -4.1, 8.1)	( 5.7,16.9)		
					Pr >  t			<.0001
		Week 24	n	77	59			
			LS Mean	15.501	1.252	14.249		
			SEM	3.088	3.326	3.162		
			95% CI	( 9.4,21.6)	( -5.3, 7.8)	( 8.0,20.5)		
					Pr >  t			<.0001
		Week 32	n	57	53			
			LS Mean	15.706	1.220	14.486		
			SEM	3.308	3.399	3.414		
			95% CI	( 9.2,22.2)	( -5.5, 7.9)	( 7.8,21.2)		
					Pr >  t			<.0001
		Week 40	n	50	44			
			LS Mean	13.353	0.985	12.368		
			SEM	3.397	3.552	3.637		
			95% CI	( 6.7,20.0)	( -6.0, 8.0)	( 5.2,19.5)		
			Pr >  t			0.0007		
Week 48	n	47	37					
	LS Mean	11.660	3.017	8.643				
	SEM	3.439	3.696	3.817				
	95% CI	( 4.9,18.4)	( -4.2,10.3)	( 1.2,16.1)				
			Pr >  t			0.0238		
Week 56	n	40	32					
	LS Mean	15.126	-0.013	15.139				
	SEM	3.563	3.830	4.056				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	95% CI	( 8.1,22.1)	( -7.5, 7.5)	( 7.2,23.1)	
	Pr >  t			0.0002	
	n	32	27		
	LS Mean	14.350	-0.034	14.384	
	SEM	3.759	4.004	4.389	
Week 72	95% CI	( 7.0,21.7)	( -7.9, 7.8)	( 5.8,23.0)	
	Pr >  t			0.0011	
	n	31	23		
	LS Mean	12.773	2.208	10.565	
	SEM	3.792	4.187	4.582	
Week 84	95% CI	( 5.3,20.2)	( -6.0,10.4)	( 1.6,19.6)	
	Pr >  t			0.0213	
	n	27	21		
	LS Mean	15.879	1.906	13.974	
	SEM	3.938	4.298	4.797	
Week 96	95% CI	( 8.1,23.6)	( -6.5,10.3)	( 4.6,23.4)	
	Pr >  t			0.0037	
	n	23	16		
	LS Mean	19.413	-1.308	20.721	
	SEM	4.110	4.675	5.279	
Week 108	95% CI	( 11.3,27.5)	( -10.5, 7.9)	( 10.4,31.1)	
	Pr >  t			<.0001	
	n	15	14		
	LS Mean	10.551	-1.480	12.031	
	SEM	4.710	4.886	5.925	
Week 120	95% CI	( 1.3,19.8)	( -11.1, 8.1)	( 0.4,23.7)	
	Pr >  t			0.0425	
	n	18	8		
	LS Mean	16.783	-2.468	19.251	
	SEM	4.432	5.995	6.689	
Week 132	95% CI	( 8.1,25.5)	( -14.2, 9.3)	( 6.1,32.4)	
	Pr >  t			0.0041	
	n	12	4		
	LS Mean	4.506	0.063	4.443	
	SEM	5.090	7.979	8.868	
Week 144	95% CI	( -5.5,14.5)	( -15.6,15.7)	( -13.0,21.8)	
	Pr >  t			0.6165	
	n	8	3		
Week 144	LS Mean	12.398	-1.810	14.208	
	SEM	5.909	9.079	10.33	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.8,24.0)	(-19.6,16.0)	( -6.1,34.5)
		Pr >  t			0.1693
	Week 156	n	5	1	
		LS Mean	20.485	0.652	19.833
		SEM	7.201	15.18	16.47
		95% CI	( 6.4,34.6)	(-29.1,30.4)	(-12.5,52.2)
		Pr >  t			0.2288
	Week 168	n	2	1	
		LS Mean	28.630	0.652	27.978
		SEM	10.90	15.18	18.39
		95% CI	( 7.2,50.0)	(-29.1,30.4)	( -8.1,64.1)
		Pr >  t			0.1284
	Week 180	n	1		
		LS Mean	51.976	NE	NE
		SEM	15.13	NE	NE
		95% CI	( 22.3,81.7)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	85.306	NE	NE
		SEM	15.13	NE	NE
		95% CI	( 55.6, 115)	NE	NE
		Pr >  t			NE
Yes	Week 8	n	38	30	
		LS Mean	14.610	4.009	10.601
		SEM	5.499	5.937	5.362
		95% CI	( 3.7,25.5)	( -7.7,15.8)	( 0.0,21.2)
		Pr >  t			0.0491
	Week 16	n	32	24	
		LS Mean	16.291	8.536	7.755
		SEM	5.643	6.191	5.865
		95% CI	( 5.1,27.5)	( -3.7,20.8)	( -3.8,19.3)
		Pr >  t			0.1871
	Week 24	n	28	22	
		LS Mean	14.470	2.299	12.171
		SEM	5.894	6.310	6.150
		95% CI	( 2.8,26.1)	(-10.2,14.8)	( 0.1,24.3)
		Pr >  t			0.0487
	Week 32	n	29	20	
		LS Mean	10.886	-2.732	13.618
		SEM	5.860	6.567	6.261

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-0.7,22.5)	(-15.7,10.2)	(-1.3,25.9)
		Pr >  t			0.0304
		n	25	18	
		LS Mean	18.097	3.937	14.160
		SEM	6.025	6.719	6.579
Week 48		95% CI	(-6.2,30.0)	(-9.3,17.2)	(-1.2,27.1)
		Pr >  t			0.0321
		n	22	14	
		LS Mean	15.349	0.341	15.007
		SEM	6.184	7.133	7.148
Week 56		95% CI	(-3.1,27.6)	(-13.7,14.4)	(-1.0,29.1)
		Pr >  t			0.0364
		n	19	13	
		LS Mean	13.340	2.114	11.226
		SEM	6.380	7.277	7.471
Week 64		95% CI	(-0.8,25.9)	(-12.2,16.5)	(-3.5,25.9)
		Pr >  t			0.1337
		n	15	15	
		LS Mean	11.612	0.895	10.717
		SEM	6.741	7.021	7.557
Week 72		95% CI	(-1.7,24.9)	(-13.0,14.7)	(-4.1,25.6)
		Pr >  t			0.1569
		n	17	12	
		LS Mean	8.542	3.573	4.968
		SEM	6.542	7.431	7.765
Week 84		95% CI	(-4.4,21.4)	(-11.1,18.2)	(-10.3,20.2)
		Pr >  t			0.5226
		n	13	12	
		LS Mean	15.853	2.170	13.683
		SEM	7.077	7.433	8.165
Week 96		95% CI	(-1.9,29.8)	(-12.5,16.8)	(-2.4,29.7)
		Pr >  t			0.0945
		n	12	8	
		LS Mean	16.463	-6.698	23.160
		SEM	7.233	8.362	9.144
Week 108		95% CI	(-2.2,30.7)	(-23.2, 9.8)	(-5.2,41.1)
		Pr >  t			0.0117
		n	11	7	
		LS Mean	9.352	0.331	9.021
		SEM	7.418	8.730	9.621



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-5.3,24.0)	(-16.8,17.5)	(-9.9,27.9)
	Pr >  t			0.3489
	n	10	8	
	LS Mean	-0.602	4.593	-5.196
Week 132	SEM	7.625	8.365	9.460
	95% CI	(-15.6,14.4)	(-11.9,21.1)	(-23.8,13.4)
	Pr >  t			0.5831
	n	8	4	
Week 144	LS Mean	14.737	0.775	13.962
	SEM	8.175	10.66	11.90
	95% CI	(-1.3,30.8)	(-20.2,21.7)	(-9.4,37.4)
	Pr >  t			0.2414
Week 156	n	7	2	
	LS Mean	10.371	1.123	9.247
	SEM	8.547	14.15	15.32
	95% CI	(-6.4,27.2)	(-26.7,28.9)	(-20.9,39.4)
Week 168	Pr >  t			0.5464
	n	5	2	
	LS Mean	10.975	1.123	9.852
	SEM	9.636	14.15	15.95
Week 180	95% CI	(-8.0,29.9)	(-26.7,28.9)	(-21.5,41.2)
	Pr >  t			0.5371
	n	2	1	
	LS Mean	11.801	1.054	10.747
Week 192	SEM	14.00	19.32	23.03
	95% CI	(-15.7,39.3)	(-36.9,39.0)	(-34.5,56.0)
	Pr >  t			0.6409
	n		1	
Week 192	LS Mean	NE	1.054	NE
	SEM	NE	19.32	NE
	95% CI	NE	(-36.9,39.0)	NE
	Pr >  t			NE
Week 192	n		1	
	LS Mean	NE	1.054	NE
	SEM	NE	19.32	NE
	95% CI	NE	(-36.9,39.0)	NE
Week 192	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134		
			LS Mean	13.449	1.607	11.842	
			SEM	1.713	1.711	2.418	
			95% CI	( 10.1,16.8)	( -1.8, 5.0)	( 7.1,16.6)	
				Pr >  t			<.0001
		Week 16	n	118	104		
			LS Mean	13.116	2.682	10.434	
			SEM	1.808	1.913	2.632	
			95% CI	( 9.6,16.7)	( -1.1, 6.4)	( 5.3,15.6)	
				Pr >  t			<.0001
		Week 24	n	100	79		
			LS Mean	13.536	0.467	13.069	
			SEM	1.937	2.147	2.890	
			95% CI	( 9.7,17.3)	( -3.7, 4.7)	( 7.4,18.7)	
				Pr >  t			<.0001
		Week 32	n	84	72		
			LS Mean	13.414	-0.936	14.350	
			SEM	2.079	2.233	3.049	
			95% CI	( 9.3,17.5)	( -5.3, 3.4)	( 8.4,20.3)	
				Pr >  t			<.0001
		Week 40	n	73	62		
			LS Mean	13.844	0.771	13.074	
			SEM	2.200	2.372	3.232	
			95% CI	( 9.5,18.2)	( -3.9, 5.4)	( 6.7,19.4)	
		Pr >  t			<.0001		
Week 48	n	67	51				
	LS Mean	12.237	1.246	10.992			
	SEM	2.276	2.569	3.429			
	95% CI	( 7.8,16.7)	( -3.8, 6.3)	( 4.3,17.7)			
		Pr >  t			0.0014		
Week 56	n	57	45				
	LS Mean	14.079	-0.439	14.518			
	SEM	2.429	2.706	3.635			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 9.3,18.8)	( -5.7, 4.9)	( 7.4,21.6)
	Pr >  t			<.0001
	n	45	42	
	LS Mean	13.015	-0.782	13.797
	SEM	2.675	2.787	3.861
Week 72	95% CI	( 7.8,18.3)	( -6.2, 4.7)	( 6.2,21.4)
	Pr >  t			0.0004
	n	46	35	
	LS Mean	10.720	1.576	9.143
	SEM	2.653	3.008	4.009
Week 84	95% CI	( 5.5,15.9)	( -4.3, 7.5)	( 1.3,17.0)
	Pr >  t			0.0227
	n	40	33	
	LS Mean	15.030	0.924	14.106
	SEM	2.811	3.085	4.171
Week 96	95% CI	( 9.5,20.5)	( -5.1, 7.0)	( 5.9,22.3)
	Pr >  t			0.0007
	n	34	24	
	LS Mean	17.698	-4.195	21.893
	SEM	3.013	3.541	4.648
Week 108	95% CI	( 11.8,23.6)	( -11.1, 2.8)	( 12.8,31.0)
	Pr >  t			<.0001
	n	26	21	
	LS Mean	9.214	-1.911	11.125
	SEM	3.387	3.758	5.057
Week 120	95% CI	( 2.6,15.9)	( -9.3, 5.5)	( 1.2,21.0)
	Pr >  t			0.0280
	n	27	16	
	LS Mean	9.666	-0.029	9.696
	SEM	3.334	4.249	5.398
Week 132	95% CI	( 3.1,16.2)	( -8.4, 8.3)	( -0.9,20.3)
	Pr >  t			0.0727
	n	20	8	
	LS Mean	7.877	-0.724	8.601
	SEM	3.807	5.862	6.988
Week 144	95% CI	( 0.4,15.3)	( -12.2,10.8)	( -5.1,22.3)
	Pr >  t			0.2186
	n	14	5	
	LS Mean	10.731	-1.656	12.387
	SEM	4.483	7.350	8.607

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 1.9,19.5)	(-16.1,12.8)	( -4.5,29.3)
		Pr >  t			0.1503
	Week 156	n	10	3	
		LS Mean	15.012	-0.315	15.327
		SEM	5.247	9.414	10.78
		95% CI	( 4.7,25.3)	(-18.8,18.2)	( -5.8,36.5)
		Pr >  t			0.1552
	Week 168	n	4	2	
		LS Mean	19.485	-0.315	19.801
		SEM	8.155	11.49	14.09
		95% CI	( 3.5,35.5)	(-22.8,22.2)	( -7.8,47.4)
		Pr >  t			0.1601
	Week 180	n	1	1	
		LS Mean	50.247	-0.423	50.669
		SEM	16.16	16.16	22.86
		95% CI	( 18.5,82.0)	(-32.1,31.3)	( 5.8,95.5)
		Pr >  t			0.0268
	Week 192	n	1	1	
		LS Mean	83.577	-0.423	83.999
		SEM	16.16	16.16	22.86
		95% CI	( 51.9, 115)	(-32.1,31.3)	( 39.2, 129)
		Pr >  t			0.0002
Prior use	Week 8	n	8	6	
		LS Mean	12.518	3.678	8.841
		SEM	7.643	8.729	11.70
		95% CI	( -3.6,28.6)	(-14.6,21.9)	(-15.7,33.4)
		Pr >  t			0.4596
	Week 16	n	6	3	
		LS Mean	13.316	0.898	12.418
		SEM	8.696	11.76	14.73
		95% CI	( -4.7,31.4)	(-23.3,25.1)	(-18.0,42.9)
		Pr >  t			0.4077
	Week 24	n	5	2	
		LS Mean	30.277	-0.562	30.839
		SEM	9.263	13.61	16.48
		95% CI	( 11.1,49.4)	(-28.4,27.3)	( -3.0,64.7)
		Pr >  t			0.0722
	Week 32	n	2	1	
		LS Mean	1.586	-0.562	2.148
		SEM	12.82	17.92	22.02

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-24.7,27.8)	(-37.3,36.2)	(-43.0,47.3)
	Pr >  t			0.9230
Week 40	n	2		
	LS Mean	18.251	NE	NE
	SEM	12.82	NE	NE
	95% CI	(-8.0,44.5)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	1.586	NE	NE
	SEM	12.82	NE	NE
	95% CI	(-24.7,27.8)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	1.586	NE	NE
	SEM	12.82	NE	NE
	95% CI	(-24.7,27.8)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	1.586	NE	NE
	SEM	12.82	NE	NE
	95% CI	(-24.7,27.8)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	1.586	NE	NE
	SEM	12.82	NE	NE
	95% CI	(-24.7,27.8)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	8.984	NE	NE
	SEM	16.71	NE	NE
	95% CI	(-25.4,43.3)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	8.984	NE	NE
	SEM	16.71	NE	NE
	95% CI	(-25.4,43.3)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	8.984	NE	NE
	SEM	16.71	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-25.4,43.3)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	17.131	3.417	13.713		
			SEM	3.281	3.449	3.397		
			95% CI	( 10.7,23.6)	( -3.4,10.2)	( 7.0,20.4)		
					Pr >  t			<.0001
		Week 16	n	70	52			
			LS Mean	17.132	7.672	9.460		
			SEM	3.381	3.772	3.718		
			95% CI	( 10.5,23.8)	( 0.3,15.1)	( 2.2,16.8)		
					Pr >  t			0.0112
		Week 24	n	61	37			
			LS Mean	19.749	0.870	18.879		
			SEM	3.497	4.143	4.141		
			95% CI	( 12.9,26.6)	( -7.3, 9.0)	( 10.7,27.0)		
					Pr >  t			<.0001
		Week 32	n	48	33			
			LS Mean	14.900	1.626	13.274		
			SEM	3.724	4.268	4.431		
			95% CI	( 7.6,22.2)	( -6.8,10.0)	( 4.6,22.0)		
					Pr >  t			0.0028
		Week 40	n	42	31			
			LS Mean	15.825	2.121	13.703		
			SEM	3.842	4.341	4.603		
			95% CI	( 8.3,23.4)	( -6.4,10.6)	( 4.7,22.7)		
			Pr >  t			0.0030		
Week 48	n	40	25					
	LS Mean	15.456	1.686	13.770				
	SEM	3.887	4.599	4.886				
	95% CI	( 7.8,23.1)	( -7.3,10.7)	( 4.2,23.4)				
			Pr >  t			0.0050		
Week 56	n	35	20					
	LS Mean	13.649	1.092	12.558				
	SEM	4.016	4.915	5.289				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 5.8,21.5)	( -8.6,10.7)	( 2.2,22.9)
		Pr >  t			0.0178
	Week 64	n	29	18	
		LS Mean	12.605	4.096	8.509
		SEM	4.216	5.083	5.598
		95% CI	( 4.3,20.9)	( -5.9,14.1)	( -2.5,19.5)
		Pr >  t			0.1289
	Week 72	n	28	18	
		LS Mean	14.874	5.999	8.875
		SEM	4.258	5.078	5.628
		95% CI	( 6.5,23.2)	( -4.0,16.0)	( -2.2,19.9)
		Pr >  t			0.1152
	Week 84	n	27	17	
		LS Mean	16.570	7.161	9.408
		SEM	4.333	5.174	5.746
		95% CI	( 8.1,25.1)	( -3.0,17.3)	( -1.9,20.7)
		Pr >  t			0.1019
	Week 96	n	23	14	
		LS Mean	20.021	-2.744	22.765
		SEM	4.527	5.512	6.205
		95% CI	( 11.1,28.9)	( -13.6, 8.1)	( 10.6,34.9)
		Pr >  t			0.0003
	Week 108	n	19	12	
		LS Mean	12.124	1.308	10.816
		SEM	4.825	5.814	6.674
		95% CI	( 2.7,21.6)	( -10.1,12.7)	( -2.3,23.9)
		Pr >  t			0.1054
	Week 120	n	18	8	
		LS Mean	12.409	5.528	6.882
		SEM	4.890	6.763	7.568
		95% CI	( 2.8,22.0)	( -7.7,18.8)	( -8.0,21.7)
		Pr >  t			0.3634
	Week 132	n	11	4	
		LS Mean	12.994	2.780	10.213
		SEM	5.841	9.007	10.14
		95% CI	( 1.5,24.5)	( -14.9,20.5)	( -9.7,30.1)
		Pr >  t			0.3139
	Week 144	n	11	4	
		LS Mean	11.731	0.936	10.795
		SEM	5.819	9.012	10.14

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.3,23.2)	(-16.8,18.6)	( -9.1,30.7)
		Pr >  t			0.2874
	Week 156	n	5	2	
		LS Mean	13.324	2.566	10.758
		SEM	8.059	12.31	14.29
		95% CI	( -2.5,29.1)	(-21.6,26.7)	(-17.3,38.8)
		Pr >  t			0.4517
	Week 168	n	1	2	
		LS Mean	16.697	2.566	14.131
		SEM	16.99	12.31	20.69
		95% CI	(-16.7,50.1)	(-21.6,26.7)	(-26.5,54.7)
		Pr >  t			0.4947
	Week 180	n		1	
		LS Mean	NE	2.390	NE
		SEM	NE	17.08	NE
		95% CI	NE	(-31.1,35.9)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	2.390	NE
		SEM	NE	17.08	NE
		95% CI	NE	(-31.1,35.9)	NE
		Pr >  t			NE
>= 65 Years	Week 8	n	63	71	
		LS Mean	7.832	-1.176	9.008
		SEM	4.447	4.423	3.338
		95% CI	( -0.9,16.6)	( -9.9, 7.5)	( 2.4,15.6)
		Pr >  t			0.0073
	Week 16	n	54	55	
		LS Mean	7.452	-3.217	10.669
		SEM	4.591	4.532	3.638
		95% CI	( -1.6,16.5)	(-12.2, 5.7)	( 3.5,17.8)
		Pr >  t			0.0035
	Week 24	n	44	44	
		LS Mean	6.764	-1.224	7.987
		SEM	4.715	4.650	3.964
		95% CI	( -2.5,16.1)	(-10.4, 7.9)	( 0.2,15.8)
		Pr >  t			0.0444
	Week 32	n	38	40	
		LS Mean	10.112	-4.494	14.606
		SEM	4.864	4.758	4.171

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 0.5,19.7)	( -13.9, 4.9)	( 6.4,22.8)
		Pr >  t			0.0005
	Week 40	n	33	31	
		LS Mean	10.868	-1.628	12.495
		SEM	4.970	4.990	4.496
		95% CI	( 1.1,20.7)	(-11.4, 8.2)	( 3.7,21.3)
		Pr >  t			0.0056
	Week 48	n	29	26	
		LS Mean	6.653	-0.425	7.078
		SEM	5.073	5.148	4.782
		95% CI	( -3.3,16.6)	(-10.6, 9.7)	( -2.3,16.5)
		Pr >  t			0.1394
	Week 56	n	24	25	
		LS Mean	13.425	-3.174	16.599
		SEM	5.246	5.183	5.004
		95% CI	( 3.1,23.7)	(-13.4, 7.0)	( 6.8,26.4)
		Pr >  t			0.0010
	Week 64	n	18	24	
		LS Mean	12.702	-6.067	18.770
		SEM	5.559	5.227	5.374
		95% CI	( 1.8,23.6)	(-16.3, 4.2)	( 8.2,29.3)
		Pr >  t			0.0005
	Week 72	n	20	17	
		LS Mean	3.700	-3.971	7.670
		SEM	5.442	5.615	5.637
		95% CI	( -7.0,14.4)	(-15.0, 7.1)	( -3.4,18.7)
		Pr >  t			0.1741
	Week 84	n	13	16	
		LS Mean	13.172	-6.619	19.791
		SEM	6.001	5.692	6.251
		95% CI	( 1.4,25.0)	(-17.8, 4.6)	( 7.5,32.1)
		Pr >  t			0.0016
	Week 96	n	12	10	
		LS Mean	13.537	-6.151	19.687
		SEM	6.131	6.439	7.049
		95% CI	( 1.5,25.6)	(-18.8, 6.5)	( 5.8,33.5)
		Pr >  t			0.0054
	Week 108	n	7	9	
		LS Mean	4.148	-6.372	10.521
		SEM	7.187	6.639	8.150

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.0,18.3)	(-19.4, 6.7)	(-5.5,26.5)
		Pr >  t			0.1972
	Week 120	n	10	8	
		LS Mean	5.329	-6.706	12.035
		SEM	6.462	6.886	7.734
		95% CI	(-7.4,18.0)	(-20.2, 6.8)	(-3.1,27.2)
		Pr >  t			0.1201
	Week 132	n	9	4	
		LS Mean	0.625	-5.283	5.908
		SEM	6.647	8.767	9.573
		95% CI	(-12.4,13.7)	(-22.5,11.9)	(-12.9,24.7)
		Pr >  t			0.5373
	Week 144	n	4	1	
		LS Mean	10.842	-4.210	15.052
		SEM	8.765	15.91	17.33
		95% CI	(-6.4,28.0)	(-35.4,27.0)	(-19.0,49.1)
		Pr >  t			0.3855
	Week 156	n	5	1	
		LS Mean	15.178	-4.210	19.388
		SEM	8.074	15.91	17.00
		95% CI	(-0.7,31.0)	(-35.4,27.0)	(-14.0,52.8)
		Pr >  t			0.2544
	Week 168	n	3		
		LS Mean	17.338	NE	NE
		SEM	9.827	NE	NE
		95% CI	(-2.0,36.6)	NE	NE
		Pr >  t			NE
	Week 180	n	1		
		LS Mean	46.436	NE	NE
		SEM	15.90	NE	NE
		95% CI	(15.2,77.7)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	79.766	NE	NE
		SEM	15.90	NE	NE
		95% CI	(48.5, 111)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	14.028	2.576	11.452		
			SEM	2.678	2.730	2.579		
			95% CI	( 8.8,19.3)	( -2.8, 7.9)	( 6.4,16.5)		
					Pr >  t			<.0001
		Week 16	n	111	91			
			LS Mean	13.897	4.329	9.568		
			SEM	2.763	2.933	2.824		
			95% CI	( 8.5,19.3)	( -1.4,10.1)	( 4.0,15.1)		
					Pr >  t			0.0007
		Week 24	n	96	70			
			LS Mean	15.621	1.228	14.392		
			SEM	2.850	3.123	3.084		
			95% CI	( 10.0,21.2)	( -4.9, 7.4)	( 8.3,20.4)		
					Pr >  t			<.0001
		Week 32	n	77	61			
			LS Mean	14.226	0.135	14.091		
			SEM	3.016	3.239	3.311		
			95% CI	( 8.3,20.1)	( -6.2, 6.5)	( 7.6,20.6)		
					Pr >  t			<.0001
		Week 40	n	69	52			
			LS Mean	14.918	0.856	14.062		
			SEM	3.088	3.383	3.504		
			95% CI	( 8.9,21.0)	( -5.8, 7.5)	( 7.2,20.9)		
			Pr >  t			<.0001		
Week 48	n	62	41					
	LS Mean	13.423	2.017	11.406				
	SEM	3.162	3.597	3.774				
	95% CI	( 7.2,19.6)	( -5.0, 9.1)	( 4.0,18.8)				
			Pr >  t			0.0026		
Week 56	n	53	35					
	LS Mean	14.138	-0.024	14.162				
	SEM	3.280	3.761	4.031				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 7.7,20.6)	( -7.4, 7.4)	( 6.3,22.1)
		Pr >  t			0.0005
	Week 64	n	44	33	
		LS Mean	11.346	0.408	10.937
		SEM	3.436	3.828	4.222
		95% CI	( 4.6,18.1)	( -7.1, 7.9)	( 2.7,19.2)
		Pr >  t			0.0097
	Week 72	n	45	28	
		LS Mean	10.552	1.803	8.750
		SEM	3.418	4.021	4.383
		95% CI	( 3.8,17.3)	( -6.1, 9.7)	( 0.2,17.3)
		Pr >  t			0.0461
	Week 84	n	39	27	
		LS Mean	15.742	2.183	13.559
		SEM	3.568	4.067	4.531
		95% CI	( 8.7,22.7)	( -5.8,10.2)	( 4.7,22.4)
		Pr >  t			0.0028
	Week 96	n	34	19	
		LS Mean	18.297	-4.294	22.591
		SEM	3.704	4.568	5.090
		95% CI	( 11.0,25.6)	(-13.3, 4.7)	( 12.6,32.6)
		Pr >  t			<.0001
	Week 108	n	26	17	
		LS Mean	9.828	-1.341	11.169
		SEM	4.036	4.754	5.489
		95% CI	( 1.9,17.7)	(-10.7, 8.0)	( 0.4,21.9)
		Pr >  t			0.0420
	Week 120	n	27	11	
		LS Mean	10.675	1.110	9.565
		SEM	3.978	5.607	6.211
		95% CI	( 2.9,18.5)	( -9.9,12.1)	( -2.6,21.7)
		Pr >  t			0.1238
	Week 132	n	20	6	
		LS Mean	8.470	0.214	8.256
		SEM	4.408	7.220	7.924
		95% CI	( -0.2,17.1)	(-13.9,14.4)	( -7.3,23.8)
		Pr >  t			0.2977
	Week 144	n	15	4	
		LS Mean	11.349	-1.245	12.594
		SEM	4.883	8.659	9.498

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 1.8,20.9)	(-18.2,15.7)	( -6.0,31.2)
		Pr >  t			0.1851
	Week 156	n	10	2	
		LS Mean	15.615	0.462	15.153
		SEM	5.749	11.95	12.93
		95% CI	( 4.3,26.9)	(-23.0,23.9)	(-10.2,40.5)
		Pr >  t			0.2415
	Week 168	n	4	2	
		LS Mean	20.068	0.462	19.607
		SEM	8.589	11.95	14.42
		95% CI	( 3.2,36.9)	(-23.0,23.9)	( -8.7,47.9)
		Pr >  t			0.1742
	Week 180	n	1	1	
		LS Mean	50.809	0.316	50.493
		SEM	16.65	16.67	23.38
		95% CI	( 18.1,83.5)	(-32.4,33.0)	( 4.6,96.4)
		Pr >  t			0.0310
	Week 192	n	1	1	
		LS Mean	84.139	0.316	83.823
		SEM	16.65	16.67	23.38
		95% CI	( 51.5, 117)	(-32.4,33.0)	( 38.0, 130)
		Pr >  t			0.0003
>= 75 Years	Week 8	n	17	19	
		LS Mean	11.318	-0.709	12.027
		SEM	4.490	4.042	6.003
		95% CI	( 2.3,20.3)	( -8.8, 7.3)	( 0.0,24.0)
		Pr >  t			0.0492
	Week 16	n	13	16	
		LS Mean	11.128	-4.537	15.664
		SEM	4.946	4.341	6.556
		95% CI	( 1.3,21.0)	(-13.2, 4.1)	( 2.6,28.7)
		Pr >  t			0.0192
	Week 24	n	9	11	
		LS Mean	6.342	-1.162	7.504
		SEM	5.583	4.945	7.433
		95% CI	( -4.7,17.4)	(-11.0, 8.6)	( -7.2,22.2)
		Pr >  t			0.3149
	Week 32	n	9	12	
		LS Mean	8.065	-4.080	12.145
		SEM	5.599	4.825	7.369



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.0,19.2)	(-2.5,26.8)
		Pr >  t		0.1022
	Week 40	n	6	10
		LS Mean	9.476	2.538
		SEM	6.401	5.098
		95% CI	(-3.2,22.1)	(-7.6,12.6)
		Pr >  t		(-9.2,23.1)
	Week 48	n	7	10
		LS Mean	3.579	-0.737
		SEM	6.076	5.116
		95% CI	(-8.4,15.6)	(-10.9, 9.4)
		Pr >  t		(-11.3,20.0)
	Week 56	n	6	10
		LS Mean	14.174	-1.298
		SEM	6.394	5.121
		95% CI	( 1.5,26.8)	(-11.4, 8.8)
		Pr >  t		(-0.7,31.6)
	Week 64	n	3	9
		LS Mean	40.559	-4.380
		SEM	8.280	5.302
		95% CI	( 24.2,56.9)	(-14.9, 6.1)
		Pr >  t		( 25.6,64.3)
	Week 72	n	3	7
		LS Mean	18.336	1.827
		SEM	8.280	5.782
		95% CI	( 2.0,34.7)	(-9.6,13.3)
		Pr >  t		(-3.4,36.4)
	Week 84	n	1	6
		LS Mean	12.082	-3.117
		SEM	13.29	6.102
		95% CI	(-14.2,38.3)	(-15.2, 8.9)
		Pr >  t		(-13.6,44.0)
	Week 96	n	1	5
		LS Mean	12.082	-2.602
		SEM	13.29	6.529
		95% CI	(-14.2,38.3)	(-15.5,10.3)
		Pr >  t		(-14.5,43.9)
	Week 108	n		4
		LS Mean	NE	-2.757
		SEM	NE	7.118
				NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-16.8,11.3)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	1.529	-2.602
		SEM	13.33	6.529
		95% CI	(-24.8,27.8)	(-15.5,10.3)
		Pr >  t		(-25.1,33.4)
	Week 132	n		2
		LS Mean	NE	-3.075
		SEM	NE	9.468
		95% CI	NE	(-21.8,15.6)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	-1.803
		SEM	NE	12.96
		95% CI	NE	(-27.4,23.8)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	-1.803
		SEM	NE	12.96
		95% CI	NE	(-27.4,23.8)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	12.673	1.577	11.096	
		SEM	3.557	3.479	2.862	
		95% CI	( 5.7,19.7)	( -5.3, 8.4)	( 5.5,16.7)	
			Pr >  t			0.0001
	Week 16	n	88	71		
		LS Mean	12.468	4.206	8.262	
		SEM	3.634	3.730	3.082	
		95% CI	( 5.3,19.6)	( -3.1,11.5)	( 2.2,14.3)	
			Pr >  t			0.0076
	Week 24	n	75	54		
		LS Mean	13.495	0.127	13.369	
		SEM	3.702	3.886	3.366	
		95% CI	( 6.2,20.8)	( -7.5, 7.8)	( 6.8,20.0)	
			Pr >  t			<.0001
	Week 32	n	62	52		
		LS Mean	12.939	0.687	12.252	
		SEM	3.815	3.912	3.507	
		95% CI	( 5.4,20.4)	( -7.0, 8.4)	( 5.4,19.1)	
			Pr >  t			0.0005
	Week 40	n	51	46		
		LS Mean	14.294	0.357	13.937	
		SEM	3.929	4.017	3.722	
		95% CI	( 6.6,22.0)	( -7.5, 8.2)	( 6.6,21.2)	
		Pr >  t			0.0002	
Week 48	n	50	37			
	LS Mean	10.887	2.136	8.751		
	SEM	3.941	4.179	3.910		
	95% CI	( 3.1,18.6)	( -6.1,10.3)	( 1.1,16.4)		
		Pr >  t			0.0254	
Week 56	n	43	33			
	LS Mean	11.858	-1.078	12.936		
	SEM	4.040	4.277	4.114		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 3.9,19.8)	( -9.5, 7.3)	( 4.9,21.0)
		Pr >  t			0.0017
	Week 64	n	35	33	
		LS Mean	11.076	0.430	10.646
		SEM	4.194	4.277	4.270
		95% CI	( 2.8,19.3)	( -8.0, 8.8)	( 2.3,19.0)
		Pr >  t			0.0128
	Week 72	n	35	31	
		LS Mean	13.342	1.764	11.578
		SEM	4.194	4.332	4.325
		95% CI	( 5.1,21.6)	( -6.7,10.3)	( 3.1,20.1)
		Pr >  t			0.0075
	Week 84	n	31	29	
		LS Mean	14.539	2.162	12.377
		SEM	4.310	4.394	4.486
		95% CI	( 6.1,23.0)	( -6.5,10.8)	( 3.6,21.2)
		Pr >  t			0.0059
	Week 96	n	27	22	
		LS Mean	14.730	-3.939	18.669
		SEM	4.426	4.685	4.890
		95% CI	( 6.0,23.4)	(-13.1, 5.3)	( 9.1,28.3)
		Pr >  t			0.0001
	Week 108	n	19	20	
		LS Mean	12.347	-1.391	13.738
		SEM	4.841	4.799	5.359
		95% CI	( 2.8,21.9)	(-10.8, 8.0)	( 3.2,24.3)
		Pr >  t			0.0105
	Week 120	n	20	15	
		LS Mean	14.557	0.652	13.905
		SEM	4.756	5.197	5.662
		95% CI	( 5.2,23.9)	( -9.5,10.9)	( 2.8,25.0)
		Pr >  t			0.0142
	Week 132	n	15	7	
		LS Mean	10.357	0.069	10.289
		SEM	5.169	6.703	7.344
		95% CI	( 0.2,20.5)	(-13.1,13.2)	( -4.1,24.7)
		Pr >  t			0.1615
	Week 144	n	10	5	
		LS Mean	16.013	-1.112	17.125
		SEM	5.849	7.646	8.679

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 4.5,27.5)	(-16.1,13.9)	( 0.1,34.2)
		Pr >  t			0.0487
	Week 156	n	6	3	
		LS Mean	14.339	0.238	14.101
		SEM	7.091	9.469	11.06
		95% CI	( 0.4,28.3)	(-18.3,18.8)	( -7.6,35.8)
		Pr >  t			0.2024
	Week 168	n	3	2	
		LS Mean	23.062	0.227	22.835
		SEM	9.454	11.35	14.16
		95% CI	( 4.5,41.6)	(-22.0,22.5)	( -4.9,50.6)
		Pr >  t			0.1070
	Week 180	n	1	1	
		LS Mean	50.528	0.172	50.356
		SEM	15.66	15.66	21.75
		95% CI	( 19.8,81.3)	(-30.6,30.9)	( 7.7,93.0)
		Pr >  t			0.0208
	Week 192	n	1	1	
		LS Mean	83.858	0.172	83.686
		SEM	15.66	15.66	21.75
		95% CI	( 53.1, 115)	(-30.6,30.9)	( 41.0, 126)
		Pr >  t			0.0001
1	Week 8	n	43	50	
		LS Mean	15.712	3.493	12.219
		SEM	4.168	4.321	4.456
		95% CI	( 7.5,23.9)	( -5.0,12.0)	( 3.4,21.0)
		Pr >  t			0.0065
	Week 16	n	35	35	
		LS Mean	15.583	1.192	14.391
		SEM	4.447	4.592	5.062
		95% CI	( 6.8,24.3)	( -7.9,10.2)	( 4.4,24.4)
		Pr >  t			0.0048
	Week 24	n	29	26	
		LS Mean	17.501	3.120	14.382
		SEM	4.714	5.060	5.602
		95% CI	( 8.2,26.8)	( -6.8,13.1)	( 3.4,25.4)
		Pr >  t			0.0107
	Week 32	n	23	21	
		LS Mean	15.872	-2.813	18.685
		SEM	5.125	5.450	6.162

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	( 5.8,26.0)	(-13.5, 7.9)	( 6.6,30.8)
		Pr >  t			0.0026
		n	23	16	
		LS Mean	15.716	4.178	11.538
		SEM	5.133	5.906	6.560
Week 48		95% CI	( 5.6,25.8)	( -7.4,15.8)	( -1.4,24.4)
		Pr >  t			0.0794
		n	18	14	
		LS Mean	15.547	0.911	14.636
		SEM	5.506	6.164	7.099
Week 56		95% CI	( 4.7,26.4)	(-11.2,13.0)	( 0.7,28.6)
		Pr >  t			0.0399
		n	15	12	
		LS Mean	19.339	3.484	15.855
		SEM	5.844	6.479	7.650
Week 64		95% CI	( 7.8,30.8)	( -9.3,16.2)	( 0.8,30.9)
		Pr >  t			0.0388
		n	11	9	
		LS Mean	20.537	-2.788	23.325
		SEM	6.477	7.175	8.718
Week 72		95% CI	( 7.8,33.3)	(-16.9,11.3)	( 6.2,40.5)
		Pr >  t			0.0078
		n	12	4	
		LS Mean	4.481	4.185	0.295
		SEM	6.298	9.917	10.98
Week 84		95% CI	( -7.9,16.9)	(-15.3,23.7)	(-21.3,21.9)
		Pr >  t			0.9785
		n	8	4	
		LS Mean	20.262	-4.147	24.409
		SEM	7.361	9.917	11.59
Week 96		95% CI	( 5.8,34.7)	(-23.6,15.3)	( 1.6,47.2)
		Pr >  t			0.0359
		n	8	2	
		LS Mean	28.595	-2.027	30.623
		SEM	7.361	13.46	14.74
Week 108		95% CI	( 14.1,43.1)	(-28.5,24.4)	( 1.6,59.6)
		Pr >  t			0.0384
		n	6	1	
	LS Mean	2.754	-2.190	4.944	
	SEM	8.247	18.62	19.90	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.5,19.0)	(-38.8,34.4)	(-34.2,44.1)
		Pr >  t			0.8039
	Week 120	n	8	1	
		LS Mean	-0.726	-2.190	1.464
		SEM	7.371	18.62	19.55
		95% CI	(-15.2,13.8)	(-38.8,34.4)	(-37.0,39.9)
		Pr >  t			0.9404
	Week 132	n	5	1	
		LS Mean	1.813	-2.190	4.003
		SEM	8.882	18.62	20.17
		95% CI	(-15.6,19.3)	(-38.8,34.4)	(-35.7,43.7)
		Pr >  t			0.8428
	Week 144	n	5		
		LS Mean	1.813	NE	NE
		SEM	8.882	NE	NE
		95% CI	(-15.6,19.3)	NE	NE
		Pr >  t			NE
	Week 156	n	4		
		LS Mean	17.091	NE	NE
		SEM	9.750	NE	NE
		95% CI	(-2.1,36.3)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	9.579	NE	NE
		SEM	18.38	NE	NE
		95% CI	(-26.6,45.7)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	92			
			LS Mean	19.909	8.622	11.287		
			SEM	3.519	3.520	2.950		
			95% CI	( 13.0,26.8)	( 1.7,15.5)	( 5.5,17.1)		
					Pr >  t			0.0001
		Week 16	n	79	68			
			LS Mean	15.956	10.209	5.747		
			SEM	3.570	3.749	3.244		
			95% CI	( 8.9,23.0)	( 2.8,17.6)	( -0.6,12.1)		
					Pr >  t			0.0770
		Week 24	n	64	55			
			LS Mean	19.777	7.809	11.968		
			SEM	3.711	3.933	3.545		
			95% CI	( 12.5,27.1)	( 0.1,15.5)	( 5.0,18.9)		
					Pr >  t			0.0008
		Week 32	n	49	53			
			LS Mean	17.479	5.883	11.596		
			SEM	3.940	3.961	3.766		
			95% CI	( 9.7,25.2)	( -1.9,13.7)	( 4.2,19.0)		
					Pr >  t			0.0022
		Week 40	n	44	45			
			LS Mean	16.190	7.807	8.383		
			SEM	4.018	4.080	3.972		
			95% CI	( 8.3,24.1)	( -0.2,15.8)	( 0.6,16.2)		
			Pr >  t			0.0351		
Week 48	n	41	36					
	LS Mean	17.111	9.481	7.630				
	SEM	4.074	4.265	4.215				
	95% CI	( 9.1,25.1)	( 1.1,17.9)	( -0.6,15.9)				
			Pr >  t			0.0706		
Week 56	n	33	32					
	LS Mean	19.354	6.159	13.195				
	SEM	4.261	4.376	4.511				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 11.0,27.7)	( -2.4,14.8)	( 4.3,22.0)
	Pr >  t			0.0035
	n	27	31	
	LS Mean	17.551	5.537	12.014
	SEM	4.461	4.409	4.735
Week 72	95% CI	( 8.8,26.3)	( -3.1,14.2)	( 2.7,21.3)
	Pr >  t			0.0113
	n	26	26	
	LS Mean	12.425	8.644	3.781
	SEM	4.504	4.595	4.948
Week 84	95% CI	( 3.6,21.3)	( -0.4,17.7)	( -5.9,13.5)
	Pr >  t			0.4449
	n	22	23	
	LS Mean	23.034	9.265	13.769
	SEM	4.726	4.737	5.259
Week 96	95% CI	( 13.8,32.3)	( -0.0,18.6)	( 3.4,24.1)
	Pr >  t			0.0090
	n	18	18	
	LS Mean	26.997	1.814	25.182
	SEM	5.002	5.064	5.790
Week 108	95% CI	( 17.2,36.8)	( -8.1,11.8)	( 13.8,36.5)
	Pr >  t			<.0001
	n	14	14	
	LS Mean	13.523	4.686	8.838
	SEM	5.407	5.463	6.473
Week 120	95% CI	( 2.9,24.1)	( -6.0,15.4)	( -3.9,21.5)
	Pr >  t			0.1725
	n	12	12	
	LS Mean	3.410	7.103	-3.693
	SEM	5.684	5.743	6.935
Week 132	95% CI	( -7.7,14.6)	( -4.2,18.4)	( -17.3, 9.9)
	Pr >  t			0.5945
	n	9	5	
	LS Mean	12.495	6.314	6.181
	SEM	6.283	7.947	9.246
Week 144	95% CI	( 0.2,24.8)	( -9.3,21.9)	( -12.0,24.3)
	Pr >  t			0.5040
	n	7	4	
	LS Mean	2.329	4.981	-2.652
	SEM	6.906	8.731	10.33

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.2,15.9)	(-12.2,22.1)	(-22.9,17.6)
		Pr >  t			0.7975
	Week 156	n	4	2	
		LS Mean	30.426	6.708	23.718
		SEM	8.675	11.86	14.10
		95% CI	( 13.4,47.4)	(-16.6,30.0)	( -3.9,51.4)
		Pr >  t			0.0928
	Week 168	n	2	1	
		LS Mean	16.070	6.815	9.255
		SEM	11.81	16.41	19.79
		95% CI	( -7.1,39.2)	(-25.4,39.0)	(-29.6,48.1)
		Pr >  t			0.6402
Yes	Week 8	n	53	48	
		LS Mean	8.179	-4.576	12.754
		SEM	3.813	3.978	3.937
		95% CI	( 0.7,15.7)	(-12.4, 3.3)	( 5.0,20.5)
		Pr >  t			0.0013
	Week 16	n	45	39	
		LS Mean	14.085	-4.417	18.502
		SEM	4.034	4.201	4.244
		95% CI	( 6.1,22.0)	(-12.7, 3.9)	( 10.2,26.8)
		Pr >  t			<.0001
	Week 24	n	41	26	
		LS Mean	10.768	-6.074	16.842
		SEM	4.106	4.604	4.756
		95% CI	( 2.7,18.9)	(-15.1, 3.0)	( 7.5,26.2)
		Pr >  t			0.0004
	Week 32	n	37	20	
		LS Mean	11.214	-6.358	17.572
		SEM	4.233	4.985	5.169
		95% CI	( 2.9,19.5)	(-16.2, 3.4)	( 7.4,27.7)
		Pr >  t			0.0007
	Week 40	n	31	17	
		LS Mean	15.182	-5.425	20.607
		SEM	4.398	5.278	5.540
		95% CI	( 6.5,23.8)	(-15.8, 5.0)	( 9.7,31.5)
		Pr >  t			0.0002
	Week 48	n	28	15	
		LS Mean	8.773	-7.847	16.620
		SEM	4.502	5.476	5.812

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-0.1,17.6)	(-18.6, 2.9)	( 5.2,28.0)
		Pr >  t			0.0044
	Week 56	n	26	13	
		LS Mean	10.012	-5.558	15.570
		SEM	4.581	5.723	6.109
		95% CI	( 1.0,19.0)	(-16.8, 5.7)	( 3.6,27.6)
		Pr >  t			0.0111
	Week 64	n	20	11	
		LS Mean	9.825	-4.983	14.808
		SEM	4.894	6.042	6.640
		95% CI	( 0.2,19.4)	(-16.9, 6.9)	( 1.8,27.8)
		Pr >  t			0.0261
	Week 72	n	22	9	
		LS Mean	11.174	-4.752	15.926
		SEM	4.779	6.462	6.942
		95% CI	( 1.8,20.6)	(-17.4, 7.9)	( 2.3,29.6)
		Pr >  t			0.0221
	Week 84	n	18	10	
		LS Mean	8.322	-8.239	16.561
		SEM	5.058	6.237	6.920
		95% CI	( -1.6,18.3)	(-20.5, 4.0)	( 3.0,30.2)
		Pr >  t			0.0170
	Week 96	n	17	6	
		LS Mean	9.982	-7.357	17.339
		SEM	5.120	7.492	8.124
		95% CI	( -0.1,20.0)	(-22.1, 7.4)	( 1.4,33.3)
		Pr >  t			0.0332
	Week 108	n	12	7	
		LS Mean	6.745	-7.263	14.008
		SEM	5.722	7.067	8.131
		95% CI	( -4.5,18.0)	(-21.1, 6.6)	( -2.0,30.0)
		Pr >  t			0.0855
	Week 120	n	16	4	
		LS Mean	15.451	-6.705	22.156
		SEM	5.217	8.807	9.405
		95% CI	( 5.2,25.7)	(-24.0,10.6)	( 3.7,40.6)
		Pr >  t			0.0188
	Week 132	n	11	3	
		LS Mean	5.322	-6.893	12.215
		SEM	5.889	9.945	10.82

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-6.2,16.9)	(-26.4,12.6)	(-9.0,33.5)
		Pr >  t			0.2593
	Week 144	n	8	1	
		LS Mean	19.762	-6.286	26.048
		SEM	6.549	16.41	17.21
		95% CI	( 6.9,32.6)	(-38.5,26.0)	(-7.8,59.9)
		Pr >  t			0.1307
	Week 156	n	6	1	
		LS Mean	5.335	-6.286	11.620
		SEM	7.350	16.41	17.51
		95% CI	(-9.1,19.8)	(-38.5,26.0)	(-22.8,46.0)
		Pr >  t			0.5073
	Week 168	n	2	1	
		LS Mean	24.885	-6.286	31.171
		SEM	11.79	16.41	19.79
		95% CI	( 1.7,48.0)	(-38.5,26.0)	(-7.7,70.1)
		Pr >  t			0.1159
	Week 180	n	1	1	
		LS Mean	48.770	-6.286	55.055
		SEM	16.29	16.41	22.76
		95% CI	( 16.8,80.8)	(-38.5,26.0)	( 10.3,99.8)
		Pr >  t			0.0159
	Week 192	n	1	1	
		LS Mean	82.100	-6.286	88.385
		SEM	16.29	16.41	22.76
		95% CI	( 50.1, 114)	(-38.5,26.0)	( 43.7, 133)
		Pr >  t			0.0001

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35			
			LS Mean	17.503	-0.631	18.134		
			SEM	4.571	4.972	4.819		
			95% CI	( 8.5,26.6)	(-10.5, 9.2)	( 8.6,27.7)		
					Pr >  t			0.0002
		Week 16	n	35	22			
			LS Mean	16.665	0.412	16.253		
			SEM	4.768	5.647	5.499		
			95% CI	( 7.2,26.1)	(-10.7,11.6)	( 5.4,27.1)		
					Pr >  t			0.0035
		Week 24	n	28	16			
			LS Mean	22.774	-1.354	24.129		
			SEM	4.962	6.065	6.122		
			95% CI	( 13.0,32.6)	(-13.3,10.6)	( 12.1,36.2)		
					Pr >  t			0.0001
		Week 32	n	22	16			
			LS Mean	15.064	-1.349	16.413		
			SEM	5.285	6.082	6.333		
			95% CI	( 4.6,25.5)	(-13.3,10.6)	( 3.9,28.9)		
					Pr >  t			0.0101
		Week 40	n	19	12			
			LS Mean	14.016	1.213	12.804		
			SEM	5.463	6.516	6.891		
			95% CI	( 3.2,24.8)	(-11.6,14.1)	( -0.8,26.4)		
			Pr >  t			0.0642		
Week 48	n	16	10					
	LS Mean	12.380	-1.879	14.259				
	SEM	5.679	6.842	7.372				
	95% CI	( 1.2,23.6)	(-15.4,11.6)	( -0.2,28.8)				
			Pr >  t			0.0540		
Week 56	n	14	7					
	LS Mean	20.731	-2.272	23.003				
		SEM	5.875	7.592	8.222			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( -9.2,32.3)	( -17.2,12.7)	( -6.8,39.2)
		Pr >  t			0.0054
	Week 64	n	8	7	
		LS Mean	4.659	-2.225	6.884
		SEM	6.852	7.592	8.966
		95% CI	( -8.8,18.1)	( -17.2,12.7)	( -10.8,24.5)
		Pr >  t			0.4431
	Week 72	n	12	6	
		LS Mean	-0.785	-2.417	1.632
		SEM	6.112	7.974	8.748
		95% CI	( -12.8,11.3)	( -18.1,13.3)	( -15.6,18.8)
		Pr >  t			0.8521
	Week 84	n	8	5	
		LS Mean	14.102	-2.635	16.736
		SEM	6.905	8.470	9.727
		95% CI	( 0.5,27.7)	( -19.3,14.0)	( -2.4,35.9)
		Pr >  t			0.0862
	Week 96	n	5	5	
		LS Mean	13.265	-2.635	15.900
		SEM	8.086	8.470	10.60
		95% CI	( -2.6,29.2)	( -19.3,14.0)	( -4.9,36.7)
		Pr >  t			0.1345
	Week 108	n	7	5	
		LS Mean	4.090	-2.635	6.725
		SEM	7.212	8.470	9.946
		95% CI	( -10.1,18.3)	( -19.3,14.0)	( -12.8,26.3)
		Pr >  t			0.4994
	Week 120	n	5	3	
		LS Mean	11.267	-3.562	14.829
		SEM	8.098	10.18	12.02
		95% CI	( -4.7,27.2)	( -23.6,16.5)	( -8.8,38.5)
		Pr >  t			0.2181
	Week 132	n	2	2	
		LS Mean	6.848	-3.974	10.822
		SEM	11.65	11.90	15.89
		95% CI	( -16.1,29.8)	( -27.4,19.4)	( -20.4,42.1)
		Pr >  t			0.4963
	Week 144	n	2		
		LS Mean	26.600	NE	NE
		SEM	11.66	NE	NE

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive	Week 156	95% CI	( 3.7,49.5)	NE	NE
		Pr >  t			NE
		n	2		
		LS Mean	4.484	NE	NE
		SEM	11.67	NE	NE
		95% CI	(-18.5,27.4)	NE	NE
	Week 168	Pr >  t			NE
		n	1		
		LS Mean	1.397	NE	NE
		SEM	15.92	NE	NE
		95% CI	(-29.9,32.7)	NE	NE
		Pr >  t			NE
	Week 8	n	98	104	
		LS Mean	11.557	2.775	8.782
		SEM	3.161	3.121	2.711
		95% CI	( 5.3,17.8)	( -3.4, 8.9)	( 3.5,14.1)
		Pr >  t			0.0013
		n	87	84	
	Week 16	LS Mean	11.475	3.556	7.919
		SEM	3.248	3.244	2.928
		95% CI	( 5.1,17.9)	( -2.8, 9.9)	( 2.2,13.7)
		Pr >  t			0.0070
		n	76	65	
		LS Mean	10.931	1.300	9.631
Week 24	SEM	3.344	3.423	3.188	
	95% CI	( 4.4,17.5)	( -5.4, 8.0)	( 3.4,15.9)	
	Pr >  t			0.0026	
	n	62	57		
	LS Mean	12.068	-0.433	12.501	
	SEM	3.485	3.534	3.413	
Week 32	95% CI	( 5.2,18.9)	( -7.4, 6.5)	( 5.8,19.2)	
	Pr >  t			0.0003	
	n	54	50		
	LS Mean	13.052	1.038	12.014	
	SEM	3.578	3.652	3.609	
	95% CI	( 6.0,20.1)	( -6.1, 8.2)	( 4.9,19.1)	
Week 40	Pr >  t			0.0009	
	n	52	41		
	LS Mean	11.876	2.340	9.535	
	SEM	3.604	3.815	3.798	
	95% CI				
	Pr >  t				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 4.8,19.0)	( -5.2, 9.8)	( 2.1,17.0)
		Pr >  t			0.0122
	Week 56	n	44	38	
		LS Mean	11.432	0.314	11.118
		SEM	3.729	3.884	3.989
		95% CI	( 4.1,18.8)	( -7.3, 7.9)	( 3.3,18.9)
		Pr >  t			0.0054
	Week 64	n	39	35	
		LS Mean	13.891	-0.049	13.940
		SEM	3.831	3.963	4.162
		95% CI	( 6.4,21.4)	( -7.8, 7.7)	( 5.8,22.1)
		Pr >  t			0.0008
	Week 72	n	36	29	
		LS Mean	13.905	2.838	11.067
		SEM	3.904	4.158	4.413
		95% CI	( 6.2,21.6)	( -5.3,11.0)	( 2.4,19.7)
		Pr >  t			0.0123
	Week 84	n	32	28	
		LS Mean	14.865	2.042	12.822
		SEM	4.032	4.197	4.552
		95% CI	( 6.9,22.8)	( -6.2,10.3)	( 3.9,21.8)
		Pr >  t			0.0049
	Week 96	n	30	19	
		LS Mean	17.746	-4.236	21.982
		SEM	4.086	4.700	5.074
		95% CI	( 9.7,25.8)	( -13.5, 5.0)	( 12.0,31.9)
		Pr >  t			<.0001
	Week 108	n	18	16	
		LS Mean	11.504	-1.356	12.860
		SEM	4.756	4.970	5.845
		95% CI	( 2.2,20.8)	( -11.1, 8.4)	( 1.4,24.3)
		Pr >  t			0.0280
	Week 120	n	23	13	
		LS Mean	8.907	1.231	7.676
		SEM	4.398	5.337	5.901
		95% CI	( 0.3,17.5)	( -9.2,11.7)	( -3.9,19.3)
		Pr >  t			0.1936
	Week 132	n	18	6	
		LS Mean	7.582	0.540	7.043
		SEM	4.756	7.200	7.830



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-1.8,16.9)	(-13.6,14.7)	(-8.3,22.4)
	Pr >  t			0.3686
Week 144	n	13	5	
	LS Mean	8.121	-0.917	9.038
	SEM	5.282	7.782	8.695
	95% CI	(-2.2,18.5)	(-16.2,14.4)	(-8.0,26.1)
	Pr >  t			0.2988
Week 156	n	8	3	
	LS Mean	17.365	0.385	16.980
	SEM	6.372	9.748	11.07
	95% CI	( 4.9,29.9)	(-18.7,19.5)	(-4.7,38.7)
	Pr >  t			0.1253
Week 168	n	3	2	
	LS Mean	24.964	0.363	24.601
	SEM	9.714	11.75	14.81
	95% CI	( 5.9,44.0)	(-22.7,23.4)	(-4.5,53.7)
	Pr >  t			0.0970
Week 180	n	1	1	
	LS Mean	50.314	0.291	50.022
	SEM	16.34	16.34	22.82
	95% CI	( 18.3,82.4)	(-31.8,32.3)	( 5.3,94.8)
	Pr >  t			0.0286
Week 192	n	1	1	
	LS Mean	83.644	0.291	83.352
	SEM	16.34	16.34	22.82
	95% CI	( 51.6, 116)	(-31.8,32.3)	( 38.6, 128)
	Pr >  t			0.0003

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
ER and PR Status (L)	Both positive	Week 8	n	96	104	
			LS Mean	11.751	2.697	9.053
			SEM	3.171	3.121	2.729
			95% CI	( 5.5,18.0)	( -3.4, 8.8)	( 3.7,14.4)
			Pr >  t			0.0010
		Week 16	n	85	84	
			LS Mean	11.691	3.464	8.227
			SEM	3.261	3.245	2.950
			95% CI	( 5.3,18.1)	( -2.9, 9.8)	( 2.4,14.0)
			Pr >  t			0.0054
		Week 24	n	75	65	
			LS Mean	11.121	1.221	9.900
			SEM	3.355	3.425	3.207
			95% CI	( 4.5,17.7)	( -5.5, 8.0)	( 3.6,16.2)
			Pr >  t			0.0021
		Week 32	n	61	57	
			LS Mean	12.301	-0.509	12.810
			SEM	3.500	3.537	3.436
			95% CI	( 5.4,19.2)	( -7.5, 6.4)	( 6.1,19.6)
			Pr >  t			0.0002
		Week 40	n	53	50	
			LS Mean	13.352	0.959	12.393
			SEM	3.597	3.656	3.636
			95% CI	( 6.3,20.4)	( -6.2, 8.1)	( 5.3,19.5)
			Pr >  t			0.0007
		Week 48	n	51	41	
			LS Mean	12.155	2.261	9.894
			SEM	3.624	3.820	3.826
95% CI	( 5.0,19.3)		( -5.2, 9.8)	( 2.4,17.4)		
Pr >  t				0.0099		
Week 56	n	43	38			
	LS Mean	11.722	0.233	11.488		
	SEM	3.756	3.889	4.023		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 4.3,19.1)	( -7.4, 7.9)	( 3.6,19.4)
	Pr >  t			0.0044
	n	39	35	
	LS Mean	14.113	-0.122	14.234
	SEM	3.839	3.970	4.179
Week 72	95% CI	( 6.6,21.7)	( -7.9, 7.7)	( 6.0,22.4)
	Pr >  t			0.0007
	n	35	29	
	LS Mean	14.241	2.764	11.477
	SEM	3.940	4.166	4.456
Week 84	95% CI	( 6.5,22.0)	( -5.4,10.9)	( 2.7,20.2)
	Pr >  t			0.0101
	n	31	28	
	LS Mean	15.249	1.970	13.279
	SEM	4.076	4.205	4.600
Week 96	95% CI	( 7.2,23.3)	( -6.3,10.2)	( 4.3,22.3)
	Pr >  t			0.0040
	n	29	19	
	LS Mean	18.240	-4.304	22.543
	SEM	4.133	4.712	5.126
Week 108	95% CI	( 10.1,26.4)	( -13.6, 4.9)	( 12.5,32.6)
	Pr >  t			<.0001
	n	18	16	
	LS Mean	11.735	-1.421	13.156
	SEM	4.771	4.984	5.871
Week 120	95% CI	( 2.4,21.1)	( -11.2, 8.4)	( 1.6,24.7)
	Pr >  t			0.0252
	n	23	13	
	LS Mean	9.134	1.173	7.962
	SEM	4.411	5.354	5.928
Week 132	95% CI	( 0.5,17.8)	( -9.3,11.7)	( -3.7,19.6)
	Pr >  t			0.1795
	n	18	6	
	LS Mean	7.817	0.469	7.348
	SEM	4.772	7.228	7.867
Week 144	95% CI	( -1.5,17.2)	( -13.7,14.6)	( -8.1,22.8)
	Pr >  t			0.3505
	n	13	5	
	LS Mean	8.351	-0.986	9.337
	SEM	5.301	7.814	8.736

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive Negative	Week 156	95% CI	(-2.1,18.8)	(-16.3,14.3)	(-7.8,26.5)
		Pr >  t			0.2854
		n	8	3	
	Week 168	LS Mean	17.605	0.308	17.298
		SEM	6.397	9.790	11.12
		95% CI	( 5.1,30.2)	(-18.9,19.5)	(-4.5,39.1)
	Week 180	Pr >  t			0.1201
		n	3	2	
		LS Mean	25.223	0.279	24.944
	Week 192	SEM	9.758	11.81	14.88
		95% CI	( 6.1,44.4)	(-22.9,23.4)	(-4.3,54.1)
		Pr >  t			0.0940
	Week 8	n	1	1	
		LS Mean	50.587	0.226	50.361
		SEM	16.41	16.41	22.93
	Week 16	95% CI	( 18.4,82.8)	(-32.0,32.4)	( 5.4,95.3)
		Pr >  t			0.0283
		n	1	1	
	Week 24	LS Mean	83.917	0.226	83.691
		SEM	16.41	16.41	22.93
		95% CI	( 51.7, 116)	(-32.0,32.4)	( 38.7, 129)
	Week 32	Pr >  t			0.0003
		n	42	35	
		LS Mean	17.503	-0.631	18.134
Week 8	SEM	4.571	4.972	4.819	
	95% CI	( 8.5,26.6)	(-10.5, 9.2)	( 8.6,27.7)	
	Pr >  t			0.0002	
Week 16	n	35	22		
	LS Mean	16.665	0.412	16.253	
	SEM	4.768	5.647	5.499	
Week 24	95% CI	( 7.2,26.1)	(-10.7,11.6)	( 5.4,27.1)	
	Pr >  t			0.0035	
	n	28	16		
Week 32	LS Mean	22.774	-1.354	24.129	
	SEM	4.962	6.065	6.122	
	95% CI	( 13.0,32.6)	(-13.3,10.6)	( 12.1,36.2)	
Week 8	Pr >  t			0.0001	
	n	22	16		
	LS Mean	15.064	-1.349	16.413	
Week 16	SEM	5.285	6.082	6.333	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	( 4.6,25.5)	(-13.3,10.6)	( 3.9,28.9)
	Pr >  t			0.0101
Week 40	n	19	12	
	LS Mean	14.016	1.213	12.804
	SEM	5.463	6.516	6.891
	95% CI	( 3.2,24.8)	(-11.6,14.1)	( -0.8,26.4)
	Pr >  t			0.0642
Week 48	n	16	10	
	LS Mean	12.380	-1.879	14.259
	SEM	5.679	6.842	7.372
	95% CI	( 1.2,23.6)	(-15.4,11.6)	( -0.2,28.8)
	Pr >  t			0.0540
Week 56	n	14	7	
	LS Mean	20.731	-2.272	23.003
	SEM	5.875	7.592	8.222
	95% CI	( 9.2,32.3)	(-17.2,12.7)	( 6.8,39.2)
	Pr >  t			0.0054
Week 64	n	8	7	
	LS Mean	4.659	-2.225	6.884
	SEM	6.852	7.592	8.966
	95% CI	( -8.8,18.1)	(-17.2,12.7)	(-10.8,24.5)
	Pr >  t			0.4431
Week 72	n	12	6	
	LS Mean	-0.785	-2.417	1.632
	SEM	6.112	7.974	8.748
	95% CI	(-12.8,11.3)	(-18.1,13.3)	(-15.6,18.8)
	Pr >  t			0.8521
Week 84	n	8	5	
	LS Mean	14.102	-2.635	16.736
	SEM	6.905	8.470	9.727
	95% CI	( 0.5,27.7)	(-19.3,14.0)	( -2.4,35.9)
	Pr >  t			0.0862
Week 96	n	5	5	
	LS Mean	13.265	-2.635	15.900
	SEM	8.086	8.470	10.60
	95% CI	( -2.6,29.2)	(-19.3,14.0)	( -4.9,36.7)
	Pr >  t			0.1345
Week 108	n	7	5	
	LS Mean	4.090	-2.635	6.725
	SEM	7.212	8.470	9.946

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-10.1,18.3)	(-19.3,14.0)	(-12.8,26.3)
	Pr >  t			0.4994
	n	5	3	
	LS Mean	11.267	-3.562	14.829
	SEM	8.098	10.18	12.02
Week 132	95% CI	(-4.7,27.2)	(-23.6,16.5)	(-8.8,38.5)
	Pr >  t			0.2181
	n	2	2	
	LS Mean	6.848	-3.974	10.822
	SEM	11.65	11.90	15.89
Week 144	95% CI	(-16.1,29.8)	(-27.4,19.4)	(-20.4,42.1)
	Pr >  t			0.4963
	n	2		
	LS Mean	26.600	NE	NE
	SEM	11.66	NE	NE
Week 156	95% CI	(-3.7,49.5)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	4.484	NE	NE
	SEM	11.67	NE	NE
Week 168	95% CI	(-18.5,27.4)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	1.397	NE	NE
	SEM	15.92	NE	NE
	95% CI	(-29.9,32.7)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	15.702	2.920	12.781
			SEM	2.947	3.044	2.894
			95% CI	( 9.9,21.5)	( -3.1, 8.9)	( 7.1,18.5)
		Pr >  t			<.0001	
		Week 16	n	90	75	
			LS Mean	14.932	5.125	9.807
			SEM	3.035	3.219	3.146
			95% CI	( 9.0,20.9)	( -1.2,11.5)	( 3.6,16.0)
		Pr >  t			0.0019	
		Week 24	n	79	62	
			LS Mean	15.347	0.647	14.700
			SEM	3.122	3.372	3.355
			95% CI	( 9.2,21.5)	( -6.0, 7.3)	( 8.1,21.3)
		Pr >  t			<.0001	
		Week 32	n	70	56	
			LS Mean	12.845	-0.668	13.513
			SEM	3.233	3.462	3.498
			95% CI	( 6.5,19.2)	( -7.5, 6.1)	( 6.6,20.4)
		Pr >  t			0.0001	
		Week 40	n	61	46	
			LS Mean	15.071	1.522	13.549
			SEM	3.321	3.631	3.731
			95% CI	( 8.5,21.6)	( -5.6, 8.7)	( 6.2,20.9)
		Pr >  t			0.0003	
		Week 48	n	56	38	
			LS Mean	13.622	0.111	13.511
			SEM	3.379	3.802	3.948
95% CI	( 7.0,20.3)		( -7.4, 7.6)	( 5.8,21.3)		
Pr >  t			0.0006			
Week 56	n	49	33			
	LS Mean	15.116	1.581	13.535		
	SEM	3.477	3.941	4.169		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	( 8.3,21.9)	( -6.2, 9.3)	( 5.4,21.7)
	Pr >  t			0.0012
	n	37	29	
	LS Mean	10.098	0.313	9.786
	SEM	3.712	4.086	4.501
Week 72	95% CI	( 2.8,17.4)	( -7.7, 8.3)	( 1.0,18.6)
	Pr >  t			0.0299
	n	40	25	
	LS Mean	9.383	4.249	5.133
	SEM	3.643	4.259	4.604
Week 84	95% CI	( 2.2,16.5)	( -4.1,12.6)	( -3.9,14.2)
	Pr >  t			0.2651
	n	32	23	
	LS Mean	16.532	3.798	12.733
	SEM	3.875	4.367	4.873
Week 96	95% CI	( 8.9,24.1)	( -4.8,12.4)	( 3.2,22.3)
	Pr >  t			0.0091
	n	29	17	
	LS Mean	17.013	-3.467	20.479
	SEM	3.974	4.806	5.349
Week 108	95% CI	( 9.2,24.8)	( -12.9, 6.0)	( 10.0,31.0)
	Pr >  t			0.0001
	n	22	15	
	LS Mean	9.280	-0.206	9.485
	SEM	4.328	5.014	5.788
Week 120	95% CI	( 0.8,17.8)	( -10.0, 9.6)	( -1.9,20.8)
	Pr >  t			0.1015
	n	23	13	
	LS Mean	10.951	2.425	8.525
	SEM	4.260	5.277	5.975
Week 132	95% CI	( 2.6,19.3)	( -7.9,12.8)	( -3.2,20.2)
	Pr >  t			0.1539
	n	17	5	
	LS Mean	11.783	0.603	11.180
	SEM	4.706	7.705	8.434
Week 144	95% CI	( 2.5,21.0)	( -14.5,15.7)	( -5.4,27.7)
	Pr >  t			0.1852
	n	14	3	
	LS Mean	12.828	-1.520	14.348
	SEM	5.024	9.680	10.43



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 3.0,22.7)	(-20.5,17.5)	( -6.1,34.8)
		Pr >  t			0.1690
	Week 156	n	9	2	
		LS Mean	10.668	0.814	9.854
		SEM	5.961	11.66	12.70
		95% CI	( -1.0,22.4)	(-22.1,23.7)	(-15.1,34.8)
		Pr >  t			0.4378
	Week 168	n	4	1	
		LS Mean	19.909	0.712	19.198
		SEM	8.421	16.23	18.00
		95% CI	( 3.4,36.4)	(-31.1,32.6)	(-16.1,54.5)
		Pr >  t			0.2865
	Week 180	n	1	1	
		LS Mean	50.486	0.712	49.775
		SEM	16.18	16.23	22.70
		95% CI	( 18.7,82.2)	(-31.1,32.6)	( 5.2,94.3)
		Pr >  t			0.0285
	Week 192	n	1	1	
		LS Mean	83.816	0.712	83.105
		SEM	16.18	16.23	22.70
		95% CI	( 52.1, 116)	(-31.1,32.6)	( 38.6, 128)
		Pr >  t			0.0003
>= 3	Week 8	n	37	45	
		LS Mean	4.260	-3.233	7.493
		SEM	6.914	6.845	4.024
		95% CI	( -9.4,17.9)	(-16.7,10.2)	( -0.4,15.4)
		Pr >  t			0.0637
	Week 16	n	34	32	
		LS Mean	6.022	-5.569	11.591
		SEM	7.182	7.251	4.424
		95% CI	( -8.1,20.2)	(-19.8, 8.7)	( 2.9,20.3)
		Pr >  t			0.0092
	Week 24	n	26	19	
		LS Mean	9.806	-1.166	10.972
		SEM	7.367	7.657	5.341
		95% CI	( -4.7,24.3)	(-16.2,13.9)	( 0.5,21.5)
		Pr >  t			0.0407
	Week 32	n	16	17	
		LS Mean	14.457	-2.891	17.348
		SEM	7.822	7.786	6.107

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-0.9,29.9)	(-18.2,12.4)	( 5.3,29.4)
		Pr >  t			0.0048
		n	14	16	
		LS Mean	9.687	-2.769	12.455
		SEM	7.986	7.849	6.391
Week 48		95% CI	(-6.0,25.4)	(-18.2,12.7)	(-0.1,25.0)
		Pr >  t			0.0521
		n	13	13	
		LS Mean	5.219	3.237	1.981
		SEM	8.072	8.099	6.800
Week 56		95% CI	(-10.7,21.1)	(-12.7,19.2)	(-11.4,15.4)
		Pr >  t			0.7709
		n	10	12	
		LS Mean	7.625	-7.380	15.005
		SEM	8.467	8.214	7.361
Week 64		95% CI	(-9.0,24.3)	(-23.5, 8.8)	( 0.5,29.5)
		Pr >  t			0.0422
		n	10	13	
		LS Mean	22.347	-5.148	27.495
		SEM	8.465	8.111	7.250
Week 72		95% CI	( 5.7,39.0)	(-21.1,10.8)	( 13.2,41.8)
		Pr >  t			0.0002
		n	8	10	
		LS Mean	16.919	-6.795	23.714
		SEM	8.839	8.476	8.083
Week 84		95% CI	(-0.5,34.3)	(-23.5, 9.9)	( 7.8,39.6)
		Pr >  t			0.0036
		n	8	10	
		LS Mean	9.678	-7.513	17.191
		SEM	8.844	8.470	8.084
Week 96		95% CI	(-7.7,27.1)	(-24.2, 9.2)	( 1.3,33.1)
		Pr >  t			0.0341
		n	6	7	
		LS Mean	21.308	-7.832	29.140
		SEM	9.452	9.121	9.361
Week 108		95% CI	( 2.7,39.9)	(-25.8,10.1)	( 10.7,47.5)
		Pr >  t			0.0020
		n	4	6	
	LS Mean	10.960	-7.816	18.776	
	SEM	10.53	9.443	10.75	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-9.7,31.7)	(-26.4,10.8)	(-2.4,39.9)
		Pr >  t			0.0816
	Week 120	n	5	3	
		LS Mean	5.349	-10.01	15.360
		SEM	9.894	11.51	12.07
		95% CI	(-14.1,24.8)	(-32.6,12.6)	(-8.4,39.1)
		Pr >  t			0.2042
	Week 132	n	3	3	
		LS Mean	-12.35	-5.719	-6.628
		SEM	11.51	11.51	13.43
		95% CI	(-35.0,10.3)	(-28.4,16.9)	(-33.0,19.8)
		Pr >  t			0.6219
	Week 144	n	1	2	
		LS Mean	-9.237	-4.891	-4.346
		SEM	17.46	13.25	19.89
		95% CI	(-43.6,25.1)	(-30.9,21.2)	(-43.5,34.8)
		Pr >  t			0.8272
	Week 156	n	1	1	
		LS Mean	57.433	-5.097	62.530
		SEM	17.46	17.47	22.90
		95% CI	(23.1,91.8)	(-39.5,29.3)	(17.5,108)
		Pr >  t			0.0067
	Week 168	n		1	
		LS Mean	NE	-5.097	NE
		SEM	NE	17.47	NE
		95% CI	NE	(-39.5,29.3)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	7.376	-5.019	12.395		
			SEM	6.730	6.966	3.587		
					95% CI	(-6.0,20.7)	(-18.8, 8.8)	( 5.3,19.4)
					Pr >  t			0.0006
				Week 16	n	59	49	
					LS Mean	7.043	-2.889	9.933
					SEM	6.780	7.064	3.892
					95% CI	(-6.4,20.5)	(-16.9,11.1)	( 2.3,17.6)
					Pr >  t			0.0110
				Week 24	n	54	41	
					LS Mean	7.550	-5.964	13.514
					SEM	6.808	7.164	4.137
					95% CI	(-5.9,21.0)	(-20.1, 8.2)	( 5.4,21.6)
					Pr >  t			0.0012
				Week 32	n	48	37	
					LS Mean	8.164	-8.655	16.818
					SEM	6.853	7.222	4.330
					95% CI	(-5.4,21.7)	(-23.0, 5.6)	( 8.3,25.3)
					Pr >  t			0.0001
				Week 40	n	43	33	
					LS Mean	7.691	-5.065	12.756
					SEM	6.901	7.293	4.534
					95% CI	(-6.0,21.4)	(-19.5, 9.4)	( 3.9,21.7)
			Pr >  t			0.0050		
		Week 48	n	41	28			
			LS Mean	7.176	-7.001	14.177		
			SEM	6.923	7.407	4.755		
			95% CI	(-6.5,20.9)	(-21.6, 7.6)	( 4.8,23.5)		
			Pr >  t			0.0030		
		Week 56	n	35	22			
			LS Mean	5.477	-6.045	11.522		
			SEM	7.004	7.609	5.191		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.4,19.3)	(-21.1, 9.0)	( 1.3,21.7)
		Pr >  t			0.0267
	Week 64	n	26	23	
		LS Mean	4.344	-5.325	9.669
		SEM	7.194	7.570	5.417
		95% CI	(-9.9,18.6)	(-20.3, 9.6)	(-1.0,20.3)
		Pr >  t			0.0747
	Week 72	n	28	18	
		LS Mean	5.233	-3.205	8.438
		SEM	7.142	7.808	5.674
		95% CI	(-8.9,19.4)	(-18.6,12.2)	(-2.7,19.6)
		Pr >  t			0.1374
	Week 84	n	22	18	
		LS Mean	8.319	-2.282	10.600
		SEM	7.395	7.808	5.923
		95% CI	(-6.3,22.9)	(-17.7,13.1)	(-1.0,22.2)
		Pr >  t			0.0739
	Week 96	n	21	13	
		LS Mean	9.639	-11.72	21.362
		SEM	7.364	8.207	6.494
		95% CI	(-4.9,24.2)	(-27.9, 4.5)	( 8.6,34.1)
		Pr >  t			0.0010
	Week 108	n	17	12	
		LS Mean	3.126	-7.458	10.583
		SEM	7.660	8.323	6.883
		95% CI	(-12.0,18.2)	(-23.9, 9.0)	(-2.9,24.1)
		Pr >  t			0.1245
	Week 120	n	18	11	
		LS Mean	5.885	-4.308	10.193
		SEM	7.510	8.457	6.980
		95% CI	(-8.9,20.7)	(-21.0,12.4)	(-3.5,23.9)
		Pr >  t			0.1445
	Week 132	n	13	5	
		LS Mean	5.568	-6.562	12.131
		SEM	7.995	10.18	9.331
		95% CI	(-10.2,21.3)	(-26.6,13.5)	(-6.2,30.4)
		Pr >  t			0.1939
	Week 144	n	12	3	
		LS Mean	7.508	-8.580	16.088
		SEM	7.996	11.96	11.33

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-8.3,23.3)	(-32.1,14.9)	(-6.2,38.3)
		Pr >  t			0.1561
	Week 156	n	7	2	
		LS Mean	5.820	-6.364	12.184
		SEM	9.125	13.84	13.94
		95% CI	(-12.1,23.8)	(-33.5,20.8)	(-15.2,39.6)
		Pr >  t			0.3825
	Week 168	n	3	1	
		LS Mean	19.370	-6.454	25.824
		SEM	11.78	18.38	19.91
		95% CI	(-3.8,42.5)	(-42.5,29.6)	(-13.3,64.9)
		Pr >  t			0.1950
	Week 180	n	1	1	
		LS Mean	44.918	-6.454	51.373
		SEM	18.27	18.38	24.32
		95% CI	( 9.0,80.8)	(-42.5,29.6)	( 3.6,99.1)
		Pr >  t			0.0350
	Week 192	n	1	1	
		LS Mean	78.248	-6.454	84.703
		SEM	18.27	18.38	24.32
		95% CI	( 42.4, 114)	(-42.5,29.6)	( 37.0, 132)
		Pr >  t			0.0005
Yes	Week 8	n	73	80	
		LS Mean	16.975	5.943	11.032
		SEM	4.129	4.170	3.176
		95% CI	( 8.8,25.1)	(-2.3,14.2)	( 4.8,17.3)
		Pr >  t			0.0006
	Week 16	n	65	58	
		LS Mean	17.214	5.730	11.484
		SEM	4.258	4.384	3.474
		95% CI	( 8.8,25.6)	(-2.9,14.4)	( 4.7,18.3)
		Pr >  t			0.0010
	Week 24	n	51	40	
		LS Mean	19.133	4.849	14.284
		SEM	4.368	4.658	3.914
		95% CI	( 10.5,27.7)	(-4.3,14.0)	( 6.6,22.0)
		Pr >  t			0.0003
	Week 32	n	38	36	
		LS Mean	15.849	4.758	11.091
		SEM	4.621	4.743	4.216

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 6.8,24.9)	( -4.6,14.1)	( 2.8,19.4)
		Pr >  t			0.0088
	Week 40	n	32	29	
		LS Mean	18.466	4.425	14.041
		SEM	4.762	4.916	4.546
		95% CI	( 9.1,27.8)	( -5.2,14.1)	( 5.1,23.0)
		Pr >  t			0.0021
	Week 48	n	28	23	
		LS Mean	14.329	7.700	6.630
		SEM	4.870	5.136	4.885
		95% CI	( 4.8,23.9)	( -2.4,17.8)	( -3.0,16.2)
		Pr >  t			0.1751
	Week 56	n	24	23	
		LS Mean	21.140	3.125	18.015
		SEM	5.018	5.136	5.026
		95% CI	( 11.3,31.0)	( -7.0,13.2)	( 8.1,27.9)
		Pr >  t			0.0004
	Week 64	n	21	19	
		LS Mean	19.443	1.265	18.177
		SEM	5.158	5.339	5.366
		95% CI	( 9.3,29.6)	( -9.2,11.8)	( 7.6,28.7)
		Pr >  t			0.0007
	Week 72	n	20	17	
		LS Mean	13.162	4.255	8.907
		SEM	5.215	5.470	5.550
		95% CI	( 2.9,23.4)	( -6.5,15.0)	( -2.0,19.8)
		Pr >  t			0.1089
	Week 84	n	18	15	
		LS Mean	19.957	1.407	18.549
		SEM	5.323	5.635	5.813
		95% CI	( 9.5,30.4)	( -9.7,12.5)	( 7.1,30.0)
		Pr >  t			0.0015
	Week 96	n	14	11	
		LS Mean	24.338	1.537	22.801
		SEM	5.658	6.106	6.548
		95% CI	( 13.2,35.5)	( -10.5,13.5)	( 9.9,35.7)
		Pr >  t			0.0005
	Week 108	n	9	9	
		LS Mean	13.020	1.312	11.708
		SEM	6.392	6.462	7.504

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 0.5,25.6)	(-11.4,14.0)	( -3.0,26.4)
		Pr >  t			0.1191
	Week 120	n	10	5	
		LS Mean	9.561	-0.063	9.624
		SEM	6.216	7.851	8.601
		95% CI	( -2.6,21.8)	(-15.5,15.4)	( -7.3,26.5)
		Pr >  t			0.2636
	Week 132	n	7	3	
		LS Mean	4.347	2.792	1.555
		SEM	6.921	9.533	10.61
		95% CI	( -9.2,17.9)	(-15.9,21.5)	(-19.3,22.4)
		Pr >  t			0.8836
	Week 144	n	3	2	
		LS Mean	3.771	3.559	0.212
		SEM	9.477	11.30	13.84
		95% CI	(-14.8,22.4)	(-18.6,25.7)	(-27.0,27.4)
		Pr >  t			0.9878
	Week 156	n	3	1	
		LS Mean	26.005	3.702	22.303
		SEM	9.489	15.44	17.38
		95% CI	( 7.4,44.6)	(-26.6,34.0)	(-11.8,56.4)
		Pr >  t			0.1999
	Week 168	n	1	1	
		LS Mean	6.279	3.702	2.577
		SEM	15.44	15.44	21.22
		95% CI	(-24.0,36.6)	(-26.6,34.0)	(-39.1,44.3)
		Pr >  t			0.9034

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	6.952	-3.280	10.233
			SEM	7.354	8.101	7.033
			95% CI	(-7.7,21.6)	(-19.5,13.0)	(-3.7,24.2)
			Pr >  t			0.1491
		Week 16	n	14	17	
			LS Mean	20.256	-3.813	24.070
			SEM	7.473	8.338	7.634
			95% CI	(5.3,35.2)	(-20.5,12.9)	(8.9,39.2)
			Pr >  t			0.0021
		Week 24	n	14	11	
			LS Mean	17.876	-3.080	20.956
			SEM	7.473	8.958	8.261
			95% CI	(3.0,32.8)	(-20.9,14.8)	(4.6,37.3)
			Pr >  t			0.0124
		Week 32	n	10	10	
			LS Mean	17.637	-3.041	20.678
			SEM	8.353	9.141	8.852
			95% CI	(1.1,34.2)	(-21.2,15.2)	(3.2,38.2)
			Pr >  t			0.0209
		Week 40	n	8	10	
			LS Mean	15.826	-6.245	22.071
			SEM	8.756	9.138	9.212
			95% CI	(-1.5,33.2)	(-24.4,12.0)	(3.9,40.3)
			Pr >  t			0.0178
		Week 48	n	7	11	
			LS Mean	15.294	2.966	12.328
			SEM	8.985	9.001	9.363
			95% CI	(-2.5,33.1)	(-15.0,20.9)	(-6.2,30.8)
			Pr >  t			0.1898
		Week 56	n	6	9	
			LS Mean	26.801	-6.693	33.494
			SEM	9.315	9.311	9.975

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	( 8.4,45.2)	(-25.2,11.8)	( 13.8,53.2)
		Pr >  t			0.0010
	Week 64	n	5	8	
		LS Mean	11.260	-2.765	14.024
		SEM	9.756	9.491	10.56
		95% CI	( -8.0,30.5)	(-21.6,16.1)	( -6.8,34.9)
		Pr >  t			0.1857
	Week 72	n	7	7	
		LS Mean	10.388	2.141	8.247
		SEM	8.972	9.741	10.08
		95% CI	( -7.4,28.2)	(-17.2,21.5)	(-11.7,28.1)
		Pr >  t			0.4145
	Week 84	n	7	7	
		LS Mean	10.388	2.142	8.246
		SEM	8.972	9.741	10.08
		95% CI	( -7.4,28.2)	(-17.2,21.5)	(-11.7,28.1)
		Pr >  t			0.4146
	Week 96	n	5	6	
		LS Mean	13.729	-7.790	21.519
		SEM	9.751	10.06	11.07
		95% CI	( -5.6,33.0)	(-27.7,12.2)	( -0.3,43.3)
		Pr >  t			0.0533
	Week 108	n	4	6	
		LS Mean	9.737	-7.790	17.528
		SEM	10.39	10.06	11.63
		95% CI	(-10.8,30.3)	(-27.7,12.2)	( -5.4,40.5)
		Pr >  t			0.1334
	Week 120	n	4	4	
		LS Mean	20.220	-9.448	29.667
		SEM	10.40	11.09	12.53
		95% CI	( -0.3,40.8)	(-31.4,12.5)	( 5.0,54.4)
		Pr >  t			0.0188
	Week 132	n	3	1	
		LS Mean	3.235	-3.906	7.141
		SEM	11.36	17.60	19.10
		95% CI	(-19.2,25.6)	(-38.6,30.8)	(-30.5,44.8)
		Pr >  t			0.7090
	Week 144	n	1	1	
		LS Mean	12.685	-11.60	24.284
		SEM	17.20	17.66	23.11

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-21.2,46.6)	(-46.4,23.2)	(-21.3,69.9)
		Pr >  t			0.2946
		n	35	37	
		LS Mean	6.921	-7.851	14.772
	Week 16	SEM	10.41	10.97	4.846
		95% CI	(-13.6,27.5)	(-29.5,13.8)	( 5.2,24.3)
		Pr >  t			0.0026
		n	34	30	
	Week 24	LS Mean	5.521	-7.844	13.365
		SEM	10.74	11.06	5.075
		95% CI	(-15.7,26.7)	(-29.7,14.0)	( 3.4,23.4)
		Pr >  t			0.0091
	Week 32	n	32	23	
		LS Mean	12.004	-8.578	20.582
		SEM	10.76	11.19	5.425
		95% CI	( -9.2,33.2)	(-30.7,13.5)	( 9.9,31.3)
	Week 40	Pr >  t			0.0002
		n	21	22	
		LS Mean	-0.466	-10.30	9.833
		SEM	10.97	11.23	5.880
	Week 48	95% CI	(-22.1,21.2)	(-32.4,11.8)	( -1.7,21.4)
		Pr >  t			0.0956
		n	20	20	
		LS Mean	0.771	-7.043	7.814
	Week 56	SEM	11.00	11.28	6.043
		95% CI	(-20.9,22.5)	(-29.3,15.2)	( -4.1,19.7)
		Pr >  t			0.1970
		n	19	12	
Week 64	LS Mean	3.305	-7.964	11.270	
	SEM	11.03	11.65	6.778	
	95% CI	(-18.4,25.0)	(-30.9,15.0)	( -2.1,24.6)	
	Pr >  t			0.0973	
Week 64	n	16	8		
	LS Mean	7.413	-11.66	19.075	
	SEM	11.14	12.11	7.693	
	95% CI	(-14.6,29.4)	(-35.5,12.2)	( 3.9,34.2)	
Week 64	Pr >  t			0.0136	
	n	12	11		
	LS Mean	6.022	-13.51	19.528	
		SEM	11.38	11.75	7.462

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.4,28.4)	(-36.7, 9.7)	( 4.9,34.2)
		Pr >  t			0.0092
	Week 72	n	13	7	
		LS Mean	1.202	-7.765	8.967
		SEM	11.32	12.30	8.213
		95% CI	(-21.1,23.5)	(-32.0,16.5)	( -7.2,25.1)
		Pr >  t			0.2756
	Week 84	n	12	6	
		LS Mean	11.103	-5.685	16.788
		SEM	11.38	12.55	8.664
		95% CI	(-11.3,33.5)	(-30.4,19.0)	( -0.2,33.8)
		Pr >  t			0.0534
	Week 96	n	7	6	
		LS Mean	9.708	-18.60	28.308
		SEM	12.01	12.55	9.477
		95% CI	(-13.9,33.4)	(-43.3, 6.1)	( 9.7,46.9)
		Pr >  t			0.0030
	Week 108	n	5	3	
		LS Mean	-1.304	-5.926	4.622
		SEM	12.58	14.10	12.06
		95% CI	(-26.1,23.5)	(-33.7,21.8)	(-19.1,28.3)
		Pr >  t			0.7018
	Week 120	n	8	3	
		LS Mean	-8.181	-17.04	8.855
		SEM	11.85	14.10	11.28
		95% CI	(-31.5,15.2)	(-44.8,10.7)	(-13.3,31.0)
		Pr >  t			0.4329
	Week 132	n	2	1	
		LS Mean	14.753	-12.65	27.400
		SEM	15.22	19.04	19.55
		95% CI	(-15.2,44.7)	(-50.1,24.8)	(-11.0,65.8)
		Pr >  t			0.1618
	Week 144	n	2		
		LS Mean	31.760	NE	NE
		SEM	15.25	NE	NE
		95% CI	( 1.8,61.7)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	-1.570	NE	NE
		SEM	15.25	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
H1047X	Week 8	95% CI	(-31.6,28.4)	NE	NE	
		Pr >  t			NE	
		n	81	64		
		LS Mean	15.863	4.924	10.939	
		SEM	3.158	3.327	3.273	
		95% CI	( 9.6,22.1)	( -1.6,11.5)	( 4.5,17.4)	
		Pr >  t			0.0009	
		Week 16	n	70	52	
		LS Mean	13.830	6.920	6.909	
		SEM	3.273	3.571	3.563	
		95% CI	( 7.4,20.3)	( -0.1,13.9)	( -0.1,13.9)	
		Pr >  t			0.0530	
		Week 24	n	54	40	
		LS Mean	13.379	4.000	9.379	
		SEM	3.476	3.852	3.984	
		95% CI	( 6.5,20.2)	( -3.6,11.6)	( 1.6,17.2)	
		Pr >  t			0.0189	
		Week 32	n	50	36	
		LS Mean	16.357	2.139	14.217	
		SEM	3.564	3.958	4.149	
		95% CI	( 9.3,23.4)	( -5.6, 9.9)	( 6.1,22.4)	
		Pr >  t			0.0006	
		Week 40	n	42	28	
		LS Mean	18.182	4.555	13.627	
		SEM	3.711	4.268	4.543	
		95% CI	( 10.9,25.5)	( -3.8,12.9)	( 4.7,22.5)	
		Pr >  t			0.0028	
		Week 48	n	38	24	
	LS Mean	14.695	2.697	11.999		
	SEM	3.804	4.463	4.802		
	95% CI	( 7.2,22.2)	( -6.1,11.5)	( 2.6,21.4)		
	Pr >  t			0.0127		
	Week 56	n	33	24		
	LS Mean	13.270	4.912	8.359		
	SEM	3.945	4.466	4.923		
	95% CI	( 5.5,21.0)	( -3.9,13.7)	( -1.3,18.0)		
	Pr >  t			0.0899		
	Week 64	n	27	19		
	LS Mean	12.797	4.021	8.776		
	SEM	4.168	4.802	5.406		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Placebo qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
		95% CI	N=169		N=172					
Week 72		( 4.6,21.0)		( -5.4,13.4)		( -1.8,19.4)				
	Pr >  t					0.1049				
	n	26		17						
Week 84	LS Mean	10.917		4.096		6.821				
	SEM	4.215		4.975		5.599				
	95% CI	( 2.6,19.2)		( -5.7,13.9)		( -4.2,17.8)				
Week 96	Pr >  t					0.2235				
	n	18		16						
	LS Mean	16.530		1.970		14.560				
Week 108	SEM	4.769		5.079		6.088				
	95% CI	( 7.2,25.9)		( -8.0,11.9)		( 2.6,26.5)				
	Pr >  t					0.0170				
Week 120	n	20		10						
	LS Mean	20.662		2.161		18.501				
	SEM	4.592		6.007		6.772				
Week 132	95% CI	( 11.6,29.7)		( -9.6,14.0)		( 5.2,31.8)				
	Pr >  t					0.0064				
	n	14		10						
Week 144	LS Mean	10.769		1.837		8.932				
	SEM	5.209		6.007		7.194				
	95% CI	( 0.5,21.0)		(-10.0,13.6)		( -5.2,23.1)				
Week 156	Pr >  t					0.2147				
	n	14		7						
	LS Mean	10.329		1.532		8.798				
Week 132	SEM	5.183		6.912		7.964				
	95% CI	( 0.2,20.5)		(-12.0,15.1)		( -6.8,24.4)				
	Pr >  t					0.2696				
Week 144	n	12		5						
	LS Mean	10.006		2.798		7.207				
	SEM	5.508		7.956		9.063				
Week 156	95% CI	( -0.8,20.8)		(-12.8,18.4)		(-10.6,25.0)				
	Pr >  t					0.4267				
	n	11		4						
Week 156	LS Mean	7.551		3.237		4.314				
	SEM	5.664		8.765		9.886				
	95% CI	( -3.6,18.7)		(-14.0,20.4)		(-15.1,23.7)				
Week 156	Pr >  t					0.6627				
	n	8		3						
	LS Mean	19.201		3.248		15.952				
	SEM	6.447		9.964		11.37				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168	95% CI	( 6.5,31.9)	(-16.3,22.8)	( -6.4,38.3)
	Pr >  t			0.1612
	n	4	2	
	LS Mean	21.189	3.298	17.891
	SEM	8.675	12.01	14.42
Week 180	95% CI	( 4.2,38.2)	(-20.3,26.9)	(-10.4,46.2)
	Pr >  t			0.2151
	n	1	1	
	LS Mean	52.066	3.104	48.962
	SEM	16.65	16.68	23.32
Week 192	95% CI	( 19.4,84.7)	(-29.6,35.9)	( 3.2,94.7)
	Pr >  t			0.0361
	n	1	1	
	LS Mean	85.396	3.104	82.292
	SEM	16.65	16.68	23.32
	95% CI	( 52.7, 118)	(-29.6,35.9)	( 36.5, 128)
	Pr >  t			0.0004

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-28i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Diarrhoea score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	15.863	4.924	10.939		
			SEM	3.158	3.327	3.273		
			95% CI	( 9.6,22.1)	( -1.6,11.5)	( 4.5,17.4)		
					Pr >  t			0.0009
		Week 16	n	70	52			
			LS Mean	13.830	6.920	6.909		
			SEM	3.273	3.571	3.563		
			95% CI	( 7.4,20.3)	( -0.1,13.9)	( -0.1,13.9)		
					Pr >  t			0.0530
		Week 24	n	54	40			
			LS Mean	13.379	4.000	9.379		
			SEM	3.476	3.852	3.984		
			95% CI	( 6.5,20.2)	( -3.6,11.6)	( 1.6,17.2)		
					Pr >  t			0.0189
		Week 32	n	50	36			
			LS Mean	16.357	2.139	14.217		
			SEM	3.564	3.958	4.149		
			95% CI	( 9.3,23.4)	( -5.6, 9.9)	( 6.1,22.4)		
					Pr >  t			0.0006
		Week 40	n	42	28			
			LS Mean	18.182	4.555	13.627		
			SEM	3.711	4.268	4.543		
			95% CI	( 10.9,25.5)	( -3.8,12.9)	( 4.7,22.5)		
			Pr >  t			0.0028		
Week 48	n	38	24					
	LS Mean	14.695	2.697	11.999				
	SEM	3.804	4.463	4.802				
	95% CI	( 7.2,22.2)	( -6.1,11.5)	( 2.6,21.4)				
			Pr >  t			0.0127		
Week 56	n	33	24					
	LS Mean	13.270	4.912	8.359				
	SEM	3.945	4.466	4.923				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	( 5.5,21.0)	( -3.9,13.7)	( -1.3,18.0)
		Pr >  t			0.0899
	Week 64	n	27	19	
		LS Mean	12.797	4.021	8.776
		SEM	4.168	4.802	5.406
		95% CI	( 4.6,21.0)	( -5.4,13.4)	( -1.8,19.4)
		Pr >  t			0.1049
	Week 72	n	26	17	
		LS Mean	10.917	4.096	6.821
		SEM	4.215	4.975	5.599
		95% CI	( 2.6,19.2)	( -5.7,13.9)	( -4.2,17.8)
		Pr >  t			0.2235
	Week 84	n	18	16	
		LS Mean	16.530	1.970	14.560
		SEM	4.769	5.079	6.088
		95% CI	( 7.2,25.9)	( -8.0,11.9)	( 2.6,26.5)
		Pr >  t			0.0170
	Week 96	n	20	10	
		LS Mean	20.662	2.161	18.501
		SEM	4.592	6.007	6.772
		95% CI	( 11.6,29.7)	( -9.6,14.0)	( 5.2,31.8)
		Pr >  t			0.0064
	Week 108	n	14	10	
		LS Mean	10.769	1.837	8.932
		SEM	5.209	6.007	7.194
		95% CI	( 0.5,21.0)	( -10.0,13.6)	( -5.2,23.1)
		Pr >  t			0.2147
	Week 120	n	14	7	
		LS Mean	10.329	1.532	8.798
		SEM	5.183	6.912	7.964
		95% CI	( 0.2,20.5)	( -12.0,15.1)	( -6.8,24.4)
		Pr >  t			0.2696
	Week 132	n	12	5	
		LS Mean	10.006	2.798	7.207
		SEM	5.508	7.956	9.063
		95% CI	( -0.8,20.8)	( -12.8,18.4)	( -10.6,25.0)
		Pr >  t			0.4267
	Week 144	n	11	4	
		LS Mean	7.551	3.237	4.314
		SEM	5.664	8.765	9.886

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-3.6,18.7)	(-14.0,20.4)	(-15.1,23.7)
		Pr >  t			0.6627
	Week 156	n	8	3	
		LS Mean	19.201	3.248	15.952
		SEM	6.447	9.964	11.37
		95% CI	( 6.5,31.9)	(-16.3,22.8)	( -6.4,38.3)
		Pr >  t			0.1612
	Week 168	n	4	2	
		LS Mean	21.189	3.298	17.891
		SEM	8.675	12.01	14.42
		95% CI	( 4.2,38.2)	(-20.3,26.9)	(-10.4,46.2)
		Pr >  t			0.2151
	Week 180	n	1	1	
		LS Mean	52.066	3.104	48.962
		SEM	16.65	16.68	23.32
		95% CI	( 19.4,84.7)	(-29.6,35.9)	( 3.2,94.7)
		Pr >  t			0.0361
	Week 192	n	1	1	
		LS Mean	85.396	3.104	82.292
		SEM	16.65	16.68	23.32
		95% CI	( 52.7, 118)	(-29.6,35.9)	( 36.5, 128)
		Pr >  t			0.0004
Exon 9	Week 8	n	53	64	
		LS Mean	11.891	-0.056	11.946
		SEM	5.467	5.843	3.812
		95% CI	( 1.1,22.7)	(-11.6,11.5)	( 4.4,19.4)
		Pr >  t			0.0019
	Week 16	n	48	48	
		LS Mean	15.252	-0.491	15.743
		SEM	5.614	5.976	4.108
		95% CI	( 4.2,26.3)	(-12.3,11.3)	( 7.7,23.8)
		Pr >  t			0.0001
	Week 24	n	46	36	
		LS Mean	19.095	-0.644	19.739
		SEM	5.637	6.149	4.385
		95% CI	( 8.0,30.2)	(-12.8,11.5)	( 11.1,28.4)
		Pr >  t			<.0001
	Week 32	n	31	33	
		LS Mean	10.600	-1.694	12.294
		SEM	5.988	6.209	4.779

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-1.2,22.4)	(-13.9,10.5)	( 2.9,21.7)
	Pr >  t			0.0104
	n	28	30	
	LS Mean	10.645	-0.507	11.152
	SEM	6.067	6.276	4.958
Week 48	95% CI	(-1.3,22.6)	(-12.9,11.9)	( 1.4,20.9)
	Pr >  t			0.0249
	n	26	23	
	LS Mean	12.035	2.696	9.340
	SEM	6.120	6.488	5.289
Week 56	95% CI	(-0.0,24.1)	(-10.1,15.5)	( -1.0,19.7)
	Pr >  t			0.0780
	n	22	17	
	LS Mean	18.234	-3.914	22.148
	SEM	6.258	6.790	5.808
Week 64	95% CI	( 5.9,30.6)	(-17.3, 9.5)	( 10.7,33.6)
	Pr >  t			0.0002
	n	17	19	
	LS Mean	12.965	-3.270	16.235
	SEM	6.516	6.669	5.957
Week 72	95% CI	( 0.1,25.8)	(-16.4, 9.9)	( 4.5,27.9)
	Pr >  t			0.0066
	n	20	14	
	LS Mean	9.357	2.373	6.984
	SEM	6.351	7.022	6.176
Week 84	95% CI	(-3.1,21.9)	(-11.4,16.2)	( -5.1,19.1)
	Pr >  t			0.2586
	n	19	13	
	LS Mean	15.373	3.511	11.862
	SEM	6.401	7.118	6.336
Week 96	95% CI	( 2.8,28.0)	(-10.5,17.5)	( -0.6,24.3)
	Pr >  t			0.0617
	n	12	12	
	LS Mean	15.636	-7.940	23.577
	SEM	6.965	7.232	7.025
Week 108	95% CI	( 1.9,29.3)	(-22.2, 6.3)	( 9.8,37.4)
	Pr >  t			0.0008
	n	9	9	
Week 108	LS Mean	7.440	-3.114	10.554
	SEM	7.439	7.695	7.941

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.2,22.1)	(-18.2,12.0)	(-5.0,26.1)
		Pr >  t			0.1843
	Week 120	n	12	7	
		LS Mean	6.521	-8.026	14.547
		SEM	6.979	8.193	8.016
		95% CI	(-7.2,20.2)	(-24.1, 8.1)	(-1.2,30.3)
		Pr >  t			0.0700
	Week 132	n	5	2	
		LS Mean	10.120	-2.970	13.090
		SEM	8.772	12.40	13.39
		95% CI	(-7.1,27.3)	(-27.3,21.4)	(-13.2,39.4)
		Pr >  t			0.3286
	Week 144	n	3	1	
		LS Mean	30.093	-9.554	39.647
		SEM	10.47	16.64	18.31
		95% CI	( 9.5,50.7)	(-42.2,23.1)	( 3.7,75.6)
		Pr >  t			0.0308
	Week 156	n	2		
		LS Mean	5.604	NE	NE
		SEM	12.28	NE	NE
		95% CI	(-18.5,29.7)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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#### 4.8.4.2 Krankheitssymptomatik: BPI-SF – 2. Datenschnitt

Tabelle 4H-49: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Stärkster Schmerz“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo	Treatment difference		
			300mg qd + Fulv N=169	qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	71		
			LS Mean	-0.296	0.230	-0.527	
			SEM	0.413	0.418	0.378	
			95% CI	(-1.1, 0.5)	(-0.6, 1.1)	(-1.3, 0.2)	
				Pr >  t		0.1648	
		Week 16		n	67	54	
	LS Mean			-0.606	0.365	-0.970	
	SEM			0.420	0.445	0.412	
	95% CI			(-1.4, 0.2)	(-0.5, 1.2)	(-1.8,-0.2)	
				Pr >  t		0.0189	
		Week 24		n	61	45	
	LS Mean			-0.125	0.554	-0.680	
	SEM			0.428	0.459	0.435	
	95% CI			(-1.0, 0.7)	(-0.3, 1.5)	(-1.5, 0.2)	
				Pr >  t		0.1185	
		Week 32		n	52	40	
	LS Mean			0.597	0.507	0.089	
	SEM			0.444	0.471	0.456	
	95% CI			(-0.3, 1.5)	(-0.4, 1.4)	(-0.8, 1.0)	
				Pr >  t		0.8451	
	Week 40		n	45	35		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 48	LS Mean	0.046	-0.055	0.101	
	SEM	0.454	0.486	0.480	
	95% CI	(-0.8, 0.9)	(-1.0, 0.9)	(-0.8, 1.0)	
	Pr >  t			0.8328	
	n	42	29		
Week 56	LS Mean	0.388	0.705	-0.317	
	SEM	0.460	0.505	0.504	
	95% CI	(-0.5, 1.3)	(-0.3, 1.7)	(-1.3, 0.7)	
	Pr >  t			0.5292	
	n	35	24		
Week 64	LS Mean	0.460	-0.213	0.672	
	SEM	0.476	0.527	0.540	
	95% CI	(-0.5, 1.4)	(-1.2, 0.8)	(-0.4, 1.7)	
	Pr >  t			0.2138	
	n	25	25		
Week 72	LS Mean	0.500	-0.177	0.678	
	SEM	0.510	0.523	0.567	
	95% CI	(-0.5, 1.5)	(-1.2, 0.8)	(-0.4, 1.8)	
	Pr >  t			0.2327	
	n	27	20		
Week 84	LS Mean	0.196	0.627	-0.432	
	SEM	0.502	0.551	0.586	
	95% CI	(-0.8, 1.2)	(-0.5, 1.7)	(-1.6, 0.7)	
	Pr >  t			0.4618	
	n	23	19		
Week 96	LS Mean	0.024	0.705	-0.681	
	SEM	0.523	0.559	0.609	
	95% CI	(-1.0, 1.1)	(-0.4, 1.8)	(-1.9, 0.5)	
	Pr >  t			0.2640	
	n	20	13		
Week 108	LS Mean	0.086	0.449	-0.364	
	SEM	0.541	0.621	0.682	
	95% CI	(-1.0, 1.1)	(-0.8, 1.7)	(-1.7, 1.0)	
	Pr >  t			0.5939	
	n	17	13		
Week 108	LS Mean	0.783	-0.198	0.981	
	SEM	0.565	0.621	0.701	
	95% CI	(-0.3, 1.9)	(-1.4, 1.0)	(-0.4, 2.4)	
	Pr >  t			0.1620	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	n	17	12	
	LS Mean	0.170	-0.503	0.673
	SEM	0.565	0.636	0.715
	95% CI	(-0.9, 1.3)	(-1.8, 0.7)	(-0.7, 2.1)
	Pr >  t			0.3469
Week 132	n	13	6	
	LS Mean	-0.167	0.054	-0.221
	SEM	0.611	0.808	0.901
	95% CI	(-1.4, 1.0)	(-1.5, 1.6)	(-2.0, 1.5)
	Pr >  t			0.8068
Week 144	n	11	4	
	LS Mean	0.541	-0.329	0.870
	SEM	0.644	0.950	1.051
	95% CI	(-0.7, 1.8)	(-2.2, 1.5)	(-1.2, 2.9)
	Pr >  t			0.4077
Week 156	n	6	2	
	LS Mean	-0.162	2.207	-2.369
	SEM	0.800	1.280	1.437
	95% CI	(-1.7, 1.4)	(-0.3, 4.7)	(-5.2, 0.5)
	Pr >  t			0.0997
Week 168	n	3	1	
	LS Mean	-0.033	0.376	-0.410
	SEM	1.063	1.766	2.009
	95% CI	(-2.1, 2.1)	(-3.1, 3.8)	(-4.4, 3.5)
	Pr >  t			0.8385
Week 180	n	1	1	
	LS Mean	1.967	0.376	1.590
	SEM	1.761	1.766	2.451
	95% CI	(-1.5, 5.4)	(-3.1, 3.8)	(-3.2, 6.4)
	Pr >  t			0.5166
Week 192	n	1	1	
	LS Mean	0.967	-0.624	1.590
	SEM	1.761	1.766	2.451
	95% CI	(-2.5, 4.4)	(-4.1, 2.8)	(-3.2, 6.4)
	Pr >  t			0.5166
Present Week 8	n	65	66	
	LS Mean	0.222	0.267	-0.045
	SEM	0.471	0.488	0.418
	95% CI	(-0.7, 1.2)	(-0.7, 1.2)	(-0.9, 0.8)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		Pr >  t			0.9152
	Week 16	n	57	51	
		LS Mean	0.595	0.873	-0.279
		SEM	0.492	0.512	0.452
		95% CI	(-0.4, 1.6)	(-0.1, 1.9)	(-1.2, 0.6)
		Pr >  t			0.5377
	Week 24	n	44	35	
		LS Mean	0.575	1.241	-0.666
		SEM	0.511	0.555	0.515
		95% CI	(-0.4, 1.6)	( 0.1, 2.3)	(-1.7, 0.3)
		Pr >  t			0.1970
	Week 32	n	34	32	
		LS Mean	0.838	0.402	0.436
		SEM	0.539	0.565	0.552
		95% CI	(-0.2, 1.9)	(-0.7, 1.5)	(-0.6, 1.5)
		Pr >  t			0.4292
	Week 40	n	30	26	
		LS Mean	0.852	0.841	0.011
		SEM	0.553	0.589	0.590
		95% CI	(-0.2, 1.9)	(-0.3, 2.0)	(-1.1, 1.2)
		Pr >  t			0.9854
	Week 48	n	27	21	
		LS Mean	0.701	1.138	-0.437
		SEM	0.565	0.619	0.630
		95% CI	(-0.4, 1.8)	(-0.1, 2.4)	(-1.7, 0.8)
		Pr >  t			0.4880
	Week 56	n	24	21	
		LS Mean	0.482	1.434	-0.953
		SEM	0.580	0.619	0.644
		95% CI	(-0.7, 1.6)	( 0.2, 2.7)	(-2.2, 0.3)
		Pr >  t			0.1393
	Week 64	n	22	17	
		LS Mean	0.263	1.055	-0.792
		SEM	0.591	0.651	0.685
		95% CI	(-0.9, 1.4)	(-0.2, 2.3)	(-2.1, 0.6)
		Pr >  t			0.2478
	Week 72	n	21	15	
		LS Mean	0.773	0.520	0.253
		SEM	0.598	0.673	0.711



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	(-0.4, 1.9)	(-0.8, 1.8)	(-1.1, 1.6)
		Pr >  t			0.7226
	Week 84	n	17	14	
		LS Mean	2.093	1.023	1.070
		SEM	0.633	0.685	0.750
		95% CI	( 0.8, 3.3)	( -0.3, 2.4)	( -0.4, 2.5)
		Pr >  t			0.1545
	Week 96	n	15	11	
		LS Mean	1.281	1.276	0.005
		SEM	0.651	0.735	0.814
		95% CI	( 0.0, 2.6)	( -0.2, 2.7)	( -1.6, 1.6)
		Pr >  t			0.9955
	Week 108	n	9	8	
		LS Mean	0.284	1.136	-0.852
		SEM	0.766	0.814	0.971
		95% CI	( -1.2, 1.8)	( -0.5, 2.7)	( -2.8, 1.1)
		Pr >  t			0.3803
	Week 120	n	11	4	
		LS Mean	0.901	1.444	-0.543
		SEM	0.715	1.054	1.149
		95% CI	( -0.5, 2.3)	( -0.6, 3.5)	( -2.8, 1.7)
		Pr >  t			0.6365
	Week 132	n	7	2	
		LS Mean	1.672	0.800	0.872
		SEM	0.836	1.409	1.542
		95% CI	( 0.0, 3.3)	( -2.0, 3.6)	( -2.2, 3.9)
		Pr >  t			0.5721
	Week 144	n	4	1	
		LS Mean	0.829	1.765	-0.936
		SEM	1.029	1.937	2.126
		95% CI	( -1.2, 2.8)	( -2.0, 5.6)	( -5.1, 3.2)
		Pr >  t			0.6600
	Week 156	n	3	1	
		LS Mean	1.349	0.765	0.584
		SEM	1.170	1.937	2.194
		95% CI	( -0.9, 3.6)	( -3.0, 4.6)	( -3.7, 4.9)
		Pr >  t			0.7901
	Week 168	n	1	1	
		LS Mean	0.380	-0.235	0.616

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
	SEM	1.931	1.937	2.678
	95% CI	( -3.4, 4.2)	( -4.0, 3.6)	( -4.6, 5.9)
	Pr >  t			0.8183

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Presence of Lung Metastases (L)	No	Week 8	n	98	82		
			LS Mean	-0.294	0.191	-0.485	
			SEM	0.332	0.353	0.337	
			95% CI	(-0.9, 0.4)	(-0.5, 0.9)	(-1.1, 0.2)	
					Pr >  t		0.1508
		Week 16	n	86	66		
			LS Mean	-0.429	0.438	-0.867	
			SEM	0.341	0.371	0.363	
			95% CI	(-1.1, 0.2)	(-0.3, 1.2)	(-1.6, -0.2)	
					Pr >  t		0.0172
		Week 24	n	73	47		
			LS Mean	0.037	0.526	-0.489	
			SEM	0.353	0.402	0.403	
			95% CI	(-0.7, 0.7)	(-0.3, 1.3)	(-1.3, 0.3)	
					Pr >  t		0.2255
		Week 32	n	60	42		
			LS Mean	0.552	0.382	0.171	
			SEM	0.371	0.415	0.426	
			95% CI	(-0.2, 1.3)	(-0.4, 1.2)	(-0.7, 1.0)	
					Pr >  t		0.6892
		Week 40	n	50	37		
			LS Mean	0.100	-0.033	0.132	
			SEM	0.386	0.430	0.452	
			95% CI	(-0.7, 0.9)	(-0.9, 0.8)	(-0.8, 1.0)	
					Pr >  t		0.7697
		Week 48	n	48	30		
			LS Mean	0.457	0.692	-0.235	
			SEM	0.389	0.453	0.477	
95% CI	(-0.3, 1.2)		(-0.2, 1.6)	(-1.2, 0.7)			
			Pr >  t		0.6219		
Week 56	n	41	25				
	LS Mean	0.410	-0.036	0.446			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.403	0.476	0.511	
	95% CI	(-0.4, 1.2)	(-1.0, 0.9)	(-0.6, 1.4)	
	Pr >  t			0.3824	
	n	30	24		
	LS Mean	0.396	-0.268	0.664	
Week 72	SEM	0.436	0.482	0.543	
	95% CI	(-0.5, 1.3)	(-1.2, 0.7)	(-0.4, 1.7)	
	Pr >  t			0.2216	
	n	32	19		
	LS Mean	0.216	0.608	-0.392	
Week 84	SEM	0.429	0.517	0.568	
	95% CI	(-0.6, 1.1)	(-0.4, 1.6)	(-1.5, 0.7)	
	Pr >  t			0.4905	
	n	26	19		
	LS Mean	0.434	0.618	-0.185	
Week 96	SEM	0.456	0.517	0.587	
	95% CI	(-0.5, 1.3)	(-0.4, 1.6)	(-1.3, 1.0)	
	Pr >  t			0.7532	
	n	23	14		
	LS Mean	0.151	0.377	-0.225	
Week 108	SEM	0.472	0.571	0.648	
	95% CI	(-0.8, 1.1)	(-0.7, 1.5)	(-1.5, 1.0)	
	Pr >  t			0.7280	
	n	19	13		
	LS Mean	0.693	-0.306	1.000	
Week 120	SEM	0.502	0.585	0.682	
	95% CI	(-0.3, 1.7)	(-1.5, 0.8)	(-0.3, 2.3)	
	Pr >  t			0.1428	
	n	19	11		
	LS Mean	0.164	-0.587	0.752	
Week 132	SEM	0.501	0.621	0.713	
	95% CI	(-0.8, 1.1)	(-1.8, 0.6)	(-0.6, 2.2)	
	Pr >  t			0.2919	
	n	15	5		
	LS Mean	0.243	0.016	0.227	
Week 144	SEM	0.543	0.848	0.940	
	95% CI	(-0.8, 1.3)	(-1.6, 1.7)	(-1.6, 2.1)	
	Pr >  t			0.8090	
	n	12	3		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.508	-0.486	0.994
		SEM	0.586	1.062	1.160
		95% CI	(-0.6, 1.7)	(-2.6, 1.6)	(-1.3, 3.3)
		Pr >  t			0.3915
	Week 156	n	6	2	
		LS Mean	-0.106	2.150	-2.256
		SEM	0.774	1.278	1.450
		95% CI	(-1.6, 1.4)	(-0.4, 4.7)	(-5.1, 0.6)
		Pr >  t			0.1200
	Week 168	n	3	1	
		LS Mean	0.031	0.307	-0.276
		SEM	1.051	1.775	2.032
		95% CI	(-2.0, 2.1)	(-3.2, 3.8)	(-4.3, 3.7)
		Pr >  t			0.8918
	Week 180	n	1	1	
		LS Mean	2.009	0.307	1.702
		SEM	1.769	1.775	2.481
		95% CI	(-1.5, 5.5)	(-3.2, 3.8)	(-3.2, 6.6)
		Pr >  t			0.4929
	Week 192	n	1	1	
		LS Mean	1.009	-0.693	1.702
		SEM	1.769	1.775	2.481
		95% CI	(-2.5, 4.5)	(-4.2, 2.8)	(-3.2, 6.6)
		Pr >  t			0.4929
Yes	Week 8	n	44	55	
		LS Mean	1.066	1.053	0.013
		SEM	0.796	0.762	0.504
		95% CI	(-0.5, 2.6)	(-0.4, 2.6)	(-1.0, 1.0)
		Pr >  t			0.9789
	Week 16	n	38	39	
		LS Mean	1.388	1.616	-0.228
		SEM	0.822	0.810	0.553
		95% CI	(-0.2, 3.0)	( 0.0, 3.2)	(-1.3, 0.9)
		Pr >  t			0.6802
	Week 24	n	32	33	
		LS Mean	1.137	2.122	-0.985
		SEM	0.836	0.822	0.590
		95% CI	(-0.5, 2.8)	( 0.5, 3.7)	(-2.1, 0.2)
		Pr >  t			0.0956

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	26	30	
	LS Mean	1.717	1.363	0.354
	SEM	0.853	0.830	0.625
	95% CI	( 0.0, 3.4)	( -0.3, 3.0)	( -0.9, 1.6)
	Pr >  t			0.5721
Week 40	n	25	24	
	LS Mean	1.658	1.669	-0.011
	SEM	0.857	0.850	0.656
	95% CI	( -0.0, 3.3)	( -0.0, 3.3)	( -1.3, 1.3)
	Pr >  t			0.9868
Week 48	n	21	20	
	LS Mean	1.342	1.992	-0.651
	SEM	0.873	0.869	0.701
	95% CI	( -0.4, 3.1)	( 0.3, 3.7)	( -2.0, 0.7)
	Pr >  t			0.3540
Week 56	n	18	20	
	LS Mean	1.282	2.101	-0.819
	SEM	0.890	0.869	0.722
	95% CI	( -0.5, 3.0)	( 0.4, 3.8)	( -2.2, 0.6)
	Pr >  t			0.2577
Week 64	n	17	18	
	LS Mean	1.048	1.975	-0.927
	SEM	0.898	0.881	0.745
	95% CI	( -0.7, 2.8)	( 0.2, 3.7)	( -2.4, 0.5)
	Pr >  t			0.2141
Week 72	n	16	16	
	LS Mean	1.596	1.424	0.171
	SEM	0.905	0.896	0.772
	95% CI	( -0.2, 3.4)	( -0.3, 3.2)	( -1.3, 1.7)
	Pr >  t			0.8243
Week 84	n	14	14	
	LS Mean	2.510	1.973	0.537
	SEM	0.923	0.914	0.813
	95% CI	( 0.7, 4.3)	( 0.2, 3.8)	( -1.1, 2.1)
	Pr >  t			0.5092
Week 96	n	12	10	
	LS Mean	2.162	2.213	-0.051
	SEM	0.946	0.970	0.900
	95% CI	( 0.3, 4.0)	( 0.3, 4.1)	( -1.8, 1.7)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.9548
	Week 108	n	7	8	
		LS Mean	1.122	2.122	-1.000
		SEM	1.054	1.016	1.056
		95% CI	(-0.9, 3.2)	( 0.1, 4.1)	(-3.1, 1.1)
		Pr >  t			0.3442
	Week 120	n	9	5	
		LS Mean	1.833	2.167	-0.335
		SEM	1.000	1.142	1.130
		95% CI	(-0.1, 3.8)	(-0.1, 4.4)	(-2.6, 1.9)
		Pr >  t			0.7673
	Week 132	n	5	3	
		LS Mean	1.829	1.624	0.205
		SEM	1.147	1.334	1.438
		95% CI	(-0.4, 4.1)	(-1.0, 4.2)	(-2.6, 3.0)
		Pr >  t			0.8866
	Week 144	n	3	2	
		LS Mean	1.827	2.098	-0.271
		SEM	1.338	1.542	1.772
		95% CI	(-0.8, 4.5)	(-0.9, 5.1)	(-3.8, 3.2)
		Pr >  t			0.8783
	Week 156	n	3	1	
		LS Mean	2.116	1.576	0.540
		SEM	1.340	2.040	2.220
		95% CI	(-0.5, 4.7)	(-2.4, 5.6)	(-3.8, 4.9)
		Pr >  t			0.8079
	Week 168	n	1	1	
		LS Mean	1.215	0.576	0.639
		SEM	2.048	2.040	2.707
		95% CI	(-2.8, 5.2)	(-3.4, 4.6)	(-4.7, 6.0)
		Pr >  t			0.8134

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Bone Lesions Only (L)	No	Week 8	n	104	109	
			LS Mean	-0.031	0.209	-0.241
			SEM	0.357	0.356	0.322
			95% CI	(-0.7, 0.7)	(-0.5, 0.9)	(-0.9, 0.4)
				Pr >  t		0.4543
		Week 16	n	92	83	
	LS Mean		0.056	0.503	-0.446	
	SEM		0.369	0.380	0.349	
	95% CI		(-0.7, 0.8)	(-0.2, 1.3)	(-1.1, 0.2)	
			Pr >  t		0.2016	
		Week 24	n	77	59	
	LS Mean		0.102	0.789	-0.687	
	SEM		0.379	0.408	0.389	
	95% CI		(-0.6, 0.8)	(-0.0, 1.6)	(-1.5, 0.1)	
			Pr >  t		0.0774	
		Week 32	n	57	53	
	LS Mean		0.693	0.406	0.287	
	SEM		0.406	0.417	0.420	
	95% CI		(-0.1, 1.5)	(-0.4, 1.2)	(-0.5, 1.1)	
			Pr >  t		0.4954	
		Week 40	n	50	44	
	LS Mean		0.277	0.374	-0.097	
	SEM		0.417	0.436	0.448	
	95% CI		(-0.5, 1.1)	(-0.5, 1.2)	(-1.0, 0.8)	
			Pr >  t		0.8288	
		Week 48	n	47	37	
	LS Mean		0.442	0.996	-0.554	
	SEM		0.423	0.454	0.470	
95% CI	(-0.4, 1.3)		( 0.1, 1.9)	(-1.5, 0.4)		
		Pr >  t		0.2390		
	Week 56	n	40	32		
LS Mean		0.443	0.737	-0.294		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.438	0.471	0.500
	95% CI	(-0.4, 1.3)	(-0.2, 1.7)	(-1.3, 0.7)
	Pr >  t			0.5562
	n	32	27	
	LS Mean	0.112	0.613	-0.501
Week 72	SEM	0.462	0.492	0.541
	95% CI	(-0.8, 1.0)	(-0.4, 1.6)	(-1.6, 0.6)
	Pr >  t			0.3545
	n	31	23	
	LS Mean	0.592	0.646	-0.054
Week 84	SEM	0.466	0.515	0.565
	95% CI	(-0.3, 1.5)	(-0.4, 1.7)	(-1.2, 1.1)
	Pr >  t			0.9235
	n	27	21	
	LS Mean	1.333	1.044	0.289
Week 96	SEM	0.485	0.529	0.592
	95% CI	( 0.4, 2.3)	( 0.0, 2.1)	(-0.9, 1.5)
	Pr >  t			0.6251
	n	23	16	
	LS Mean	0.714	0.796	-0.082
Week 108	SEM	0.506	0.576	0.652
	95% CI	(-0.3, 1.7)	(-0.3, 1.9)	(-1.4, 1.2)
	Pr >  t			0.8994
	n	15	14	
	LS Mean	0.340	0.717	-0.377
Week 120	SEM	0.580	0.602	0.732
	95% CI	(-0.8, 1.5)	(-0.5, 1.9)	(-1.8, 1.1)
	Pr >  t			0.6065
	n	18	8	
	LS Mean	0.613	0.636	-0.023
Week 132	SEM	0.546	0.740	0.826
	95% CI	(-0.5, 1.7)	(-0.8, 2.1)	(-1.6, 1.6)
	Pr >  t			0.9776
	n	12	4	
	LS Mean	0.379	0.804	-0.425
Week 144	SEM	0.628	0.985	1.096
	95% CI	(-0.9, 1.6)	(-1.1, 2.7)	(-2.6, 1.7)
	Pr >  t			0.6985
	n	8	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.137	0.190	-0.052
		SEM	0.729	1.122	1.277
		95% CI	(-1.3, 1.6)	(-2.0, 2.4)	(-2.6, 2.5)
		Pr >  t			0.9673
	Week 156	n	5	1	
		LS Mean	1.152	0.404	0.748
		SEM	0.889	1.876	2.036
		95% CI	(-0.6, 2.9)	(-3.3, 4.1)	(-3.2, 4.7)
		Pr >  t			0.7133
	Week 168	n	2	1	
		LS Mean	0.147	-0.596	0.743
		SEM	1.347	1.876	2.273
		95% CI	(-2.5, 2.8)	(-4.3, 3.1)	(-3.7, 5.2)
		Pr >  t			0.7439
	Week 180	n	1		
		LS Mean	2.242	NE	NE
		SEM	1.871	NE	NE
		95% CI	(-1.4, 5.9)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	1.242	NE	NE
		SEM	1.871	NE	NE
		95% CI	(-2.4, 4.9)	NE	NE
		Pr >  t			NE
Yes	Week 8	n	38	28	
		LS Mean	-0.123	0.467	-0.590
		SEM	0.631	0.685	0.580
		95% CI	(-1.4, 1.1)	(-0.9, 1.8)	(-1.7, 0.6)
		Pr >  t			0.3103
	Week 16	n	32	22	
		LS Mean	-0.381	1.016	-1.398
		SEM	0.642	0.708	0.628
		95% CI	(-1.7, 0.9)	(-0.4, 2.4)	(-2.6,-0.2)
		Pr >  t			0.0272
	Week 24	n	28	21	
		LS Mean	0.452	1.152	-0.700
		SEM	0.662	0.713	0.647
		95% CI	(-0.9, 1.8)	(-0.3, 2.6)	(-2.0, 0.6)
		Pr >  t			0.2806

Subgroup	Time Window	Alpelisib		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		300mg qd + Fulv N=169	Placebo qd + Fulv N=172	
Week 32	n	29	19	
	LS Mean	0.790	0.704	0.086
	SEM	0.659	0.734	0.657
	95% CI	(-0.5, 2.1)	(-0.7, 2.2)	(-1.2, 1.4)
	Pr >  t			0.8955
Week 40	n	25	17	
	LS Mean	0.644	0.335	0.309
	SEM	0.672	0.747	0.685
	95% CI	(-0.7, 2.0)	(-1.1, 1.8)	(-1.0, 1.7)
	Pr >  t			0.6519
Week 48	n	22	13	
	LS Mean	0.762	0.750	0.012
	SEM	0.684	0.782	0.735
	95% CI	(-0.6, 2.1)	(-0.8, 2.3)	(-1.4, 1.5)
	Pr >  t			0.9869
Week 56	n	19	13	
	LS Mean	0.602	0.191	0.411
	SEM	0.698	0.783	0.751
	95% CI	(-0.8, 2.0)	(-1.4, 1.7)	(-1.1, 1.9)
	Pr >  t			0.5849
Week 64	n	15	15	
	LS Mean	0.929	-0.037	0.965
	SEM	0.726	0.763	0.758
	95% CI	(-0.5, 2.4)	(-1.5, 1.5)	(-0.5, 2.5)
	Pr >  t			0.2037
Week 72	n	17	12	
	LS Mean	0.209	0.605	-0.395
	SEM	0.711	0.795	0.775
	95% CI	(-1.2, 1.6)	(-1.0, 2.2)	(-1.9, 1.1)
	Pr >  t			0.6103
Week 84	n	13	12	
	LS Mean	0.063	0.623	-0.560
	SEM	0.751	0.795	0.808
	95% CI	(-1.4, 1.5)	(-0.9, 2.2)	(-2.2, 1.0)
	Pr >  t			0.4888
Week 96	n	12	8	
	LS Mean	0.398	0.985	-0.588
	SEM	0.764	0.868	0.891
	95% CI	(-1.1, 1.9)	(-0.7, 2.7)	(-2.3, 1.2)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		Pr >  t			0.5099
	Week 108	n	11	7	
		LS Mean	1.128	-0.261	1.390
		SEM	0.778	0.897	0.932
		95% CI	(-0.4, 2.7)	(-2.0, 1.5)	(-0.4, 3.2)
		Pr >  t			0.1365
	Week 120	n	10	8	
		LS Mean	0.269	-0.351	0.620
		SEM	0.794	0.868	0.918
		95% CI	(-1.3, 1.8)	(-2.1, 1.4)	(-1.2, 2.4)
		Pr >  t			0.4998
	Week 132	n	8	4	
		LS Mean	0.764	-0.013	0.777
		SEM	0.838	1.054	1.128
		95% CI	(-0.9, 2.4)	(-2.1, 2.1)	(-1.4, 3.0)
		Pr >  t			0.4912
	Week 144	n	7	2	
		LS Mean	1.418	0.482	0.935
		SEM	0.868	1.351	1.427
		95% CI	(-0.3, 3.1)	(-2.2, 3.1)	(-1.9, 3.7)
		Pr >  t			0.5124
	Week 156	n	4	2	
		LS Mean	-0.497	2.482	-2.979
		SEM	1.028	1.351	1.530
		95% CI	(-2.5, 1.5)	(-0.2, 5.1)	(-6.0, 0.0)
		Pr >  t			0.0521
	Week 168	n	2	1	
		LS Mean	0.267	0.653	-0.387
		SEM	1.328	1.802	2.113
		95% CI	(-2.3, 2.9)	(-2.9, 4.2)	(-4.5, 3.8)
		Pr >  t			0.8549
	Week 180	n		1	
		LS Mean	NE	0.653	NE
		SEM	NE	1.802	NE
		95% CI	NE	(-2.9, 4.2)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-0.347	NE
		SEM	NE	1.802	NE

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
	95% CI	NE	(-3.9, 3.2)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
PTEN Loss of Expression (L)	No	Week 8	n	137	128	
			LS Mean	-0.043	0.240	-0.282
			SEM	0.311	0.318	0.287
			95% CI	(-0.7, 0.6)	(-0.4, 0.9)	(-0.8, 0.3)
				Pr >  t		0.3250
		Week 16	n	119	96	
	LS Mean		-0.013	0.625	-0.638	
	SEM		0.320	0.339	0.313	
	95% CI		(-0.6, 0.6)	(-0.0, 1.3)	(-1.3,-0.0)	
			Pr >  t		0.0418	
		Week 24	n	100	74	
	LS Mean		0.116	0.917	-0.802	
	SEM		0.330	0.357	0.341	
	95% CI		(-0.5, 0.8)	( 0.2, 1.6)	(-1.5,-0.1)	
			Pr >  t		0.0189	
		Week 32	n	82	68	
	LS Mean		0.669	0.425	0.244	
	SEM		0.345	0.365	0.359	
	95% CI		(-0.0, 1.3)	(-0.3, 1.1)	(-0.5, 0.9)	
			Pr >  t		0.4963	
		Week 40	n	73	57	
	LS Mean		0.415	0.332	0.083	
	SEM		0.352	0.379	0.380	
	95% CI		(-0.3, 1.1)	(-0.4, 1.1)	(-0.7, 0.8)	
			Pr >  t		0.8269	
		Week 48	n	66	47	
	LS Mean		0.471	0.899	-0.429	
	SEM		0.359	0.396	0.402	
95% CI	(-0.2, 1.2)		( 0.1, 1.7)	(-1.2, 0.4)		
		Pr >  t		0.2868		
	Week 56	n	56	43		
LS Mean		0.463	0.429	0.034		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	0.371	0.422
		95% CI	( -0.3, 1.2)	( -0.8, 0.9)
		Pr >  t		0.9362
	Week 64	n	45	41
		LS Mean	0.341	0.356
		SEM	0.389	0.409
		95% CI	( -0.4, 1.1)	( -0.9, 0.9)
		Pr >  t		0.9731
	Week 72	n	46	34
		LS Mean	0.479	0.616
		SEM	0.388	0.429
		95% CI	( -0.3, 1.2)	( -0.2, 1.5)
		Pr >  t		0.7657
	Week 84	n	37	32
		LS Mean	0.965	0.882
		SEM	0.410	0.436
		95% CI	( 0.2, 1.8)	( 0.0, 1.7)
		Pr >  t		0.8635
	Week 96	n	33	23
		LS Mean	0.548	0.855
		SEM	0.422	0.479
		95% CI	( -0.3, 1.4)	( -0.1, 1.8)
		Pr >  t		0.5640
	Week 108	n	24	20
		LS Mean	0.518	0.260
		SEM	0.464	0.500
		95% CI	( -0.4, 1.4)	( -0.7, 1.2)
		Pr >  t		0.6583
	Week 120	n	25	16
		LS Mean	0.235	0.093
		SEM	0.458	0.539
		95% CI	( -0.7, 1.1)	( -1.0, 1.2)
		Pr >  t		0.8178
	Week 132	n	19	8
		LS Mean	0.676	0.355
		SEM	0.500	0.698
		95% CI	( -0.3, 1.7)	( -1.0, 1.7)
		Pr >  t		0.6825
	Week 144	n	14	5



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		LS Mean	0.801	0.260	0.542
		SEM	0.555	0.852	0.954
		95% CI	(-0.3, 1.9)	(-1.4, 1.9)	(-1.3, 2.4)
		Pr >  t			0.5704
	Week 156	n	9	3	
		LS Mean	0.402	1.789	-1.387
		SEM	0.659	1.070	1.206
		95% CI	(-0.9, 1.7)	(-0.3, 3.9)	(-3.8, 1.0)
		Pr >  t			0.2503
	Week 168	n	4	2	
		LS Mean	0.202	0.026	0.176
		SEM	0.933	1.292	1.554
		95% CI	(-1.6, 2.0)	(-2.5, 2.6)	(-2.9, 3.2)
		Pr >  t			0.9098
	Week 180	n	1	1	
		LS Mean	2.242	0.615	1.627
		SEM	1.796	1.798	2.517
		95% CI	(-1.3, 5.8)	(-2.9, 4.1)	(-3.3, 6.6)
		Pr >  t			0.5182
	Week 192	n	1	1	
		LS Mean	1.242	-0.385	1.627
		SEM	1.796	1.798	2.517
		95% CI	(-2.3, 4.8)	(-3.9, 3.1)	(-3.3, 6.6)
		Pr >  t			0.5182
Yes	Week 8	n	5	8	
		LS Mean	-1.016	-0.082	-0.934
		SEM	1.137	0.882	1.454
		95% CI	(-3.3, 1.3)	(-1.9, 1.7)	(-3.9, 2.0)
		Pr >  t			0.5250
	Week 16	n	5	8	
		LS Mean	-1.816	-0.019	-1.796
		SEM	1.137	0.878	1.456
		95% CI	(-4.1, 0.5)	(-1.8, 1.8)	(-4.8, 1.2)
		Pr >  t			0.2255
	Week 24	n	5	5	
		LS Mean	0.984	-0.170	1.154
		SEM	1.137	1.105	1.600
		95% CI	(-1.3, 3.3)	(-2.4, 2.1)	(-2.1, 4.4)
		Pr >  t			0.4752

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 32	n	4	3		
	LS Mean	1.212	1.066	0.146	
	SEM	1.255	1.409	1.906	
	95% CI	(-1.3, 3.7)	(-1.8, 3.9)	(-3.7, 4.0)	
	Pr >  t			0.9394	
Week 40	n	2	3		
	LS Mean	-1.246	-0.406	-0.841	
	SEM	1.699	1.411	2.200	
	95% CI	(-4.7, 2.2)	(-3.2, 2.4)	(-5.3, 3.6)	
	Pr >  t			0.7041	
Week 48	n	3	2		
	LS Mean	1.449	-0.876	2.325	
	SEM	1.423	1.727	2.211	
	95% CI	(-1.4, 4.3)	(-4.3, 2.6)	(-2.1, 6.8)	
	Pr >  t			0.2982	
Week 56	n	3	1		
	LS Mean	0.449	5.536	-5.086	
	SEM	1.423	2.398	2.810	
	95% CI	(-2.4, 3.3)	( 0.7,10.4)	(-10.7, 0.6)	
	Pr >  t			0.0765	
Week 64	n	2			
	LS Mean	0.254	NE	NE	
	SEM	1.699	NE	NE	
	95% CI	(-3.2, 3.7)	NE	NE	
	Pr >  t			NE	
Week 72	n	2			
	LS Mean	-0.859	NE	NE	
	SEM	1.698	NE	NE	
	95% CI	(-4.3, 2.6)	NE	NE	
	Pr >  t			NE	
Week 84	n	3			
	LS Mean	-0.217	NE	NE	
	SEM	1.423	NE	NE	
	95% CI	(-3.1, 2.7)	NE	NE	
	Pr >  t			NE	
Week 96	n	2			
	LS Mean	0.754	NE	NE	
	SEM	1.699	NE	NE	
	95% CI	(-2.7, 4.2)	NE	NE	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	1.953	NE	NE
		SEM	1.710	NE	NE
		95% CI	(-1.5, 5.4)	NE	NE
		Pr >  t			NE
	Week 120	n	3		
		LS Mean	2.116	NE	NE
		SEM	1.423	NE	NE
		95% CI	(-0.8, 5.0)	NE	NE
		Pr >  t			NE
	Week 132	n	1		
		LS Mean	-2.935	NE	NE
		SEM	2.350	NE	NE
		95% CI	(-7.7, 1.8)	NE	NE
		Pr >  t			NE
	Week 144	n	1		
		LS Mean	-0.935	NE	NE
		SEM	2.350	NE	NE
		95% CI	(-5.7, 3.8)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	118			
			LS Mean	-0.117	0.334	-0.451		
			SEM	0.319	0.326	0.303		
			95% CI	(-0.7, 0.5)	(-0.3, 1.0)	(-1.0, 0.1)		
					Pr >  t			0.1367
		Week 16	n	111	89			
			LS Mean	-0.094	0.643	-0.737		
			SEM	0.328	0.348	0.329		
			95% CI	(-0.7, 0.6)	(-0.0, 1.3)	(-1.4,-0.1)		
					Pr >  t			0.0253
		Week 24	n	96	69			
			LS Mean	0.167	0.798	-0.631		
			SEM	0.337	0.367	0.356		
			95% CI	(-0.5, 0.8)	( 0.1, 1.5)	(-1.3, 0.1)		
					Pr >  t			0.0763
		Week 32	n	77	60			
			LS Mean	0.695	0.495	0.200		
			SEM	0.354	0.380	0.380		
			95% CI	(-0.0, 1.4)	(-0.3, 1.2)	(-0.5, 0.9)		
					Pr >  t			0.5993
		Week 40	n	69	51			
			LS Mean	0.298	0.439	-0.141		
			SEM	0.361	0.395	0.400		
			95% CI	(-0.4, 1.0)	(-0.3, 1.2)	(-0.9, 0.6)		
					Pr >  t			0.7250
		Week 48	n	62	40			
			LS Mean	0.600	0.964	-0.363		
			SEM	0.369	0.418	0.430		
95% CI	(-0.1, 1.3)		( 0.1, 1.8)	(-1.2, 0.5)				
			Pr >  t			0.3976		
Week 56	n	53	35					
	LS Mean	0.543	0.594	-0.051				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.381	0.432	0.454	
	95% CI	(-0.2, 1.3)	(-0.3, 1.4)	(-0.9, 0.8)	
	Pr >  t			0.9110	
	n	44	33		
	LS Mean	0.388	-0.102	0.490	
Week 72	SEM	0.397	0.439	0.474	
	95% CI	(-0.4, 1.2)	(-1.0, 0.8)	(-0.4, 1.4)	
	Pr >  t			0.3018	
	n	45	28		
	LS Mean	0.467	0.750	-0.283	
Week 84	SEM	0.395	0.459	0.491	
	95% CI	(-0.3, 1.2)	(-0.1, 1.7)	(-1.2, 0.7)	
	Pr >  t			0.5644	
	n	39	27		
	LS Mean	0.952	0.931	0.022	
Week 96	SEM	0.410	0.464	0.507	
	95% CI	( 0.1, 1.8)	( 0.0, 1.8)	(-1.0, 1.0)	
	Pr >  t			0.9658	
	n	34	19		
	LS Mean	0.580	1.054	-0.474	
Week 108	SEM	0.424	0.516	0.566	
	95% CI	(-0.3, 1.4)	( 0.0, 2.1)	(-1.6, 0.6)	
	Pr >  t			0.4028	
	n	26	17		
	LS Mean	0.663	0.439	0.223	
Week 120	SEM	0.458	0.535	0.608	
	95% CI	(-0.2, 1.6)	(-0.6, 1.5)	(-1.0, 1.4)	
	Pr >  t			0.7136	
	n	27	11		
	LS Mean	0.458	-0.497	0.955	
Week 132	SEM	0.453	0.625	0.686	
	95% CI	(-0.4, 1.3)	(-1.7, 0.7)	(-0.4, 2.3)	
	Pr >  t			0.1637	
	n	20	6		
	LS Mean	0.530	0.368	0.162	
Week 144	SEM	0.497	0.797	0.869	
	95% CI	(-0.4, 1.5)	(-1.2, 1.9)	(-1.5, 1.9)	
	Pr >  t			0.8525	
	n	15	4		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
>= 75 Years	Week 156	LS Mean	0.729	0.267	0.461
		SEM	0.547	0.951	1.039
		95% CI	(-0.3, 1.8)	(-1.6, 2.1)	(-1.6, 2.5)
		Pr >  t			0.6572
		n	9	2	
	Week 168	LS Mean	0.412	2.584	-2.172
		SEM	0.666	1.306	1.422
		95% CI	(-0.9, 1.7)	( 0.0, 5.1)	(-5.0, 0.6)
		Pr >  t			0.1270
		n	4	2	
	Week 180	LS Mean	0.213	0.084	0.129
		SEM	0.942	1.306	1.571
		95% CI	(-1.6, 2.1)	(-2.5, 2.6)	(-3.0, 3.2)
		Pr >  t			0.9346
		n	1	1	
	Week 192	LS Mean	2.248	0.653	1.595
		SEM	1.813	1.816	2.542
		95% CI	(-1.3, 5.8)	(-2.9, 4.2)	(-3.4, 6.6)
		Pr >  t			0.5303
		n	1	1	
	Week 8	LS Mean	1.248	-0.347	1.595
		SEM	1.813	1.816	2.542
		95% CI	(-2.3, 4.8)	(-3.9, 3.2)	(-3.4, 6.6)
		Pr >  t			0.5303
n		17	19		
Week 16	LS Mean	-0.050	-0.815	0.765	
	SEM	0.565	0.509	0.755	
	95% CI	(-1.2, 1.1)	(-1.8, 0.2)	(-0.7, 2.3)	
	Pr >  t			0.3133	
	n	13	16		
Week 24	LS Mean	-0.280	-0.089	-0.191	
	SEM	0.633	0.553	0.841	
	95% CI	(-1.5, 1.0)	(-1.2, 1.0)	(-1.9, 1.5)	
	Pr >  t			0.8210	
	n	9	11		
		LS Mean	-0.101	0.867	-0.967
		SEM	0.726	0.643	0.970
		95% CI	(-1.5, 1.3)	(-0.4, 2.1)	(-2.9, 1.0)
		Pr >  t			0.3202

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	N=172	
Week 32	n	9	12		
	LS Mean	0.514	-0.136		0.651
	SEM	0.727	0.625		0.959
	95% CI	(-0.9, 2.0)	(-1.4, 1.1)		(-1.2, 2.5)
	Pr >  t				0.4988
Week 40	n	6	10		
	LS Mean	1.117	-0.623		1.739
	SEM	0.851	0.667		1.081
	95% CI	(-0.6, 2.8)	(-1.9, 0.7)		(-0.4, 3.9)
	Pr >  t				0.1097
Week 48	n	7	10		
	LS Mean	-0.345	0.220		-0.565
	SEM	0.801	0.668		1.041
	95% CI	(-1.9, 1.2)	(-1.1, 1.5)		(-2.6, 1.5)
	Pr >  t				0.5879
Week 56	n	6	10		
	LS Mean	-0.326	-0.072		-0.254
	SEM	0.848	0.670		1.078
	95% CI	(-2.0, 1.3)	(-1.4, 1.3)		(-2.4, 1.9)
	Pr >  t				0.8139
Week 64	n	3	9		
	LS Mean	-0.270	1.537		-1.807
	SEM	1.124	0.697		1.320
	95% CI	(-2.5, 1.9)	(0.2, 2.9)		(-4.4, 0.8)
	Pr >  t				0.1728
Week 72	n	3	7		
	LS Mean	-0.270	-0.464		0.194
	SEM	1.124	0.769		1.359
	95% CI	(-2.5, 1.9)	(-2.0, 1.1)		(-2.5, 2.9)
	Pr >  t				0.8865
Week 84	n	1	6		
	LS Mean	-1.227	0.050		-1.277
	SEM	1.852	0.817		2.023
	95% CI	(-4.9, 2.4)	(-1.6, 1.7)		(-5.3, 2.7)
	Pr >  t				0.5285
Week 96	n	1	5		
	LS Mean	0.773	-0.550		1.323
	SEM	1.852	0.880		2.049
	95% CI	(-2.9, 4.4)	(-2.3, 1.2)		(-2.7, 5.4)
	Pr >  t				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 108	Pr >  t			0.5194
		n		4	
		LS Mean	NE	-0.571	NE
		SEM	NE	0.967	NE
		95% CI	NE	(-2.5, 1.3)	NE
	Week 120	Pr >  t			NE
		n	1	5	
		LS Mean	0.880	0.850	0.029
		SEM	1.851	0.880	2.048
		95% CI	(-2.8, 4.5)	(-0.9, 2.6)	(-4.0, 4.1)
	Week 132	Pr >  t			0.9885
		n		2	
		LS Mean	NE	-0.206	NE
		SEM	NE	1.308	NE
		95% CI	NE	(-2.8, 2.4)	NE
	Week 144	Pr >  t			NE
		n		1	
		LS Mean	NE	-0.333	NE
		SEM	NE	1.809	NE
		95% CI	NE	(-3.9, 3.2)	NE
	Week 156	Pr >  t			NE
		n		1	
		LS Mean	NE	-0.333	NE
		SEM	NE	1.809	NE
		95% CI	NE	(-3.9, 3.2)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Endocrine Status (L) Primary resistant	Week 8	n	21	15	
		LS Mean	-0.452	0.623	-1.075
		SEM	0.616	0.717	0.757
		95% CI	(-1.7, 0.8)	(-0.8, 2.1)	(-2.6, 0.4)
		Pr >  t			0.1603
	Week 16	n	17	9	
		LS Mean	0.563	0.837	-0.274
		SEM	0.665	0.853	0.902
		95% CI	(-0.8, 1.9)	(-0.9, 2.5)	(-2.1, 1.5)
		Pr >  t			0.7621
	Week 24	n	9	5	
		LS Mean	-0.335	0.879	-1.214
		SEM	0.778	1.024	1.172
		95% CI	(-1.9, 1.2)	(-1.2, 2.9)	(-3.5, 1.1)
		Pr >  t			0.3024
	Week 32	n	8	4	
		LS Mean	-0.954	0.725	-1.678
		SEM	0.811	1.104	1.265
		95% CI	(-2.6, 0.7)	(-1.5, 2.9)	(-4.2, 0.8)
		Pr >  t			0.1873
	Week 40	n	5	4	
		LS Mean	-0.609	-0.775	0.166
		SEM	0.935	1.104	1.360
		95% CI	(-2.5, 1.2)	(-3.0, 1.4)	(-2.5, 2.9)
	Pr >  t			0.9031	
Week 48	n	5	3		
	LS Mean	-0.609	0.515	-1.124	
	SEM	0.935	1.216	1.450	
	95% CI	(-2.5, 1.2)	(-1.9, 2.9)	(-4.0, 1.7)	
	Pr >  t			0.4398	
Week 56	n	4	3		
	LS Mean	-0.210	-0.485	0.275	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	1.009	1.216	1.503
	95% CI	(-2.2, 1.8)	(-2.9, 1.9)	(-2.7, 3.3)
	Pr >  t			0.8552
	n	4	3	
	LS Mean	0.040	-0.152	0.192
Week 72	SEM	1.009	1.216	1.503
	95% CI	(-2.0, 2.0)	(-2.6, 2.3)	(-2.8, 3.2)
	Pr >  t			0.8988
	n	4	3	
	LS Mean	0.540	0.515	0.025
Week 84	SEM	1.009	1.216	1.503
	95% CI	(-1.5, 2.5)	(-1.9, 2.9)	(-3.0, 3.0)
	Pr >  t			0.9868
	n	2	3	
	LS Mean	1.108	1.515	-0.408
Week 96	SEM	1.342	1.216	1.729
	95% CI	(-1.6, 3.8)	(-0.9, 3.9)	(-3.8, 3.0)
	Pr >  t			0.8141
	n	1	3	
	LS Mean	-0.870	1.182	-2.052
Week 108	SEM	1.793	1.216	2.124
	95% CI	(-4.4, 2.7)	(-1.2, 3.6)	(-6.3, 2.2)
	Pr >  t			0.3364
	n		2	
	LS Mean	NE	1.260	NE
Week 120	SEM	NE	1.403	NE
	95% CI	NE	(-1.5, 4.0)	NE
	Pr >  t			NE
	n	1	1	
	LS Mean	-0.870	-1.314	0.444
Week 132	SEM	1.793	1.850	2.544
	95% CI	(-4.4, 2.7)	(-5.0, 2.4)	(-4.6, 5.5)
	Pr >  t			0.8619
	n		1	
	LS Mean	NE	1.686	NE
Week 144	SEM	NE	1.850	NE
	95% CI	NE	(-2.0, 5.4)	NE
	Pr >  t			NE
	n	1		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169			Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv				
		LS Mean	SEM	95% CI	Pr >  t	LS Mean	SEM	95% CI	Pr >  t	
Secondary resistant	Week 8	LS Mean	-0.870	NE	NE	NE	NE	NE	NE	
		SEM	1.793	NE	NE	NE	NE	NE	NE	
		95% CI	(-4.4, 2.7)	NE	NE	NE	NE	NE	NE	NE
		Pr >  t								
	Week 16	n	98	104						
		LS Mean	-0.021	0.279						
		SEM	0.389	0.389						
		95% CI	(-0.8, 0.7)	(-0.5, 1.0)						
	Week 24	Pr >  t								0.3701
		n	83	80						
		LS Mean	-0.134	0.742						
		SEM	0.400	0.409						
	Week 32	95% CI	(-0.9, 0.7)	(-0.1, 1.5)						(-1.6,-0.2)
		Pr >  t								0.0165
		n	75	61						
		LS Mean	0.285	1.109						
	Week 40	SEM	0.409	0.431						0.393
		95% CI	(-0.5, 1.1)	(0.3, 2.0)						(-1.6,-0.1)
		Pr >  t								0.0362
		n	59	55						
	Week 48	LS Mean	0.854	0.587						0.268
		SEM	0.432	0.439						0.419
		95% CI	(0.0, 1.7)	(-0.3, 1.4)						(-0.6, 1.1)
		Pr >  t								0.5232
Week 56	n	52	47							
	LS Mean	0.712	0.444						0.268	
	SEM	0.442	0.454						0.442	
	95% CI	(-0.2, 1.6)	(-0.4, 1.3)						(-0.6, 1.1)	
Week 8	Pr >  t								0.5448	
	n	47	36							
	LS Mean	0.842	1.189						-0.346	
	SEM	0.450	0.479						0.476	
Week 16	95% CI	(-0.0, 1.7)	(0.2, 2.1)						(-1.3, 0.6)	
	Pr >  t								0.4671	
	n	41	31							
	LS Mean	0.932	0.824						0.108	
Week 24	SEM	0.462	0.496						0.504	
	95% CI	(0.0, 1.8)	(-0.1, 1.8)						(-0.9, 1.1)	
	Pr >  t								0.8304	
	n									

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	n	32	28		
	LS Mean	0.566	0.603	-0.037	
	SEM	0.487	0.508	0.539	
	95% CI	(-0.4, 1.5)	(-0.4, 1.6)	(-1.1, 1.0)	
	Pr >  t			0.9445	
Week 72	n	29	22		
	LS Mean	0.576	0.305	0.272	
	SEM	0.499	0.541	0.580	
	95% CI	(-0.4, 1.6)	(-0.8, 1.4)	(-0.9, 1.4)	
	Pr >  t			0.6391	
Week 84	n	26	21		
	LS Mean	0.746	0.705	0.041	
	SEM	0.512	0.547	0.597	
	95% CI	(-0.3, 1.8)	(-0.4, 1.8)	(-1.1, 1.2)	
	Pr >  t			0.9456	
Week 96	n	23	14		
	LS Mean	0.759	0.974	-0.215	
	SEM	0.529	0.618	0.676	
	95% CI	(-0.3, 1.8)	(-0.2, 2.2)	(-1.5, 1.1)	
	Pr >  t			0.7502	
Week 108	n	18	13		
	LS Mean	1.207	-0.150	1.357	
	SEM	0.567	0.633	0.719	
	95% CI	( 0.1, 2.3)	(-1.4, 1.1)	(-0.1, 2.8)	
	Pr >  t			0.0594	
Week 120	n	19	10		
	LS Mean	0.786	-0.236	1.021	
	SEM	0.559	0.693	0.766	
	95% CI	(-0.3, 1.9)	(-1.6, 1.1)	(-0.5, 2.5)	
	Pr >  t			0.1825	
Week 132	n	13	4		
	LS Mean	0.861	0.102	0.759	
	SEM	0.628	0.994	1.085	
	95% CI	(-0.4, 2.1)	(-1.8, 2.1)	(-1.4, 2.9)	
	Pr >  t			0.4845	
Week 144	n	8	1		
	LS Mean	1.227	0.900	0.327	
	SEM	0.747	1.880	1.971	
	95% CI	(-0.2, 2.7)	(-2.8, 4.6)	(-3.5, 4.2)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Sensitive	Week 156	Pr >  t			0.8683
		n	4	1	
		LS Mean	0.672	4.900	-4.228
		SEM	0.990	1.880	2.075
	Week 168	95% CI	(-1.3, 2.6)	(1.2, 8.6)	(-8.3,-0.2)
		Pr >  t			0.0419
		n	3	1	
		LS Mean	-0.412	0.900	-1.312
	Week 180	SEM	1.123	1.880	2.142
		95% CI	(-2.6, 1.8)	(-2.8, 4.6)	(-5.5, 2.9)
		Pr >  t			0.5404
		n	1	1	
	Week 192	LS Mean	2.394	0.900	1.494
		SEM	1.872	1.880	2.613
		95% CI	(-1.3, 6.1)	(-2.8, 4.6)	(-3.6, 6.6)
		Pr >  t			0.5676
	Week 8	n	1	1	
		LS Mean	1.394	-0.100	1.494
		SEM	1.872	1.880	2.613
		95% CI	(-2.3, 5.1)	(-3.8, 3.6)	(-3.6, 6.6)
Week 16	Pr >  t			0.5676	
	n	17	16		
	LS Mean	-0.592	-0.366	-0.226	
	SEM	0.545	0.557	0.771	
Week 24	95% CI	(-1.7, 0.5)	(-1.5, 0.7)	(-1.8, 1.3)	
	Pr >  t			0.7700	
	n	18	14		
	LS Mean	-0.659	-0.727	0.068	
Week 32	SEM	0.535	0.588	0.794	
	95% CI	(-1.7, 0.4)	(-1.9, 0.4)	(-1.5, 1.6)	
	Pr >  t			0.9317	
	n	16	13		
Week 8	LS Mean	-0.320	-0.653	0.333	
	SEM	0.559	0.602	0.821	
	95% CI	(-1.4, 0.8)	(-1.8, 0.5)	(-1.3, 2.0)	
Week 16	Pr >  t			0.6853	
	n	15	13		
	LS Mean	0.515	-0.573	1.088	
Week 24	SEM	0.568	0.604	0.828	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-0.6, 1.6)	(-1.8, 0.6)	(-0.6, 2.7)	
	Pr >  t			0.1918	
	n	14	10		
	LS Mean	-0.616	-0.107	-0.509	
	SEM	0.584	0.658	0.879	
Week 48	95% CI	(-1.8, 0.5)	(-1.4, 1.2)	(-2.2, 1.2)	
	Pr >  t			0.5634	
	n	14	11		
	LS Mean	-0.045	-0.435	0.391	
	SEM	0.584	0.639	0.865	
Week 56	95% CI	(-1.2, 1.1)	(-1.7, 0.8)	(-1.3, 2.1)	
	Pr >  t			0.6525	
	n	11	11		
	LS Mean	-0.800	-0.526	-0.274	
	SEM	0.630	0.639	0.898	
Week 64	95% CI	(-2.0, 0.4)	(-1.8, 0.7)	(-2.0, 1.5)	
	Pr >  t			0.7604	
	n	8	11		
	LS Mean	-0.147	-0.799	0.652	
	SEM	0.700	0.639	0.949	
Week 72	95% CI	(-1.5, 1.2)	(-2.1, 0.5)	(-1.2, 2.5)	
	Pr >  t			0.4929	
	n	11	10		
	LS Mean	-0.164	0.576	-0.740	
	SEM	0.630	0.660	0.912	
Week 84	95% CI	(-1.4, 1.1)	(-0.7, 1.9)	(-2.5, 1.1)	
	Pr >  t			0.4189	
	n	9	9		
	LS Mean	1.525	0.324	1.201	
	SEM	0.672	0.682	0.959	
Week 96	95% CI	( 0.2, 2.9)	(-1.0, 1.7)	(-0.7, 3.1)	
	Pr >  t			0.2122	
	n	8	7		
	LS Mean	0.491	-0.383	0.874	
	SEM	0.701	0.743	1.022	
Week 108	95% CI	(-0.9, 1.9)	(-1.8, 1.1)	(-1.1, 2.9)	
	Pr >  t			0.3938	
	n	7	6		
	LS Mean	-0.796	0.409	-1.205	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 120	SEM	0.735	0.786	1.078	
	95% CI	(-2.2, 0.7)	(-1.1, 2.0)	(-3.3, 0.9)	
	Pr >  t			0.2648	
	n	6	5		
	LS Mean	-0.228	0.411	-0.638	
Week 132	SEM	0.779	0.843	1.148	
	95% CI	(-1.8, 1.3)	(-1.3, 2.1)	(-2.9, 1.6)	
	Pr >  t			0.5788	
	n	5	3		
	LS Mean	-0.091	-0.460	0.369	
Week 144	SEM	0.835	1.033	1.330	
	95% CI	(-1.7, 1.6)	(-2.5, 1.6)	(-2.2, 3.0)	
	Pr >  t			0.7817	
	n	5	4		
	LS Mean	0.109	-0.614	0.723	
Week 156	SEM	0.835	0.919	1.243	
	95% CI	(-1.5, 1.8)	(-2.4, 1.2)	(-1.7, 3.2)	
	Pr >  t			0.5615	
	n	4	2		
	LS Mean	-0.027	-0.522	0.495	
Week 168	SEM	0.911	1.230	1.532	
	95% CI	(-1.8, 1.8)	(-2.9, 1.9)	(-2.5, 3.5)	
	Pr >  t			0.7467	
	n	1	1		
	LS Mean	2.165	-1.578	3.742	
Week 168	SEM	1.681	1.688	2.383	
	95% CI	(-1.1, 5.5)	(-4.9, 1.7)	(-0.9, 8.4)	
	Pr >  t			0.1175	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	65		
			LS Mean	0.056	0.534	-0.478	
			SEM	0.556	0.543	0.416	
			95% CI	(-1.0, 1.2)	(-0.5, 1.6)	(-1.3, 0.3)	
					Pr >  t	0.2523	
		Week 16	n	60	51		
			LS Mean	-0.091	0.600	-0.690	
			SEM	0.566	0.568	0.441	
			95% CI	(-1.2, 1.0)	(-0.5, 1.7)	(-1.6, 0.2)	
					Pr >  t	0.1186	
		Week 24	n	51	42		
			LS Mean	0.403	0.742	-0.340	
			SEM	0.574	0.580	0.468	
			95% CI	(-0.7, 1.5)	(-0.4, 1.9)	(-1.3, 0.6)	
					Pr >  t	0.4681	
		Week 32	n	46	36		
			LS Mean	0.789	0.512	0.277	
			SEM	0.583	0.595	0.489	
			95% CI	(-0.4, 1.9)	(-0.7, 1.7)	(-0.7, 1.2)	
					Pr >  t	0.5710	
		Week 40	n	40	33		
			LS Mean	0.685	0.559	0.126	
			SEM	0.592	0.602	0.507	
			95% CI	(-0.5, 1.9)	(-0.6, 1.7)	(-0.9, 1.1)	
			Pr >  t	0.8037			
Week 48	n	37	28				
	LS Mean	0.323	1.395	-1.071			
	SEM	0.597	0.615	0.528			
	95% CI	(-0.9, 1.5)	( 0.2, 2.6)	(-2.1,-0.0)			
			Pr >  t	0.0428			
Week 56	n	33	23				
	LS Mean	0.674	0.532	0.142			



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		SEM	0.605	0.633	0.558
		95% CI	(-0.5, 1.9)	(-0.7, 1.8)	(-1.0, 1.2)
		Pr >  t			0.7995
	Week 64	n	26	20	
		LS Mean	0.342	0.207	0.135
		SEM	0.623	0.647	0.594
		95% CI	(-0.9, 1.6)	(-1.1, 1.5)	(-1.0, 1.3)
		Pr >  t			0.8205
	Week 72	n	28	17	
		LS Mean	0.209	0.708	-0.499
		SEM	0.617	0.666	0.608
		95% CI	(-1.0, 1.4)	(-0.6, 2.0)	(-1.7, 0.7)
		Pr >  t			0.4121
	Week 84	n	23	17	
		LS Mean	0.886	0.808	0.078
		SEM	0.634	0.667	0.626
		95% CI	(-0.4, 2.1)	(-0.5, 2.1)	(-1.2, 1.3)
		Pr >  t			0.9003
	Week 96	n	23	11	
		LS Mean	0.543	1.235	-0.692
		SEM	0.635	0.731	0.694
		95% CI	(-0.7, 1.8)	(-0.2, 2.7)	(-2.1, 0.7)
		Pr >  t			0.3187
	Week 108	n	15	13	
		LS Mean	1.019	0.901	0.118
		SEM	0.683	0.704	0.712
		95% CI	(-0.3, 2.4)	(-0.5, 2.3)	(-1.3, 1.5)
		Pr >  t			0.8684
	Week 120	n	16	9	
		LS Mean	0.824	0.566	0.257
		SEM	0.675	0.768	0.768
		95% CI	(-0.5, 2.2)	(-0.9, 2.1)	(-1.3, 1.8)
		Pr >  t			0.7377
	Week 132	n	14	5	
		LS Mean	0.807	0.937	-0.130
		SEM	0.693	0.912	0.925
		95% CI	(-0.6, 2.2)	(-0.9, 2.7)	(-1.9, 1.7)
		Pr >  t			0.8881
	Week 144	n	8	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Neoadjuvant	Week 156	LS Mean	0.119	1.081	-0.962
		SEM	0.791	1.094	1.169
		95% CI	(-1.4, 1.7)	(-1.1, 3.2)	(-3.3, 1.3)
		Pr >  t			0.4109
		n	7	2	
	Week 168	LS Mean	0.550	2.834	-2.284
		SEM	0.821	1.284	1.367
		95% CI	(-1.1, 2.2)	(0.3, 5.4)	(-5.0, 0.4)
		Pr >  t			0.0952
		n	4	2	
	Week 180	LS Mean	0.312	0.334	-0.021
		SEM	0.982	1.284	1.470
		95% CI	(-1.6, 2.2)	(-2.2, 2.9)	(-2.9, 2.9)
		Pr >  t			0.9883
		n	1	1	
	Week 192	LS Mean	2.324	0.968	1.356
		SEM	1.732	1.732	2.355
		95% CI	(-1.1, 5.7)	(-2.4, 4.4)	(-3.3, 6.0)
		Pr >  t			0.5649
		n	1	1	
	Week 8	LS Mean	1.324	-0.032	1.356
		SEM	1.732	1.732	2.355
		95% CI	(-2.1, 4.7)	(-3.4, 3.4)	(-3.3, 6.0)
		Pr >  t			0.5649
n		18	17		
Week 16	LS Mean	-0.390	0.210	-0.599	
	SEM	0.591	0.619	0.855	
	95% CI	(-1.6, 0.8)	(-1.0, 1.4)	(-2.3, 1.1)	
	Pr >  t			0.4854	
	n	17	11		
Week 24	LS Mean	0.439	0.517	-0.078	
	SEM	0.604	0.744	0.959	
	95% CI	(-0.8, 1.6)	(-1.0, 2.0)	(-2.0, 1.8)	
	Pr >  t			0.9357	
	n	15	5		
	LS Mean	-0.148	1.636	-1.784	
	SEM	0.633	1.027	1.207	
	95% CI	(-1.4, 1.1)	(-0.4, 3.7)	(-4.2, 0.6)	
	Pr >  t			0.1416	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	13	5	
	LS Mean	1.513	-0.564	2.076
	SEM	0.668	1.027	1.226
	95% CI	( 0.2, 2.8)	( -2.6, 1.5)	( -0.3, 4.5)
	Pr >  t			0.0925
Week 40	n	11	5	
	LS Mean	0.031	0.036	-0.006
	SEM	0.709	1.027	1.249
	95% CI	( -1.4, 1.4)	( -2.0, 2.1)	( -2.5, 2.5)
	Pr >  t			0.9964
Week 48	n	11	2	
	LS Mean	2.557	-0.005	2.563
	SEM	0.709	1.485	1.647
	95% CI	( 1.2, 4.0)	( -2.9, 2.9)	( -0.7, 5.8)
	Pr >  t			0.1216
Week 56	n	8	2	
	LS Mean	1.105	0.495	0.610
	SEM	0.795	1.485	1.687
	95% CI	( -0.5, 2.7)	( -2.4, 3.4)	( -2.7, 3.9)
	Pr >  t			0.7179
Week 64	n	7	3	
	LS Mean	0.053	-1.032	1.085
	SEM	0.835	1.258	1.512
	95% CI	( -1.6, 1.7)	( -3.5, 1.5)	( -1.9, 4.1)
	Pr >  t			0.4739
Week 72	n	7	3	
	LS Mean	0.660	-0.699	1.359
	SEM	0.837	1.258	1.513
	95% CI	( -1.0, 2.3)	( -3.2, 1.8)	( -1.6, 4.3)
	Pr >  t			0.3704
Week 84	n	7	2	
	LS Mean	0.517	-1.005	1.522
	SEM	0.837	1.485	1.706
	95% CI	( -1.1, 2.2)	( -3.9, 1.9)	( -1.8, 4.9)
	Pr >  t			0.3735
Week 96	n	6	3	
	LS Mean	0.471	0.301	0.170
	SEM	0.888	1.258	1.541
	95% CI	( -1.3, 2.2)	( -2.2, 2.8)	( -2.9, 3.2)
	Pr >  t			

Subgroup	Time Window		Alpelisib	Placebo	Treatment difference
			300mg qd + Fulv N=169	qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 108	Pr >  t			0.9124
		n	7	2	
		LS Mean	0.088	0.133	-0.045
		SEM	0.837	1.483	1.705
		95% CI	(-1.6, 1.7)	(-2.8, 3.1)	(-3.4, 3.3)
	Week 120	Pr >  t			0.9791
		n	6	1	
		LS Mean	-0.196	-1.086	0.890
		SEM	0.888	2.019	2.207
		95% CI	(-1.9, 1.6)	(-5.1, 2.9)	(-3.5, 5.2)
	Week 132	Pr >  t			0.6871
		n	4		
		LS Mean	1.133	NE	NE
		SEM	1.044	NE	NE
		95% CI	(-0.9, 3.2)	NE	NE
	Week 144	Pr >  t			NE
		n	5		
		LS Mean	2.465	NE	NE
		SEM	0.954	NE	NE
		95% CI	( 0.6, 4.3)	NE	NE
	Week 156	Pr >  t			NE
		n	2		
		LS Mean	0.427	NE	NE
		SEM	1.411	NE	NE
		95% CI	(-2.4, 3.2)	NE	NE
	Week 8	Pr >  t			NE
No Prior Use		n	59	55	
		LS Mean	-0.294	-0.214	-0.080
		SEM	0.385	0.408	0.431
		95% CI	(-1.1, 0.5)	(-1.0, 0.6)	(-0.9, 0.8)
	Week 16	Pr >  t			0.8537
		n	47	42	
		LS Mean	-0.443	0.470	-0.913
		SEM	0.409	0.442	0.483
		95% CI	(-1.2, 0.4)	(-0.4, 1.3)	(-1.9, 0.0)
	Week 24	Pr >  t			0.0596
		n	39	33	
		LS Mean	-0.206	0.766	-0.973
		SEM	0.434	0.478	0.532

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169			Placebo qd + Fulv N=172			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv							
		95% CI	Pr >  t	n	LS Mean	SEM	95% CI	Pr >  t	n	LS Mean	SEM	95% CI	Pr >  t		
		(-1.1, 0.6)		27	0.005	0.490	(-1.0, 1.0)		31	0.427	0.487	(-0.2, 1.7)		(-2.0, 0.1)	0.0683
	Week 32														
	Week 40														
	Week 48														
	Week 56														
	Week 64														
	Week 72														
	Week 84														
	Week 96														

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		SEM	0.859	0.712	1.054
		95% CI	(-0.7, 2.7)	(-1.1, 1.7)	(-1.3, 2.8)
		Pr >  t			0.4862
	Week 108	n	4	6	
		LS Mean	0.628	-0.860	1.488
		SEM	1.031	0.873	1.297
		95% CI	(-1.4, 2.7)	(-2.6, 0.9)	(-1.1, 4.0)
		Pr >  t			0.2518
	Week 120	n	6	6	
		LS Mean	0.309	-0.519	0.827
		SEM	0.859	0.873	1.169
		95% CI	(-1.4, 2.0)	(-2.2, 1.2)	(-1.5, 3.1)
		Pr >  t			0.4794
	Week 132	n	2	3	
		LS Mean	-2.059	-0.587	-1.472
		SEM	1.416	1.178	1.803
		95% CI	(-4.8, 0.7)	(-2.9, 1.7)	(-5.0, 2.1)
		Pr >  t			0.4148
	Week 144	n	2	2	
		LS Mean	-0.826	-0.968	0.143
		SEM	1.410	1.423	1.973
		95% CI	(-3.6, 1.9)	(-3.8, 1.8)	(-3.7, 4.0)
		Pr >  t			0.9425
	Week 156	n		1	
		LS Mean	NE	-0.214	NE
		SEM	NE	1.972	NE
		95% CI	NE	(-4.1, 3.7)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Prior Tamoxifen Use (L) No	Week 8	n	89	89		
		LS Mean	0.179	0.311	-0.131	
		SEM	0.413	0.416	0.350	
		95% CI	(-0.6, 1.0)	(-0.5, 1.1)	(-0.8, 0.6)	
					Pr >  t	0.7078
	Week 16	n	79	66		
		LS Mean	0.069	0.885	-0.817	
		SEM	0.419	0.444	0.385	
		95% CI	(-0.8, 0.9)	(0.0, 1.8)	(-1.6,-0.1)	
					Pr >  t	0.0342
	Week 24	n	64	54		
		LS Mean	0.435	1.045	-0.610	
		SEM	0.436	0.465	0.420	
		95% CI	(-0.4, 1.3)	(0.1, 2.0)	(-1.4, 0.2)	
					Pr >  t	0.1472
	Week 32	n	49	52		
		LS Mean	1.008	0.605	0.403	
		SEM	0.463	0.469	0.446	
		95% CI	(0.1, 1.9)	(-0.3, 1.5)	(-0.5, 1.3)	
					Pr >  t	0.3664
	Week 40	n	44	44		
		LS Mean	0.469	0.512	-0.043	
		SEM	0.473	0.484	0.472	
		95% CI	(-0.5, 1.4)	(-0.4, 1.5)	(-1.0, 0.9)	
				Pr >  t	0.9283	
Week 48	n	41	35			
	LS Mean	0.554	0.969	-0.415		
	SEM	0.480	0.507	0.502		
	95% CI	(-0.4, 1.5)	(-0.0, 2.0)	(-1.4, 0.6)		
				Pr >  t	0.4080	
Week 56	n	33	32			
	LS Mean	0.436	0.740	-0.305		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	0.502	0.517	0.534
		95% CI	(-0.6, 1.4)	(-0.3, 1.8)	(-1.4, 0.7)
		Pr >  t			0.5685
	Week 64	n	27	31	
		LS Mean	0.616	0.279	0.337
		SEM	0.526	0.521	0.561
		95% CI	(-0.4, 1.6)	(-0.7, 1.3)	(-0.8, 1.4)
		Pr >  t			0.5485
	Week 72	n	26	26	
		LS Mean	0.597	0.707	-0.110
		SEM	0.531	0.543	0.586
		95% CI	(-0.4, 1.6)	(-0.4, 1.8)	(-1.3, 1.0)
		Pr >  t			0.8514
	Week 84	n	22	23	
		LS Mean	1.512	0.903	0.609
		SEM	0.558	0.560	0.623
		95% CI	( 0.4, 2.6)	(-0.2, 2.0)	(-0.6, 1.8)
		Pr >  t			0.3289
	Week 96	n	18	18	
		LS Mean	1.225	0.940	0.285
		SEM	0.590	0.599	0.686
		95% CI	( 0.1, 2.4)	(-0.2, 2.1)	(-1.1, 1.6)
		Pr >  t			0.6778
	Week 108	n	14	14	
		LS Mean	1.219	0.267	0.952
		SEM	0.638	0.646	0.767
		95% CI	(-0.0, 2.5)	(-1.0, 1.5)	(-0.6, 2.5)
		Pr >  t			0.2148
	Week 120	n	12	12	
		LS Mean	0.126	-0.043	0.169
		SEM	0.671	0.679	0.822
		95% CI	(-1.2, 1.4)	(-1.4, 1.3)	(-1.4, 1.8)
		Pr >  t			0.8370
	Week 132	n	9	5	
		LS Mean	0.787	0.327	0.460
		SEM	0.743	0.941	1.096
		95% CI	(-0.7, 2.2)	(-1.5, 2.2)	(-1.7, 2.6)
		Pr >  t			0.6745
	Week 144	n	7	4	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Yes	Week 156	LS Mean	0.321	0.182	0.139
		SEM	0.817	1.034	1.225
		95% CI	(-1.3, 1.9)	(-1.8, 2.2)	(-2.3, 2.5)
		Pr >  t			0.9097
		n	4	2	
	Week 168	LS Mean	-0.263	0.340	-0.602
		SEM	1.027	1.405	1.671
		95% CI	(-2.3, 1.8)	(-2.4, 3.1)	(-3.9, 2.7)
		Pr >  t			0.7187
		n	2	1	
	Week 8	LS Mean	0.424	-0.588	1.012
		SEM	1.398	1.945	2.346
		95% CI	(-2.3, 3.2)	(-4.4, 3.2)	(-3.6, 5.6)
		Pr >  t			0.6664
		n	53	48	
	Week 16	LS Mean	-0.277	0.251	-0.528
		SEM	0.484	0.503	0.479
		95% CI	(-1.2, 0.7)	(-0.7, 1.2)	(-1.5, 0.4)
		Pr >  t			0.2717
		n	45	39	
Week 24	LS Mean	-0.106	0.286	-0.392	
	SEM	0.503	0.523	0.507	
	95% CI	(-1.1, 0.9)	(-0.7, 1.3)	(-1.4, 0.6)	
	Pr >  t			0.4407	
	n	41	26		
Week 32	LS Mean	-0.042	0.680	-0.722	
	SEM	0.510	0.559	0.556	
	95% CI	(-1.0, 1.0)	(-0.4, 1.8)	(-1.8, 0.4)	
	Pr >  t			0.1946	
	n	37	20		
Week 40	LS Mean	0.443	0.354	0.089	
	SEM	0.520	0.591	0.592	
	95% CI	(-0.6, 1.5)	(-0.8, 1.5)	(-1.1, 1.3)	
	Pr >  t			0.8804	
	n	31	17		
		LS Mean	0.460	0.169	0.292
		SEM	0.534	0.616	0.625
		95% CI	(-0.6, 1.5)	(-1.0, 1.4)	(-0.9, 1.5)
		Pr >  t			0.6409

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 48	n	28	15	
	LS Mean	0.688	0.987	-0.299
	SEM	0.543	0.633	0.650
	95% CI	(-0.4, 1.8)	(-0.3, 2.2)	(-1.6, 1.0)
	Pr >  t			0.6455
Week 56	n	26	13	
	LS Mean	0.711	0.342	0.370
	SEM	0.549	0.655	0.677
	95% CI	(-0.4, 1.8)	(-0.9, 1.6)	(-1.0, 1.7)
	Pr >  t			0.5853
Week 64	n	20	11	
	LS Mean	0.226	0.847	-0.621
	SEM	0.576	0.683	0.724
	95% CI	(-0.9, 1.4)	(-0.5, 2.2)	(-2.0, 0.8)
	Pr >  t			0.3916
Week 72	n	22	9	
	LS Mean	0.399	0.483	-0.084
	SEM	0.566	0.720	0.752
	95% CI	(-0.7, 1.5)	(-0.9, 1.9)	(-1.6, 1.4)
	Pr >  t			0.9110
Week 84	n	18	10	
	LS Mean	0.309	0.936	-0.627
	SEM	0.589	0.700	0.751
	95% CI	(-0.9, 1.5)	(-0.4, 2.3)	(-2.1, 0.8)
	Pr >  t			0.4039
Week 96	n	17	6	
	LS Mean	0.077	0.754	-0.676
	SEM	0.595	0.813	0.862
	95% CI	(-1.1, 1.2)	(-0.8, 2.4)	(-2.4, 1.0)
	Pr >  t			0.4330
Week 108	n	12	7	
	LS Mean	0.137	0.687	-0.549
	SEM	0.647	0.775	0.863
	95% CI	(-1.1, 1.4)	(-0.8, 2.2)	(-2.2, 1.1)
	Pr >  t			0.5246
Week 120	n	16	4	
	LS Mean	0.829	0.862	-0.032
	SEM	0.603	0.935	0.984
	95% CI	(-0.4, 2.0)	(-1.0, 2.7)	(-2.0, 1.9)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.9737
	Week 132	n	11	3	
		LS Mean	0.412	0.628	-0.216
		SEM	0.662	1.042	1.118
		95% CI	(-0.9, 1.7)	(-1.4, 2.7)	(-2.4, 2.0)
		Pr >  t			0.8470
	Week 144	n	8	1	
		LS Mean	1.191	1.011	0.180
		SEM	0.721	1.667	1.741
		95% CI	(-0.2, 2.6)	(-2.3, 4.3)	(-3.2, 3.6)
		Pr >  t			0.9176
	Week 156	n	5	1	
		LS Mean	1.087	5.011	-3.925
		SEM	0.844	1.667	1.794
		95% CI	(-0.6, 2.7)	( 1.7, 8.3)	(-7.4,-0.4)
		Pr >  t			0.0291
	Week 168	n	2	1	
		LS Mean	0.214	1.011	-0.797
		SEM	1.214	1.667	1.995
		95% CI	(-2.2, 2.6)	(-2.3, 4.3)	(-4.7, 3.1)
		Pr >  t			0.6895
	Week 180	n	1	1	
		LS Mean	2.302	1.011	1.291
		SEM	1.651	1.667	2.288
		95% CI	(-0.9, 5.5)	(-2.3, 4.3)	(-3.2, 5.8)
		Pr >  t			0.5728
	Week 192	n	1	1	
		LS Mean	1.302	0.011	1.291
		SEM	1.651	1.667	2.288
		95% CI	(-1.9, 4.5)	(-3.3, 3.3)	(-3.2, 5.8)
		Pr >  t			0.5728

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
95% CI	NE		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	NE	NE	NE			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Positive	Week 72	SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
	Week 84	95% CI	NE	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
	Week 96	Pr >  t			NE
		n	1		
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 8	n	140	137	
		LS Mean	-0.037	0.239	-0.276
		SEM	0.310	0.314	0.280
		95% CI	(-0.6, 0.6)	(-0.4, 0.9)	(-0.8, 0.3)
		Pr >  t			0.3251
		n	122	105	
Week 16	LS Mean	-0.040	0.601	-0.641	
	SEM	0.318	0.333	0.304	
	95% CI	(-0.7, 0.6)	(-0.1, 1.3)	(-1.2,-0.0)	
	Pr >  t			0.0356	
	n	104	80		
	LS Mean	0.211	0.866	-0.655	
Week 24	SEM	0.327	0.351	0.332	
	95% CI	(-0.4, 0.9)	( 0.2, 1.6)	(-1.3,-0.0)	
	Pr >  t			0.0485	
	n	85	72		
	LS Mean	0.658	0.463	0.196	
	SEM	0.342	0.360	0.351	
Week 32	95% CI	(-0.0, 1.3)	(-0.2, 1.2)	(-0.5, 0.9)	
	Pr >  t			0.5775	
	n	74	61		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	LS Mean	0.415	0.338	0.077	
	SEM	0.351	0.373	0.372	
	95% CI	(-0.3, 1.1)	(-0.4, 1.1)	(-0.7, 0.8)	
	Pr >  t			0.8362	
	n	68	50		
Week 56	LS Mean	0.548	0.902	-0.354	
	SEM	0.357	0.389	0.394	
	95% CI	(-0.2, 1.2)	( 0.1, 1.7)	(-1.1, 0.4)	
	Pr >  t			0.3689	
	n	58	45		
Week 64	LS Mean	0.532	0.545	-0.013	
	SEM	0.368	0.399	0.414	
	95% CI	(-0.2, 1.3)	(-0.2, 1.3)	(-0.8, 0.8)	
	Pr >  t			0.9744	
	n	47	42		
Week 72	LS Mean	0.395	0.348	0.046	
	SEM	0.385	0.406	0.436	
	95% CI	(-0.4, 1.2)	(-0.4, 1.1)	(-0.8, 0.9)	
	Pr >  t			0.9152	
	n	47	35		
Week 84	LS Mean	0.501	0.597	-0.096	
	SEM	0.386	0.425	0.454	
	95% CI	(-0.3, 1.3)	(-0.2, 1.4)	(-1.0, 0.8)	
	Pr >  t			0.8322	
	n	39	33		
Week 96	LS Mean	0.959	0.854	0.105	
	SEM	0.405	0.431	0.475	
	95% CI	( 0.2, 1.8)	( 0.0, 1.7)	(-0.8, 1.0)	
	Pr >  t			0.8249	
	n	34	24		
Week 108	LS Mean	0.673	0.818	-0.145	
	SEM	0.419	0.473	0.525	
	95% CI	(-0.1, 1.5)	(-0.1, 1.7)	(-1.2, 0.9)	
	Pr >  t			0.7826	
	n	26	21		
Week 108	LS Mean	0.691	0.343	0.348	
	SEM	0.454	0.493	0.569	
	95% CI	(-0.2, 1.6)	(-0.6, 1.3)	(-0.8, 1.5)	
	Pr >  t			0.5414	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	n	28	16		
	LS Mean	0.515	0.097		0.418
	SEM	0.443	0.539		0.603
	95% CI	(-0.4, 1.4)	(-1.0, 1.2)		(-0.8, 1.6)
	Pr >  t				0.4884
Week 132	n	20	8		
	LS Mean	0.559	0.360		0.199
	SEM	0.493	0.701		0.781
	95% CI	(-0.4, 1.5)	(-1.0, 1.7)		(-1.3, 1.7)
	Pr >  t				0.7992
Week 144	n	15	5		
	LS Mean	0.757	0.263		0.494
	SEM	0.543	0.856		0.951
	95% CI	(-0.3, 1.8)	(-1.4, 1.9)		(-1.4, 2.4)
	Pr >  t				0.6035
Week 156	n	9	3		
	LS Mean	0.444	1.792		-1.348
	SEM	0.662	1.076		1.213
	95% CI	(-0.9, 1.7)	(-0.3, 3.9)		(-3.7, 1.0)
	Pr >  t				0.2663
Week 168	n	4	2		
	LS Mean	0.243	0.031		0.212
	SEM	0.939	1.299		1.564
	95% CI	(-1.6, 2.1)	(-2.5, 2.6)		(-2.9, 3.3)
	Pr >  t				0.8920
Week 180	n	1	1		
	LS Mean	2.276	0.619		1.657
	SEM	1.808	1.810		2.534
	95% CI	(-1.3, 5.8)	(-2.9, 4.2)		(-3.3, 6.6)
	Pr >  t				0.5133
Week 192	n	1	1		
	LS Mean	1.276	-0.381		1.657
	SEM	1.808	1.810		2.534
	95% CI	(-2.3, 4.8)	(-3.9, 3.2)		(-3.3, 6.6)
	Pr >  t				0.5133

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)



counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	93			
			LS Mean	-0.171	0.206	-0.377		
			SEM	0.347	0.359	0.337		
			95% CI	(-0.9, 0.5)	(-0.5, 0.9)	(-1.0, 0.3)		
					Pr >  t			0.2642
		Week 16	n	90	73			
			LS Mean	-0.246	0.442	-0.688		
			SEM	0.357	0.379	0.365		
			95% CI	(-0.9, 0.5)	(-0.3, 1.2)	(-1.4, 0.0)		
					Pr >  t			0.0599
		Week 24	n	79	61			
			LS Mean	0.129	0.626	-0.496		
			SEM	0.366	0.394	0.387		
			95% CI	(-0.6, 0.8)	(-0.1, 1.4)	(-1.3, 0.3)		
					Pr >  t			0.2003
		Week 32	n	70	55			
			LS Mean	0.671	0.501	0.170		
			SEM	0.377	0.404	0.403		
			95% CI	(-0.1, 1.4)	(-0.3, 1.3)	(-0.6, 1.0)		
					Pr >  t			0.6728
		Week 40	n	61	45			
			LS Mean	0.342	0.165	0.177		
			SEM	0.387	0.423	0.428		
			95% CI	(-0.4, 1.1)	(-0.7, 1.0)	(-0.7, 1.0)		
					Pr >  t			0.6791
		Week 48	n	56	37			
			LS Mean	0.554	0.926	-0.372		
			SEM	0.393	0.441	0.452		
95% CI	(-0.2, 1.3)		( 0.1, 1.8)	(-1.3, 0.5)				
			Pr >  t			0.4114		
Week 56	n	49	33					
	LS Mean	0.517	0.043	0.474				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.403	0.453	0.473	
	95% CI	(-0.3, 1.3)	(-0.8, 0.9)	(-0.5, 1.4)	
	Pr >  t			0.3169	
	n	37	29		
	LS Mean	0.228	0.014	0.214	
Week 72	SEM	0.428	0.469	0.509	
	95% CI	(-0.6, 1.1)	(-0.9, 0.9)	(-0.8, 1.2)	
	Pr >  t			0.6743	
	n	40	25		
	LS Mean	0.424	0.505	-0.081	
Week 84	SEM	0.421	0.487	0.520	
	95% CI	(-0.4, 1.3)	(-0.5, 1.5)	(-1.1, 0.9)	
	Pr >  t			0.8766	
	n	32	23		
	LS Mean	0.779	1.067	-0.288	
Week 96	SEM	0.445	0.499	0.549	
	95% CI	(-0.1, 1.7)	( 0.1, 2.0)	(-1.4, 0.8)	
	Pr >  t			0.6001	
	n	29	17		
	LS Mean	0.447	0.570	-0.123	
Week 108	SEM	0.456	0.546	0.601	
	95% CI	(-0.4, 1.3)	(-0.5, 1.6)	(-1.3, 1.1)	
	Pr >  t			0.8375	
	n	22	15		
	LS Mean	0.673	-0.251	0.924	
Week 120	SEM	0.493	0.568	0.648	
	95% CI	(-0.3, 1.6)	(-1.4, 0.9)	(-0.3, 2.2)	
	Pr >  t			0.1543	
	n	23	13		
	LS Mean	0.222	0.032	0.191	
Week 132	SEM	0.486	0.596	0.669	
	95% CI	(-0.7, 1.2)	(-1.1, 1.2)	(-1.1, 1.5)	
	Pr >  t			0.7755	
	n	17	5		
	LS Mean	0.578	0.209	0.370	
Week 144	SEM	0.534	0.859	0.937	
	95% CI	(-0.5, 1.6)	(-1.5, 1.9)	(-1.5, 2.2)	
	Pr >  t			0.6932	
	n	14	3		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.712	-0.291	1.003
		SEM	0.568	1.075	1.155
		95% CI	(-0.4, 1.8)	(-2.4, 1.8)	(-1.3, 3.3)
		Pr >  t			0.3852
	Week 156	n	8	2	
		LS Mean	0.263	2.353	-2.090
		SEM	0.700	1.292	1.419
		95% CI	(-1.1, 1.6)	(-0.2, 4.9)	(-4.9, 0.7)
		Pr >  t			0.1410
	Week 168	n	4	1	
		LS Mean	0.148	0.528	-0.380
		SEM	0.937	1.794	1.987
		95% CI	(-1.7, 2.0)	(-3.0, 4.0)	(-4.3, 3.5)
		Pr >  t			0.8484
	Week 180	n	1	1	
		LS Mean	2.179	0.528	1.651
		SEM	1.788	1.794	2.504
		95% CI	(-1.3, 5.7)	(-3.0, 4.0)	(-3.3, 6.6)
		Pr >  t			0.5098
	Week 192	n	1	1	
		LS Mean	1.179	-0.472	1.651
		SEM	1.788	1.794	2.504
		95% CI	(-2.3, 4.7)	(-4.0, 3.0)	(-3.3, 6.6)
		Pr >  t			0.5098
>= 3	Week 8	n	37	44	
		LS Mean	0.326	0.420	-0.095
		SEM	0.868	0.862	0.504
		95% CI	(-1.4, 2.0)	(-1.3, 2.1)	(-1.1, 0.9)
		Pr >  t			0.8513
	Week 16	n	34	32	
		LS Mean	0.527	1.100	-0.572
		SEM	0.899	0.907	0.552
		95% CI	(-1.2, 2.3)	(-0.7, 2.9)	(-1.7, 0.5)
		Pr >  t			0.3011
	Week 24	n	26	19	
		LS Mean	0.403	1.728	-1.326
		SEM	0.921	0.955	0.661
		95% CI	(-1.4, 2.2)	(-0.2, 3.6)	(-2.6,-0.0)
		Pr >  t			0.0456

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	16	17	
	LS Mean	0.810	0.418	0.392
	SEM	0.974	0.969	0.750
	95% CI	(-1.1, 2.7)	(-1.5, 2.3)	(-1.1, 1.9)
	Pr >  t			0.6014
Week 40	n	14	16	
	LS Mean	0.553	0.941	-0.388
	SEM	0.992	0.976	0.783
	95% CI	(-1.4, 2.5)	(-1.0, 2.9)	(-1.9, 1.2)
	Pr >  t			0.6208
Week 48	n	13	13	
	LS Mean	0.413	0.949	-0.536
	SEM	1.002	1.005	0.831
	95% CI	(-1.6, 2.4)	(-1.0, 2.9)	(-2.2, 1.1)
	Pr >  t			0.5193
Week 56	n	10	12	
	LS Mean	0.256	2.059	-1.803
	SEM	1.047	1.018	0.896
	95% CI	(-1.8, 2.3)	( 0.1, 4.1)	(-3.6,-0.0)
	Pr >  t			0.0451
Week 64	n	10	13	
	LS Mean	0.880	1.270	-0.390
	SEM	1.047	1.006	0.883
	95% CI	(-1.2, 2.9)	(-0.7, 3.2)	(-2.1, 1.3)
	Pr >  t			0.6593
Week 72	n	8	10	
	LS Mean	0.466	0.979	-0.513
	SEM	1.090	1.048	0.980
	95% CI	(-1.7, 2.6)	(-1.1, 3.0)	(-2.4, 1.4)
	Pr >  t			0.6008
Week 84	n	8	10	
	LS Mean	1.417	0.536	0.881
	SEM	1.091	1.047	0.980
	95% CI	(-0.7, 3.6)	(-1.5, 2.6)	(-1.0, 2.8)
	Pr >  t			0.3694
Week 96	n	6	7	
	LS Mean	1.273	1.590	-0.316
	SEM	1.160	1.121	1.129
	95% CI	(-1.0, 3.6)	(-0.6, 3.8)	(-2.5, 1.9)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.7794
	Week 108	n	4	6	
		LS Mean	0.518	2.014	-1.496
		SEM	1.284	1.158	1.291
		95% CI	(-2.0, 3.0)	(-0.3, 4.3)	(-4.0, 1.0)
		Pr >  t			0.2472
	Week 120	n	5	3	
		LS Mean	1.654	0.348	1.306
		SEM	1.211	1.397	1.446
		95% CI	(-0.7, 4.0)	(-2.4, 3.1)	(-1.5, 4.1)
		Pr >  t			0.3671
	Week 132	n	3	3	
		LS Mean	0.165	0.931	-0.766
		SEM	1.397	1.397	1.606
		95% CI	(-2.6, 2.9)	(-1.8, 3.7)	(-3.9, 2.4)
		Pr >  t			0.6338
	Week 144	n	1	2	
		LS Mean	0.392	1.397	-1.005
		SEM	2.093	1.599	2.369
		95% CI	(-3.7, 4.5)	(-1.7, 4.5)	(-5.7, 3.7)
		Pr >  t			0.6717
	Week 156	n	1	1	
		LS Mean	1.392	0.941	0.451
		SEM	2.093	2.092	2.725
		95% CI	(-2.7, 5.5)	(-3.2, 5.1)	(-4.9, 5.8)
		Pr >  t			0.8687
	Week 168	n		1	
		LS Mean	NE	-0.059	NE
		SEM	NE	2.092	NE
		95% CI	NE	(-4.2, 4.1)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-29i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Worst Pain Item**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Visceral Disease (L)	No	Week 8	n	69	58		
			LS Mean	-1.173	-0.668	-0.505	
				SEM	0.864	0.895	0.406
				95% CI	(-2.9, 0.5)	(-2.4, 1.1)	(-1.3, 0.3)
				Pr >  t			0.2148
		Week 16	n	59	47		
			LS Mean	-1.458	-0.509	-0.950	
			SEM	0.868	0.904	0.437	
			95% CI	(-3.2, 0.3)	(-2.3, 1.3)	(-1.8,-0.1)	
			Pr >  t			0.0303	
		Week 24	n	54	40		
			LS Mean	-1.088	-0.241	-0.847	
			SEM	0.870	0.912	0.459	
			95% CI	(-2.8, 0.6)	(-2.0, 1.6)	(-1.7, 0.1)	
			Pr >  t			0.0654	
		Week 32	n	48	36		
			LS Mean	-0.369	-0.364	-0.004	
			SEM	0.874	0.917	0.477	
			95% CI	(-2.1, 1.4)	(-2.2, 1.5)	(-0.9, 0.9)	
			Pr >  t			0.9926	
		Week 40	n	43	32		
			LS Mean	-0.851	-1.042	0.191	
			SEM	0.877	0.923	0.497	
			95% CI	(-2.6, 0.9)	(-2.9, 0.8)	(-0.8, 1.2)	
		Pr >  t			0.7002		
	Week 48	n	41	27			
		LS Mean	-0.384	-0.275	-0.109		
		SEM	0.879	0.933	0.518		
		95% CI	(-2.1, 1.4)	(-2.1, 1.6)	(-1.1, 0.9)		
		Pr >  t			0.8336		
	Week 56	n	35	22			
		LS Mean	-0.525	-1.157	0.631		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.886	0.947	0.555
		95% CI	(-2.3, 1.2)	(-3.0, 0.7)	(-0.5, 1.7)
		Pr >  t			0.2556
	Week 64	n	26	23	
		LS Mean	-0.407	-1.116	0.708
		SEM	0.900	0.944	0.576
		95% CI	(-2.2, 1.4)	(-3.0, 0.8)	(-0.4, 1.8)
		Pr >  t			0.2192
	Week 72	n	28	18	
		LS Mean	-0.701	-0.173	-0.529
		SEM	0.897	0.963	0.600
		95% CI	(-2.5, 1.1)	(-2.1, 1.7)	(-1.7, 0.6)
		Pr >  t			0.3787
	Week 84	n	22	18	
		LS Mean	-0.947	-0.162	-0.785
		SEM	0.917	0.963	0.624
		95% CI	(-2.8, 0.9)	(-2.1, 1.7)	(-2.0, 0.4)
		Pr >  t			0.2085
	Week 96	n	21	13	
		LS Mean	-0.850	-0.459	-0.392
		SEM	0.914	0.995	0.678
		95% CI	(-2.7, 1.0)	(-2.4, 1.5)	(-1.7, 0.9)
		Pr >  t			0.5636
	Week 108	n	17	12	
		LS Mean	-0.138	-1.123	0.985
		SEM	0.938	1.005	0.715
		95% CI	(-2.0, 1.7)	(-3.1, 0.9)	(-0.4, 2.4)
		Pr >  t			0.1690
	Week 120	n	18	11	
		LS Mean	-0.775	-1.456	0.681
		SEM	0.926	1.016	0.724
		95% CI	(-2.6, 1.1)	(-3.5, 0.5)	(-0.7, 2.1)
		Pr >  t			0.3472
	Week 132	n	13	5	
		LS Mean	-1.090	-0.850	-0.239
		SEM	0.965	1.162	0.952
		95% CI	(-3.0, 0.8)	(-3.1, 1.4)	(-2.1, 1.6)
		Pr >  t			0.8016
	Week 144	n	12	3	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		LS Mean	-0.448	-1.356	0.907
		SEM	0.965	1.320	1.147
		95% CI	(-2.4, 1.5)	(-4.0, 1.2)	(-1.3, 3.2)
		Pr >  t			0.4293
	Week 156	n	6	2	
		LS Mean	-1.084	1.286	-2.370
		SEM	1.092	1.491	1.428
		95% CI	(-3.2, 1.1)	(-1.6, 4.2)	(-5.2, 0.4)
		Pr >  t			0.0974
	Week 168	n	3	1	
		LS Mean	-0.953	-0.554	-0.398
		SEM	1.294	1.917	1.994
		95% CI	(-3.5, 1.6)	(-4.3, 3.2)	(-4.3, 3.5)
		Pr >  t			0.8416
	Week 180	n	1	1	
		LS Mean	1.048	-0.554	1.603
		SEM	1.901	1.917	2.432
		95% CI	(-2.7, 4.8)	(-4.3, 3.2)	(-3.2, 6.4)
		Pr >  t			0.5100
	Week 192	n	1	1	
		LS Mean	0.048	-1.554	1.603
		SEM	1.901	1.917	2.432
		95% CI	(-3.7, 3.8)	(-5.3, 2.2)	(-3.2, 6.4)
		Pr >  t			0.5100
Yes	Week 8	n	73	79	
		LS Mean	0.360	0.545	-0.185
		SEM	0.499	0.507	0.390
		95% CI	(-0.6, 1.3)	(-0.5, 1.5)	(-1.0, 0.6)
		Pr >  t			0.6349
	Week 16	n	65	58	
		LS Mean	0.639	1.045	-0.406
		SEM	0.516	0.533	0.425
		95% CI	(-0.4, 1.7)	(-0.0, 2.1)	(-1.2, 0.4)
		Pr >  t			0.3400
	Week 24	n	51	40	
		LS Mean	0.795	1.320	-0.525
		SEM	0.530	0.569	0.482
		95% CI	(-0.2, 1.8)	( 0.2, 2.4)	(-1.5, 0.4)
		Pr >  t			0.2763

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 32	n	38	36		
	LS Mean	1.118	0.646	0.473	
	SEM	0.563	0.580	0.521	
	95% CI	( 0.0, 2.2)	( -0.5, 1.8)	( -0.5, 1.5)	
	Pr >  t			0.3643	
Week 40	n	32	29		
	LS Mean	0.994	1.103	-0.109	
	SEM	0.582	0.602	0.563	
	95% CI	( -0.1, 2.1)	( -0.1, 2.3)	( -1.2, 1.0)	
	Pr >  t			0.8466	
Week 48	n	28	23		
	LS Mean	0.676	1.449	-0.772	
	SEM	0.596	0.631	0.607	
	95% CI	( -0.5, 1.8)	( 0.2, 2.7)	( -2.0, 0.4)	
	Pr >  t			0.2038	
Week 56	n	24	23		
	LS Mean	0.769	1.589	-0.820	
	SEM	0.615	0.631	0.625	
	95% CI	( -0.4, 2.0)	( 0.3, 2.8)	( -2.0, 0.4)	
	Pr >  t			0.1899	
Week 64	n	21	19		
	LS Mean	0.395	1.232	-0.838	
	SEM	0.634	0.657	0.669	
	95% CI	( -0.8, 1.6)	( -0.1, 2.5)	( -2.2, 0.5)	
	Pr >  t			0.2106	
Week 72	n	20	17		
	LS Mean	0.929	0.698	0.231	
	SEM	0.641	0.674	0.692	
	95% CI	( -0.3, 2.2)	( -0.6, 2.0)	( -1.1, 1.6)	
	Pr >  t			0.7388	
Week 84	n	18	15		
	LS Mean	2.254	1.197	1.057	
	SEM	0.655	0.695	0.726	
	95% CI	( 1.0, 3.5)	( -0.2, 2.6)	( -0.4, 2.5)	
	Pr >  t			0.1458	
Week 96	n	14	11		
	LS Mean	1.543	1.463	0.080	
	SEM	0.698	0.756	0.820	
	95% CI	( 0.2, 2.9)	( -0.0, 2.9)	( -1.5, 1.7)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		Pr >  t			0.9226
	Week 108	n	9	9	
		LS Mean	0.460	1.285	-0.825
		SEM	0.793	0.802	0.942
		95% CI	(-1.1, 2.0)	(-0.3, 2.9)	(-2.7, 1.0)
		Pr >  t			0.3813
	Week 120	n	10	5	
		LS Mean	1.166	1.498	-0.333
		SEM	0.770	0.980	1.081
		95% CI	(-0.3, 2.7)	(-0.4, 3.4)	(-2.5, 1.8)
		Pr >  t			0.7583
	Week 132	n	7	3	
		LS Mean	1.854	0.970	0.884
		SEM	0.861	1.195	1.337
		95% CI	( 0.2, 3.5)	(-1.4, 3.3)	(-1.7, 3.5)
		Pr >  t			0.5087
	Week 144	n	3	2	
		LS Mean	1.280	1.443	-0.163
		SEM	1.189	1.421	1.747
		95% CI	(-1.1, 3.6)	(-1.3, 4.2)	(-3.6, 3.3)
		Pr >  t			0.9255
	Week 156	n	3	1	
		LS Mean	1.552	0.915	0.637
		SEM	1.190	1.946	2.195
		95% CI	(-0.8, 3.9)	(-2.9, 4.7)	(-3.7, 4.9)
		Pr >  t			0.7718
	Week 168	n	1	1	
		LS Mean	0.588	-0.085	0.673
		SEM	1.946	1.946	2.681
		95% CI	(-3.2, 4.4)	(-3.9, 3.7)	(-4.6, 5.9)
		Pr >  t			0.8019

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

Tabelle 4H-50: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Schweregrad-Index“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Presence of Lung Metastases (L)	No	Week 8	n	98	82	
			LS Mean	-0.126	0.154	-0.280
			SEM	0.249	0.265	0.249
			95% CI	(-0.6, 0.4)	(-0.4, 0.7)	(-0.8, 0.2)
			Pr >  t			0.2617
	Week 16	n	86	66		
		LS Mean	-0.167	0.334	-0.501	
		SEM	0.256	0.277	0.268	
		95% CI	(-0.7, 0.3)	(-0.2, 0.9)	(-1.0, 0.0)	
		Pr >  t			0.0615	
	Week 24	n	73	47		
		LS Mean	0.181	0.421	-0.240	
		SEM	0.263	0.299	0.296	
		95% CI	(-0.3, 0.7)	(-0.2, 1.0)	(-0.8, 0.3)	
		Pr >  t			0.4178	
	Week 32	n	60	42		
		LS Mean	0.401	0.281	0.120	
		SEM	0.276	0.307	0.312	
		95% CI	(-0.1, 0.9)	(-0.3, 0.9)	(-0.5, 0.7)	
		Pr >  t			0.7004	
Week 40	n	50	37			
	LS Mean	0.169	-0.045	0.214		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	SEM	0.286	0.317	0.329
	95% CI	(-0.4, 0.7)	(-0.7, 0.6)	(-0.4, 0.9)
	Pr >  t			0.5151
	n	48	30	
	LS Mean	0.545	0.398	0.148
Week 56	SEM	0.288	0.333	0.347
	95% CI	(-0.0, 1.1)	(-0.3, 1.1)	(-0.5, 0.8)
	Pr >  t			0.6700
	n	41	25	
	LS Mean	0.500	-0.062	0.562
Week 64	SEM	0.298	0.349	0.370
	95% CI	(-0.1, 1.1)	(-0.7, 0.6)	(-0.2, 1.3)
	Pr >  t			0.1295
	n	30	24	
	LS Mean	0.407	-0.227	0.634
Week 72	SEM	0.320	0.353	0.392
	95% CI	(-0.2, 1.0)	(-0.9, 0.5)	(-0.1, 1.4)
	Pr >  t			0.1064
	n	32	19	
	LS Mean	0.458	0.394	0.065
Week 84	SEM	0.315	0.377	0.410
	95% CI	(-0.2, 1.1)	(-0.3, 1.1)	(-0.7, 0.9)
	Pr >  t			0.8747
	n	26	19	
	LS Mean	0.253	0.581	-0.328
Week 96	SEM	0.334	0.377	0.423
	95% CI	(-0.4, 0.9)	(-0.2, 1.3)	(-1.2, 0.5)
	Pr >  t			0.4386
	n	23	14	
	LS Mean	0.248	0.275	-0.027
Week 108	SEM	0.344	0.414	0.465
	95% CI	(-0.4, 0.9)	(-0.5, 1.1)	(-0.9, 0.9)
	Pr >  t			0.9543
	n	19	13	
	LS Mean	0.634	-0.448	1.082
Week 120	SEM	0.365	0.424	0.489
	95% CI	(-0.1, 1.4)	(-1.3, 0.4)	( 0.1, 2.0)
	Pr >  t			0.0271
	n	19	11	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference	
		N=169	Placebo qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	0.466	-0.420	0.886
		SEM	0.364	0.449	0.511
		95% CI	(-0.2, 1.2)	(-1.3, 0.5)	(-0.1, 1.9)
		Pr >  t			0.0831
	Week 132	n	15	5	
		LS Mean	0.227	0.112	0.116
		SEM	0.394	0.607	0.670
		95% CI	(-0.5, 1.0)	(-1.1, 1.3)	(-1.2, 1.4)
		Pr >  t			0.8632
	Week 144	n	12	3	
		LS Mean	0.237	-0.466	0.703
		SEM	0.424	0.757	0.825
		95% CI	(-0.6, 1.1)	(-2.0, 1.0)	(-0.9, 2.3)
		Pr >  t			0.3939
	Week 156	n	6	2	
		LS Mean	-0.077	1.031	-1.108
		SEM	0.554	0.909	1.029
		95% CI	(-1.2, 1.0)	(-0.8, 2.8)	(-3.1, 0.9)
		Pr >  t			0.2820
	Week 168	n	3	1	
		LS Mean	-0.163	0.141	-0.304
		SEM	0.748	1.260	1.440
		95% CI	(-1.6, 1.3)	(-2.3, 2.6)	(-3.1, 2.5)
		Pr >  t			0.8326
	Week 180	n	1	1	
		LS Mean	1.495	0.391	1.104
		SEM	1.255	1.260	1.758
		95% CI	(-1.0, 4.0)	(-2.1, 2.9)	(-2.3, 4.6)
		Pr >  t			0.5301
	Week 192	n	1	1	
		LS Mean	0.495	-0.359	0.854
		SEM	1.255	1.260	1.758
		95% CI	(-2.0, 3.0)	(-2.8, 2.1)	(-2.6, 4.3)
		Pr >  t			0.6272
Yes	Week 8	n	44	55	
		LS Mean	1.026	1.041	-0.015
		SEM	0.660	0.631	0.416
		95% CI	(-0.3, 2.3)	(-0.2, 2.3)	(-0.8, 0.8)
		Pr >  t			0.9707

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 16	n	38	39		
	LS Mean	1.159	1.532	-0.374	
	SEM	0.680	0.668	0.454	
	95% CI	(-0.2, 2.5)	( 0.2, 2.8)	(-1.3, 0.5)	
	Pr >  t			0.4108	
Week 24	n	32	33		
	LS Mean	1.043	1.823	-0.779	
	SEM	0.690	0.676	0.481	
	95% CI	(-0.3, 2.4)	( 0.5, 3.2)	(-1.7, 0.2)	
	Pr >  t			0.1064	
Week 32	n	26	30		
	LS Mean	1.350	1.478	-0.128	
	SEM	0.703	0.683	0.508	
	95% CI	(-0.0, 2.7)	( 0.1, 2.8)	(-1.1, 0.9)	
	Pr >  t			0.8006	
Week 40	n	25	24		
	LS Mean	1.255	1.852	-0.597	
	SEM	0.706	0.697	0.531	
	95% CI	(-0.1, 2.6)	( 0.5, 3.2)	(-1.6, 0.4)	
	Pr >  t			0.2620	
Week 48	n	21	20		
	LS Mean	1.409	1.835	-0.426	
	SEM	0.717	0.711	0.565	
	95% CI	(-0.0, 2.8)	( 0.4, 3.2)	(-1.5, 0.7)	
	Pr >  t			0.4512	
Week 56	n	18	20		
	LS Mean	1.172	2.074	-0.903	
	SEM	0.730	0.711	0.580	
	95% CI	(-0.3, 2.6)	( 0.7, 3.5)	(-2.0, 0.2)	
	Pr >  t			0.1206	
Week 64	n	17	18		
	LS Mean	0.921	1.942	-1.021	
	SEM	0.735	0.720	0.598	
	95% CI	(-0.5, 2.4)	( 0.5, 3.4)	(-2.2, 0.2)	
	Pr >  t			0.0883	
Week 72	n	16	16		
	LS Mean	1.295	1.459	-0.164	
	SEM	0.741	0.731	0.617	
	95% CI	(-0.2, 2.8)	( 0.0, 2.9)	(-1.4, 1.0)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.7905
	Week 84	n	14	14
		LS Mean	2.297	1.981
		SEM	0.753	0.744
		95% CI	( 0.8, 3.8)	( 0.5, 3.4)
		Pr >  t		0.6266
	Week 96	n	12	10
		LS Mean	2.177	2.006
		SEM	0.771	0.785
		95% CI	( 0.7, 3.7)	( 0.5, 3.5)
		Pr >  t		0.8107
	Week 108	n	7	8
		LS Mean	1.268	2.250
		SEM	0.850	0.819
		95% CI	( -0.4, 2.9)	( 0.6, 3.9)
		Pr >  t		0.2387
	Week 120	n	9	5
		LS Mean	1.281	2.460
		SEM	0.811	0.913
		95% CI	( -0.3, 2.9)	( 0.7, 4.3)
		Pr >  t		0.1848
	Week 132	n	5	3
		LS Mean	1.572	1.767
		SEM	0.920	1.057
		95% CI	( -0.2, 3.4)	( -0.3, 3.8)
		Pr >  t		0.8624
	Week 144	n	3	2
		LS Mean	1.076	1.818
		SEM	1.063	1.215
		95% CI	( -1.0, 3.2)	( -0.6, 4.2)
		Pr >  t		0.5909
	Week 156	n	3	1
		LS Mean	1.702	1.694
		SEM	1.064	1.594
		95% CI	( -0.4, 3.8)	( -1.4, 4.8)
		Pr >  t		0.9963
	Week 168	n	1	1
		LS Mean	1.084	0.694
		SEM	1.602	1.594
				2.100



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-2.1, 4.2)	(-2.4, 3.8)	(-3.7, 4.5)
	Pr >  t			0.8527

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference		
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Presence of Liver Metastases (L)	No	Week 8	n	104	96		
			LS Mean	-0.186	-0.015	-0.172	
				SEM	0.311	0.309	0.261
				95% CI	(-0.8, 0.4)	(-0.6, 0.6)	(-0.7, 0.3)
				Pr >  t			0.5109
		Week 16	n	92	75		
			LS Mean	-0.202	0.296	-0.498	
			SEM	0.315	0.326	0.280	
			95% CI	(-0.8, 0.4)	(-0.3, 0.9)	(-1.0, 0.1)	
			Pr >  t			0.0762	
		Week 24	n	83	65		
			LS Mean	-0.047	0.588	-0.635	
			SEM	0.320	0.333	0.293	
			95% CI	(-0.7, 0.6)	(-0.1, 1.2)	(-1.2, -0.1)	
			Pr >  t			0.0305	
		Week 32	n	72	59		
			LS Mean	0.408	0.290	0.118	
			SEM	0.326	0.339	0.305	
			95% CI	(-0.2, 1.0)	(-0.4, 1.0)	(-0.5, 0.7)	
			Pr >  t			0.6983	
		Week 40	n	64	50		
			LS Mean	0.129	0.243	-0.113	
			SEM	0.331	0.349	0.320	
			95% CI	(-0.5, 0.8)	(-0.4, 0.9)	(-0.7, 0.5)	
			Pr >  t			0.7230	
		Week 48	n	58	44		
			LS Mean	0.486	0.334	0.151	
			SEM	0.336	0.356	0.333	
	95% CI		(-0.2, 1.1)	(-0.4, 1.0)	(-0.5, 0.8)		
		Pr >  t			0.6489		
	Week 56	n	49	38			
		LS Mean	0.296	0.020	0.276		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.344	0.366	0.351
	95% CI	(-0.4, 1.0)	(-0.7, 0.7)	(-0.4, 1.0)
	Pr >  t			0.4323
	n	39	37	
	LS Mean	0.211	0.218	-0.006
Week 72	SEM	0.357	0.368	0.366
	95% CI	(-0.5, 0.9)	(-0.5, 0.9)	(-0.7, 0.7)
	Pr >  t			0.9867
	n	41	32	
	LS Mean	0.347	0.319	0.028
Week 84	SEM	0.354	0.378	0.374
	95% CI	(-0.3, 1.0)	(-0.4, 1.1)	(-0.7, 0.8)
	Pr >  t			0.9404
	n	33	29	
	LS Mean	0.464	0.769	-0.305
Week 96	SEM	0.370	0.386	0.395
	95% CI	(-0.3, 1.2)	( 0.0, 1.5)	(-1.1, 0.5)
	Pr >  t			0.4397
	n	31	21	
	LS Mean	0.524	0.513	0.011
Week 108	SEM	0.374	0.415	0.428
	95% CI	(-0.2, 1.3)	(-0.3, 1.3)	(-0.8, 0.9)
	Pr >  t			0.9796
	n	23	18	
	LS Mean	0.526	0.075	0.451
Week 120	SEM	0.401	0.432	0.466
	95% CI	(-0.3, 1.3)	(-0.8, 0.9)	(-0.5, 1.4)
	Pr >  t			0.3341
	n	25	15	
	LS Mean	0.241	0.187	0.054
Week 132	SEM	0.392	0.454	0.481
	95% CI	(-0.5, 1.0)	(-0.7, 1.1)	(-0.9, 1.0)
	Pr >  t			0.9106
	n	17	8	
	LS Mean	0.169	0.277	-0.108
Week 144	SEM	0.433	0.555	0.606
	95% CI	(-0.7, 1.0)	(-0.8, 1.4)	(-1.3, 1.1)
	Pr >  t			0.8582
	n	15	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
	Week 156	LS Mean	0.140	-0.038	0.178
		SEM	0.447	0.664	0.716
		95% CI	(-0.7, 1.0)	(-1.3, 1.3)	(-1.2, 1.6)
		Pr >  t			0.8036
	Week 168	n	9	3	
		LS Mean	0.101	0.888	-0.787
		SEM	0.528	0.821	0.907
		95% CI	(-0.9, 1.1)	(-0.7, 2.5)	(-2.6, 1.0)
	Week 180	n	4	2	
		LS Mean	-0.178	-0.206	0.028
		SEM	0.723	0.982	1.165
		95% CI	(-1.6, 1.2)	(-2.1, 1.7)	(-2.3, 2.3)
Week 192	n	1	1		
	LS Mean	1.446	0.547	0.899	
	SEM	1.353	1.354	1.881	
	95% CI	(-1.2, 4.1)	(-2.1, 3.2)	(-2.8, 4.6)	
Yes Week 8	n	38	41		
	LS Mean	0.556	0.783	-0.227	
	SEM	0.385	0.419	0.391	
	95% CI	(-0.2, 1.3)	(-0.0, 1.6)	(-1.0, 0.5)	
Week 16	n	32	30		
	LS Mean	0.636	1.007	-0.371	
	SEM	0.411	0.440	0.430	
	95% CI	(-0.2, 1.4)	( 0.1, 1.9)	(-1.2, 0.5)	
Week 24	n	22	15		
	LS Mean	1.089	0.738	0.351	
	SEM	0.439	0.519	0.533	
	95% CI	( 0.2, 2.0)	(-0.3, 1.8)	(-0.7, 1.4)	
		Pr >  t		0.5114	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	14	13	
	LS Mean	0.363	0.773	-0.411
	SEM	0.502	0.539	0.596
	95% CI	(-0.6, 1.4)	(-0.3, 1.8)	(-1.6, 0.8)
	Pr >  t			0.4917
Week 40	n	11	11	
	LS Mean	0.649	0.710	-0.061
	SEM	0.537	0.563	0.647
	95% CI	(-0.4, 1.7)	(-0.4, 1.8)	(-1.3, 1.2)
	Pr >  t			0.9247
Week 48	n	11	6	
	LS Mean	0.694	2.126	-1.432
	SEM	0.537	0.673	0.745
	95% CI	(-0.4, 1.8)	( 0.8, 3.5)	(-2.9, 0.0)
	Pr >  t			0.0556
Week 56	n	10	7	
	LS Mean	1.033	2.692	-1.659
	SEM	0.552	0.642	0.727
	95% CI	(-0.1, 2.1)	( 1.4, 4.0)	(-3.1,-0.2)
	Pr >  t			0.0233
Week 64	n	8	5	
	LS Mean	0.444	0.330	0.114
	SEM	0.590	0.712	0.817
	95% CI	(-0.7, 1.6)	(-1.1, 1.7)	(-1.5, 1.7)
	Pr >  t			0.8889
Week 72	n	7	3	
	LS Mean	0.774	0.678	0.095
	SEM	0.615	0.856	0.962
	95% CI	(-0.4, 2.0)	(-1.0, 2.4)	(-1.8, 2.0)
	Pr >  t			0.9211
Week 84	n	7	4	
	LS Mean	1.452	0.252	1.200
	SEM	0.615	0.770	0.886
	95% CI	( 0.2, 2.7)	(-1.3, 1.8)	(-0.5, 2.9)
	Pr >  t			0.1767
Week 96	n	4	3	
	LS Mean	0.777	0.845	-0.068
	SEM	0.747	0.856	1.052
	95% CI	(-0.7, 2.2)	(-0.8, 2.5)	(-2.1, 2.0)
	Pr >  t			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.9487
	Week 108	n	3	3	
		LS Mean	0.543	1.044	-0.501
		SEM	0.835	0.858	1.117
		95% CI	(-1.1, 2.2)	(-0.6, 2.7)	(-2.7, 1.7)
		Pr >  t			0.6543
	Week 120	n	3	1	
		LS Mean	1.678	-0.381	2.059
		SEM	0.835	1.357	1.534
		95% CI	(0.0, 3.3)	(-3.1, 2.3)	(-1.0, 5.1)
		Pr >  t			0.1809
	Week 132	n	3		
		LS Mean	1.279	NE	NE
		SEM	0.835	NE	NE
		95% CI	(-0.4, 2.9)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	128			
			LS Mean	0.087	0.228	-0.141		
			SEM	0.248	0.253	0.225		
			95% CI	( -0.4, 0.6)	( -0.3, 0.7)	( -0.6, 0.3)		
					Pr >  t			0.5301
		Week 16	n	119	96			
			LS Mean	0.111	0.569	-0.458		
			SEM	0.254	0.268	0.244		
			95% CI	( -0.4, 0.6)	( 0.0, 1.1)	( -0.9, 0.0)		
					Pr >  t			0.0607
		Week 24	n	100	74			
			LS Mean	0.267	0.763	-0.496		
			SEM	0.261	0.281	0.264		
			95% CI	( -0.2, 0.8)	( 0.2, 1.3)	( -1.0, 0.0)		
					Pr >  t			0.0606
		Week 32	n	82	68			
			LS Mean	0.537	0.467	0.070		
			SEM	0.271	0.286	0.277		
			95% CI	( 0.0, 1.1)	( -0.1, 1.0)	( -0.5, 0.6)		
					Pr >  t			0.8000
		Week 40	n	73	57			
			LS Mean	0.375	0.435	-0.060		
			SEM	0.277	0.296	0.291		
			95% CI	( -0.2, 0.9)	( -0.1, 1.0)	( -0.6, 0.5)		
					Pr >  t			0.8356
		Week 48	n	66	47			
			LS Mean	0.631	0.682	-0.051		
			SEM	0.281	0.308	0.307		
95% CI	( 0.1, 1.2)		( 0.1, 1.3)	( -0.7, 0.6)				
			Pr >  t			0.8689		
Week 56	n	56	43					
	LS Mean	0.530	0.444	0.086				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	0.290	0.314	0.321
		95% CI	( -0.0, 1.1)	( -0.2, 1.1)	( -0.5, 0.7)
		Pr >  t			0.7891
	Week 64	n	45	41	
		LS Mean	0.351	0.390	-0.039
		SEM	0.303	0.317	0.336
		95% CI	( -0.2, 0.9)	( -0.2, 1.0)	( -0.7, 0.6)
		Pr >  t			0.9077
	Week 72	n	46	34	
		LS Mean	0.600	0.533	0.067
		SEM	0.301	0.331	0.348
		95% CI	( 0.0, 1.2)	( -0.1, 1.2)	( -0.6, 0.8)
		Pr >  t			0.8476
	Week 84	n	37	32	
		LS Mean	0.899	0.886	0.013
		SEM	0.317	0.336	0.366
		95% CI	( 0.3, 1.5)	( 0.2, 1.5)	( -0.7, 0.7)
		Pr >  t			0.9711
	Week 96	n	33	23	
		LS Mean	0.777	0.722	0.056
		SEM	0.326	0.367	0.401
		95% CI	( 0.1, 1.4)	( 0.0, 1.4)	( -0.7, 0.8)
		Pr >  t			0.8896
	Week 108	n	24	20	
		LS Mean	0.580	0.278	0.302
		SEM	0.355	0.382	0.438
		95% CI	( -0.1, 1.3)	( -0.5, 1.0)	( -0.6, 1.2)
		Pr >  t			0.4912
	Week 120	n	25	16	
		LS Mean	0.349	0.335	0.014
		SEM	0.351	0.409	0.460
		95% CI	( -0.3, 1.0)	( -0.5, 1.1)	( -0.9, 0.9)
		Pr >  t			0.9765
	Week 132	n	19	8	
		LS Mean	0.631	0.503	0.127
		SEM	0.381	0.524	0.583
		95% CI	( -0.1, 1.4)	( -0.5, 1.5)	( -1.0, 1.3)
		Pr >  t			0.8273
	Week 144	n	14	5	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Yes	Week 156	LS Mean	0.406	0.191	0.215
		SEM	0.420	0.636	0.709
		95% CI	(-0.4, 1.2)	(-1.1, 1.4)	(-1.2, 1.6)
		Pr >  t			0.7612
		n	9	3	
	Week 168	LS Mean	0.342	1.116	-0.773
		SEM	0.495	0.795	0.893
		95% CI	(-0.6, 1.3)	(-0.4, 2.7)	(-2.5, 1.0)
		Pr >  t			0.3869
		n	4	2	
	Week 180	LS Mean	0.061	0.020	0.041
		SEM	0.695	0.958	1.149
		95% CI	(-1.3, 1.4)	(-1.9, 1.9)	(-2.2, 2.3)
		Pr >  t			0.9716
		n	1	1	
	Week 192	LS Mean	1.691	0.773	0.919
		SEM	1.328	1.330	1.858
		95% CI	(-0.9, 4.3)	(-1.8, 3.4)	(-2.7, 4.6)
		Pr >  t			0.6212
		n	1	1	
	Week 8	LS Mean	0.691	0.023	0.669
		SEM	1.328	1.330	1.858
		95% CI	(-1.9, 3.3)	(-2.6, 2.6)	(-3.0, 4.3)
		Pr >  t			0.7191
n		5	8		
Week 16	LS Mean	-1.208	-0.044	-1.165	
	SEM	0.719	0.568	0.934	
	95% CI	(-2.7, 0.2)	(-1.2, 1.1)	(-3.1, 0.7)	
	Pr >  t			0.2196	
	n	5	8		
Week 24	LS Mean	-1.708	-0.548	-1.161	
	SEM	0.719	0.561	0.928	
	95% CI	(-3.2,-0.3)	(-1.7, 0.6)	(-3.0, 0.7)	
	Pr >  t			0.2183	
	n	5	5		
		LS Mean	-0.258	-0.550	0.291
		SEM	0.719	0.707	1.019
		95% CI	(-1.7, 1.2)	(-2.0, 0.9)	(-1.8, 2.3)
		Pr >  t			0.7765

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169			Placebo qd + Fulv N=172			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		n	LS Mean	SEM	95% CI	n	LS Mean		SEM
Week 32	n	4			3				
	LS Mean		-0.293			0.327			-0.620
	SEM		0.794			0.909			1.215
	95% CI		(-1.9, 1.3)			(-1.5, 2.2)			(-3.1, 1.8)
	Pr >  t								0.6120
Week 40	n	2			3				
	LS Mean		-1.470			-0.409			-1.061
	SEM		1.102			0.913			1.426
	95% CI		(-3.7, 0.7)			(-2.2, 1.4)			(-3.9, 1.8)
	Pr >  t								0.4601
Week 48	n	3			2				
	LS Mean		0.395			-0.925			1.320
	SEM		0.910			1.131			1.437
	95% CI		(-1.4, 2.2)			(-3.2, 1.3)			(-1.6, 4.2)
	Pr >  t								0.3631
Week 56	n	3			1				
	LS Mean		0.145			4.624			-4.479
	SEM		0.910			1.572			1.826
	95% CI		(-1.7, 2.0)			( 1.5, 7.8)			(-8.1,-0.8)
	Pr >  t								0.0178
Week 64	n	2							
	LS Mean		0.030			NE			NE
	SEM		1.102			NE			NE
	95% CI		(-2.2, 2.2)			NE			NE
	Pr >  t								NE
Week 72	n	2							
	LS Mean		-1.242			NE			NE
	SEM		1.098			NE			NE
	95% CI		(-3.4, 1.0)			NE			NE
	Pr >  t								NE
Week 84	n	3							
	LS Mean		-1.688			NE			NE
	SEM		0.910			NE			NE
	95% CI		(-3.5, 0.1)			NE			NE
	Pr >  t								NE
Week 96	n	2							
	LS Mean		-1.345			NE			NE
	SEM		1.102			NE			NE
	95% CI		(-3.6, 0.9)			NE			NE
	Pr >  t								NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	1.272	NE	NE
		SEM	1.110	NE	NE
		95% CI	( -1.0, 3.5)	NE	NE
		Pr >  t			NE
	Week 120	n	3		
		LS Mean	1.395	NE	NE
		SEM	0.910	NE	NE
		95% CI	( -0.4, 3.2)	NE	NE
		Pr >  t			NE
	Week 132	n	1		
		LS Mean	-3.331	NE	NE
		SEM	1.548	NE	NE
		95% CI	( -6.4,-0.2)	NE	NE
		Pr >  t			NE
	Week 144	n	1		
		LS Mean	-1.081	NE	NE
		SEM	1.548	NE	NE
		95% CI	( -4.2, 2.0)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	118			
			LS Mean	0.034	0.273	-0.239		
			SEM	0.252	0.258	0.236		
			95% CI	(-0.5, 0.5)	(-0.2, 0.8)	(-0.7, 0.2)		
					Pr >  t			0.3111
		Week 16	n	111	89			
			LS Mean	0.054	0.536	-0.482		
			SEM	0.258	0.273	0.255		
			95% CI	(-0.5, 0.6)	(-0.0, 1.1)	(-1.0, 0.0)		
					Pr >  t			0.0592
		Week 24	n	96	69			
			LS Mean	0.264	0.674	-0.410		
			SEM	0.265	0.287	0.274		
			95% CI	(-0.3, 0.8)	( 0.1, 1.2)	(-0.9, 0.1)		
					Pr >  t			0.1355
		Week 32	n	77	60			
			LS Mean	0.516	0.533	-0.016		
			SEM	0.276	0.296	0.291		
			95% CI	(-0.0, 1.1)	(-0.0, 1.1)	(-0.6, 0.6)		
					Pr >  t			0.9552
		Week 40	n	69	51			
			LS Mean	0.260	0.500	-0.240		
			SEM	0.282	0.306	0.306		
			95% CI	(-0.3, 0.8)	(-0.1, 1.1)	(-0.8, 0.4)		
					Pr >  t			0.4333
		Week 48	n	62	40			
			LS Mean	0.682	0.744	-0.062		
			SEM	0.287	0.322	0.327		
95% CI	( 0.1, 1.2)		( 0.1, 1.4)	(-0.7, 0.6)				
			Pr >  t			0.8488		
Week 56	n	53	35					
	LS Mean	0.577	0.544	0.033				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.296	0.333	0.345	
	95% CI	(-0.0, 1.2)	(-0.1, 1.2)	(-0.6, 0.7)	
	Pr >  t			0.9235	
	n	44	33		
	LS Mean	0.372	0.006	0.366	
Week 72	SEM	0.307	0.337	0.359	
	95% CI	(-0.2, 1.0)	(-0.7, 0.7)	(-0.3, 1.1)	
	Pr >  t			0.3084	
	n	45	28		
	LS Mean	0.532	0.627	-0.094	
Week 84	SEM	0.305	0.352	0.371	
	95% CI	(-0.1, 1.1)	(-0.1, 1.3)	(-0.8, 0.6)	
	Pr >  t			0.7993	
	n	39	27		
	LS Mean	0.775	0.850	-0.075	
Week 96	SEM	0.316	0.355	0.383	
	95% CI	( 0.2, 1.4)	( 0.2, 1.5)	(-0.8, 0.7)	
	Pr >  t			0.8449	
	n	34	19		
	LS Mean	0.666	0.883	-0.216	
Week 108	SEM	0.326	0.392	0.425	
	95% CI	( 0.0, 1.3)	( 0.1, 1.7)	(-1.1, 0.6)	
	Pr >  t			0.6113	
	n	26	17		
	LS Mean	0.673	0.339	0.334	
Week 120	SEM	0.350	0.406	0.456	
	95% CI	(-0.0, 1.4)	(-0.5, 1.1)	(-0.6, 1.2)	
	Pr >  t			0.4643	
	n	27	11		
	LS Mean	0.526	-0.136	0.661	
Week 132	SEM	0.346	0.471	0.512	
	95% CI	(-0.2, 1.2)	(-1.1, 0.8)	(-0.3, 1.7)	
	Pr >  t			0.1969	
	n	20	6		
	LS Mean	0.460	0.499	-0.039	
Week 144	SEM	0.378	0.595	0.646	
	95% CI	(-0.3, 1.2)	(-0.7, 1.7)	(-1.3, 1.2)	
	Pr >  t			0.9517	
	n	15	4		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
>= 75 Years	Week 156	LS Mean	0.355	0.149	0.206
		SEM	0.414	0.708	0.771
		95% CI	(-0.5, 1.2)	(-1.2, 1.5)	(-1.3, 1.7)
		Pr >  t			0.7895
		n	9	2	
	Week 168	LS Mean	0.317	1.531	-1.214
		SEM	0.500	0.968	1.052
		95% CI	(-0.7, 1.3)	(-0.4, 3.4)	(-3.3, 0.9)
		Pr >  t			0.2490
		n	4	2	
	Week 180	LS Mean	0.036	0.031	0.005
		SEM	0.701	0.968	1.162
		95% CI	(-1.3, 1.4)	(-1.9, 1.9)	(-2.3, 2.3)
		Pr >  t			0.9967
		n	1	1	
	Week 192	LS Mean	1.665	0.768	0.897
		SEM	1.341	1.343	1.877
		95% CI	(-1.0, 4.3)	(-1.9, 3.4)	(-2.8, 4.6)
		Pr >  t			0.6328
		n	1	1	
	Week 8	LS Mean	0.665	0.018	0.647
		SEM	1.341	1.343	1.877
		95% CI	(-2.0, 3.3)	(-2.6, 2.7)	(-3.0, 4.3)
		Pr >  t			0.7303
n		17	19		
Week 16	LS Mean	-0.176	-0.398	0.222	
	SEM	0.440	0.392	0.585	
	95% CI	(-1.1, 0.7)	(-1.2, 0.4)	(-0.9, 1.4)	
	Pr >  t			0.7054	
	n	13	16		
Week 24	LS Mean	-0.338	0.066	-0.404	
	SEM	0.488	0.424	0.645	
	95% CI	(-1.3, 0.6)	(-0.8, 0.9)	(-1.7, 0.9)	
	Pr >  t			0.5326	
	n	9	11		
	LS Mean	-0.086	0.540	-0.626	
	SEM	0.554	0.488	0.738	
	95% CI	(-1.2, 1.0)	(-0.4, 1.5)	(-2.1, 0.8)	
	Pr >  t			0.3977	

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32		n	9	12	
		LS Mean	0.148	-0.194	0.342
		SEM	0.555	0.476	0.730
		95% CI	(-1.0, 1.2)	(-1.1, 0.7)	(-1.1, 1.8)
		Pr >  t			0.6403
Week 40		n	6	10	
		LS Mean	0.794	-0.364	1.158
		SEM	0.643	0.505	0.817
		95% CI	(-0.5, 2.1)	(-1.4, 0.6)	(-0.5, 2.8)
		Pr >  t			0.1584
Week 48		n	7	10	
		LS Mean	-0.096	0.063	-0.158
		SEM	0.607	0.507	0.789
		95% CI	(-1.3, 1.1)	(-0.9, 1.1)	(-1.7, 1.4)
		Pr >  t			0.8413
Week 56		n	6	10	
		LS Mean	-0.200	0.132	-0.331
		SEM	0.641	0.508	0.815
		95% CI	(-1.5, 1.1)	(-0.9, 1.1)	(-1.9, 1.3)
		Pr >  t			0.6848
Week 64		n	3	9	
		LS Mean	-0.147	1.341	-1.488
		SEM	0.838	0.527	0.988
		95% CI	(-1.8, 1.5)	(0.3, 2.4)	(-3.4, 0.5)
		Pr >  t			0.1337
Week 72		n	3	7	
		LS Mean	0.186	-0.325	0.511
		SEM	0.838	0.579	1.016
		95% CI	(-1.5, 1.8)	(-1.5, 0.8)	(-1.5, 2.5)
		Pr >  t			0.6155
Week 84		n	1	6	
		LS Mean	-0.704	0.482	-1.186
		SEM	1.366	0.613	1.496
		95% CI	(-3.4, 2.0)	(-0.7, 1.7)	(-4.1, 1.8)
		Pr >  t			0.4289
Week 96		n	1	5	
		LS Mean	1.296	-0.439	1.735
		SEM	1.366	0.658	1.515
		95% CI	(-1.4, 4.0)	(-1.7, 0.9)	(-1.3, 4.7)
		Pr >  t			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.2537
	Week 108	n		4	
		LS Mean	NE	-0.168	NE
		SEM	NE	0.721	NE
		95% CI	NE	(-1.6, 1.3)	NE
		Pr >  t			NE
	Week 120	n	1	5	
		LS Mean	0.568	0.911	-0.343
		SEM	1.365	0.658	1.514
		95% CI	(-2.1, 3.3)	(-0.4, 2.2)	(-3.3, 2.6)
		Pr >  t			0.8208
	Week 132	n		2	
		LS Mean	NE	0.055	NE
		SEM	NE	0.967	NE
		95% CI	NE	(-1.9, 2.0)	NE
		Pr >  t			NE
	Week 144	n		1	
		LS Mean	NE	-0.149	NE
		SEM	NE	1.331	NE
		95% CI	NE	(-2.8, 2.5)	NE
		Pr >  t			NE
	Week 156	n		1	
		LS Mean	NE	-0.149	NE
		SEM	NE	1.331	NE
		95% CI	NE	(-2.8, 2.5)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
		N=169	N=172			
Prior Tamoxifen Use (L) No	Week 8	n	89	89		
		LS Mean	0.239	0.269	-0.030	
		SEM	0.323	0.325	0.271	
		95% CI	(-0.4, 0.9)	(-0.4, 0.9)	(-0.6, 0.5)	
	Week 16	Pr >  t				0.9126
		n	79	66		
		LS Mean	0.139	0.769	-0.630	
		SEM	0.327	0.345	0.296	
	Week 24	95% CI	(-0.5, 0.8)	(0.1, 1.4)	(-1.2, -0.0)	
		Pr >  t				0.0341
		n	64	54		
		LS Mean	0.450	0.820	-0.370	
	Week 32	SEM	0.339	0.361	0.322	
		95% CI	(-0.2, 1.1)	(0.1, 1.5)	(-1.0, 0.3)	
		Pr >  t				0.2519
		n	49	52		
	Week 40	LS Mean	0.855	0.619	0.236	
		SEM	0.359	0.363	0.341	
		95% CI	(0.1, 1.6)	(-0.1, 1.3)	(-0.4, 0.9)	
		Pr >  t				0.4899
	Week 48	n	44	44		
		LS Mean	0.421	0.574	-0.152	
		SEM	0.366	0.374	0.360	
		95% CI	(-0.3, 1.1)	(-0.2, 1.3)	(-0.9, 0.6)	
	Week 56	Pr >  t				0.6726
		n	41	35		
		LS Mean	0.701	0.737	-0.036	
		SEM	0.371	0.391	0.382	
	95% CI	(-0.0, 1.4)	(-0.0, 1.5)	(-0.8, 0.7)		
	Pr >  t				0.9244	
	n	33	32			
	LS Mean	0.497	0.673	-0.176		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	0.387	0.398	0.406
		95% CI	(-0.3, 1.3)	(-0.1, 1.5)	(-1.0, 0.6)
		Pr >  t			0.6644
	Week 64	n	27	31	
		LS Mean	0.604	0.311	0.293
		SEM	0.404	0.401	0.426
		95% CI	(-0.2, 1.4)	(-0.5, 1.1)	(-0.5, 1.1)
		Pr >  t			0.4918
	Week 72	n	26	26	
		LS Mean	0.755	0.563	0.192
		SEM	0.408	0.417	0.444
		95% CI	(-0.0, 1.6)	(-0.3, 1.4)	(-0.7, 1.1)
		Pr >  t			0.6659
	Week 84	n	22	23	
		LS Mean	1.186	0.875	0.311
		SEM	0.427	0.429	0.471
		95% CI	( 0.3, 2.0)	( 0.0, 1.7)	(-0.6, 1.2)
		Pr >  t			0.5098
	Week 96	n	18	18	
		LS Mean	1.128	0.765	0.363
		SEM	0.451	0.458	0.518
		95% CI	( 0.2, 2.0)	(-0.1, 1.7)	(-0.7, 1.4)
		Pr >  t			0.4834
	Week 108	n	14	14	
		LS Mean	1.049	0.239	0.810
		SEM	0.486	0.492	0.578
		95% CI	( 0.1, 2.0)	(-0.7, 1.2)	(-0.3, 1.9)
		Pr >  t			0.1613
	Week 120	n	12	12	
		LS Mean	0.315	0.207	0.108
		SEM	0.510	0.517	0.619
		95% CI	(-0.7, 1.3)	(-0.8, 1.2)	(-1.1, 1.3)
		Pr >  t			0.8614
	Week 132	n	9	5	
		LS Mean	0.665	0.334	0.330
		SEM	0.563	0.709	0.822
		95% CI	(-0.4, 1.8)	(-1.1, 1.7)	(-1.3, 1.9)
		Pr >  t			0.6877
	Week 144	n	7	4	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Yes	Week 156	LS Mean	0.215	0.114	0.101
		SEM	0.617	0.778	0.918
		95% CI	(-1.0, 1.4)	(-1.4, 1.6)	(-1.7, 1.9)
		Pr >  t			0.9123
	Week 168	n	4	2	
		LS Mean	-0.394	0.394	-0.788
		SEM	0.773	1.053	1.250
		95% CI	(-1.9, 1.1)	(-1.7, 2.5)	(-3.2, 1.7)
	Week 8	Pr >  t			0.5287
		n	2	1	
		LS Mean	0.320	-0.492	0.812
		SEM	1.048	1.455	1.753
	Week 16	95% CI	(-1.7, 2.4)	(-3.3, 2.4)	(-2.6, 4.3)
		Pr >  t			0.6435
		n	53	48	
		LS Mean	-0.151	0.315	-0.466
	Week 24	SEM	0.390	0.405	0.379
		95% CI	(-0.9, 0.6)	(-0.5, 1.1)	(-1.2, 0.3)
		Pr >  t			0.2208
		n	45	39	
	Week 32	LS Mean	0.042	0.271	-0.229
		SEM	0.403	0.419	0.399
		95% CI	(-0.8, 0.8)	(-0.6, 1.1)	(-1.0, 0.6)
		Pr >  t			0.5660
Week 40	n	41	26		
	LS Mean	0.072	0.661	-0.589	
	SEM	0.407	0.442	0.430	
	95% CI	(-0.7, 0.9)	(-0.2, 1.5)	(-1.4, 0.3)	
Week 8	Pr >  t			0.1720	
	n	37	20		
	LS Mean	0.117	0.338	-0.221	
	SEM	0.413	0.463	0.454	
Week 16	95% CI	(-0.7, 0.9)	(-0.6, 1.3)	(-1.1, 0.7)	
	Pr >  t			0.6262	
	n	31	17		
	LS Mean	0.290	0.290	-0.001	
Week 24	SEM	0.422	0.479	0.476	
	95% CI	(-0.5, 1.1)	(-0.7, 1.2)	(-0.9, 0.9)	
	Pr >  t			0.9990	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 48	n	28	15	
	LS Mean	0.633	0.782	-0.149
	SEM	0.428	0.490	0.493
	95% CI	(-0.2, 1.5)	(-0.2, 1.7)	(-1.1, 0.8)
	Pr >  t			0.7622
Week 56	n	26	13	
	LS Mean	0.654	0.461	0.194
	SEM	0.432	0.504	0.511
	95% CI	(-0.2, 1.5)	(-0.5, 1.5)	(-0.8, 1.2)
	Pr >  t			0.7043
Week 64	n	20	11	
	LS Mean	0.130	0.831	-0.701
	SEM	0.449	0.523	0.543
	95% CI	(-0.8, 1.0)	(-0.2, 1.9)	(-1.8, 0.4)
	Pr >  t			0.1973
Week 72	n	22	9	
	LS Mean	0.326	0.564	-0.239
	SEM	0.443	0.548	0.562
	95% CI	(-0.5, 1.2)	(-0.5, 1.6)	(-1.3, 0.9)
	Pr >  t			0.6709
Week 84	n	18	10	
	LS Mean	0.263	0.992	-0.730
	SEM	0.458	0.534	0.561
	95% CI	(-0.6, 1.2)	(-0.1, 2.0)	(-1.8, 0.4)
	Pr >  t			0.1937
Week 96	n	17	6	
	LS Mean	0.295	0.721	-0.426
	SEM	0.462	0.610	0.637
	95% CI	(-0.6, 1.2)	(-0.5, 1.9)	(-1.7, 0.8)
	Pr >  t			0.5036
Week 108	n	12	7	
	LS Mean	0.284	0.684	-0.400
	SEM	0.496	0.584	0.638
	95% CI	(-0.7, 1.3)	(-0.5, 1.8)	(-1.7, 0.9)
	Pr >  t			0.5305
Week 120	n	16	4	
	LS Mean	0.708	0.979	-0.271
	SEM	0.467	0.693	0.721
	95% CI	(-0.2, 1.6)	(-0.4, 2.3)	(-1.7, 1.1)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.7065
	Week 132	n	11	3	
		LS Mean	0.309	0.983	-0.674
		SEM	0.506	0.767	0.814
		95% CI	(-0.7, 1.3)	(-0.5, 2.5)	(-2.3, 0.9)
		Pr >  t			0.4081
	Week 144	n	8	1	
		LS Mean	0.493	0.845	-0.352
		SEM	0.545	1.203	1.251
		95% CI	(-0.6, 1.6)	(-1.5, 3.2)	(-2.8, 2.1)
		Pr >  t			0.7788
	Week 156	n	5	1	
		LS Mean	0.935	2.845	-1.910
		SEM	0.629	1.203	1.289
		95% CI	(-0.3, 2.2)	( 0.5, 5.2)	(-4.4, 0.6)
		Pr >  t			0.1390
	Week 168	n	2	1	
		LS Mean	-0.121	0.845	-0.966
		SEM	0.884	1.203	1.431
		95% CI	(-1.9, 1.6)	(-1.5, 3.2)	(-3.8, 1.8)
		Pr >  t			0.5000
	Week 180	n	1	1	
		LS Mean	1.623	1.095	0.528
		SEM	1.191	1.203	1.638
		95% CI	(-0.7, 4.0)	(-1.3, 3.5)	(-2.7, 3.7)
		Pr >  t			0.7473
	Week 192	n	1	1	
		LS Mean	0.623	0.345	0.278
		SEM	1.191	1.203	1.638
		95% CI	(-1.7, 3.0)	(-2.0, 2.7)	(-2.9, 3.5)
		Pr >  t			0.8653

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	NE	NE	NE	
			SEM	NE	NE	NE	
			95% CI	NE	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
			95% CI	NE	NE	NE	NE
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	NE	NE	NE	NE
			SEM	NE	NE	NE	NE
95% CI	NE		NE	NE	NE		
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	NE	NE	NE	NE		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 72	n	1		
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 84	n	1		
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 96	n	1		
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Positive	n	140	137	
	Week 8	LS Mean	0.070	0.237	-0.167
		SEM	0.245	0.249	0.218
		95% CI	(-0.4, 0.6)	(-0.3, 0.7)	(-0.6, 0.3)
		Pr >  t			0.4457
	Week 16	n	122	105	
		LS Mean	0.073	0.526	-0.453
		SEM	0.251	0.262	0.236
		95% CI	(-0.4, 0.6)	(0.0, 1.0)	(-0.9, 0.0)
		Pr >  t			0.0554
	Week 24	n	104	80	
		LS Mean	0.289	0.709	-0.420
		SEM	0.258	0.275	0.256
		95% CI	(-0.2, 0.8)	(0.2, 1.2)	(-0.9, 0.1)
		Pr >  t			0.1013
	Week 32	n	85	72	
		LS Mean	0.507	0.476	0.031
		SEM	0.268	0.281	0.270
		95% CI	(-0.0, 1.0)	(-0.1, 1.0)	(-0.5, 0.6)
		Pr >  t			0.9092
	Week 40	n	74	61	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	LS Mean	0.352	0.425	-0.073	
	SEM	0.274	0.290	0.285	
	95% CI	( -0.2, 0.9)	( -0.1, 1.0)	( -0.6, 0.5)	
	Pr >  t			0.7971	
	n	68	50		
Week 56	LS Mean	0.652	0.684	-0.032	
	SEM	0.278	0.302	0.300	
	95% CI	( 0.1, 1.2)	( 0.1, 1.3)	( -0.6, 0.6)	
	Pr >  t			0.9156	
	n	58	45		
Week 64	LS Mean	0.572	0.540	0.032	
	SEM	0.286	0.309	0.315	
	95% CI	( 0.0, 1.1)	( -0.1, 1.1)	( -0.6, 0.6)	
	Pr >  t			0.9201	
	n	47	42		
Week 72	LS Mean	0.382	0.379	0.002	
	SEM	0.299	0.314	0.331	
	95% CI	( -0.2, 1.0)	( -0.2, 1.0)	( -0.6, 0.7)	
	Pr >  t			0.9942	
	n	47	35		
Week 84	LS Mean	0.571	0.516	0.056	
	SEM	0.299	0.327	0.344	
	95% CI	( -0.0, 1.2)	( -0.1, 1.2)	( -0.6, 0.7)	
	Pr >  t			0.8715	
	n	39	33		
Week 96	LS Mean	0.768	0.857	-0.089	
	SEM	0.312	0.332	0.359	
	95% CI	( 0.2, 1.4)	( 0.2, 1.5)	( -0.8, 0.6)	
	Pr >  t			0.8040	
	n	34	24		
Week 108	LS Mean	0.745	0.691	0.053	
	SEM	0.323	0.361	0.395	
	95% CI	( 0.1, 1.4)	( -0.0, 1.4)	( -0.7, 0.8)	
	Pr >  t			0.8930	
	n	26	21		
Week 108	LS Mean	0.695	0.327	0.368	
	SEM	0.347	0.376	0.428	
	95% CI	( 0.0, 1.4)	( -0.4, 1.1)	( -0.5, 1.2)	
	Pr >  t			0.3906	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 120	n	28	16		
	LS Mean	0.564	0.331		0.232
	SEM	0.340	0.410		0.453
	95% CI	(-0.1, 1.2)	(-0.5, 1.1)		(-0.7, 1.1)
	Pr >  t				0.6079
Week 132	n	20	8		
	LS Mean	0.481	0.501		-0.019
	SEM	0.375	0.527		0.583
	95% CI	(-0.3, 1.2)	(-0.5, 1.5)		(-1.2, 1.1)
	Pr >  t				0.9733
Week 144	n	15	5		
	LS Mean	0.376	0.186		0.190
	SEM	0.411	0.640		0.708
	95% CI	(-0.4, 1.2)	(-1.1, 1.4)		(-1.2, 1.6)
	Pr >  t				0.7885
Week 156	n	9	3		
	LS Mean	0.341	1.111		-0.771
	SEM	0.498	0.801		0.901
	95% CI	(-0.6, 1.3)	(-0.5, 2.7)		(-2.5, 1.0)
	Pr >  t				0.3925
Week 168	n	4	2		
	LS Mean	0.058	0.016		0.041
	SEM	0.700	0.966		1.160
	95% CI	(-1.3, 1.4)	(-1.9, 1.9)		(-2.2, 2.3)
	Pr >  t				0.9715
Week 180	n	1	1		
	LS Mean	1.687	0.768		0.919
	SEM	1.342	1.343		1.877
	95% CI	(-0.9, 4.3)	(-1.9, 3.4)		(-2.8, 4.6)
	Pr >  t				0.6245
Week 192	n	1	1		
	LS Mean	0.687	0.018		0.669
	SEM	1.342	1.343		1.877
	95% CI	(-1.9, 3.3)	(-2.6, 2.7)		(-3.0, 4.4)
	Pr >  t				0.7216

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	0.388	-0.016	0.404
		SEM	0.443	0.489	0.470	
		95% CI	(-0.5, 1.3)	(-1.0, 1.0)	(-0.5, 1.3)	
		Pr >  t			0.3913	
		Week 16	n	35	22	
			LS Mean	0.445	0.061	0.383
			SEM	0.461	0.553	0.533
			95% CI	(-0.5, 1.4)	(-1.0, 1.2)	(-0.7, 1.4)
			Pr >  t			0.4725
		Week 24	n	28	16	
			LS Mean	0.721	0.645	0.076
			SEM	0.479	0.589	0.588
			95% CI	(-0.2, 1.7)	(-0.5, 1.8)	(-1.1, 1.2)
			Pr >  t			0.8977
		Week 32	n	22	16	
			LS Mean	0.566	0.831	-0.265
			SEM	0.508	0.591	0.608
			95% CI	(-0.4, 1.6)	(-0.3, 2.0)	(-1.5, 0.9)
			Pr >  t			0.6630
		Week 40	n	19	12	
			LS Mean	0.496	0.390	0.106
			SEM	0.524	0.629	0.659
			95% CI	(-0.5, 1.5)	(-0.9, 1.6)	(-1.2, 1.4)
			Pr >  t			0.8724
		Week 48	n	16	10	
			LS Mean	1.111	1.002	0.109
			SEM	0.544	0.659	0.702
95% CI	(0.0, 2.2)		(-0.3, 2.3)	(-1.3, 1.5)		
Pr >  t				0.8769		
Week 56	n	14	7			
	LS Mean	0.791	0.504	0.287		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.562	0.726	0.780
	95% CI	(-0.3, 1.9)	(-0.9, 1.9)	(-1.2, 1.8)
	Pr >  t			0.7127
	n	8	7	
	LS Mean	0.713	0.106	0.607
Week 72	SEM	0.652	0.726	0.849
	95% CI	(-0.6, 2.0)	(-1.3, 1.5)	(-1.1, 2.3)
	Pr >  t			0.4749
	n	12	6	
	LS Mean	0.865	-0.118	0.983
Week 84	SEM	0.584	0.761	0.828
	95% CI	(-0.3, 2.0)	(-1.6, 1.4)	(-0.6, 2.6)
	Pr >  t			0.2361
	n	8	5	
	LS Mean	0.852	0.240	0.612
Week 96	SEM	0.657	0.806	0.918
	95% CI	(-0.4, 2.1)	(-1.3, 1.8)	(-1.2, 2.4)
	Pr >  t			0.5055
	n	5	5	
	LS Mean	0.833	0.190	0.643
Week 108	SEM	0.765	0.806	1.000
	95% CI	(-0.7, 2.3)	(-1.4, 1.8)	(-1.3, 2.6)
	Pr >  t			0.5207
	n	7	5	
	LS Mean	1.184	0.440	0.744
Week 120	SEM	0.684	0.806	0.939
	95% CI	(-0.2, 2.5)	(-1.1, 2.0)	(-1.1, 2.6)
	Pr >  t			0.4286
	n	5	3	
	LS Mean	0.869	1.686	-0.817
Week 132	SEM	0.766	0.963	1.131
	95% CI	(-0.6, 2.4)	(-0.2, 3.6)	(-3.0, 1.4)
	Pr >  t			0.4704
	n	2	2	
	LS Mean	1.140	-0.188	1.327
Week 144	SEM	1.096	1.122	1.492
	95% CI	(-1.0, 3.3)	(-2.4, 2.0)	(-1.6, 4.3)
	Pr >  t			0.3742
	n	2		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Positive	Week 156	LS Mean	2.609	NE	NE
		SEM	1.097	NE	NE
		95% CI	( 0.5, 4.8)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	0.487	NE	NE
		SEM	1.495	NE	NE
		95% CI	( -2.5, 3.4)	NE	NE
	Week 8	Pr >  t			NE
		n	1		
		LS Mean	0.487	NE	NE
		SEM	1.495	NE	NE
	Week 16	95% CI	( -2.5, 3.4)	NE	NE
		Pr >  t			NE
		n	98	101	
		LS Mean	-0.114	0.207	-0.321
	Week 24	SEM	0.298	0.296	0.247
		95% CI	( -0.7, 0.5)	( -0.4, 0.8)	( -0.8, 0.2)
		Pr >  t			0.1944
		n	87	82	
	Week 32	LS Mean	-0.137	0.557	-0.695
		SEM	0.305	0.305	0.264
		95% CI	( -0.7, 0.5)	( -0.0, 1.2)	( -1.2,-0.2)
		Pr >  t			0.0086
Week 40	n	76	64		
	LS Mean	0.053	0.633	-0.581	
	SEM	0.311	0.318	0.283	
	95% CI	( -0.6, 0.7)	( 0.0, 1.3)	( -1.1,-0.0)	
Week 8	Pr >  t			0.0407	
	n	62	56		
	LS Mean	0.457	0.282	0.175	
	SEM	0.322	0.326	0.301	
Week 16	95% CI	( -0.2, 1.1)	( -0.4, 0.9)	( -0.4, 0.8)	
	Pr >  t			0.5604	
	n	54	49		
	LS Mean	0.196	0.349	-0.153	
Week 24	SEM	0.329	0.335	0.316	
	95% CI	( -0.4, 0.8)	( -0.3, 1.0)	( -0.8, 0.5)	
	Pr >  t			0.6291	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 48	n	52	40	
	LS Mean	0.369	0.520	-0.151
	SEM	0.330	0.347	0.331
	95% CI	(-0.3, 1.0)	(-0.2, 1.2)	(-0.8, 0.5)
	Pr >  t			0.6476
Week 56	n	44	38	
	LS Mean	0.364	0.470	-0.106
	SEM	0.340	0.351	0.343
	95% CI	(-0.3, 1.0)	(-0.2, 1.2)	(-0.8, 0.6)
	Pr >  t			0.7582
Week 64	n	39	35	
	LS Mean	0.184	0.358	-0.173
	SEM	0.347	0.356	0.357
	95% CI	(-0.5, 0.9)	(-0.3, 1.1)	(-0.9, 0.5)
	Pr >  t			0.6269
Week 72	n	36	29	
	LS Mean	0.363	0.573	-0.210
	SEM	0.352	0.370	0.376
	95% CI	(-0.3, 1.1)	(-0.2, 1.3)	(-0.9, 0.5)
	Pr >  t			0.5769
Week 84	n	32	28	
	LS Mean	0.633	0.896	-0.263
	SEM	0.361	0.373	0.386
	95% CI	(-0.1, 1.3)	( 0.2, 1.6)	(-1.0, 0.5)
	Pr >  t			0.4965
Week 96	n	30	19	
	LS Mean	0.559	0.741	-0.181
	SEM	0.365	0.410	0.427
	95% CI	(-0.2, 1.3)	(-0.1, 1.5)	(-1.0, 0.7)
	Pr >  t			0.6710
Week 108	n	18	16	
	LS Mean	0.485	0.195	0.290
	SEM	0.415	0.431	0.486
	95% CI	(-0.3, 1.3)	(-0.6, 1.0)	(-0.7, 1.2)
	Pr >  t			0.5514
Week 120	n	23	13	
	LS Mean	0.375	-0.057	0.431
	SEM	0.388	0.458	0.491
	95% CI	(-0.4, 1.1)	(-1.0, 0.8)	(-0.5, 1.4)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.3796
	Week 132	n	18	6	
		LS Mean	0.255	0.642	-0.388
		SEM	0.415	0.601	0.642
		95% CI	(-0.6, 1.1)	(-0.5, 1.8)	(-1.6, 0.9)
		Pr >  t			0.5464
	Week 144	n	13	5	
		LS Mean	-0.105	0.128	-0.233
		SEM	0.454	0.647	0.711
		95% CI	(-1.0, 0.8)	(-1.1, 1.4)	(-1.6, 1.2)
		Pr >  t			0.7431
	Week 156	n	8	3	
		LS Mean	0.165	1.058	-0.893
		SEM	0.537	0.801	0.900
		95% CI	(-0.9, 1.2)	(-0.5, 2.6)	(-2.7, 0.9)
		Pr >  t			0.3211
	Week 168	n	3	2	
		LS Mean	-0.169	-0.036	-0.133
		SEM	0.798	0.960	1.199
		95% CI	(-1.7, 1.4)	(-1.9, 1.8)	(-2.5, 2.2)
		Pr >  t			0.9118
	Week 180	n	1	1	
		LS Mean	1.479	0.687	0.792
		SEM	1.325	1.325	1.841
		95% CI	(-1.1, 4.1)	(-1.9, 3.3)	(-2.8, 4.4)
		Pr >  t			0.6670
	Week 192	n	1	1	
		LS Mean	0.479	-0.063	0.542
		SEM	1.325	1.325	1.841
		95% CI	(-2.1, 3.1)	(-2.7, 2.5)	(-3.1, 4.2)
		Pr >  t			0.7684

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final





**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	101			
			LS Mean	-0.104	0.200	-0.304		
			SEM	0.300	0.297	0.249		
			95% CI	(-0.7, 0.5)	(-0.4, 0.8)	(-0.8, 0.2)		
					Pr >  t			0.2227
		Week 16	n	85	82			
			LS Mean	-0.127	0.550	-0.677		
			SEM	0.307	0.306	0.266		
			95% CI	(-0.7, 0.5)	(-0.1, 1.2)	(-1.2,-0.2)		
					Pr >  t			0.0111
		Week 24	n	75	64			
			LS Mean	0.066	0.627	-0.560		
			SEM	0.313	0.319	0.285		
			95% CI	(-0.5, 0.7)	(-0.0, 1.3)	(-1.1,-0.0)		
					Pr >  t			0.0497
		Week 32	n	61	56			
			LS Mean	0.429	0.275	0.154		
			SEM	0.324	0.327	0.303		
			95% CI	(-0.2, 1.1)	(-0.4, 0.9)	(-0.4, 0.7)		
					Pr >  t			0.6110
		Week 40	n	53	49			
			LS Mean	0.208	0.342	-0.134		
			SEM	0.331	0.336	0.318		
			95% CI	(-0.4, 0.9)	(-0.3, 1.0)	(-0.8, 0.5)		
					Pr >  t			0.6738
		Week 48	n	51	40			
			LS Mean	0.369	0.513	-0.144		
			SEM	0.333	0.348	0.333		
95% CI	(-0.3, 1.0)		(-0.2, 1.2)	(-0.8, 0.5)				
			Pr >  t			0.6661		
Week 56	n	43	38					
	LS Mean	0.400	0.463	-0.063				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.342	0.352	0.346	
	95% CI	(-0.3, 1.1)	(-0.2, 1.2)	(-0.7, 0.6)	
	Pr >  t			0.8545	
	n	39	35		
	LS Mean	0.196	0.351	-0.155	
Week 72	SEM	0.348	0.357	0.358	
	95% CI	(-0.5, 0.9)	(-0.4, 1.1)	(-0.9, 0.5)	
	Pr >  t			0.6648	
	n	35	29		
	LS Mean	0.396	0.566	-0.170	
Week 84	SEM	0.356	0.371	0.379	
	95% CI	(-0.3, 1.1)	(-0.2, 1.3)	(-0.9, 0.6)	
	Pr >  t			0.6545	
	n	31	28		
	LS Mean	0.646	0.889	-0.243	
Week 96	SEM	0.365	0.374	0.390	
	95% CI	(-0.1, 1.4)	(0.2, 1.6)	(-1.0, 0.5)	
	Pr >  t			0.5330	
	n	29	19		
	LS Mean	0.605	0.734	-0.129	
Week 108	SEM	0.369	0.412	0.430	
	95% CI	(-0.1, 1.3)	(-0.1, 1.5)	(-1.0, 0.7)	
	Pr >  t			0.7640	
	n	18	16		
	LS Mean	0.497	0.189	0.309	
Week 120	SEM	0.416	0.432	0.488	
	95% CI	(-0.3, 1.3)	(-0.7, 1.0)	(-0.6, 1.3)	
	Pr >  t			0.5269	
	n	23	13		
	LS Mean	0.387	-0.063	0.450	
Week 132	SEM	0.390	0.459	0.492	
	95% CI	(-0.4, 1.2)	(-1.0, 0.8)	(-0.5, 1.4)	
	Pr >  t			0.3612	
	n	18	6		
	LS Mean	0.267	0.636	-0.368	
Week 144	SEM	0.416	0.603	0.644	
	95% CI	(-0.5, 1.1)	(-0.5, 1.8)	(-1.6, 0.9)	
	Pr >  t			0.5675	
	n	13	5		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Positive Negative	Week 156	LS Mean	-0.093	0.121	-0.214
		SEM	0.456	0.648	0.713
		95% CI	(-1.0, 0.8)	(-1.2, 1.4)	(-1.6, 1.2)
		Pr >  t			0.7644
		n	8	3	
	Week 168	LS Mean	0.178	1.051	-0.873
		SEM	0.539	0.803	0.902
		95% CI	(-0.9, 1.2)	(-0.5, 2.6)	(-2.6, 0.9)
		Pr >  t			0.3331
		n	3	2	
	Week 180	LS Mean	-0.156	-0.043	-0.113
		SEM	0.800	0.962	1.202
		95% CI	(-1.7, 1.4)	(-1.9, 1.8)	(-2.5, 2.2)
		Pr >  t			0.9250
		n	1	1	
	Week 192	LS Mean	1.492	0.681	0.811
		SEM	1.328	1.328	1.846
		95% CI	(-1.1, 4.1)	(-1.9, 3.3)	(-2.8, 4.4)
		Pr >  t			0.6604
		n	1	1	
	Week 8	LS Mean	0.492	-0.069	0.561
		SEM	1.328	1.328	1.846
		95% CI	(-2.1, 3.1)	(-2.7, 2.5)	(-3.1, 4.2)
		Pr >  t			0.7611
n		42	35		
Week 16	LS Mean	0.388	-0.016	0.404	
	SEM	0.443	0.489	0.470	
	95% CI	(-0.5, 1.3)	(-1.0, 1.0)	(-0.5, 1.3)	
	Pr >  t			0.3913	
	n	35	22		
Week 24	LS Mean	0.445	0.061	0.383	
	SEM	0.461	0.553	0.533	
	95% CI	(-0.5, 1.4)	(-1.0, 1.2)	(-0.7, 1.4)	
	Pr >  t			0.4725	
	n	28	16		
	LS Mean	0.721	0.645	0.076	
	SEM	0.479	0.589	0.588	
	95% CI	(-0.2, 1.7)	(-0.5, 1.8)	(-1.1, 1.2)	
	Pr >  t			0.8977	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	22	16	
	LS Mean	0.566	0.831	-0.265
	SEM	0.508	0.591	0.608
	95% CI	(-0.4, 1.6)	(-0.3, 2.0)	(-1.5, 0.9)
	Pr >  t			0.6630
Week 40	n	19	12	
	LS Mean	0.496	0.390	0.106
	SEM	0.524	0.629	0.659
	95% CI	(-0.5, 1.5)	(-0.9, 1.6)	(-1.2, 1.4)
	Pr >  t			0.8724
Week 48	n	16	10	
	LS Mean	1.111	1.002	0.109
	SEM	0.544	0.659	0.702
	95% CI	( 0.0, 2.2)	(-0.3, 2.3)	(-1.3, 1.5)
	Pr >  t			0.8769
Week 56	n	14	7	
	LS Mean	0.791	0.504	0.287
	SEM	0.562	0.726	0.780
	95% CI	(-0.3, 1.9)	(-0.9, 1.9)	(-1.2, 1.8)
	Pr >  t			0.7127
Week 64	n	8	7	
	LS Mean	0.713	0.106	0.607
	SEM	0.652	0.726	0.849
	95% CI	(-0.6, 2.0)	(-1.3, 1.5)	(-1.1, 2.3)
	Pr >  t			0.4749
Week 72	n	12	6	
	LS Mean	0.865	-0.118	0.983
	SEM	0.584	0.761	0.828
	95% CI	(-0.3, 2.0)	(-1.6, 1.4)	(-0.6, 2.6)
	Pr >  t			0.2361
Week 84	n	8	5	
	LS Mean	0.852	0.240	0.612
	SEM	0.657	0.806	0.918
	95% CI	(-0.4, 2.1)	(-1.3, 1.8)	(-1.2, 2.4)
	Pr >  t			0.5055
Week 96	n	5	5	
	LS Mean	0.833	0.190	0.643
	SEM	0.765	0.806	1.000
	95% CI	(-0.7, 2.3)	(-1.4, 1.8)	(-1.3, 2.6)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 108	Pr >  t			0.5207
		n	7	5	
		LS Mean	1.184	0.440	0.744
		SEM	0.684	0.806	0.939
		95% CI	(-0.2, 2.5)	(-1.1, 2.0)	(-1.1, 2.6)
	Week 120	Pr >  t			0.4286
		n	5	3	
		LS Mean	0.869	1.686	-0.817
		SEM	0.766	0.963	1.131
		95% CI	(-0.6, 2.4)	(-0.2, 3.6)	(-3.0, 1.4)
	Week 132	Pr >  t			0.4704
		n	2	2	
		LS Mean	1.140	-0.188	1.327
		SEM	1.096	1.122	1.492
		95% CI	(-1.0, 3.3)	(-2.4, 2.0)	(-1.6, 4.3)
	Week 144	Pr >  t			0.3742
		n	2		
		LS Mean	2.609	NE	NE
		SEM	1.097	NE	NE
		95% CI	( 0.5, 4.8)	NE	NE
	Week 156	Pr >  t			NE
		n	1		
		LS Mean	0.487	NE	NE
		SEM	1.495	NE	NE
		95% CI	(-2.5, 3.4)	NE	NE
	Week 168	Pr >  t			NE
		n	1		
		LS Mean	0.487	NE	NE
		SEM	1.495	NE	NE
		95% CI	(-2.5, 3.4)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	93			
			LS Mean	-0.075	0.183	-0.258		
			SEM	0.272	0.282	0.260		
			95% CI	(-0.6, 0.5)	(-0.4, 0.7)	(-0.8, 0.3)		
					Pr >  t			0.3219
		Week 16	n	90	73			
			LS Mean	-0.043	0.341	-0.384		
			SEM	0.279	0.295	0.280		
			95% CI	(-0.6, 0.5)	(-0.2, 0.9)	(-0.9, 0.2)		
					Pr >  t			0.1705
		Week 24	n	79	61			
			LS Mean	0.216	0.524	-0.308		
			SEM	0.285	0.306	0.295		
			95% CI	(-0.3, 0.8)	(-0.1, 1.1)	(-0.9, 0.3)		
					Pr >  t			0.2966
		Week 32	n	70	55			
			LS Mean	0.449	0.493	-0.043		
			SEM	0.293	0.313	0.306		
			95% CI	(-0.1, 1.0)	(-0.1, 1.1)	(-0.6, 0.6)		
					Pr >  t			0.8877
		Week 40	n	61	45			
			LS Mean	0.279	0.267	0.012		
			SEM	0.299	0.325	0.324		
			95% CI	(-0.3, 0.9)	(-0.4, 0.9)	(-0.6, 0.6)		
					Pr >  t			0.9715
		Week 48	n	56	37			
			LS Mean	0.658	0.596	0.061		
			SEM	0.303	0.338	0.341		
95% CI	( 0.1, 1.3)		(-0.1, 1.3)	(-0.6, 0.7)				
			Pr >  t			0.8576		
Week 56	n	49	33					
	LS Mean	0.553	0.084	0.469				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 64	SEM	0.310	0.346	0.355	
	95% CI	(-0.1, 1.2)	(-0.6, 0.8)	(-0.2, 1.2)	
	Pr >  t			0.1869	
	n	37	29		
	LS Mean	0.214	0.022	0.192	
Week 72	SEM	0.327	0.357	0.380	
	95% CI	(-0.4, 0.9)	(-0.7, 0.7)	(-0.6, 0.9)	
	Pr >  t			0.6140	
	n	40	25		
	LS Mean	0.499	0.378	0.121	
Week 84	SEM	0.322	0.370	0.388	
	95% CI	(-0.1, 1.1)	(-0.3, 1.1)	(-0.6, 0.9)	
	Pr >  t			0.7553	
	n	32	23		
	LS Mean	0.634	1.017	-0.383	
Week 96	SEM	0.339	0.377	0.408	
	95% CI	(-0.0, 1.3)	( 0.3, 1.8)	(-1.2, 0.4)	
	Pr >  t			0.3484	
	n	29	17		
	LS Mean	0.531	0.485	0.046	
Week 108	SEM	0.346	0.410	0.445	
	95% CI	(-0.1, 1.2)	(-0.3, 1.3)	(-0.8, 0.9)	
	Pr >  t			0.9177	
	n	22	15		
	LS Mean	0.694	-0.297	0.991	
Week 120	SEM	0.372	0.426	0.478	
	95% CI	(-0.0, 1.4)	(-1.1, 0.5)	( 0.1, 1.9)	
	Pr >  t			0.0385	
	n	23	13		
	LS Mean	0.401	0.138	0.263	
Week 132	SEM	0.367	0.445	0.493	
	95% CI	(-0.3, 1.1)	(-0.7, 1.0)	(-0.7, 1.2)	
	Pr >  t			0.5941	
	n	17	5		
	LS Mean	0.464	0.325	0.138	
Week 144	SEM	0.400	0.631	0.684	
	95% CI	(-0.3, 1.2)	(-0.9, 1.6)	(-1.2, 1.5)	
	Pr >  t			0.8400	
	n	14	3		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
>= 3	Week 156	LS Mean	0.336	-0.249	0.585
		SEM	0.424	0.785	0.840
		95% CI	(-0.5, 1.2)	(-1.8, 1.3)	(-1.1, 2.2)
		Pr >  t			0.4861
	Week 168	n	8	2	
		LS Mean	0.259	1.253	-0.994
		SEM	0.517	0.941	1.030
		95% CI	(-0.8, 1.3)	(-0.6, 3.1)	(-3.0, 1.0)
	Week 180	Pr >  t			0.3347
		n	4	1	
		LS Mean	-0.019	0.381	-0.400
		SEM	0.685	1.301	1.439
Week 192	95% CI	(-1.4, 1.3)	(-2.2, 2.9)	(-3.2, 2.4)	
	Pr >  t			0.7810	
	n	1	1		
	LS Mean	1.605	0.631	0.974	
Week 204	SEM	1.297	1.301	1.812	
	95% CI	(-0.9, 4.1)	(-1.9, 3.2)	(-2.6, 4.5)	
	Pr >  t			0.5910	
	n	1	1		
Week 8	LS Mean	0.605	-0.119	0.724	
	SEM	1.297	1.301	1.812	
	95% CI	(-1.9, 3.1)	(-2.7, 2.4)	(-2.8, 4.3)	
	Pr >  t			0.6895	
Week 16	n	37	44		
	LS Mean	0.742	0.698	0.044	
	SEM	0.685	0.680	0.397	
	95% CI	(-0.6, 2.1)	(-0.6, 2.0)	(-0.7, 0.8)	
Week 24	Pr >  t			0.9117	
	n	34	32		
	LS Mean	0.683	1.306	-0.623	
	SEM	0.709	0.715	0.435	
Week 32	95% CI	(-0.7, 2.1)	(-0.1, 2.7)	(-1.5, 0.2)	
	Pr >  t			0.1530	
	n	26	19		
	LS Mean	0.716	1.563	-0.847	
Week 40	SEM	0.726	0.752	0.518	
	95% CI	(-0.7, 2.1)	( 0.1, 3.0)	(-1.9, 0.2)	
	Pr >  t			0.1030	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	16	17	
	LS Mean	0.951	0.674	0.278
	SEM	0.766	0.762	0.587
	95% CI	(-0.6, 2.5)	(-0.8, 2.2)	(-0.9, 1.4)
	Pr >  t			0.6369
Week 40	n	14	16	
	LS Mean	0.717	1.160	-0.443
	SEM	0.780	0.768	0.613
	95% CI	(-0.8, 2.3)	(-0.4, 2.7)	(-1.6, 0.8)
	Pr >  t			0.4707
Week 48	n	13	13	
	LS Mean	0.710	1.234	-0.524
	SEM	0.788	0.790	0.649
	95% CI	(-0.8, 2.3)	(-0.3, 2.8)	(-1.8, 0.8)
	Pr >  t			0.4198
Week 56	n	10	12	
	LS Mean	0.581	2.120	-1.539
	SEM	0.822	0.800	0.700
	95% CI	(-1.0, 2.2)	( 0.5, 3.7)	(-2.9,-0.2)
	Pr >  t			0.0285
Week 64	n	10	13	
	LS Mean	1.123	1.558	-0.435
	SEM	0.822	0.791	0.690
	95% CI	(-0.5, 2.7)	( 0.0, 3.1)	(-1.8, 0.9)
	Pr >  t			0.5292
Week 72	n	8	10	
	LS Mean	0.857	1.215	-0.358
	SEM	0.855	0.823	0.764
	95% CI	(-0.8, 2.5)	(-0.4, 2.8)	(-1.9, 1.1)
	Pr >  t			0.6397
Week 84	n	8	10	
	LS Mean	1.408	0.850	0.558
	SEM	0.855	0.822	0.764
	95% CI	(-0.3, 3.1)	(-0.8, 2.5)	(-0.9, 2.1)
	Pr >  t			0.4655
Week 96	n	6	7	
	LS Mean	1.652	1.549	0.103
	SEM	0.909	0.879	0.879
	95% CI	(-0.1, 3.4)	(-0.2, 3.3)	(-1.6, 1.8)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.9067
	Week 108	n	4	6	
		LS Mean	0.686	2.256	-1.570
		SEM	1.004	0.907	1.004
		95% CI	(-1.3, 2.7)	(0.5, 4.0)	(-3.5, 0.4)
		Pr >  t			0.1188
	Week 120	n	5	3	
		LS Mean	1.370	1.270	0.099
		SEM	0.948	1.090	1.123
		95% CI	(-0.5, 3.2)	(-0.9, 3.4)	(-2.1, 2.3)
		Pr >  t			0.9298
	Week 132	n	3	3	
		LS Mean	0.549	1.332	-0.783
		SEM	1.090	1.090	1.247
		95% CI	(-1.6, 2.7)	(-0.8, 3.5)	(-3.2, 1.7)
		Pr >  t			0.5307
	Week 144	n	1	2	
		LS Mean	0.258	1.371	-1.113
		SEM	1.626	1.246	1.838
		95% CI	(-2.9, 3.5)	(-1.1, 3.8)	(-4.7, 2.5)
		Pr >  t			0.5453
	Week 156	n	1	1	
		LS Mean	0.758	1.311	-0.553
		SEM	1.626	1.626	2.113
		95% CI	(-2.4, 4.0)	(-1.9, 4.5)	(-4.7, 3.6)
		Pr >  t			0.7936
	Week 168	n		1	
		LS Mean	NE	0.311	NE
		SEM	NE	1.626	NE
		95% CI	NE	(-2.9, 3.5)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-30i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Severity Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo	Treatment difference		
			300mg qd + Fulv N=169	qd + Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Visceral Disease (L)	No	Week 8	n	69	58		
			LS Mean	-0.899	-0.410	-0.489	
			SEM	0.652	0.676	0.298	
			95% CI	(-2.2, 0.4)	(-1.7, 0.9)	(-1.1, 0.1)	
					Pr >  t	0.1018	
		Week 16	n	59	47		
			LS Mean	-0.973	-0.364	-0.609	
			SEM	0.654	0.682	0.320	
			95% CI	(-2.3, 0.3)	(-1.7, 1.0)	(-1.2, 0.0)	
					Pr >  t	0.0576	
		Week 24	n	54	40		
			LS Mean	-0.745	-0.081	-0.664	
			SEM	0.656	0.687	0.335	
			95% CI	(-2.0, 0.6)	(-1.4, 1.3)	(-1.3,-0.0)	
					Pr >  t	0.0481	
		Week 32	n	48	36		
			LS Mean	-0.338	-0.315	-0.023	
			SEM	0.658	0.691	0.348	
			95% CI	(-1.6, 1.0)	(-1.7, 1.1)	(-0.7, 0.7)	
					Pr >  t	0.9479	
		Week 40	n	43	32		
			LS Mean	-0.617	-0.698	0.081	
			SEM	0.660	0.695	0.361	
			95% CI	(-1.9, 0.7)	(-2.1, 0.7)	(-0.6, 0.8)	
			Pr >  t	0.8223			
Week 48	n	41	27				
	LS Mean	-0.152	-0.318	0.165			
	SEM	0.662	0.701	0.376			
	95% CI	(-1.5, 1.2)	(-1.7, 1.1)	(-0.6, 0.9)			
			Pr >  t	0.6606			
Week 56		n	35	22			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		LS Mean	-0.249	-0.821	0.571
		SEM	0.666	0.711	0.402
		95% CI	(-1.6, 1.1)	(-2.2, 0.6)	(-0.2, 1.4)
		Pr >  t			0.1553
	Week 64	n	26	23	
		LS Mean	-0.293	-0.838	0.544
		SEM	0.676	0.709	0.416
		95% CI	(-1.6, 1.0)	(-2.2, 0.6)	(-0.3, 1.4)
		Pr >  t			0.1916
	Week 72	n	28	18	
		LS Mean	-0.295	-0.161	-0.134
		SEM	0.673	0.721	0.433
		95% CI	(-1.6, 1.0)	(-1.6, 1.3)	(-1.0, 0.7)
		Pr >  t			0.7570
	Week 84	n	22	18	
		LS Mean	-0.689	0.036	-0.725
		SEM	0.687	0.721	0.450
		95% CI	(-2.0, 0.7)	(-1.4, 1.5)	(-1.6, 0.2)
		Pr >  t			0.1074
	Week 96	n	21	13	
		LS Mean	-0.526	-0.283	-0.243
		SEM	0.685	0.743	0.487
		95% CI	(-1.9, 0.8)	(-1.8, 1.2)	(-1.2, 0.7)
		Pr >  t			0.6177
	Week 108	n	17	12	
		LS Mean	-0.050	-0.918	0.868
		SEM	0.701	0.750	0.513
		95% CI	(-1.4, 1.3)	(-2.4, 0.6)	(-0.1, 1.9)
		Pr >  t			0.0912
	Week 120	n	18	11	
		LS Mean	-0.268	-1.024	0.756
		SEM	0.693	0.757	0.520
		95% CI	(-1.6, 1.1)	(-2.5, 0.5)	(-0.3, 1.8)
		Pr >  t			0.1461
	Week 132	n	13	5	
		LS Mean	-0.658	-0.493	-0.165
		SEM	0.719	0.856	0.679
		95% CI	(-2.1, 0.8)	(-2.2, 1.2)	(-1.5, 1.2)
		Pr >  t			0.8079

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Yes	Week 144	n	12	3	
		LS Mean	-0.523	-1.072	0.549
		SEM	0.719	0.964	0.817
		95% CI	(-1.9, 0.9)	(-3.0, 0.8)	(-1.1, 2.2)
		Pr >  t			0.5015
	Week 156	n	6	2	
		LS Mean	-0.850	0.428	-1.278
		SEM	0.805	1.082	1.015
		95% CI	(-2.4, 0.7)	(-1.7, 2.6)	(-3.3, 0.7)
		Pr >  t			0.2084
	Week 168	n	3	1	
		LS Mean	-0.936	-0.461	-0.475
		SEM	0.944	1.378	1.415
		95% CI	(-2.8, 0.9)	(-3.2, 2.2)	(-3.3, 2.3)
		Pr >  t			0.7370
	Week 180	n	1	1	
		LS Mean	0.730	-0.211	0.941
		SEM	1.365	1.378	1.724
		95% CI	(-1.9, 3.4)	(-2.9, 2.5)	(-2.4, 4.3)
		Pr >  t			0.5852
Week 192	n	1	1		
	LS Mean	-0.270	-0.961	0.691	
	SEM	1.365	1.378	1.724	
	95% CI	(-2.9, 2.4)	(-3.7, 1.7)	(-2.7, 4.1)	
	Pr >  t			0.6885	
Week 8	n	73	79		
	LS Mean	0.480	0.465	0.015	
	SEM	0.412	0.417	0.316	
	95% CI	(-0.3, 1.3)	(-0.4, 1.3)	(-0.6, 0.6)	
	Pr >  t			0.9631	
Week 16	n	65	58		
	LS Mean	0.572	0.931	-0.359	
	SEM	0.424	0.437	0.343	
	95% CI	(-0.3, 1.4)	( 0.1, 1.8)	(-1.0, 0.3)	
	Pr >  t			0.2958	
Week 24	n	51	40		
	LS Mean	0.778	1.023	-0.246	
	SEM	0.434	0.463	0.385	
	95% CI	(-0.1, 1.6)	( 0.1, 1.9)	(-1.0, 0.5)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		Pr >  t			0.5236
	Week 32	n	38	36	
		LS Mean	0.842	0.807	0.035
		SEM	0.458	0.471	0.414
		95% CI	(-0.1, 1.7)	(-0.1, 1.7)	(-0.8, 0.8)
		Pr >  t			0.9336
	Week 40	n	32	29	
		LS Mean	0.765	1.118	-0.352
		SEM	0.471	0.487	0.446
		95% CI	(-0.2, 1.7)	( 0.2, 2.1)	(-1.2, 0.5)
		Pr >  t			0.4292
	Week 48	n	28	23	
		LS Mean	0.847	1.258	-0.410
		SEM	0.481	0.508	0.478
		95% CI	(-0.1, 1.8)	( 0.3, 2.3)	(-1.3, 0.5)
		Pr >  t			0.3907
	Week 56	n	24	23	
		LS Mean	0.735	1.435	-0.699
		SEM	0.495	0.508	0.491
		95% CI	(-0.2, 1.7)	( 0.4, 2.4)	(-1.7, 0.3)
		Pr >  t			0.1551
	Week 64	n	21	19	
		LS Mean	0.437	1.200	-0.764
		SEM	0.509	0.527	0.524
		95% CI	(-0.6, 1.4)	( 0.2, 2.2)	(-1.8, 0.3)
		Pr >  t			0.1451
	Week 72	n	20	17	
		LS Mean	0.808	0.722	0.086
		SEM	0.514	0.539	0.541
		95% CI	(-0.2, 1.8)	(-0.3, 1.8)	(-1.0, 1.1)
		Pr >  t			0.8737
	Week 84	n	18	15	
		LS Mean	1.776	1.199	0.577
		SEM	0.524	0.555	0.566
		95% CI	( 0.7, 2.8)	( 0.1, 2.3)	(-0.5, 1.7)
		Pr >  t			0.3085
	Week 96	n	14	11	
		LS Mean	1.557	1.209	0.348
		SEM	0.556	0.599	0.637



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		95% CI	( 0.5, 2.6)	( 0.0, 2.4)	(-0.9, 1.6)
		Pr >  t			0.5851
	Week 108	n	9	9	
		LS Mean	0.682	1.231	-0.550
		SEM	0.626	0.633	0.728
		95% CI	(-0.5, 1.9)	(-0.0, 2.5)	(-2.0, 0.9)
		Pr >  t			0.4507
	Week 120	n	10	5	
		LS Mean	0.735	1.739	-1.004
		SEM	0.609	0.766	0.834
		95% CI	(-0.5, 1.9)	( 0.2, 3.2)	(-2.6, 0.6)
		Pr >  t			0.2287
	Week 132	n	7	3	
		LS Mean	1.204	1.065	0.139
		SEM	0.676	0.926	1.027
		95% CI	(-0.1, 2.5)	(-0.8, 2.9)	(-1.9, 2.2)
		Pr >  t			0.8923
	Week 144	n	3	2	
		LS Mean	0.576	1.117	-0.541
		SEM	0.921	1.096	1.338
		95% CI	(-1.2, 2.4)	(-1.0, 3.3)	(-3.2, 2.1)
		Pr >  t			0.6859
	Week 156	n	3	1	
		LS Mean	1.190	0.985	0.205
		SEM	0.922	1.493	1.679
		95% CI	(-0.6, 3.0)	(-1.9, 3.9)	(-3.1, 3.5)
		Pr >  t			0.9026
	Week 168	n	1	1	
		LS Mean	0.534	-0.015	0.549
		SEM	1.493	1.493	2.049
		95% CI	(-2.4, 3.5)	(-2.9, 2.9)	(-3.5, 4.6)
		Pr >  t			0.7890

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

Tabelle 4H-51: Ergebnisse für den Endpunkt „Krankheitssymptomatik (BPI-SF): Schmerz-Interferenz-Index“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	71	
		LS Mean	-0.148	-0.029	-0.119	
		SEM	0.337	0.341	0.312	
		95% CI	(-0.8, 0.5)	(-0.7, 0.6)	(-0.7, 0.5)	
			Pr >  t			0.7025
	Week 16	n	67	54		
		LS Mean	-0.207	0.175	-0.382	
		SEM	0.343	0.364	0.341	
		95% CI	(-0.9, 0.5)	(-0.5, 0.9)	(-1.1, 0.3)	
			Pr >  t			0.2628
	Week 24	n	61	44		
		LS Mean	-0.045	0.371	-0.416	
		SEM	0.351	0.378	0.362	
		95% CI	(-0.7, 0.6)	(-0.4, 1.1)	(-1.1, 0.3)	
			Pr >  t			0.2507
	Week 32	n	52	40		
		LS Mean	0.369	0.145	0.224	
		SEM	0.364	0.387	0.379	
		95% CI	(-0.3, 1.1)	(-0.6, 0.9)	(-0.5, 1.0)	
			Pr >  t			0.5544
Week 40	n	45	35			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		LS Mean	0.380	0.291	0.090
		SEM	0.373	0.400	0.399
		95% CI	(-0.4, 1.1)	(-0.5, 1.1)	(-0.7, 0.9)
		Pr >  t			0.8223
	Week 48	n	42	29	
		LS Mean	0.730	0.228	0.502
		SEM	0.378	0.416	0.420
		95% CI	(-0.0, 1.5)	(-0.6, 1.0)	(-0.3, 1.3)
		Pr >  t			0.2322
	Week 56	n	35	24	
		LS Mean	0.019	-0.130	0.149
		SEM	0.392	0.436	0.451
		95% CI	(-0.8, 0.8)	(-1.0, 0.7)	(-0.7, 1.0)
		Pr >  t			0.7417
	Week 64	n	25	25	
		LS Mean	0.260	0.216	0.044
		SEM	0.422	0.432	0.475
		95% CI	(-0.6, 1.1)	(-0.6, 1.1)	(-0.9, 1.0)
		Pr >  t			0.9255
	Week 72	n	27	20	
		LS Mean	0.294	0.126	0.168
		SEM	0.415	0.456	0.491
		95% CI	(-0.5, 1.1)	(-0.8, 1.0)	(-0.8, 1.1)
		Pr >  t			0.7323
	Week 84	n	23	19	
		LS Mean	0.225	0.730	-0.505
		SEM	0.433	0.463	0.511
		95% CI	(-0.6, 1.1)	(-0.2, 1.6)	(-1.5, 0.5)
		Pr >  t			0.3226
	Week 96	n	20	13	
		LS Mean	0.282	0.065	0.217
		SEM	0.449	0.517	0.573
		95% CI	(-0.6, 1.2)	(-0.9, 1.1)	(-0.9, 1.3)
		Pr >  t			0.7043
	Week 108	n	17	13	
		LS Mean	0.696	-0.217	0.914
		SEM	0.470	0.517	0.589
		95% CI	(-0.2, 1.6)	(-1.2, 0.8)	(-0.2, 2.1)
		Pr >  t			0.1212

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 120	n	17	12		
	LS Mean	0.645	-0.410	1.054	
	SEM	0.470	0.530	0.601	
	95% CI	(-0.3, 1.6)	(-1.5, 0.6)	(-0.1, 2.2)	
Week 132	n	13	6		
	LS Mean	0.115	0.553	-0.438	
	SEM	0.509	0.677	0.760	
	95% CI	(-0.9, 1.1)	(-0.8, 1.9)	(-1.9, 1.1)	
Week 144	n	11	4		
	LS Mean	0.391	-0.335	0.726	
	SEM	0.538	0.799	0.887	
	95% CI	(-0.7, 1.4)	(-1.9, 1.2)	(-1.0, 2.5)	
Week 156	n	6	2		
	LS Mean	-0.258	0.981	-1.239	
	SEM	0.671	1.081	1.216	
	95% CI	(-1.6, 1.1)	(-1.1, 3.1)	(-3.6, 1.1)	
Week 168	n	3	1		
	LS Mean	-0.722	-0.321	-0.401	
	SEM	0.896	1.493	1.701	
	95% CI	(-2.5, 1.0)	(-3.3, 2.6)	(-3.7, 2.9)	
Week 180	n	1	1		
	LS Mean	2.419	0.249	2.171	
	SEM	1.490	1.493	2.076	
	95% CI	(-0.5, 5.3)	(-2.7, 3.2)	(-1.9, 6.2)	
Week 192	n	1	1		
	LS Mean	0.269	-0.461	0.731	
	SEM	1.490	1.493	2.076	
	95% CI	(-2.7, 3.2)	(-3.4, 2.5)	(-3.3, 4.8)	
Present Week 8	n	65	66		
	LS Mean	0.297	0.312	-0.015	
	SEM	0.363	0.374	0.314	
	95% CI	(-0.4, 1.0)	(-0.4, 1.1)	(-0.6, 0.6)	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.9616
	Week 16	n	57	51
		LS Mean	0.404	0.357
		SEM	0.376	0.390
		95% CI	(-0.3, 1.1)	(-0.4, 1.1)
		Pr >  t		0.8875
	Week 24	n	44	35
		LS Mean	0.445	0.386
		SEM	0.388	0.418
		95% CI	(-0.3, 1.2)	(-0.4, 1.2)
		Pr >  t		0.8757
	Week 32	n	34	32
		LS Mean	0.149	0.548
		SEM	0.406	0.424
		95% CI	(-0.6, 0.9)	(-0.3, 1.4)
		Pr >  t		0.3203
	Week 40	n	30	26
		LS Mean	0.433	0.411
		SEM	0.415	0.439
		95% CI	(-0.4, 1.2)	(-0.5, 1.3)
		Pr >  t		0.9593
	Week 48	n	27	21
		LS Mean	0.791	0.789
		SEM	0.422	0.458
		95% CI	(-0.0, 1.6)	(-0.1, 1.7)
		Pr >  t		0.9963
	Week 56	n	24	21
		LS Mean	0.304	0.672
		SEM	0.431	0.458
		95% CI	(-0.5, 1.2)	(-0.2, 1.6)
		Pr >  t		0.4252
	Week 64	n	22	17
		LS Mean	0.264	0.775
		SEM	0.438	0.478
		95% CI	(-0.6, 1.1)	(-0.2, 1.7)
		Pr >  t		0.2957
	Week 72	n	21	15
		LS Mean	0.173	0.240
		SEM	0.443	0.492

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 84	95% CI	(-0.7, 1.0)	(-0.7, 1.2)	(-1.1, 0.9)	
	Pr >  t			0.8953	
	n	17	14		
	LS Mean	0.964	0.530	0.435	
	SEM	0.464	0.500	0.531	
Week 96	95% CI	( 0.1, 1.9)	( -0.5, 1.5)	( -0.6, 1.5)	
	Pr >  t			0.4129	
	n	15	11		
	LS Mean	0.365	0.654	-0.289	
	SEM	0.476	0.532	0.572	
Week 108	95% CI	( -0.6, 1.3)	( -0.4, 1.7)	( -1.4, 0.8)	
	Pr >  t			0.6141	
	n	9	8		
	LS Mean	0.432	0.501	-0.069	
	SEM	0.549	0.583	0.676	
Week 120	95% CI	( -0.6, 1.5)	( -0.6, 1.6)	( -1.4, 1.3)	
	Pr >  t			0.9186	
	n	11	4		
	LS Mean	0.477	0.631	-0.154	
	SEM	0.517	0.739	0.795	
Week 132	95% CI	( -0.5, 1.5)	( -0.8, 2.1)	( -1.7, 1.4)	
	Pr >  t			0.8465	
	n	7	2		
	LS Mean	0.476	0.546	-0.070	
	SEM	0.594	0.975	1.058	
Week 144	95% CI	( -0.7, 1.6)	( -1.4, 2.5)	( -2.1, 2.0)	
	Pr >  t			0.9472	
	n	4	1		
	LS Mean	0.951	0.102	0.849	
	SEM	0.721	1.329	1.452	
Week 156	95% CI	( -0.5, 2.4)	( -2.5, 2.7)	( -2.0, 3.7)	
	Pr >  t			0.5590	
	n	3	1		
	LS Mean	0.685	-0.038	0.723	
	SEM	0.814	1.329	1.498	
Week 168	95% CI	( -0.9, 2.3)	( -2.6, 2.6)	( -2.2, 3.7)	
	Pr >  t			0.6296	
	n	1	1		
	LS Mean	-0.189	0.102	-0.291	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	1.324	1.329	1.826
		95% CI	(-2.8, 2.4)	(-2.5, 2.7)	(-3.9, 3.3)
		Pr >  t			0.8735

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Stratum 2 - Prior CDK4/6 inhibitor (L) No prior use	Week 8	n	134	131	
		LS Mean	-0.157	-0.082	-0.076
		SEM	0.161	0.163	0.229
		95% CI	(-0.5, 0.2)	(-0.4, 0.2)	(-0.5, 0.4)
	Week 16	Pr >  t			0.7404
		n	118	102	
		LS Mean	-0.121	0.017	-0.138
		SEM	0.169	0.180	0.247
	Week 24	95% CI	(-0.5, 0.2)	(-0.3, 0.4)	(-0.6, 0.3)
		Pr >  t			0.5771
		n	100	77	
		LS Mean	-0.077	0.148	-0.226
	Week 32	SEM	0.180	0.200	0.269
		95% CI	(-0.4, 0.3)	(-0.2, 0.5)	(-0.8, 0.3)
		Pr >  t			0.4010
		n	84	71	
	Week 40	LS Mean	0.100	0.108	-0.008
		SEM	0.191	0.206	0.281
		95% CI	(-0.3, 0.5)	(-0.3, 0.5)	(-0.6, 0.5)
		Pr >  t			0.9771
	Week 48	n	73	61	
		LS Mean	0.220	0.125	0.095
		SEM	0.201	0.218	0.296
		95% CI	(-0.2, 0.6)	(-0.3, 0.6)	(-0.5, 0.7)
	Week 56	Pr >  t			0.7476
		n	67	50	
		LS Mean	0.573	0.249	0.324
		SEM	0.207	0.234	0.313
Week 56	95% CI	(0.2, 1.0)	(-0.2, 0.7)	(-0.3, 0.9)	
	Pr >  t			0.3004	
		n	57	45	
		LS Mean	-0.057	0.017	-0.075



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.220	0.244	0.328
	95% CI	(-0.5, 0.4)	(-0.5, 0.5)	(-0.7, 0.6)
	Pr >  t			0.8201
	n	45	42	
	LS Mean	0.026	0.233	-0.207
Week 72	SEM	0.240	0.250	0.347
	95% CI	(-0.4, 0.5)	(-0.3, 0.7)	(-0.9, 0.5)
	Pr >  t			0.5509
	n	46	35	
	LS Mean	0.012	-0.044	0.056
Week 84	SEM	0.238	0.269	0.359
	95% CI	(-0.5, 0.5)	(-0.6, 0.5)	(-0.6, 0.8)
	Pr >  t			0.8765
	n	40	33	
	LS Mean	0.340	0.427	-0.088
Week 96	SEM	0.251	0.275	0.372
	95% CI	(-0.2, 0.8)	(-0.1, 1.0)	(-0.8, 0.6)
	Pr >  t			0.8136
	n	34	24	
	LS Mean	0.120	0.103	0.018
Week 108	SEM	0.268	0.313	0.412
	95% CI	(-0.4, 0.6)	(-0.5, 0.7)	(-0.8, 0.8)
	Pr >  t			0.9659
	n	26	21	
	LS Mean	0.423	-0.141	0.565
Week 120	SEM	0.299	0.331	0.446
	95% CI	(-0.2, 1.0)	(-0.8, 0.5)	(-0.3, 1.4)
	Pr >  t			0.2058
	n	27	16	
	LS Mean	0.412	-0.306	0.718
Week 132	SEM	0.295	0.372	0.475
	95% CI	(-0.2, 1.0)	(-1.0, 0.4)	(-0.2, 1.6)
	Pr >  t			0.1308
	n	20	8	
	LS Mean	0.065	0.407	-0.342
Week 144	SEM	0.334	0.509	0.608
	95% CI	(-0.6, 0.7)	(-0.6, 1.4)	(-1.5, 0.9)
	Pr >  t			0.5737
	n	14	5	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Prior use	Week 156	LS Mean	0.418	-0.372	0.790
		SEM	0.391	0.635	0.746
		95% CI	(-0.3, 1.2)	(-1.6, 0.9)	(-0.7, 2.3)
		Pr >  t			0.2894
		n	9	3	
	Week 168	LS Mean	-0.104	0.473	-0.577
		SEM	0.478	0.811	0.942
		95% CI	(-1.0, 0.8)	(-1.1, 2.1)	(-2.4, 1.3)
		Pr >  t			0.5402
		n	4	2	
	Week 180	LS Mean	-0.744	-0.325	-0.419
		SEM	0.703	0.989	1.213
		95% CI	(-2.1, 0.6)	(-2.3, 1.6)	(-2.8, 2.0)
		Pr >  t			0.7298
		n	1	1	
	Week 192	LS Mean	2.333	0.178	2.156
		SEM	1.388	1.389	1.964
		95% CI	(-0.4, 5.1)	(-2.5, 2.9)	(-1.7, 6.0)
		Pr >  t			0.2725
		n	1	1	
	Week 8	LS Mean	0.183	-0.532	0.716
		SEM	1.388	1.389	1.964
		95% CI	(-2.5, 2.9)	(-3.3, 2.2)	(-3.1, 4.6)
		Pr >  t			0.7156
n		8	6		
Week 16	LS Mean	-0.081	0.363	-0.444	
	SEM	0.645	0.736	0.967	
	95% CI	(-1.5, 1.3)	(-1.2, 1.9)	(-2.5, 1.6)	
	Pr >  t			0.6523	
	n	6	3		
Week 24	LS Mean	-0.230	1.428	-1.658	
	SEM	0.721	1.020	1.223	
	95% CI	(-1.7, 1.3)	(-0.7, 3.5)	(-4.2, 0.9)	
	Pr >  t			0.1886	
	n	5	2		
		LS Mean	1.090	1.377	-0.287
		SEM	0.761	1.165	1.370
		95% CI	(-0.5, 2.7)	(-1.0, 3.8)	(-3.1, 2.5)
		Pr >  t			0.8354

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 32	n	2	1	
	LS Mean	0.161	0.740	-0.579
	SEM	1.062	1.498	1.831
	95% CI	(-2.0, 2.3)	(-2.3, 3.8)	(-4.3, 3.2)
	Pr >  t			0.7544
Week 40	n	2		
	LS Mean	0.306	NE	NE
	SEM	1.062	NE	NE
	95% CI	(-1.9, 2.5)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	0.591	NE	NE
	SEM	1.062	NE	NE
	95% CI	(-1.6, 2.8)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	0.306	NE	NE
	SEM	1.062	NE	NE
	95% CI	(-1.9, 2.5)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	1.161	NE	NE
	SEM	1.062	NE	NE
	95% CI	(-1.0, 3.3)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	1.231	NE	NE
	SEM	1.062	NE	NE
	95% CI	(-0.9, 3.4)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	0.394	NE	NE
	SEM	1.379	NE	NE
	95% CI	(-2.4, 3.2)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	0.394	NE	NE
	SEM	1.379	NE	NE
	95% CI	(-2.4, 3.2)	NE	NE
	Pr >  t			NE

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 144	Pr >  t  n	1		NE
		LS Mean	0.394	NE	NE
		SEM	1.379	NE	NE
		95% CI	(-2.4, 3.2)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	118			
			LS Mean	0.044	0.158	-0.113		
			SEM	0.258	0.263	0.242		
			95% CI	(-0.5, 0.6)	(-0.4, 0.7)	(-0.6, 0.4)		
					Pr >  t			0.6390
		Week 16	n	111	89			
			LS Mean	0.092	0.251	-0.159		
			SEM	0.264	0.280	0.262		
			95% CI	(-0.4, 0.6)	(-0.3, 0.8)	(-0.7, 0.4)		
					Pr >  t			0.5428
		Week 24	n	96	69			
			LS Mean	0.217	0.352	-0.135		
			SEM	0.271	0.294	0.282		
			95% CI	(-0.3, 0.7)	(-0.2, 0.9)	(-0.7, 0.4)		
					Pr >  t			0.6330
		Week 32	n	77	60			
			LS Mean	0.310	0.356	-0.046		
			SEM	0.283	0.303	0.300		
			95% CI	(-0.2, 0.9)	(-0.2, 1.0)	(-0.6, 0.5)		
					Pr >  t			0.8784
		Week 40	n	69	51			
			LS Mean	0.397	0.343	0.054		
			SEM	0.289	0.314	0.315		
			95% CI	(-0.2, 1.0)	(-0.3, 1.0)	(-0.6, 0.7)		
					Pr >  t			0.8646
		Week 48	n	62	40			
			LS Mean	0.784	0.380	0.403		
			SEM	0.294	0.331	0.337		
95% CI	( 0.2, 1.4)		(-0.3, 1.0)	(-0.3, 1.1)				
			Pr >  t			0.2319		
Week 56	n	53	35					
	LS Mean	0.183	0.063	0.119				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.303	0.342	0.356	
	95% CI	(-0.4, 0.8)	(-0.6, 0.7)	(-0.6, 0.8)	
	Pr >  t			0.7377	
	n	44	33		
	LS Mean	0.243	0.216	0.027	
Week 72	SEM	0.315	0.347	0.371	
	95% CI	(-0.4, 0.9)	(-0.5, 0.9)	(-0.7, 0.8)	
	Pr >  t			0.9409	
	n	45	28		
	LS Mean	0.245	0.148	0.097	
Week 84	SEM	0.314	0.362	0.383	
	95% CI	(-0.4, 0.9)	(-0.6, 0.9)	(-0.7, 0.8)	
	Pr >  t			0.8004	
	n	39	27		
	LS Mean	0.581	0.297	0.283	
Week 96	SEM	0.325	0.365	0.395	
	95% CI	(-0.1, 1.2)	(-0.4, 1.0)	(-0.5, 1.1)	
	Pr >  t			0.4734	
	n	34	19		
	LS Mean	0.307	0.405	-0.098	
Week 108	SEM	0.335	0.404	0.440	
	95% CI	(-0.4, 1.0)	(-0.4, 1.2)	(-1.0, 0.8)	
	Pr >  t			0.8242	
	n	26	17		
	LS Mean	0.646	-0.098	0.744	
Week 120	SEM	0.361	0.419	0.472	
	95% CI	(-0.1, 1.4)	(-0.9, 0.7)	(-0.2, 1.7)	
	Pr >  t			0.1151	
	n	27	11		
	LS Mean	0.668	-0.349	1.017	
Week 132	SEM	0.356	0.486	0.530	
	95% CI	(-0.0, 1.4)	(-1.3, 0.6)	(-0.0, 2.1)	
	Pr >  t			0.0553	
	n	20	6		
	LS Mean	0.287	0.694	-0.407	
Week 144	SEM	0.390	0.616	0.670	
	95% CI	(-0.5, 1.1)	(-0.5, 1.9)	(-1.7, 0.9)	
	Pr >  t			0.5435	
	n	15	4		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
>= 75 Years	Week 156	LS Mean	0.610	-0.486	1.096
		SEM	0.427	0.734	0.799
		95% CI	(-0.2, 1.4)	(-1.9, 1.0)	(-0.5, 2.7)
		Pr >  t			0.1703
		n	9	2	
	Week 168	LS Mean	0.115	0.977	-0.861
		SEM	0.517	1.004	1.092
		95% CI	(-0.9, 1.1)	(-1.0, 2.9)	(-3.0, 1.3)
		Pr >  t			0.4304
		n	4	2	
	Week 180	LS Mean	-0.521	-0.168	-0.353
		SEM	0.726	1.004	1.205
		95% CI	(-1.9, 0.9)	(-2.1, 1.8)	(-2.7, 2.0)
		Pr >  t			0.7697
		n	1	1	
	Week 192	LS Mean	2.555	0.330	2.225
		SEM	1.391	1.393	1.947
		95% CI	(-0.2, 5.3)	(-2.4, 3.1)	(-1.6, 6.0)
		Pr >  t			0.2535
		n	1	1	
	Week 8	LS Mean	0.405	-0.380	0.785
		SEM	1.391	1.393	1.947
		95% CI	(-2.3, 3.1)	(-3.1, 2.4)	(-3.0, 4.6)
		Pr >  t			0.6869
n		17	19		
Week 16	LS Mean	0.050	-0.094	0.144	
	SEM	0.463	0.405	0.610	
	95% CI	(-0.9, 1.0)	(-0.9, 0.7)	(-1.1, 1.4)	
	Pr >  t			0.8138	
	n	13	16		
Week 24	LS Mean	-0.109	0.260	-0.369	
	SEM	0.513	0.440	0.679	
	95% CI	(-1.1, 0.9)	(-0.6, 1.1)	(-1.7, 1.0)	
	Pr >  t			0.5876	
	n	9	10		
	LS Mean	-0.265	0.572	-0.837	
	SEM	0.590	0.533	0.797	
	95% CI	(-1.4, 0.9)	(-0.5, 1.6)	(-2.4, 0.7)	
	Pr >  t			0.2954	
	n				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172		Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	n	9	12		
	LS Mean	0.303	0.185		0.118
	SEM	0.591	0.499		0.775
	95% CI	(-0.9, 1.5)	(-0.8, 1.2)		(-1.4, 1.7)
	Pr >  t				0.8793
Week 40	n	6	10		
	LS Mean	0.822	0.324		0.498
	SEM	0.691	0.533		0.874
	95% CI	(-0.5, 2.2)	(-0.7, 1.4)		(-1.2, 2.2)
	Pr >  t				0.5696
Week 48	n	7	10		
	LS Mean	0.753	0.862		-0.109
	SEM	0.650	0.535		0.842
	95% CI	(-0.5, 2.0)	(-0.2, 1.9)		(-1.8, 1.6)
	Pr >  t				0.8970
Week 56	n	6	10		
	LS Mean	-0.035	0.887		-0.922
	SEM	0.688	0.537		0.873
	95% CI	(-1.4, 1.3)	(-0.2, 1.9)		(-2.6, 0.8)
	Pr >  t				0.2928
Week 64	n	3	9		
	LS Mean	0.821	1.352		-0.531
	SEM	0.911	0.559		1.069
	95% CI	(-1.0, 2.6)	(0.2, 2.5)		(-2.6, 1.6)
	Pr >  t				0.6200
Week 72	n	3	7		
	LS Mean	0.631	0.326		0.305
	SEM	0.911	0.618		1.102
	95% CI	(-1.2, 2.4)	(-0.9, 1.5)		(-1.9, 2.5)
	Pr >  t				0.7825
Week 84	n	1	6		
	LS Mean	-0.044	2.226		-2.270
	SEM	1.500	0.658		1.640
	95% CI	(-3.0, 2.9)	(0.9, 3.5)		(-5.5, 1.0)
	Pr >  t				0.1682
Week 96	n	1	5		
	LS Mean	1.526	0.061		1.465
	SEM	1.500	0.709		1.661
	95% CI	(-1.4, 4.5)	(-1.3, 1.5)		(-1.8, 4.7)
	Pr >  t				



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 108	Pr >  t			0.3790
		n		4	
		LS Mean	NE	0.837	NE
		SEM	NE	0.780	NE
		95% CI	NE	(-0.7, 2.4)	NE
		Pr >  t			NE
	Week 120	n	1	5	
		LS Mean	-0.789	0.633	-1.422
		SEM	1.499	0.709	1.660
		95% CI	(-3.7, 2.2)	(-0.8, 2.0)	(-4.7, 1.9)
		Pr >  t			0.3929
	Week 132	n		2	
		LS Mean	NE	0.506	NE
		SEM	NE	1.058	NE
		95% CI	NE	(-1.6, 2.6)	NE
		Pr >  t			NE
	Week 144	n		1	
		LS Mean	NE	1.117	NE
		SEM	NE	1.464	NE
		95% CI	NE	(-1.8, 4.0)	NE
		Pr >  t			NE
	Week 156	n		1	
		LS Mean	NE	0.257	NE
		SEM	NE	1.464	NE
		95% CI	NE	(-2.6, 3.1)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Pooled Race Group 1 (L)	Asian	Week 8	n	32	34	
			LS Mean	0.287	-0.425	0.713
			SEM	0.464	0.439	0.393
			95% CI	(-0.6, 1.2)	(-1.3, 0.4)	(-0.1, 1.5)
				Pr >  t		0.0716
		Week 16	n	30	29	
	LS Mean		0.342	-0.078	0.420	
	SEM		0.466	0.457	0.410	
	95% CI		(-0.6, 1.3)	(-1.0, 0.8)	(-0.4, 1.2)	
			Pr >  t		0.3067	
		Week 24	n	21	25	
	LS Mean		0.366	-0.135	0.501	
	SEM		0.490	0.466	0.450	
	95% CI		(-0.6, 1.3)	(-1.1, 0.8)	(-0.4, 1.4)	
			Pr >  t		0.2661	
		Week 32	n	19	23	
	LS Mean		0.308	0.192	0.116	
	SEM		0.497	0.472	0.465	
	95% CI		(-0.7, 1.3)	(-0.7, 1.1)	(-0.8, 1.0)	
			Pr >  t		0.8031	
		Week 40	n	16	18	
	LS Mean		0.105	0.280	-0.175	
	SEM		0.511	0.496	0.501	
	95% CI		(-0.9, 1.1)	(-0.7, 1.3)	(-1.2, 0.8)	
			Pr >  t		0.7268	
		Week 48	n	16	17	
	LS Mean		0.679	0.437	0.242	
	SEM		0.511	0.501	0.505	
95% CI	(-0.3, 1.7)		(-0.6, 1.4)	(-0.8, 1.2)		
		Pr >  t		0.6328		
	Week 56	n	12	14		
LS Mean		0.208	0.089	0.119		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.538	0.519	0.552
		95% CI	(-0.9, 1.3)	(-0.9, 1.1)	(-1.0, 1.2)
		Pr >  t			0.8291
	Week 64	n	12	11	
		LS Mean	0.707	0.496	0.212
		SEM	0.538	0.546	0.578
		95% CI	(-0.4, 1.8)	(-0.6, 1.6)	(-0.9, 1.3)
		Pr >  t			0.7145
	Week 72	n	10	9	
		LS Mean	0.484	0.073	0.411
		SEM	0.560	0.573	0.622
		95% CI	(-0.6, 1.6)	(-1.1, 1.2)	(-0.8, 1.6)
		Pr >  t			0.5092
	Week 84	n	8	8	
		LS Mean	0.384	0.538	-0.154
		SEM	0.596	0.590	0.665
		95% CI	(-0.8, 1.6)	(-0.6, 1.7)	(-1.5, 1.2)
		Pr >  t			0.8166
	Week 96	n	6	6	
		LS Mean	0.225	0.335	-0.110
		SEM	0.643	0.638	0.749
		95% CI	(-1.0, 1.5)	(-0.9, 1.6)	(-1.6, 1.4)
		Pr >  t			0.8833
	Week 108	n	4	5	
		LS Mean	0.768	0.514	0.255
		SEM	0.728	0.675	0.852
		95% CI	(-0.7, 2.2)	(-0.8, 1.8)	(-1.4, 1.9)
		Pr >  t			0.7650
	Week 120	n	4	4	
		LS Mean	0.411	0.558	-0.147
		SEM	0.728	0.725	0.893
		95% CI	(-1.0, 1.8)	(-0.9, 2.0)	(-1.9, 1.6)
		Pr >  t			0.8691
	Week 132	n	3	2	
		LS Mean	0.530	0.109	0.422
		SEM	0.803	0.933	1.121
		95% CI	(-1.0, 2.1)	(-1.7, 1.9)	(-1.8, 2.6)
		Pr >  t			0.7072
	Week 144	n	3	1	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Other	Week 156	LS Mean	1.104	0.802	0.301
		SEM	0.803	1.250	1.396
		95% CI	(-0.5, 2.7)	(-1.7, 3.3)	(-2.4, 3.0)
		Pr >  t			0.8292
		n	2	1	
	Week 168	LS Mean	0.546	-0.058	0.604
		SEM	0.935	1.250	1.476
		95% CI	(-1.3, 2.4)	(-2.5, 2.4)	(-2.3, 3.5)
		Pr >  t			0.6825
		n	1		
	Week 8	LS Mean	0.265	NE	NE
		SEM	1.249	NE	NE
		95% CI	(-2.2, 2.7)	NE	NE
		Pr >  t			NE
		n	16	17	
		LS Mean	-0.062	0.694	-0.756
		SEM	1.137	1.113	0.701
		95% CI	(-2.3, 2.2)	(-1.5, 2.9)	(-2.1, 0.6)
		Pr >  t			0.2830
		n	15	14	
Week 16	LS Mean	-0.102	0.492	-0.594	
	SEM	1.143	1.031	0.764	
	95% CI	(-2.4, 2.2)	(-1.6, 2.5)	(-2.1, 0.9)	
	Pr >  t			0.4382	
	n	12	10		
Week 24	LS Mean	-0.299	0.775	-1.074	
	SEM	1.169	1.172	0.856	
	95% CI	(-2.6, 2.0)	(-1.5, 3.1)	(-2.8, 0.6)	
	Pr >  t			0.2123	
	n	8	9		
Week 32	LS Mean	-0.307	1.375	-1.682	
	SEM	1.228	1.188	0.950	
	95% CI	(-2.7, 2.1)	(-1.0, 3.7)	(-3.6, 0.2)	
	Pr >  t			0.0790	
	n	6	7		
Week 40	LS Mean	0.450	1.049	-0.600	
	SEM	1.284	1.229	1.064	
	95% CI	(-2.1, 3.0)	(-1.4, 3.5)	(-2.7, 1.5)	
	Pr >  t			0.5738	
	n				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 48	n	4	6		
	LS Mean	1.761	1.503		0.258
	SEM	1.388	1.260		1.220
	95% CI	(-1.0, 4.5)	(-1.0, 4.0)		(-2.2, 2.7)
	Pr >  t				0.8326
Week 56	n	4	6		
	LS Mean	-0.111	1.795		-1.906
	SEM	1.386	1.263		1.221
	95% CI	(-2.9, 2.6)	(-0.7, 4.3)		(-4.3, 0.5)
	Pr >  t				0.1206
Week 64	n	4	4		
	LS Mean	-0.180	3.031		-3.210
	SEM	1.389	1.363		1.324
	95% CI	(-2.9, 2.6)	(0.3, 5.7)		(-5.8, -0.6)
	Pr >  t				0.0166
Week 72	n	4	4		
	LS Mean	-0.790	0.673		-1.463
	SEM	1.389	1.363		1.324
	95% CI	(-3.5, 2.0)	(-2.0, 3.4)		(-4.1, 1.2)
	Pr >  t				0.2711
Week 84	n	4	4		
	LS Mean	0.688	0.638		0.050
	SEM	1.388	1.363		1.325
	95% CI	(-2.1, 3.4)	(-2.1, 3.3)		(-2.6, 2.7)
	Pr >  t				0.9698
Week 96	n	3	2		
	LS Mean	-0.179	0.343		-0.522
	SEM	1.481	1.627		1.675
	95% CI	(-3.1, 2.7)	(-2.9, 3.6)		(-3.8, 2.8)
	Pr >  t				0.7557
Week 108	n	3	3		
	LS Mean	0.774	-0.492		1.266
	SEM	1.481	1.460		1.514
	95% CI	(-2.2, 3.7)	(-3.4, 2.4)		(-1.7, 4.3)
	Pr >  t				0.4045
Week 120	n	2	1		
	LS Mean	-0.313	-0.058		-0.255
	SEM	1.651	2.051		2.213
	95% CI	(-3.6, 2.9)	(-4.1, 4.0)		(-4.6, 4.1)
	Pr >  t				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
	Week 132	Pr >  t  n	2	1	0.9085
		LS Mean	2.231	0.652	1.579
		SEM	1.647	2.051	2.212
		95% CI	(-1.0, 5.5)	(-3.4, 4.7)	(-2.8, 6.0)
	Week 156	Pr >  t  n	1		0.4766
		LS Mean	-0.627	NE	NE
		SEM	2.072	NE	NE
		95% CI	(-4.7, 3.5)	NE	NE
	Week 168	Pr >  t  n	1		NE
		LS Mean	-0.627	NE	NE
		SEM	2.072	NE	NE
		95% CI	(-4.7, 3.5)	NE	NE
White	Week 8	Pr >  t  n	93	84	NE
		LS Mean	0.104	0.425	-0.321
		SEM	0.306	0.323	0.290
		95% CI	(-0.5, 0.7)	(-0.2, 1.1)	(-0.9, 0.2)
		Pr >  t			0.2692
	Week 16	n	79	60	
		LS Mean	0.104	0.494	-0.390
		SEM	0.317	0.349	0.321
		95% CI	(-0.5, 0.7)	(-0.2, 1.2)	(-1.0, 0.2)
		Pr >  t			0.2238
	Week 24	n	71	43	
		LS Mean	0.278	0.730	-0.452
		SEM	0.323	0.371	0.349
		95% CI	(-0.4, 0.9)	(0.0, 1.5)	(-1.1, 0.2)
		Pr >  t			0.1961
	Week 32	n	59	39	
		LS Mean	0.502	0.345	0.156
		SEM	0.337	0.380	0.366
		95% CI	(-0.2, 1.2)	(-0.4, 1.1)	(-0.6, 0.9)
		Pr >  t			0.6694
Week 40	n	52	35		
	LS Mean	0.561	0.432	0.129	
	SEM	0.344	0.388	0.381	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-0.1, 1.2)	(-0.3, 1.2)	(-0.6, 0.9)
		Pr >  t			0.7348
	Week 48	n	48	26	
		LS Mean	0.876	0.517	0.359
		SEM	0.349	0.414	0.411
		95% CI	( 0.2, 1.6)	(-0.3, 1.3)	(-0.4, 1.2)
		Pr >  t			0.3827
	Week 56	n	42	24	
		LS Mean	0.256	0.205	0.050
		SEM	0.357	0.422	0.426
		95% CI	(-0.4, 1.0)	(-0.6, 1.0)	(-0.8, 0.9)
		Pr >  t			0.9058
	Week 64	n	30	26	
		LS Mean	0.340	0.246	0.095
		SEM	0.382	0.414	0.441
		95% CI	(-0.4, 1.1)	(-0.6, 1.1)	(-0.8, 1.0)
		Pr >  t			0.8302
	Week 72	n	34	21	
		LS Mean	0.435	0.264	0.171
		SEM	0.372	0.436	0.453
		95% CI	(-0.3, 1.2)	(-0.6, 1.1)	(-0.7, 1.1)
		Pr >  t			0.7052
	Week 84	n	28	20	
		LS Mean	0.714	0.964	-0.250
		SEM	0.389	0.441	0.471
		95% CI	(-0.1, 1.5)	( 0.1, 1.8)	(-1.2, 0.7)
		Pr >  t			0.5954
	Week 96	n	26	15	
		LS Mean	0.519	0.434	0.085
		SEM	0.395	0.477	0.510
		95% CI	(-0.3, 1.3)	(-0.5, 1.4)	(-0.9, 1.1)
		Pr >  t			0.8680
	Week 108	n	19	12	
		LS Mean	0.680	0.224	0.455
		SEM	0.430	0.510	0.567
		95% CI	(-0.2, 1.5)	(-0.8, 1.2)	(-0.7, 1.6)
		Pr >  t			0.4216
	Week 120	n	22	10	
		LS Mean	0.821	-0.110	0.931

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 132	SEM	0.413	0.541	0.583	
	95% CI	( 0.0, 1.6)	( -1.2, 1.0)	( -0.2, 2.1)	
	Pr >  t			0.1104	
	n	15	4		
	LS Mean	0.064	0.854	-0.790	
Week 144	SEM	0.460	0.764	0.819	
	95% CI	( -0.8, 1.0)	( -0.6, 2.4)	( -2.4, 0.8)	
	Pr >  t			0.3350	
	n	12	4		
	LS Mean	0.592	-0.286	0.878	
Week 156	SEM	0.493	0.764	0.839	
	95% CI	( -0.4, 1.6)	( -1.8, 1.2)	( -0.8, 2.5)	
	Pr >  t			0.2958	
	n	6	2		
	LS Mean	0.148	1.174	-1.026	
Week 168	SEM	0.636	1.032	1.160	
	95% CI	( -1.1, 1.4)	( -0.9, 3.2)	( -3.3, 1.3)	
	Pr >  t			0.3765	
	n	2	2		
	LS Mean	-0.913	0.029	-0.943	
Week 180	SEM	1.022	1.032	1.409	
	95% CI	( -2.9, 1.1)	( -2.0, 2.1)	( -3.7, 1.8)	
	Pr >  t			0.5037	
	n	1	1		
	LS Mean	2.605	0.531	2.074	
Week 192	SEM	1.417	1.422	1.976	
	95% CI	( -0.2, 5.4)	( -2.3, 3.3)	( -1.8, 6.0)	
	Pr >  t			0.2942	
	n	1	1		
	LS Mean	0.455	-0.179	0.634	
Week 192	SEM	1.417	1.422	1.976	
	95% CI	( -2.3, 3.2)	( -3.0, 2.6)	( -3.2, 4.5)	
	Pr >  t			0.7484	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Tamoxifen Use (L)	No	Week 8	n	89	89			
			LS Mean	0.092	0.030	0.062		
			SEM	0.348	0.350	0.286		
			95% CI	(-0.6, 0.8)	(-0.7, 0.7)	(-0.5, 0.6)		
					Pr >  t			0.8288
		Week 16	n	79	66			
			LS Mean	0.128	0.263	-0.135		
			SEM	0.352	0.370	0.311		
			95% CI	(-0.6, 0.8)	(-0.5, 1.0)	(-0.7, 0.5)		
					Pr >  t			0.6638
		Week 24	n	64	53			
			LS Mean	0.279	0.113	0.167		
			SEM	0.364	0.385	0.337		
			95% CI	(-0.4, 1.0)	(-0.6, 0.9)	(-0.5, 0.8)		
					Pr >  t			0.6212
		Week 32	n	49	52			
			LS Mean	0.488	0.349	0.139		
			SEM	0.382	0.387	0.355		
			95% CI	(-0.3, 1.2)	(-0.4, 1.1)	(-0.6, 0.8)		
					Pr >  t			0.6950
		Week 40	n	44	44			
			LS Mean	0.328	0.316	0.012		
			SEM	0.389	0.397	0.373		
			95% CI	(-0.4, 1.1)	(-0.5, 1.1)	(-0.7, 0.7)		
					Pr >  t			0.9751
		Week 48	n	41	35			
			LS Mean	0.796	0.357	0.440		
			SEM	0.393	0.412	0.394		
95% CI	( 0.0, 1.6)		(-0.5, 1.2)	(-0.3, 1.2)				
			Pr >  t			0.2646		
Week 56	n	33	32					
	LS Mean	-0.009	0.117	-0.126				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.409	0.419	0.417
	95% CI	(-0.8, 0.8)	(-0.7, 0.9)	(-0.9, 0.7)
	Pr >  t			0.7626
	n	27	31	
	LS Mean	0.500	0.334	0.165
Week 72	SEM	0.425	0.422	0.436
	95% CI	(-0.3, 1.3)	(-0.5, 1.2)	(-0.7, 1.0)
	Pr >  t			0.7041
	n	26	26	
	LS Mean	0.321	0.057	0.263
Week 84	SEM	0.428	0.437	0.453
	95% CI	(-0.5, 1.2)	(-0.8, 0.9)	(-0.6, 1.2)
	Pr >  t			0.5614
	n	22	23	
	LS Mean	0.905	0.653	0.253
Week 96	SEM	0.446	0.449	0.480
	95% CI	( 0.0, 1.8)	(-0.2, 1.5)	(-0.7, 1.2)
	Pr >  t			0.5988
	n	18	18	
	LS Mean	0.728	0.121	0.607
Week 108	SEM	0.469	0.476	0.525
	95% CI	(-0.2, 1.6)	(-0.8, 1.1)	(-0.4, 1.6)
	Pr >  t			0.2481
	n	14	14	
	LS Mean	0.836	0.047	0.789
Week 120	SEM	0.502	0.509	0.584
	95% CI	(-0.2, 1.8)	(-1.0, 1.0)	(-0.4, 1.9)
	Pr >  t			0.1766
	n	12	12	
	LS Mean	-0.150	-0.440	0.290
Week 132	SEM	0.525	0.532	0.623
	95% CI	(-1.2, 0.9)	(-1.5, 0.6)	(-0.9, 1.5)
	Pr >  t			0.6423
	n	9	5	
	LS Mean	0.377	0.329	0.048
Week 144	SEM	0.576	0.718	0.823
	95% CI	(-0.8, 1.5)	(-1.1, 1.7)	(-1.6, 1.7)
	Pr >  t			0.9537
	n	7	4	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Yes	Week 156	LS Mean	0.143	-0.471	0.614
		SEM	0.629	0.785	0.917
		95% CI	(-1.1, 1.4)	(-2.0, 1.1)	(-1.2, 2.4)
		Pr >  t			0.5031
	Week 168	n	4	2	
		LS Mean	-0.536	-0.257	-0.279
		SEM	0.780	1.055	1.245
		95% CI	(-2.1, 1.0)	(-2.3, 1.8)	(-2.7, 2.2)
	Week 8	Pr >  t			0.8227
		n	2	1	
		LS Mean	-0.559	-0.199	-0.360
		SEM	1.050	1.452	1.744
	Week 16	95% CI	(-2.6, 1.5)	(-3.0, 2.7)	(-3.8, 3.1)
		Pr >  t			0.8365
		n	53	48	
		LS Mean	-0.001	0.362	-0.363
	Week 24	SEM	0.356	0.375	0.359
		95% CI	(-0.7, 0.7)	(-0.4, 1.1)	(-1.1, 0.3)
		Pr >  t			0.3129
		n	45	39	
	Week 32	LS Mean	0.009	0.320	-0.311
		SEM	0.374	0.392	0.384
		95% CI	(-0.7, 0.7)	(-0.5, 1.1)	(-1.1, 0.4)
		Pr >  t			0.4188
Week 40	n	41	26		
	LS Mean	0.035	0.987	-0.952	
	SEM	0.379	0.423	0.425	
	95% CI	(-0.7, 0.8)	(0.2, 1.8)	(-1.8,-0.1)	
Week 8	Pr >  t			0.0259	
	n	37	20		
	LS Mean	0.087	0.266	-0.179	
	SEM	0.389	0.452	0.457	
Week 16	95% CI	(-0.7, 0.9)	(-0.6, 1.2)	(-1.1, 0.7)	
	Pr >  t			0.6959	
	n	31	17		
	LS Mean	0.606	0.438	0.168	
Week 24	SEM	0.401	0.474	0.486	
	95% CI	(-0.2, 1.4)	(-0.5, 1.4)	(-0.8, 1.1)	
	Pr >  t			0.7299	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 48	n	28	15	
	LS Mean	0.779	0.766	0.013
	SEM	0.409	0.489	0.508
	95% CI	(-0.0, 1.6)	(-0.2, 1.7)	(-1.0, 1.0)
	Pr >  t			0.9800
Week 56	n	26	13	
	LS Mean	0.394	0.553	-0.159
	SEM	0.415	0.508	0.531
	95% CI	(-0.4, 1.2)	(-0.4, 1.6)	(-1.2, 0.9)
	Pr >  t			0.7646
Week 64	n	20	11	
	LS Mean	0.003	0.780	-0.777
	SEM	0.439	0.532	0.573
	95% CI	(-0.9, 0.9)	(-0.3, 1.8)	(-1.9, 0.3)
	Pr >  t			0.1753
Week 72	n	22	9	
	LS Mean	0.213	0.478	-0.265
	SEM	0.430	0.565	0.597
	95% CI	(-0.6, 1.1)	(-0.6, 1.6)	(-1.4, 0.9)
	Pr >  t			0.6575
Week 84	n	18	10	
	LS Mean	0.153	0.675	-0.523
	SEM	0.451	0.548	0.595
	95% CI	(-0.7, 1.0)	(-0.4, 1.8)	(-1.7, 0.6)
	Pr >  t			0.3804
Week 96	n	17	6	
	LS Mean	-0.065	0.902	-0.967
	SEM	0.456	0.646	0.691
	95% CI	(-1.0, 0.8)	(-0.4, 2.2)	(-2.3, 0.4)
	Pr >  t			0.1623
Week 108	n	12	7	
	LS Mean	0.408	0.205	0.204
	SEM	0.502	0.613	0.692
	95% CI	(-0.6, 1.4)	(-1.0, 1.4)	(-1.2, 1.6)
	Pr >  t			0.7687
Week 120	n	16	4	
	LS Mean	1.183	0.975	0.208
	SEM	0.463	0.751	0.794
	95% CI	( 0.3, 2.1)	(-0.5, 2.5)	(-1.4, 1.8)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.7940
	Week 132	n	11	3	
		LS Mean	0.203	1.252	-1.049
		SEM	0.515	0.842	0.909
		95% CI	(-0.8, 1.2)	(-0.4, 2.9)	(-2.8, 0.7)
		Pr >  t			0.2488
	Week 144	n	8	1	
		LS Mean	1.009	1.023	-0.014
		SEM	0.567	1.368	1.431
		95% CI	(-0.1, 2.1)	(-1.7, 3.7)	(-2.8, 2.8)
		Pr >  t			0.9922
	Week 156	n	5	1	
		LS Mean	0.630	2.733	-2.103
		SEM	0.674	1.368	1.475
		95% CI	(-0.7, 2.0)	( 0.0, 5.4)	(-5.0, 0.8)
		Pr >  t			0.1547
	Week 168	n	2	1	
		LS Mean	-0.497	0.303	-0.799
		SEM	0.988	1.368	1.643
		95% CI	(-2.4, 1.4)	(-2.4, 3.0)	(-4.0, 2.4)
		Pr >  t			0.6267
	Week 180	n	1	1	
		LS Mean	2.601	0.873	1.729
		SEM	1.356	1.368	1.887
		95% CI	(-0.1, 5.3)	(-1.8, 3.6)	(-2.0, 5.4)
		Pr >  t			0.3600
	Week 192	n	1	1	
		LS Mean	0.451	0.163	0.289
		SEM	1.356	1.368	1.887
		95% CI	(-2.2, 3.1)	(-2.5, 2.8)	(-3.4, 4.0)
		Pr >  t			0.8785

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	-0.137	NE	NE	
			SEM	0.356	NE	NE	
			95% CI	(-4.7, 4.4)	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	-0.637	NE	NE	
			SEM	0.356	NE	NE	
			95% CI	(-5.2, 3.9)	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	-0.388	NE	NE	
			SEM	0.542	NE	NE	
			95% CI	(-7.3, 6.5)	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	0.613	NE	NE	
			SEM	0.542	NE	NE	
			95% CI	(-6.3, 7.5)	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	0.113	NE	NE	
			SEM	0.579	NE	NE	
			95% CI	(-7.2, 7.5)	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	0.403	NE	NE	
			SEM	0.579	NE	NE	
95% CI	(-7.0, 7.8)		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	-0.747	NE	NE			



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Positive	Week 72	SEM	0.579	NE	NE
		95% CI	(-8.1, 6.6)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-0.388	NE	NE
	Week 84	SEM	0.542	NE	NE
		95% CI	(-7.3, 6.5)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	0.753	NE	NE
	Week 96	SEM	0.542	NE	NE
		95% CI	(-6.1, 7.6)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-0.388	NE	NE
	Week 8	SEM	0.542	NE	NE
		95% CI	(-7.3, 6.5)	NE	NE
		Pr >  t			NE
		n	140	137	
		LS Mean	NE	NE	NE
	Week 16	SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
		n	122	105	
LS Mean		NE	NE	NE	
Week 24	SEM	NE	NE	NE	
	95% CI	NE	NE	NE	
	Pr >  t			NE	
	n	104	79		
	LS Mean	NE	NE	NE	
Week 32	SEM	NE	NE	NE	
	95% CI	NE	NE	NE	
	Pr >  t			NE	
	n	85	72		
	LS Mean	NE	NE	NE	
Week 40	SEM	NE	NE	NE	
	95% CI	NE	NE	NE	
	Pr >  t			NE	
	n	74	61		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 48	n	68	50	
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 56	n	58	45	
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 64	n	47	42	
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 72	n	47	35	
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 84	n	39	33	
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 96	n	34	24	
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE
	Week 108	n	26	21	
		LS Mean	NE	NE	NE
		SEM	NE	NE	NE
		95% CI	NE	NE	NE
		Pr >  t			NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 120	n	28	16	
	LS Mean	NE	NE	NE
	SEM	NE	NE	NE
	95% CI	NE	NE	NE
	Pr >  t			NE
Week 132	n	20	8	
	LS Mean	NE	NE	NE
	SEM	NE	NE	NE
	95% CI	NE	NE	NE
	Pr >  t			NE
Week 144	n	15	5	
	LS Mean	NE	NE	NE
	SEM	NE	NE	NE
	95% CI	NE	NE	NE
	Pr >  t			NE
Week 156	n	9	3	
	LS Mean	NE	NE	NE
	SEM	NE	NE	NE
	95% CI	NE	NE	NE
	Pr >  t			NE
Week 168	n	4	2	
	LS Mean	NE	NE	NE
	SEM	NE	NE	NE
	95% CI	NE	NE	NE
	Pr >  t			NE
Week 180	n	1	1	
	LS Mean	NE	NE	NE
	SEM	NE	NE	NE
	95% CI	NE	NE	NE
	Pr >  t			NE
Week 192	n	1	1	
	LS Mean	NE	NE	NE
	SEM	NE	NE	NE
	95% CI	NE	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks)

counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	0.395	0.011	0.384
		SEM	0.415	0.457	0.447	
		95% CI	(-0.4, 1.2)	(-0.9, 0.9)	(-0.5, 1.3)	
		Pr >  t			0.3920	
		Week 16	n	35	22	
			LS Mean	0.302	-0.052	0.354
			SEM	0.436	0.527	0.515
			95% CI	(-0.6, 1.2)	(-1.1, 1.0)	(-0.7, 1.4)
		Week 24	n	28	15	
			LS Mean	0.565	0.755	-0.190
			SEM	0.456	0.577	0.586
			95% CI	(-0.3, 1.5)	(-0.4, 1.9)	(-1.3, 1.0)
		Week 32	n	22	16	
			LS Mean	0.318	0.613	-0.296
			SEM	0.490	0.569	0.597
			95% CI	(-0.6, 1.3)	(-0.5, 1.7)	(-1.5, 0.9)
		Week 40	n	19	12	
			LS Mean	0.287	0.904	-0.617
			SEM	0.508	0.613	0.654
			95% CI	(-0.7, 1.3)	(-0.3, 2.1)	(-1.9, 0.7)
		Week 48	n	16	10	
			LS Mean	1.182	1.256	-0.074
			SEM	0.531	0.646	0.702
			95% CI	(0.1, 2.2)	(-0.0, 2.5)	(-1.5, 1.3)
		Week 56	n	14	7	
			LS Mean	0.369	0.814	-0.445

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		SEM	0.551	0.721	0.787
		95% CI	(-0.7, 1.5)	(-0.6, 2.2)	(-2.0, 1.1)
		Pr >  t			0.5726
	Week 64	n	8	7	
		LS Mean	0.697	1.481	-0.784
		SEM	0.651	0.721	0.862
		95% CI	(-0.6, 2.0)	( 0.1, 2.9)	(-2.5, 0.9)
		Pr >  t			0.3640
	Week 72	n	12	6	
		LS Mean	0.627	0.420	0.207
		SEM	0.575	0.760	0.840
		95% CI	(-0.5, 1.8)	(-1.1, 1.9)	(-1.4, 1.9)
		Pr >  t			0.8058
	Week 84	n	8	5	
		LS Mean	0.549	0.562	-0.013
		SEM	0.657	0.809	0.938
		95% CI	(-0.7, 1.8)	(-1.0, 2.2)	(-1.9, 1.8)
		Pr >  t			0.9888
	Week 96	n	5	5	
		LS Mean	0.233	0.220	0.013
		SEM	0.775	0.809	1.025
		95% CI	(-1.3, 1.8)	(-1.4, 1.8)	(-2.0, 2.0)
		Pr >  t			0.9898
	Week 108	n	7	5	
		LS Mean	0.865	0.876	-0.012
		SEM	0.687	0.809	0.960
		95% CI	(-0.5, 2.2)	(-0.7, 2.5)	(-1.9, 1.9)
		Pr >  t			0.9904
	Week 120	n	5	3	
		LS Mean	0.591	0.992	-0.401
		SEM	0.777	0.981	1.166
		95% CI	(-0.9, 2.1)	(-0.9, 2.9)	(-2.7, 1.9)
		Pr >  t			0.7314
	Week 132	n	2	2	
		LS Mean	0.806	0.685	0.121
		SEM	1.132	1.153	1.551
		95% CI	(-1.4, 3.0)	(-1.6, 3.0)	(-2.9, 3.2)
		Pr >  t			0.9379
	Week 144	n	2		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Positive	Week 156	LS Mean	2.658	NE	NE
		SEM	1.134	NE	NE
		95% CI	( 0.4, 4.9)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-0.161	NE	NE
		SEM	1.557	NE	NE
		95% CI	( -3.2, 2.9)	NE	NE
	Week 8	n	1		
		LS Mean	-0.161	NE	NE
		SEM	1.557	NE	NE
		95% CI	( -3.2, 2.9)	NE	NE
	Week 16	n	98	101	
		LS Mean	-0.118	0.118	-0.236
		SEM	0.320	0.319	0.264
		95% CI	( -0.7, 0.5)	( -0.5, 0.7)	( -0.8, 0.3)
	Week 24	n	87	82	
		LS Mean	-0.050	0.278	-0.328
		SEM	0.327	0.329	0.281
		95% CI	( -0.7, 0.6)	( -0.4, 0.9)	( -0.9, 0.2)
	Week 32	n	76	64	
		LS Mean	-0.007	0.235	-0.242
		SEM	0.334	0.342	0.302
		95% CI	( -0.7, 0.6)	( -0.4, 0.9)	( -0.8, 0.4)
Week 40	n	62	56		
	LS Mean	0.252	0.193	0.059	
	SEM	0.344	0.350	0.320	
	95% CI	( -0.4, 0.9)	( -0.5, 0.9)	( -0.6, 0.7)	
Week 8	n	54	49		
	LS Mean	0.386	0.163	0.223	
	SEM	0.351	0.359	0.335	
	95% CI	( -0.3, 1.1)	( -0.5, 0.9)	( -0.4, 0.9)	
				Pr >  t	0.5055

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 48	n	52	40	
	LS Mean	0.594	0.231	0.363
	SEM	0.353	0.371	0.350
	95% CI	(-0.1, 1.3)	(-0.5, 1.0)	(-0.3, 1.1)
	Pr >  t			0.3004
Week 56	n	44	38	
	LS Mean	0.026	0.072	-0.046
	SEM	0.363	0.375	0.364
	95% CI	(-0.7, 0.7)	(-0.7, 0.8)	(-0.8, 0.7)
	Pr >  t			0.9001
Week 64	n	39	35	
	LS Mean	0.098	0.198	-0.100
	SEM	0.370	0.381	0.377
	95% CI	(-0.6, 0.8)	(-0.5, 0.9)	(-0.8, 0.6)
	Pr >  t			0.7903
Week 72	n	36	29	
	LS Mean	0.082	0.083	-0.000
	SEM	0.376	0.395	0.397
	95% CI	(-0.7, 0.8)	(-0.7, 0.9)	(-0.8, 0.8)
	Pr >  t			0.9990
Week 84	n	32	28	
	LS Mean	0.489	0.612	-0.123
	SEM	0.385	0.398	0.408
	95% CI	(-0.3, 1.2)	(-0.2, 1.4)	(-0.9, 0.7)
	Pr >  t			0.7633
Week 96	n	30	19	
	LS Mean	0.258	0.327	-0.068
	SEM	0.389	0.436	0.449
	95% CI	(-0.5, 1.0)	(-0.5, 1.2)	(-1.0, 0.8)
	Pr >  t			0.8792
Week 108	n	18	16	
	LS Mean	0.540	-0.184	0.724
	SEM	0.439	0.457	0.511
	95% CI	(-0.3, 1.4)	(-1.1, 0.7)	(-0.3, 1.7)
	Pr >  t			0.1569
Week 120	n	23	13	
	LS Mean	0.532	-0.366	0.898
	SEM	0.413	0.485	0.516
	95% CI	(-0.3, 1.3)	(-1.3, 0.6)	(-0.1, 1.9)



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.0820
	Week 132	n	18	6	
		LS Mean	0.118	0.610	-0.493
		SEM	0.440	0.633	0.673
		95% CI	(-0.7, 1.0)	(-0.6, 1.9)	(-1.8, 0.8)
		Pr >  t			0.4645
	Week 144	n	13	5	
		LS Mean	0.198	-0.272	0.471
		SEM	0.481	0.680	0.745
		95% CI	(-0.7, 1.1)	(-1.6, 1.1)	(-1.0, 1.9)
		Pr >  t			0.5275
	Week 156	n	8	3	
		LS Mean	0.023	0.580	-0.557
		SEM	0.566	0.840	0.941
		95% CI	(-1.1, 1.1)	(-1.1, 2.2)	(-2.4, 1.3)
		Pr >  t			0.5544
	Week 168	n	3	2	
		LS Mean	-0.742	-0.219	-0.523
		SEM	0.837	1.005	1.253
		95% CI	(-2.4, 0.9)	(-2.2, 1.8)	(-3.0, 1.9)
		Pr >  t			0.6763
	Week 180	n	1	1	
		LS Mean	2.407	0.279	2.128
		SEM	1.385	1.386	1.923
		95% CI	(-0.3, 5.1)	(-2.4, 3.0)	(-1.6, 5.9)
		Pr >  t			0.2687
	Week 192	n	1	1	
		LS Mean	0.257	-0.431	0.688
		SEM	1.385	1.386	1.923
		95% CI	(-2.5, 3.0)	(-3.1, 2.3)	(-3.1, 4.5)
		Pr >  t			0.7205

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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Final



**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	101			
			LS Mean	-0.117	0.111	-0.228		
			SEM	0.322	0.320	0.267		
			95% CI	(-0.8, 0.5)	(-0.5, 0.7)	(-0.8, 0.3)		
					Pr >  t			0.3939
		Week 16	n	85	82			
			LS Mean	-0.035	0.271	-0.305		
			SEM	0.329	0.330	0.284		
			95% CI	(-0.7, 0.6)	(-0.4, 0.9)	(-0.9, 0.3)		
					Pr >  t			0.2830
		Week 24	n	75	64			
			LS Mean	0.003	0.228	-0.225		
			SEM	0.336	0.343	0.304		
			95% CI	(-0.7, 0.7)	(-0.4, 0.9)	(-0.8, 0.4)		
					Pr >  t			0.4588
		Week 32	n	61	56			
			LS Mean	0.250	0.186	0.065		
			SEM	0.347	0.352	0.322		
			95% CI	(-0.4, 0.9)	(-0.5, 0.9)	(-0.6, 0.7)		
					Pr >  t			0.8411
		Week 40	n	53	49			
			LS Mean	0.394	0.155	0.239		
			SEM	0.354	0.360	0.338		
			95% CI	(-0.3, 1.1)	(-0.6, 0.9)	(-0.4, 0.9)		
					Pr >  t			0.4797
		Week 48	n	51	40			
			LS Mean	0.601	0.224	0.377		
			SEM	0.356	0.373	0.353		
95% CI	(-0.1, 1.3)		(-0.5, 1.0)	(-0.3, 1.1)				
			Pr >  t			0.2860		
Week 56	n	43	38					
	LS Mean	0.047	0.065	-0.017				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.366	0.376	0.367	
	95% CI	(-0.7, 0.8)	(-0.7, 0.8)	(-0.7, 0.7)	
	Pr >  t			0.9623	
	n	39	35		
	LS Mean	0.106	0.191	-0.085	
Week 72	SEM	0.372	0.382	0.379	
	95% CI	(-0.6, 0.8)	(-0.6, 0.9)	(-0.8, 0.7)	
	Pr >  t			0.8225	
	n	35	29		
	LS Mean	0.099	0.076	0.024	
Week 84	SEM	0.379	0.397	0.401	
	95% CI	(-0.6, 0.8)	(-0.7, 0.9)	(-0.8, 0.8)	
	Pr >  t			0.9524	
	n	31	28		
	LS Mean	0.484	0.605	-0.121	
Week 96	SEM	0.389	0.400	0.412	
	95% CI	(-0.3, 1.2)	(-0.2, 1.4)	(-0.9, 0.7)	
	Pr >  t			0.7691	
	n	29	19		
	LS Mean	0.284	0.320	-0.036	
Week 108	SEM	0.394	0.438	0.454	
	95% CI	(-0.5, 1.1)	(-0.5, 1.2)	(-0.9, 0.9)	
	Pr >  t			0.9373	
	n	18	16		
	LS Mean	0.549	-0.191	0.740	
Week 120	SEM	0.442	0.459	0.514	
	95% CI	(-0.3, 1.4)	(-1.1, 0.7)	(-0.3, 1.7)	
	Pr >  t			0.1502	
	n	23	13		
	LS Mean	0.540	-0.373	0.913	
Week 132	SEM	0.415	0.487	0.519	
	95% CI	(-0.3, 1.4)	(-1.3, 0.6)	(-0.1, 1.9)	
	Pr >  t			0.0785	
	n	18	6		
	LS Mean	0.127	0.604	-0.477	
Week 144	SEM	0.442	0.636	0.677	
	95% CI	(-0.7, 1.0)	(-0.6, 1.9)	(-1.8, 0.9)	
	Pr >  t			0.4808	
	n	13	5		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Positive Negative	Week 156	LS Mean	0.207	-0.279	0.486
		SEM	0.483	0.683	0.748
		95% CI	(-0.7, 1.2)	(-1.6, 1.1)	(-1.0, 2.0)
		Pr >  t			0.5157
		n	8	3	
	Week 168	LS Mean	0.032	0.573	-0.541
		SEM	0.569	0.844	0.945
		95% CI	(-1.1, 1.1)	(-1.1, 2.2)	(-2.4, 1.3)
		Pr >  t			0.5676
		n	3	2	
	Week 180	LS Mean	-0.733	-0.226	-0.507
		SEM	0.840	1.010	1.259
		95% CI	(-2.4, 0.9)	(-2.2, 1.8)	(-3.0, 2.0)
		Pr >  t			0.6872
		n	1	1	
	Week 192	LS Mean	2.417	0.272	2.145
		SEM	1.391	1.392	1.932
		95% CI	(-0.3, 5.1)	(-2.5, 3.0)	(-1.6, 5.9)
		Pr >  t			0.2671
		n	1	1	
	Week 8	LS Mean	0.267	-0.438	0.705
		SEM	1.391	1.392	1.932
		95% CI	(-2.5, 3.0)	(-3.2, 2.3)	(-3.1, 4.5)
		Pr >  t			0.7153
n		42	35		
Week 16	LS Mean	0.395	0.011	0.384	
	SEM	0.415	0.457	0.447	
	95% CI	(-0.4, 1.2)	(-0.9, 0.9)	(-0.5, 1.3)	
	Pr >  t			0.3920	
	n	35	22		
Week 24	LS Mean	0.302	-0.052	0.354	
	SEM	0.436	0.527	0.515	
	95% CI	(-0.6, 1.2)	(-1.1, 1.0)	(-0.7, 1.4)	
	Pr >  t			0.4927	
	n	28	15		
	LS Mean	0.565	0.755	-0.190	
	SEM	0.456	0.577	0.586	
	95% CI	(-0.3, 1.5)	(-0.4, 1.9)	(-1.3, 1.0)	
	Pr >  t			0.7464	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	n	22	16	
	LS Mean	0.318	0.613	-0.296
	SEM	0.490	0.569	0.597
	95% CI	(-0.6, 1.3)	(-0.5, 1.7)	(-1.5, 0.9)
	Pr >  t			0.6211
Week 40	n	19	12	
	LS Mean	0.287	0.904	-0.617
	SEM	0.508	0.613	0.654
	95% CI	(-0.7, 1.3)	(-0.3, 2.1)	(-1.9, 0.7)
	Pr >  t			0.3459
Week 48	n	16	10	
	LS Mean	1.182	1.256	-0.074
	SEM	0.531	0.646	0.702
	95% CI	(0.1, 2.2)	(-0.0, 2.5)	(-1.5, 1.3)
	Pr >  t			0.9158
Week 56	n	14	7	
	LS Mean	0.369	0.814	-0.445
	SEM	0.551	0.721	0.787
	95% CI	(-0.7, 1.5)	(-0.6, 2.2)	(-2.0, 1.1)
	Pr >  t			0.5726
Week 64	n	8	7	
	LS Mean	0.697	1.481	-0.784
	SEM	0.651	0.721	0.862
	95% CI	(-0.6, 2.0)	(0.1, 2.9)	(-2.5, 0.9)
	Pr >  t			0.3640
Week 72	n	12	6	
	LS Mean	0.627	0.420	0.207
	SEM	0.575	0.760	0.840
	95% CI	(-0.5, 1.8)	(-1.1, 1.9)	(-1.4, 1.9)
	Pr >  t			0.8058
Week 84	n	8	5	
	LS Mean	0.549	0.562	-0.013
	SEM	0.657	0.809	0.938
	95% CI	(-0.7, 1.8)	(-1.0, 2.2)	(-1.9, 1.8)
	Pr >  t			0.9888
Week 96	n	5	5	
	LS Mean	0.233	0.220	0.013
	SEM	0.775	0.809	1.025
	95% CI	(-1.3, 1.8)	(-1.4, 1.8)	(-2.0, 2.0)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.9898
	Week 108	n	7	5	
		LS Mean	0.865	0.876	-0.012
		SEM	0.687	0.809	0.960
		95% CI	(-0.5, 2.2)	(-0.7, 2.5)	(-1.9, 1.9)
		Pr >  t			0.9904
	Week 120	n	5	3	
		LS Mean	0.591	0.992	-0.401
		SEM	0.777	0.981	1.166
		95% CI	(-0.9, 2.1)	(-0.9, 2.9)	(-2.7, 1.9)
		Pr >  t			0.7314
	Week 132	n	2	2	
		LS Mean	0.806	0.685	0.121
		SEM	1.132	1.153	1.551
		95% CI	(-1.4, 3.0)	(-1.6, 3.0)	(-2.9, 3.2)
		Pr >  t			0.9379
	Week 144	n	2		
		LS Mean	2.658	NE	NE
		SEM	1.134	NE	NE
		95% CI	( 0.4, 4.9)	NE	NE
		Pr >  t			NE
	Week 156	n	1		
		LS Mean	-0.161	NE	NE
		SEM	1.557	NE	NE
		95% CI	(-3.2, 2.9)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-0.161	NE	NE
		SEM	1.557	NE	NE
		95% CI	(-3.2, 2.9)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.





**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib	Placebo qd +	Treatment difference	
			300mg qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Visceral Disease (L)	No	Week 8	n	69	58	
			LS Mean	-0.760	-0.667	-0.092
			SEM	0.701	0.726	0.338
			95% CI	(-2.1, 0.6)	(-2.1, 0.8)	(-0.8, 0.6)
				Pr >  t		0.7847
		Week 16	n	59	47	
	LS Mean		-0.834	-0.399	-0.434	
	SEM		0.704	0.733	0.364	
	95% CI		(-2.2, 0.6)	(-1.9, 1.1)	(-1.2, 0.3)	
			Pr >  t		0.2340	
		Week 24	n	54	39	
	LS Mean		-0.770	-0.144	-0.626	
	SEM		0.707	0.741	0.385	
	95% CI		(-2.2, 0.6)	(-1.6, 1.3)	(-1.4, 0.1)	
			Pr >  t		0.1051	
		Week 32	n	48	36	
	LS Mean		-0.282	-0.414	0.132	
	SEM		0.710	0.745	0.399	
	95% CI		(-1.7, 1.1)	(-1.9, 1.1)	(-0.7, 0.9)	
			Pr >  t		0.7413	
		Week 40	n	43	32	
	LS Mean		-0.286	-0.394	0.108	
	SEM		0.713	0.750	0.416	
	95% CI		(-1.7, 1.1)	(-1.9, 1.1)	(-0.7, 0.9)	
		Pr >  t		0.7954		
	Week 48	n	41	27		
LS Mean		0.115	-0.378	0.493		
SEM		0.715	0.759	0.435		
95% CI		(-1.3, 1.5)	(-1.9, 1.1)	(-0.4, 1.3)		
		Pr >  t		0.2575		
	Week 56	n	35	22		
LS Mean		-0.669	-0.723	0.054		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		
		N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	SEM	0.720	0.771	0.467
	95% CI	(-2.1, 0.8)	(-2.2, 0.8)	(-0.9, 1.0)
	Pr >  t			0.9084
	n	26	23	
	LS Mean	-0.402	-0.398	-0.004
Week 72	SEM	0.734	0.768	0.485
	95% CI	(-1.9, 1.1)	(-1.9, 1.1)	(-1.0, 0.9)
	Pr >  t			0.9940
	n	28	18	
	LS Mean	-0.364	-0.493	0.128
Week 84	SEM	0.730	0.786	0.506
	95% CI	(-1.8, 1.1)	(-2.0, 1.1)	(-0.9, 1.1)
	Pr >  t			0.8000
	n	22	18	
	LS Mean	-0.470	0.159	-0.629
Week 96	SEM	0.748	0.786	0.526
	95% CI	(-2.0, 1.0)	(-1.4, 1.7)	(-1.7, 0.4)
	Pr >  t			0.2325
	n	21	13	
	LS Mean	-0.383	-0.546	0.163
Week 108	SEM	0.746	0.814	0.573
	95% CI	(-1.9, 1.1)	(-2.2, 1.1)	(-1.0, 1.3)
	Pr >  t			0.7769
	n	17	12	
	LS Mean	0.034	-0.851	0.885
Week 120	SEM	0.767	0.823	0.605
	95% CI	(-1.5, 1.6)	(-2.5, 0.8)	(-0.3, 2.1)
	Pr >  t			0.1441
	n	18	11	
	LS Mean	-0.042	-1.062	1.019
Week 132	SEM	0.756	0.833	0.613
	95% CI	(-1.5, 1.5)	(-2.7, 0.6)	(-0.2, 2.2)
	Pr >  t			0.0968
	n	13	5	
	LS Mean	-0.549	0.044	-0.593
Week 144	SEM	0.792	0.962	0.809
	95% CI	(-2.1, 1.0)	(-1.9, 1.9)	(-2.2, 1.0)
	Pr >  t			0.4638
	n	12	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
		LS Mean	-0.287	-1.086	0.799
		SEM	0.792	1.100	0.977
		95% CI	(-1.9, 1.3)	(-3.2, 1.1)	(-1.1, 2.7)
		Pr >  t			0.4133
	Week 156	n	6	2	
		LS Mean	-0.921	0.369	-1.289
		SEM	0.904	1.251	1.217
		95% CI	(-2.7, 0.9)	(-2.1, 2.8)	(-3.7, 1.1)
		Pr >  t			0.2899
	Week 168	n	3	1	
		LS Mean	-1.385	-0.934	-0.451
		SEM	1.081	1.620	1.701
		95% CI	(-3.5, 0.7)	(-4.1, 2.2)	(-3.8, 2.9)
		Pr >  t			0.7911
	Week 180	n	1	1	
		LS Mean	1.760	-0.364	2.124
		SEM	1.607	1.620	2.076
		95% CI	(-1.4, 4.9)	(-3.5, 2.8)	(-2.0, 6.2)
		Pr >  t			0.3064
	Week 192	n	1	1	
		LS Mean	-0.390	-1.074	0.684
		SEM	1.607	1.620	2.076
		95% CI	(-3.5, 2.8)	(-4.3, 2.1)	(-3.4, 4.8)
		Pr >  t			0.7417
Yes	Week 8	n	73	79	
		LS Mean	0.221	0.279	-0.058
		SEM	0.389	0.395	0.297
		95% CI	(-0.5, 1.0)	(-0.5, 1.1)	(-0.6, 0.5)
		Pr >  t			0.8453
	Week 16	n	65	58	
		LS Mean	0.333	0.299	0.034
		SEM	0.400	0.413	0.321
		95% CI	(-0.5, 1.1)	(-0.5, 1.1)	(-0.6, 0.7)
		Pr >  t			0.9156
	Week 24	n	51	40	
		LS Mean	0.489	0.293	0.195
		SEM	0.409	0.435	0.358
		95% CI	(-0.3, 1.3)	(-0.6, 1.1)	(-0.5, 0.9)
		Pr >  t			0.5853

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 32	n	38	36		
	LS Mean	0.194	0.447	-0.253	
	SEM	0.429	0.442	0.383	
	95% CI	(-0.7, 1.0)	(-0.4, 1.3)	(-1.0, 0.5)	
	Pr >  t			0.5093	
Week 40	n	32	29		
	LS Mean	0.459	0.475	-0.016	
	SEM	0.441	0.456	0.411	
	95% CI	(-0.4, 1.3)	(-0.4, 1.4)	(-0.8, 0.8)	
	Pr >  t			0.9695	
Week 48	n	28	23		
	LS Mean	0.733	0.732	0.001	
	SEM	0.450	0.475	0.440	
	95% CI	(-0.2, 1.6)	(-0.2, 1.7)	(-0.9, 0.9)	
	Pr >  t			0.9974	
Week 56	n	24	23		
	LS Mean	0.348	0.581	-0.233	
	SEM	0.462	0.475	0.452	
	95% CI	(-0.6, 1.3)	(-0.4, 1.5)	(-1.1, 0.7)	
	Pr >  t			0.6067	
Week 64	n	21	19		
	LS Mean	0.257	0.721	-0.464	
	SEM	0.474	0.491	0.480	
	95% CI	(-0.7, 1.2)	(-0.2, 1.7)	(-1.4, 0.5)	
	Pr >  t			0.3349	
Week 72	n	20	17		
	LS Mean	0.155	0.238	-0.083	
	SEM	0.478	0.502	0.496	
	95% CI	(-0.8, 1.1)	(-0.7, 1.2)	(-1.1, 0.9)	
	Pr >  t			0.8665	
Week 84	n	18	15		
	LS Mean	0.974	0.480	0.494	
	SEM	0.487	0.515	0.518	
	95% CI	( 0.0, 1.9)	(-0.5, 1.5)	(-0.5, 1.5)	
	Pr >  t			0.3409	
Week 96	n	14	11		
	LS Mean	0.367	0.609	-0.242	
	SEM	0.515	0.555	0.581	
	95% CI	(-0.6, 1.4)	(-0.5, 1.7)	(-1.4, 0.9)	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.6775
	Week 108	n	9	9	
		LS Mean	0.434	0.457	-0.023
		SEM	0.576	0.585	0.663
		95% CI	(-0.7, 1.6)	(-0.7, 1.6)	(-1.3, 1.3)
		Pr >  t			0.9722
	Week 120	n	10	5	
		LS Mean	0.497	0.556	-0.059
		SEM	0.562	0.702	0.757
		95% CI	(-0.6, 1.6)	(-0.8, 1.9)	(-1.5, 1.4)
		Pr >  t			0.9376
	Week 132	n	7	3	
		LS Mean	0.482	0.481	0.000
		SEM	0.621	0.844	0.930
		95% CI	(-0.7, 1.7)	(-1.2, 2.1)	(-1.8, 1.8)
		Pr >  t			0.9997
	Week 144	n	3	2	
		LS Mean	1.181	0.247	0.934
		SEM	0.838	0.996	1.209
		95% CI	(-0.5, 2.8)	(-1.7, 2.2)	(-1.4, 3.3)
		Pr >  t			0.4401
	Week 156	n	3	1	
		LS Mean	0.705	-0.077	0.782
		SEM	0.840	1.352	1.516
		95% CI	(-0.9, 2.4)	(-2.7, 2.6)	(-2.2, 3.8)
		Pr >  t			0.6060
	Week 168	n	1	1	
		LS Mean	-0.176	0.063	-0.239
		SEM	1.351	1.352	1.849
		95% CI	(-2.8, 2.5)	(-2.6, 2.7)	(-3.9, 3.4)
		Pr >  t			0.8971

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-31i**  
**Linear mixed effects model analysis on change from baseline in BPI-SF Pain Interference Index**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	63			
			LS Mean	0.134	0.333	-0.199		
			SEM	0.323	0.337	0.319		
			95% CI	(-0.5, 0.8)	(-0.3, 1.0)	(-0.8, 0.4)		
					Pr >  t			0.5332
		Week 16	n	70	51			
			LS Mean	0.074	0.182	-0.108		
			SEM	0.332	0.356	0.342		
			95% CI	(-0.6, 0.7)	(-0.5, 0.9)	(-0.8, 0.6)		
					Pr >  t			0.7510
		Week 24	n	54	39			
			LS Mean	0.265	0.128	0.137		
			SEM	0.346	0.377	0.375		
			95% CI	(-0.4, 0.9)	(-0.6, 0.9)	(-0.6, 0.9)		
					Pr >  t			0.7161
		Week 32	n	50	35			
			LS Mean	0.374	0.474	-0.100		
			SEM	0.352	0.385	0.388		
			95% CI	(-0.3, 1.1)	(-0.3, 1.2)	(-0.9, 0.7)		
					Pr >  t			0.7968
		Week 40	n	42	27			
			LS Mean	0.321	0.052	0.269		
			SEM	0.363	0.409	0.419		
			95% CI	(-0.4, 1.0)	(-0.8, 0.9)	(-0.6, 1.1)		
					Pr >  t			0.5206
		Week 48	n	38	23			
			LS Mean	0.995	0.439	0.556		
			SEM	0.370	0.424	0.440		
95% CI	(0.3, 1.7)		(-0.4, 1.3)	(-0.3, 1.4)				
			Pr >  t			0.2065		
Week 56	n	33	24					
	LS Mean	0.288	0.272	0.015				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
Week 64	SEM	0.380	0.420	0.445	
	95% CI	(-0.5, 1.0)	(-0.6, 1.1)	(-0.9, 0.9)	
	Pr >  t			0.9727	
	n	27	19		
	LS Mean	0.440	0.734	-0.293	
Week 72	SEM	0.396	0.445	0.482	
	95% CI	(-0.3, 1.2)	(-0.1, 1.6)	(-1.2, 0.7)	
	Pr >  t			0.5428	
	n	26	17		
	LS Mean	0.537	0.015	0.522	
Week 84	SEM	0.399	0.458	0.497	
	95% CI	(-0.2, 1.3)	(-0.9, 0.9)	(-0.5, 1.5)	
	Pr >  t			0.2936	
	n	18	16		
	LS Mean	0.641	0.664	-0.024	
Week 96	SEM	0.440	0.466	0.535	
	95% CI	(-0.2, 1.5)	(-0.3, 1.6)	(-1.1, 1.0)	
	Pr >  t			0.9649	
	n	20	10		
	LS Mean	0.456	0.209	0.247	
Week 108	SEM	0.427	0.536	0.588	
	95% CI	(-0.4, 1.3)	(-0.8, 1.3)	(-0.9, 1.4)	
	Pr >  t			0.6743	
	n	14	10		
	LS Mean	0.530	-0.286	0.816	
Week 120	SEM	0.473	0.536	0.622	
	95% CI	(-0.4, 1.5)	(-1.3, 0.8)	(-0.4, 2.0)	
	Pr >  t			0.1897	
	n	14	7		
	LS Mean	0.387	-0.265	0.652	
Week 132	SEM	0.471	0.606	0.683	
	95% CI	(-0.5, 1.3)	(-1.5, 0.9)	(-0.7, 2.0)	
	Pr >  t			0.3395	
	n	12	5		
	LS Mean	-0.084	0.624	-0.708	
Week 144	SEM	0.495	0.688	0.771	
	95% CI	(-1.1, 0.9)	(-0.7, 2.0)	(-2.2, 0.8)	
	Pr >  t			0.3588	
	n	11	4		



Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Exon 9	Week 156	LS Mean	0.466	0.408	0.058
		SEM	0.507	0.752	0.837
		95% CI	(-0.5, 1.5)	(-1.1, 1.9)	(-1.6, 1.7)
		Pr >  t			0.9443
	Week 168	n	8	3	
		LS Mean	0.185	0.700	-0.515
		SEM	0.567	0.848	0.958
		95% CI	(-0.9, 1.3)	(-1.0, 2.4)	(-2.4, 1.4)
	Week 180	Pr >  t			0.5908
		n	4	2	
		LS Mean	-0.494	-0.099	-0.396
		SEM	0.743	1.013	1.206
	Week 192	95% CI	(-2.0, 1.0)	(-2.1, 1.9)	(-2.8, 2.0)
		Pr >  t			0.7429
		n	1	1	
		LS Mean	2.586	0.410	2.176
	Week 192	SEM	1.390	1.394	1.936
		95% CI	(-0.1, 5.3)	(-2.3, 3.1)	(-1.6, 6.0)
		Pr >  t			0.2615
		n	1	1	
	Week 8	LS Mean	0.436	-0.300	0.736
		SEM	1.390	1.394	1.936
		95% CI	(-2.3, 3.2)	(-3.0, 2.4)	(-3.1, 4.5)
		Pr >  t			0.7039
Week 16	n	53	63		
	LS Mean	-0.137	-0.302	0.166	
	SEM	0.499	0.539	0.348	
	95% CI	(-1.1, 0.8)	(-1.4, 0.8)	(-0.5, 0.9)	
Week 24	Pr >  t			0.6346	
	n	48	48		
	LS Mean	-0.058	0.033	-0.091	
	SEM	0.511	0.551	0.372	
Week 24	95% CI	(-1.1, 1.0)	(-1.1, 1.1)	(-0.8, 0.6)	
	Pr >  t			0.8061	
	n	46	35		
	LS Mean	-0.202	0.371	-0.573	
Week 24	SEM	0.513	0.566	0.397	
	95% CI	(-1.2, 0.8)	(-0.7, 1.5)	(-1.4, 0.2)	
	Pr >  t			0.1504	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	n	31	33	
	LS Mean	0.005	-0.009	0.014
	SEM	0.543	0.570	0.429
	95% CI	(-1.1, 1.1)	(-1.1, 1.1)	(-0.8, 0.9)
	Pr >  t			0.9736
Week 40	n	28	30	
	LS Mean	0.177	0.429	-0.251
	SEM	0.549	0.575	0.444
	95% CI	(-0.9, 1.3)	(-0.7, 1.6)	(-1.1, 0.6)
	Pr >  t			0.5716
Week 48	n	26	23	
	LS Mean	0.227	0.362	-0.135
	SEM	0.554	0.593	0.473
	95% CI	(-0.9, 1.3)	(-0.8, 1.5)	(-1.1, 0.8)
	Pr >  t			0.7757
Week 56	n	22	17	
	LS Mean	-0.078	-0.000	-0.078
	SEM	0.566	0.619	0.518
	95% CI	(-1.2, 1.0)	(-1.2, 1.2)	(-1.1, 0.9)
	Pr >  t			0.8801
Week 64	n	17	19	
	LS Mean	-0.091	0.044	-0.135
	SEM	0.588	0.609	0.530
	95% CI	(-1.2, 1.1)	(-1.2, 1.2)	(-1.2, 0.9)
	Pr >  t			0.7990
Week 72	n	20	14	
	LS Mean	-0.108	0.193	-0.301
	SEM	0.574	0.639	0.549
	95% CI	(-1.2, 1.0)	(-1.1, 1.5)	(-1.4, 0.8)
	Pr >  t			0.5838
Week 84	n	19	13	
	LS Mean	0.462	0.588	-0.126
	SEM	0.578	0.647	0.563
	95% CI	(-0.7, 1.6)	(-0.7, 1.9)	(-1.2, 1.0)
	Pr >  t			0.8227
Week 96	n	12	12	
	LS Mean	-0.096	0.208	-0.304
	SEM	0.626	0.656	0.622
	95% CI	(-1.3, 1.1)	(-1.1, 1.5)	(-1.5, 0.9)

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t			0.6251
	Week 108	n	9	9	
		LS Mean	0.450	0.247	0.203
		SEM	0.666	0.695	0.701
		95% CI	(-0.9, 1.8)	(-1.1, 1.6)	(-1.2, 1.6)
		Pr >  t			0.7723
	Week 120	n	12	7	
		LS Mean	0.950	-0.137	1.088
		SEM	0.627	0.737	0.707
		95% CI	(-0.3, 2.2)	(-1.6, 1.3)	(-0.3, 2.5)
		Pr >  t			0.1246
	Week 132	n	5	2	
		LS Mean	0.857	0.797	0.060
		SEM	0.779	1.096	1.172
		95% CI	(-0.7, 2.4)	(-1.4, 2.9)	(-2.2, 2.4)
		Pr >  t			0.9589
	Week 144	n	3	1	
		LS Mean	1.309	-2.667	3.976
		SEM	0.925	1.464	1.600
		95% CI	(-0.5, 3.1)	(-5.5, 0.2)	( 0.8, 7.1)
		Pr >  t			0.0133
	Week 156	n	1		
		LS Mean	-0.433	NE	NE
		SEM	1.443	NE	NE
		95% CI	(-3.3, 2.4)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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#### 4.8.4.3 Gesundheitszustand: EQ-5D-VAS – 2. Datenschnitt

Tabelle 4H-52: Ergebnisse für den Endpunkt „Gesundheitszustand (EQ-5D VAS)“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Bone Lesions Only (L)	No	Week 8	n	104	111	
			LS Mean	-4.513	-3.199	-1.314
			SEM	2.583	2.577	2.312
			95% CI	(-9.6, 0.6)	(-8.3, 1.9)	(-5.9, 3.2)
			Pr >  t			0.5700
	Week 16	n	93	83		
		LS Mean	-1.853	-1.282	-0.570	
		SEM	2.661	2.752	2.513	
		95% CI	(-7.1, 3.4)	(-6.7, 4.1)	(-5.5, 4.4)	
		Pr >  t			0.8205	
	Week 24	n	77	60		
		LS Mean	-5.240	-2.469	-2.771	
		SEM	2.736	2.939	2.790	
		95% CI	(-10.6, 0.1)	(-8.2, 3.3)	(-8.2, 2.7)	
		Pr >  t			0.3209	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	n		57	53	
	LS Mean		-2.107	-1.747	-0.360
	SEM		2.930	3.011	3.022
	95% CI		(-7.9, 3.6)	(-7.7, 4.2)	(-6.3, 5.6)
	Pr >  t				0.9051
Week 40	n		50	44	
	LS Mean		-0.092	-4.536	4.444
	SEM		3.010	3.146	3.220
	95% CI		(-6.0, 5.8)	(-10.7, 1.6)	(-1.9, 10.8)
	Pr >  t				0.1679
Week 48	n		47	37	
	LS Mean		-5.200	-3.777	-1.424
	SEM		3.047	3.274	3.380
	95% CI		(-11.2, 0.8)	(-10.2, 2.7)	(-8.1, 5.2)
	Pr >  t				0.6737
Week 56	n		40	32	
	LS Mean		-1.553	-0.829	-0.724
	SEM		3.157	3.392	3.591
	95% CI		(-7.8, 4.6)	(-7.5, 5.8)	(-7.8, 6.3)
	Pr >  t				0.8403
Week 64	n		32	27	
	LS Mean		-1.454	-4.992	3.538
	SEM		3.330	3.546	3.885
	95% CI		(-8.0, 5.1)	(-12.0, 2.0)	(-4.1, 11.2)
	Pr >  t				0.3628
Week 72	n		31	23	
	LS Mean		-2.163	-3.482	1.319
	SEM		3.360	3.707	4.057
	95% CI		(-8.8, 4.4)	(-10.8, 3.8)	(-6.6, 9.3)
	Pr >  t				0.7453
Week 84	n		27	21	
	LS Mean		0.915	-5.478	6.393
	SEM		3.489	3.807	4.248
	95% CI		(-5.9, 7.8)	(-12.9, 2.0)	(-1.9, 14.7)
	Pr >  t				0.1326
Week 96	n		24	16	
	LS Mean		1.961	-12.33	14.292
	SEM		3.597	4.140	4.640
	95% CI		(-5.1, 9.0)	(-20.5, -4.2)	( 5.2, 23.4)
	Pr >  t				0.0021

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	n		15	14	
	LS Mean		-3.062	-5.121	2.059
	SEM		4.172	4.328	5.247
	95% CI		(-11.2, 5.1)	(-13.6, 3.4)	(-8.2,12.4)
	Pr >  t				0.6949
Week 120	n		18	8	
	LS Mean		1.246	-2.124	3.370
	SEM		3.927	5.310	5.924
	95% CI		(-6.5, 9.0)	(-12.5, 8.3)	(-8.3,15.0)
	Pr >  t				0.5695
Week 132	n		12	4	
	LS Mean		-2.802	-14.42	11.622
	SEM		4.509	7.066	7.853
	95% CI		(-11.6, 6.0)	(-28.3,-0.6)	(-3.8,27.0)
	Pr >  t				0.1392
Week 144	n		8	3	
	LS Mean		-4.592	1.036	-5.628
	SEM		5.233	8.039	9.147
	95% CI		(-14.9, 5.7)	(-14.7,16.8)	(-23.6,12.3)
	Pr >  t				0.5385
Week 156	n		5	1	
	LS Mean		-1.883	-5.258	3.375
	SEM		6.377	13.44	14.58
	95% CI		(-14.4,10.6)	(-31.6,21.1)	(-25.2,32.0)
	Pr >  t				0.8170
Week 168	n		2	1	
	LS Mean		-2.688	-5.258	2.570
	SEM		9.649	13.44	16.28
	95% CI		(-21.6,16.2)	(-31.6,21.1)	(-29.4,34.5)
	Pr >  t				0.8746
Week 180	n		1		
	LS Mean		-3.697	NE	NE
	SEM		13.40	NE	NE
	95% CI		(-30.0,22.6)	NE	NE
	Pr >  t				NE
Week 192	n		1		
	LS Mean		-5.697	NE	NE
	SEM		13.40	NE	NE
	95% CI		(-32.0,20.6)	NE	NE
	Pr >  t				NE

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Yes	Week 8	n	38	30	
		LS Mean	-7.771	1.820	-9.592
		SEM	4.200	4.506	3.739
		95% CI	(-16.1, 0.6)	(-7.1, 10.8)	(-17.0, -2.2)
		Pr >  t			0.0113
	Week 16	n	32	24	
		LS Mean	-3.952	-2.939	-1.013
		SEM	4.268	4.631	4.018
		95% CI	(-12.4, 4.5)	(-12.1, 6.2)	(-8.9, 6.9)
		Pr >  t			0.8012
	Week 24	n	28	22	
		LS Mean	-3.619	-3.566	-0.053
		SEM	4.389	4.686	4.165
		95% CI	(-12.3, 5.1)	(-12.9, 5.7)	(-8.3, 8.2)
		Pr >  t			0.9899
	Week 32	n	29	20	
		LS Mean	-9.822	-2.440	-7.382
		SEM	4.374	4.806	4.223
		95% CI	(-18.5, -1.1)	(-12.0, 7.1)	(-15.7, 0.9)
		Pr >  t			0.0819
Week 40	n	25	18		
	LS Mean	-7.114	-1.728	-5.386	
	SEM	4.450	4.875	4.385	
	95% CI	(-15.9, 1.7)	(-11.4, 7.9)	(-14.0, 3.3)	
	Pr >  t			0.2206	
Week 48	n	22	14		
	LS Mean	-3.845	0.416	-4.261	
	SEM	4.522	5.068	4.674	
	95% CI	(-12.8, 5.1)	(-9.6, 10.4)	(-13.5, 4.9)	
	Pr >  t			0.3628	
Week 56	n	19	13		
	LS Mean	-4.130	-4.329	0.198	
	SEM	4.611	5.137	4.841	
	95% CI	(-13.3, 5.0)	(-14.5, 5.8)	(-9.3, 9.7)	
	Pr >  t			0.9673	
Week 64	n	15	15		
	LS Mean	-7.801	-2.907	-4.894	
	SEM	4.778	5.017	4.884	
	95% CI	(-17.2, 1.6)	(-12.8, 7.0)	(-14.5, 4.7)	
	Pr >  t			0.3172	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72	n		17	12	
	LS Mean		-4.693	-0.736	-3.956
	SEM		4.686	5.209	4.992
	95% CI		(-14.0, 4.6)	(-11.0, 9.6)	(-13.8, 5.9)
	Pr >  t				0.4286
Week 84	n		13	12	
	LS Mean		-7.746	-1.630	-6.116
	SEM		4.933	5.211	5.200
	95% CI		(-17.5, 2.0)	(-11.9, 8.7)	(-16.3, 4.1)
	Pr >  t				0.2403
Week 96	n		12	8	
	LS Mean		-6.738	-6.175	-0.562
	SEM		5.007	5.658	5.715
	95% CI		(-16.6, 3.1)	(-17.3, 5.0)	(-11.8,10.7)
	Pr >  t				0.9217
Week 108	n		11	7	
	LS Mean		-3.474	-5.581	2.107
	SEM		5.097	5.839	5.970
	95% CI		(-13.5, 6.6)	(-17.1, 5.9)	( -9.6,13.8)
	Pr >  t				0.7243
Week 120	n		11	8	
	LS Mean		-13.78	-3.045	-10.74
	SEM		5.095	5.660	5.793
	95% CI		(-23.8,-3.7)	(-14.2, 8.1)	(-22.1, 0.6)
	Pr >  t				0.0645
Week 132	n		8	4	
	LS Mean		-2.993	-2.543	-0.450
	SEM		5.465	6.812	7.201
	95% CI		(-13.8, 7.8)	(-15.9,10.9)	(-14.6,13.7)
	Pr >  t				0.9502
Week 144	n		7	2	
	LS Mean		-5.984	-4.109	-1.875
	SEM		5.650	8.663	9.086
	95% CI		(-17.1, 5.1)	(-21.1,12.9)	(-19.7,16.0)
	Pr >  t				0.8366
Week 156	n		5	2	
	LS Mean		-3.293	-7.609	4.316
	SEM		6.202	8.663	9.439
	95% CI		(-15.5, 8.9)	(-24.6, 9.4)	(-14.2,22.9)
	Pr >  t				0.6477



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	Week 168	n	2	1	
		LS Mean	1.410	3.585	-2.175
		SEM	8.511	11.49	13.42
		95% CI	(-15.3,18.1)	(-19.0,26.2)	(-28.5,24.2)
		Pr >  t			0.8713
	Week 180	n		1	
		LS Mean	NE	-4.415	NE
		SEM	NE	11.49	NE
		95% CI	NE	(-27.0,18.2)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-0.415	NE
		SEM	NE	11.49	NE
		95% CI	NE	(-23.0,22.2)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	131			
			LS Mean	-5.990	-2.615	-3.375		
			SEM	2.234	2.282	2.041		
			95% CI	(-10.4,-1.6)	(-7.1, 1.9)	(-7.4, 0.6)		
					Pr >  t			0.0986
		Week 16	n	120	97			
			LS Mean	-2.888	-2.081	-0.807		
			SEM	2.296	2.426	2.228		
			95% CI	(-7.4, 1.6)	(-6.8, 2.7)	(-5.2, 3.6)		
					Pr >  t			0.7173
		Week 24	n	100	76			
			LS Mean	-5.559	-3.956	-1.603		
			SEM	2.367	2.547	2.418		
			95% CI	(-10.2,-0.9)	(-9.0, 1.0)	(-6.3, 3.1)		
					Pr >  t			0.5076
		Week 32	n	82	69			
			LS Mean	-5.067	-2.740	-2.326		
			SEM	2.470	2.604	2.549		
			95% CI	(-9.9,-0.2)	(-7.9, 2.4)	(-7.3, 2.7)		
					Pr >  t			0.3616
		Week 40	n	73	58			
			LS Mean	-3.024	-5.148	2.124		
			SEM	2.522	2.702	2.692		
			95% CI	(-8.0, 1.9)	(-10.5, 0.2)	(-3.2, 7.4)		
			Pr >  t			0.4303		
Week 48	n	66	48					
	LS Mean	-5.152	-3.434	-1.717				
	SEM	2.569	2.813	2.846				
	95% CI	(-10.2,-0.1)	(-9.0, 2.1)	(-7.3, 3.9)				
			Pr >  t			0.5464		
Week 56	n	56	43					
	LS Mean	-2.714	-2.861	0.146				
	SEM	2.653	2.885	2.995				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.9, 2.5)	(-8.5, 2.8)	(-5.7, 6.0)
	Pr >  t			0.9610
	n	45	41	
	LS Mean	-3.988	-5.192	1.204
	SEM	2.781	2.918	3.142
Week 72	95% CI	(-9.4, 1.5)	(-10.9, 0.5)	(-5.0, 7.4)
	Pr >  t			0.7017
	n	46	34	
	LS Mean	-3.214	-3.459	0.245
	SEM	2.769	3.055	3.259
Week 84	95% CI	(-8.6, 2.2)	(-9.5, 2.5)	(-6.1, 6.6)
	Pr >  t			0.9400
	n	37	32	
	LS Mean	-3.032	-5.181	2.149
	SEM	2.927	3.104	3.430
Week 96	95% CI	(-8.8, 2.7)	(-11.3, 0.9)	(-4.6, 8.9)
	Pr >  t			0.5311
	n	34	23	
	LS Mean	-1.500	-11.54	10.041
	SEM	2.987	3.407	3.758
Week 108	95% CI	(-7.4, 4.4)	(-18.2, -4.9)	( 2.7, 17.4)
	Pr >  t			0.0076
	n	24	20	
	LS Mean	-3.005	-5.125	2.120
	SEM	3.304	3.558	4.139
Week 120	95% CI	(-9.5, 3.5)	(-12.1, 1.9)	(-6.0, 10.2)
	Pr >  t			0.6085
	n	26	16	
	LS Mean	-4.028	-3.581	-0.448
	SEM	3.221	3.828	4.317
Week 132	95% CI	(-10.3, 2.3)	(-11.1, 3.9)	(-8.9, 8.0)
	Pr >  t			0.9174
	n	19	8	
	LS Mean	-3.539	-9.452	5.913
	SEM	3.555	4.950	5.541
Week 144	95% CI	(-10.5, 3.4)	(-19.2, 0.3)	(-5.0, 16.8)
	Pr >  t			0.2861
	n	14	5	
	LS Mean	-4.612	-2.005	-2.607
	SEM	3.941	6.032	6.749

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.3, 3.1)	(-13.8, 9.8)	(-15.8,10.6)
		Pr >  t			0.6994
	Week 156	n	10	3	
		LS Mean	-2.339	-7.963	5.625
		SEM	4.484	7.568	8.423
		95% CI	(-11.1, 6.5)	(-22.8, 6.9)	(-10.9,22.1)
		Pr >  t			0.5044
	Week 168	n	4	2	
		LS Mean	-0.452	-1.824	1.372
		SEM	6.605	9.134	10.98
		95% CI	(-13.4,12.5)	(-19.7,16.1)	(-20.2,22.9)
		Pr >  t			0.9006
	Week 180	n	1	1	
		LS Mean	-4.899	-6.083	1.184
		SEM	12.70	12.71	17.78
		95% CI	(-29.8,20.0)	(-31.0,18.8)	(-33.7,36.1)
		Pr >  t			0.9469
	Week 192	n	1	1	
		LS Mean	-6.899	-2.083	-4.816
		SEM	12.70	12.71	17.78
		95% CI	(-31.8,18.0)	(-27.0,22.8)	(-39.7,30.1)
		Pr >  t			0.7866
Yes	Week 8	n	5	9	
		LS Mean	13.585	9.708	3.876
		SEM	7.427	5.420	9.113
		95% CI	(-1.7,28.9)	(-1.4,20.8)	(-14.8,22.6)
		Pr >  t			0.6740
	Week 16	n	5	9	
		LS Mean	13.985	7.154	6.831
		SEM	7.427	5.324	9.124
		95% CI	(-1.3,29.3)	(-3.7,18.1)	(-11.9,25.6)
		Pr >  t			0.4607
	Week 24	n	5	5	
		LS Mean	16.785	14.701	2.083
		SEM	7.427	6.740	10.05
		95% CI	( 1.5,32.1)	( 1.1,28.3)	(-18.4,22.5)
		Pr >  t			0.8371
	Week 32	n	4	3	
		LS Mean	9.720	7.853	1.866
		SEM	7.957	8.264	11.53

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.6,26.0)	(-8.7,24.5)	(-21.4,25.1)
		Pr >  t			0.8722
	Week 40	n	2	3	
		LS Mean	19.359	20.215	-0.856
		SEM	10.10	8.374	13.09
		95% CI	(-1.0,39.7)	( 3.4,37.0)	(-27.2,25.5)
		Pr >  t			0.9482
	Week 48	n	3	2	
		LS Mean	9.602	11.144	-1.542
		SEM	8.761	9.963	13.18
		95% CI	(-8.2,27.4)	(-8.9,31.1)	(-28.0,25.0)
		Pr >  t			0.9073
	Week 56	n	3	1	
		LS Mean	11.269	17.356	-6.087
		SEM	8.761	13.41	16.12
		95% CI	(-6.5,29.0)	(-9.6,44.3)	(-38.4,26.3)
		Pr >  t			0.7072
	Week 64	n	2		
		LS Mean	13.859	NE	NE
		SEM	10.10	NE	NE
		95% CI	(-6.5,34.2)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	7.553	NE	NE
		SEM	10.08	NE	NE
		95% CI	(-12.7,27.8)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	21.602	NE	NE
		SEM	8.761	NE	NE
		95% CI	( 3.8,39.4)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	16.859	NE	NE
		SEM	10.10	NE	NE
		95% CI	(-3.5,37.2)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	7.895	NE	NE
		SEM	10.14	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.5,28.3)	NE
		Pr >  t		NE
	Week 120	n	3	
		LS Mean	5.602	NE
		SEM	8.761	NE
		95% CI	(-12.2,23.4)	NE
		Pr >  t		NE
	Week 132	n	1	
		LS Mean	24.701	NE
		SEM	13.36	NE
		95% CI	(-2.1,51.5)	NE
		Pr >  t		NE
	Week 144	n	1	
		LS Mean	4.701	NE
		SEM	13.36	NE
		95% CI	(-22.1,31.5)	NE
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-4.815	-2.030	-2.785		
			SEM	2.284	2.328	2.144		
			95% CI	(-9.3, -0.3)	(-6.6, 2.5)	(-7.0, 1.4)		
					Pr >  t			0.1945
		Week 16	n	112	91			
			LS Mean	-2.450	-1.272	-1.177		
			SEM	2.343	2.478	2.323		
			95% CI	(-7.1, 2.2)	(-6.1, 3.6)	(-5.7, 3.4)		
					Pr >  t			0.6125
		Week 24	n	96	71			
			LS Mean	-4.404	-3.409	-0.994		
			SEM	2.408	2.608	2.511		
			95% CI	(-9.1, 0.3)	(-8.5, 1.7)	(-5.9, 3.9)		
					Pr >  t			0.6922
		Week 32	n	77	61			
			LS Mean	-4.628	-2.802	-1.826		
			SEM	2.524	2.696	2.684		
			95% CI	(-9.6, 0.3)	(-8.1, 2.5)	(-7.1, 3.4)		
					Pr >  t			0.4965
		Week 40	n	69	52			
			LS Mean	-2.365	-3.115	0.750		
			SEM	2.576	2.798	2.826		
			95% CI	(-7.4, 2.7)	(-8.6, 2.4)	(-4.8, 6.3)		
			Pr >  t			0.7908		
Week 48	n	62	41					
	LS Mean	-4.820	-2.693	-2.128				
	SEM	2.628	2.951	3.023				
	95% CI	(-10.0, 0.3)	(-8.5, 3.1)	(-8.1, 3.8)				
			Pr >  t			0.4817		
Week 56	n	53	35					
	LS Mean	-2.668	-2.584	-0.085				
		SEM	2.712	3.068	3.211			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.0, 2.7)	(-8.6, 3.4)	(-6.4, 6.2)
		Pr >  t			0.9790
	Week 64	n	44	33	
		LS Mean	-3.002	-3.593	0.591
		SEM	2.823	3.116	3.352
		95% CI	(-8.5, 2.5)	(-9.7, 2.5)	(-6.0, 7.2)
		Pr >  t			0.8600
	Week 72	n	45	28	
		LS Mean	-3.906	-2.217	-1.689
		SEM	2.810	3.255	3.471
		95% CI	(-9.4, 1.6)	(-8.6, 4.2)	(-8.5, 5.1)
		Pr >  t			0.6265
	Week 84	n	39	27	
		LS Mean	-2.295	-3.690	1.395
		SEM	2.916	3.288	3.580
		95% CI	(-8.0, 3.4)	(-10.1, 2.8)	(-5.6, 8.4)
		Pr >  t			0.6967
	Week 96	n	35	19	
		LS Mean	-1.299	-12.16	10.861
		SEM	2.991	3.651	3.977
		95% CI	(-7.2, 4.6)	(-19.3,-5.0)	( 3.1,18.7)
		Pr >  t			0.0064
	Week 108	n	26	17	
		LS Mean	-3.048	-4.947	1.899
		SEM	3.252	3.788	4.291
		95% CI	(-9.4, 3.3)	(-12.4, 2.5)	(-6.5,10.3)
		Pr >  t			0.6582
	Week 120	n	28	11	
		LS Mean	-4.747	-1.034	-3.713
		SEM	3.179	4.416	4.810
		95% CI	(-11.0, 1.5)	(-9.7, 7.6)	(-13.1, 5.7)
		Pr >  t			0.4403
	Week 132	n	20	6	
		LS Mean	-2.593	-7.824	5.231
		SEM	3.523	5.617	6.120
		95% CI	(-9.5, 4.3)	(-18.8, 3.2)	(-6.8,17.2)
		Pr >  t			0.3928
	Week 144	n	15	4	
		LS Mean	-4.754	-0.560	-4.194
		SEM	3.871	6.699	7.310



Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
>= 75 Years	Week 156	95% CI	(-12.3, 2.8)	(-13.7,12.6)	(-18.5,10.1)
		Pr >  t			0.5662
		n	10	2	
	Week 168	LS Mean	-1.973	-8.039	6.066
		SEM	4.511	9.189	9.914
		95% CI	(-10.8, 6.9)	(-26.1,10.0)	(-13.4,25.5)
	Week 180	Pr >  t			0.5407
		n	4	2	
		LS Mean	-0.084	-1.039	0.954
	Week 192	SEM	6.637	9.189	11.05
		95% CI	(-13.1,12.9)	(-19.1,17.0)	(-20.7,22.6)
		Pr >  t			0.9312
	Week 8	n	1	1	
		LS Mean	-4.552	-5.234	0.682
		SEM	12.75	12.77	17.86
	Week 16	95% CI	(-29.6,20.5)	(-30.3,19.8)	(-34.4,35.7)
		Pr >  t			0.9695
		n	1	1	
	Week 24	LS Mean	-6.552	-1.234	-5.318
		SEM	12.75	12.77	17.86
		95% CI	(-31.6,18.5)	(-26.3,23.8)	(-40.4,29.7)
	Week 32	Pr >  t			0.7660
		n	17	20	
		LS Mean	-8.900	-2.109	-6.791
Week 8	SEM	3.732	3.395	5.012	
	95% CI	(-16.3,-1.5)	(-8.9, 4.6)	(-16.8, 3.2)	
	Pr >  t			0.1790	
Week 16	n	13	16		
	LS Mean	-0.621	-4.097	3.476	
	SEM	4.154	3.720	5.541	
Week 24	95% CI	(-8.9, 7.6)	(-11.5, 3.3)	(-7.5,14.5)	
	Pr >  t			0.5319	
	n	9	11		
Week 32	LS Mean	-7.496	-0.209	-7.287	
	SEM	4.777	4.256	6.368	
	95% CI	(-16.9, 2.0)	(-8.6, 8.2)	(-19.9, 5.3)	
Week 8	Pr >  t			0.2546	
	n	9	12		
	LS Mean	-3.759	1.379	-5.138	
Week 16	SEM	4.777	4.136	6.288	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.2, 5.7)	(-6.8, 9.6)	(-17.6, 7.3)
		Pr >  t			0.4154
	Week 40	n	6	10	
		LS Mean	-1.463	-7.534	6.071
		SEM	5.589	4.409	7.093
		95% CI	(-12.5, 9.6)	(-16.3, 1.2)	(-7.9, 20.1)
		Pr >  t			0.3934
	Week 48	n	7	10	
		LS Mean	-2.603	-2.910	0.307
		SEM	5.268	4.420	6.844
		95% CI	(-13.0, 7.8)	(-11.7, 5.8)	(-13.2, 13.8)
		Pr >  t			0.9643
	Week 56	n	6	10	
		LS Mean	1.875	0.387	1.488
		SEM	5.578	4.426	7.081
		95% CI	(-9.1, 12.9)	(-8.4, 9.1)	(-12.5, 15.5)
		Pr >  t			0.8338
	Week 64	n	3	9	
		LS Mean	-7.905	-7.108	-0.798
		SEM	7.403	4.602	8.681
		95% CI	(-22.5, 6.7)	(-16.2, 2.0)	(-17.9, 16.3)
		Pr >  t			0.9269
	Week 72	n	3	7	
		LS Mean	13.095	-4.305	17.400
		SEM	7.403	5.068	8.935
		95% CI	(-1.5, 27.7)	(-14.3, 5.7)	(-0.2, 35.0)
		Pr >  t			0.0531
	Week 84	n	1	6	
		LS Mean	14.457	-6.564	21.022
		SEM	12.14	5.385	13.26
		95% CI	(-9.5, 38.4)	(-17.2, 4.1)	(-5.2, 47.2)
		Pr >  t			0.1147
	Week 96	n	1	5	
		LS Mean	13.457	-3.661	17.118
		SEM	12.14	5.798	13.43
		95% CI	(-10.5, 37.4)	(-15.1, 7.8)	(-9.4, 43.6)
		Pr >  t			0.2043
	Week 108	n		4	
		LS Mean	NE	-7.069	NE
		SEM	NE	6.365	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-19.6, 5.5)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	9.560	-6.661
		SEM	12.17	5.798
		95% CI	(-14.5,33.6)	(-18.1, 4.8)
		Pr >  t		0.2299
	Week 132	n		2
		LS Mean	NE	-11.33
		SEM	NE	8.597
		95% CI	NE	(-28.3, 5.6)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	-4.018
		SEM	NE	11.87
		95% CI	NE	(-27.5,19.4)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	-6.018
		SEM	NE	11.87
		95% CI	NE	(-29.5,17.4)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	74			
			LS Mean	-8.462	-3.904	-4.557		
			SEM	7.280	7.499	2.812		
			95% CI	(-22.8, 5.9)	(-18.7,10.9)	(-10.1, 1.0)		
					Pr >  t			0.1060
		Week 16	n	69	55			
			LS Mean	-5.434	-3.913	-1.521		
			SEM	7.295	7.562	3.016		
			95% CI	(-19.8, 9.0)	(-18.8,11.0)	( -7.5, 4.4)		
					Pr >  t			0.6144
		Week 24	n	54	46			
			LS Mean	-7.339	-7.829	0.490		
			SEM	7.327	7.601	3.248		
			95% CI	(-21.8, 7.1)	(-22.8, 7.2)	( -5.9, 6.9)		
					Pr >  t			0.8802
		Week 32	n	49	41			
			LS Mean	-10.05	-5.261	-4.788		
			SEM	7.412	7.628	3.372		
			95% CI	(-24.7, 4.6)	(-20.3, 9.8)	(-11.4, 1.8)		
					Pr >  t			0.1562
		Week 40	n	40	33			
			LS Mean	-3.874	-7.057	3.183		
			SEM	7.467	7.689	3.630		
			95% CI	(-18.6,10.9)	(-22.2, 8.1)	( -3.9,10.3)		
					Pr >  t			0.3809
		Week 48	n	38	28			
			LS Mean	-7.297	-4.636	-2.661		
			SEM	7.483	7.750	3.782		
95% CI	(-22.1, 7.5)		(-19.9,10.7)	(-10.1, 4.8)				
			Pr >  t			0.4820		
Week 56	n	32	28					
	LS Mean	-4.163	-3.057	-1.107				
	SEM	7.538	7.751	3.890				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-19.0,10.7)	(-18.4,12.2)	(-8.7, 6.5)
	Pr >  t			0.7761
	n	23	26	
	LS Mean	-6.307	-3.859	-2.447
	SEM	7.668	7.777	4.187
Week 72	95% CI	(-21.4, 8.8)	(-19.2,11.5)	(-10.7, 5.8)
	Pr >  t			0.5590
	n	27	25	
	LS Mean	-2.242	-3.810	1.569
	SEM	7.600	7.791	4.094
Week 84	95% CI	(-17.2,12.8)	(-19.2,11.6)	(-6.5, 9.6)
	Pr >  t			0.7017
	n	23	22	
	LS Mean	-5.087	-6.637	1.551
	SEM	7.667	7.846	4.319
Week 96	95% CI	(-20.2,10.0)	(-22.1, 8.8)	(-6.9,10.0)
	Pr >  t			0.7197
	n	21	16	
	LS Mean	-4.135	-12.32	8.183
	SEM	7.707	8.015	4.692
Week 108	95% CI	(-19.3,11.1)	(-28.1, 3.5)	(-1.0,17.4)
	Pr >  t			0.0815
	n	20	14	
	LS Mean	-5.576	-5.483	-0.094
	SEM	7.735	8.103	4.880
Week 120	95% CI	(-20.8, 9.7)	(-21.5,10.5)	(-9.7, 9.5)
	Pr >  t			0.9847
	n	17	11	
	LS Mean	-3.480	-5.113	1.633
	SEM	7.824	8.286	5.313
Week 132	95% CI	(-18.9,11.9)	(-21.4,11.2)	(-8.8,12.1)
	Pr >  t			0.7586
	n	13	6	
	LS Mean	-5.837	-11.25	5.417
	SEM	7.999	8.965	6.537
Week 144	95% CI	(-21.6, 9.9)	(-28.9, 6.4)	(-7.4,18.2)
	Pr >  t			0.4075
	n	10	5	
	LS Mean	-7.731	-3.391	-4.341
	SEM	8.219	9.247	7.177

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-23.9, 8.5)	(-21.6,14.8)	(-18.4, 9.7)
		Pr >  t			0.5455
	Week 156	n	7	3	
		LS Mean	-3.647	-9.355	5.708
		SEM	8.613	10.30	8.867
		95% CI	(-20.6,13.3)	(-29.6,10.9)	(-11.7,23.1)
		Pr >  t			0.5199
	Week 168	n	3	2	
		LS Mean	-0.378	-3.239	2.861
		SEM	10.17	11.48	11.56
		95% CI	(-20.4,19.6)	(-25.8,19.3)	(-19.8,25.5)
		Pr >  t			0.8046
	Week 180	n		1	
		LS Mean	NE	-7.548	NE
		SEM	NE	14.43	NE
		95% CI	NE	(-35.9,20.8)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-3.548	NE
		SEM	NE	14.43	NE
		95% CI	NE	(-31.9,24.8)	NE
		Pr >  t			NE
Second Line	Week 8	n	66	67	
		LS Mean	-5.029	-3.240	-1.789
		SEM	2.512	2.521	2.772
		95% CI	(-10.0,-0.1)	(-8.2, 1.7)	(-7.2, 3.7)
		Pr >  t			0.5192
	Week 16	n	54	52	
		LS Mean	-2.328	-2.273	-0.055
		SEM	2.664	2.739	3.048
		95% CI	(-7.6, 2.9)	(-7.7, 3.1)	(-6.0, 5.9)
		Pr >  t			0.9855
	Week 24	n	49	36	
		LS Mean	-4.389	-0.216	-4.173
		SEM	2.745	3.034	3.362
		95% CI	(-9.8, 1.0)	(-6.2, 5.7)	(-10.8, 2.4)
		Pr >  t			0.2152
	Week 32	n	36	32	
		LS Mean	-0.880	-1.515	0.635
		SEM	2.992	3.143	3.634

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-6.8, 5.0)	(-7.7, 4.7)	(-6.5, 7.8)
	Pr >  t			0.8613
	n	33	29	
	LS Mean	-2.813	-3.228	0.415
	SEM	3.061	3.250	3.770
Week 48	95% CI	(-8.8, 3.2)	(-9.6, 3.2)	(-7.0, 7.8)
	Pr >  t			0.9124
	n	29	23	
	LS Mean	-3.286	-3.602	0.316
	SEM	3.171	3.470	4.048
Week 56	95% CI	(-9.5, 2.9)	(-10.4, 3.2)	(-7.6, 8.3)
	Pr >  t			0.9377
	n	25	17	
	LS Mean	-4.389	-4.655	0.265
	SEM	3.304	3.811	4.450
Week 64	95% CI	(-10.9, 2.1)	(-12.1, 2.8)	(-8.5, 9.0)
	Pr >  t			0.9524
	n	22	16	
	LS Mean	-2.699	-9.594	6.895
	SEM	3.431	3.890	4.612
Week 72	95% CI	(-9.4, 4.0)	(-17.2,-2.0)	(-2.2,16.0)
	Pr >  t			0.1354
	n	20	10	
	LS Mean	-7.480	-6.312	-1.168
	SEM	3.533	4.595	5.291
Week 84	95% CI	(-14.4,-0.5)	(-15.3, 2.7)	(-11.6, 9.2)
	Pr >  t			0.8253
	n	16	11	
	LS Mean	-0.781	-4.774	3.993
	SEM	3.818	4.435	5.339
Week 96	95% CI	(-8.3, 6.7)	(-13.5, 3.9)	(-6.5,14.5)
	Pr >  t			0.4548
	n	15	8	
	LS Mean	0.217	-11.90	12.120
	SEM	3.894	5.001	5.876
Week 108	95% CI	(-7.4, 7.9)	(-21.7,-2.1)	( 0.6,23.7)
	Pr >  t			0.0395
	n	6	7	
	LS Mean	-2.375	-10.54	8.161
	SEM	5.546	5.274	7.269

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-13.3, 8.5)	(-20.9,-0.2)	(-6.1,22.4)
	Pr >  t			0.2620
Week 120	n	12	5	
	LS Mean	-8.971	-3.886	-5.084
	SEM	4.223	6.059	6.994
	95% CI	(-17.3,-0.7)	(-15.8, 8.0)	(-18.8, 8.6)
	Pr >  t			0.4675
Week 132	n	7	2	
	LS Mean	-0.825	-9.002	8.177
	SEM	5.204	9.117	10.22
	95% CI	(-11.0, 9.4)	(-26.9, 8.9)	(-11.9,28.2)
	Pr >  t			0.4240
Week 144	n	5		
	LS Mean	-3.472	NE	NE
	SEM	5.975	NE	NE
	95% CI	(-15.2, 8.3)	NE	NE
	Pr >  t			NE
Week 156	n	3		
	LS Mean	-3.460	NE	NE
	SEM	7.515	NE	NE
	95% CI	(-18.2,11.3)	NE	NE
	Pr >  t			NE
Week 168	n	1		
	LS Mean	-5.889	NE	NE
	SEM	12.61	NE	NE
	95% CI	(-30.7,18.9)	NE	NE
	Pr >  t			NE
Week 180	n	1		
	LS Mean	-4.889	NE	NE
	SEM	12.61	NE	NE
	95% CI	(-29.7,19.9)	NE	NE
	Pr >  t			NE
Week 192	n	1		
	LS Mean	-6.889	NE	NE
	SEM	12.61	NE	NE
	95% CI	(-31.7,17.9)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis



-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-9.456	-8.414	-1.042		
			SEM	3.941	3.826	2.930		
			95% CI	(-17.2,-1.7)	(-16.0,-0.9)	(-6.8, 4.7)		
					Pr >  t			0.7224
		Week 16	n	61	51			
			LS Mean	-7.355	-7.755	0.401		
			SEM	4.003	4.017	3.112		
			95% CI	(-15.2, 0.5)	(-15.7, 0.2)	(-5.7, 6.5)		
					Pr >  t			0.8976
		Week 24	n	51	43			
			LS Mean	-8.759	-9.423	0.664		
			SEM	4.066	4.091	3.294		
			95% CI	(-16.8,-0.7)	(-17.5,-1.4)	(-5.8, 7.1)		
					Pr >  t			0.8403
		Week 32	n	46	36			
			LS Mean	-8.841	-9.756	0.915		
			SEM	4.135	4.209	3.455		
			95% CI	(-17.0,-0.7)	(-18.0,-1.5)	(-5.9, 7.7)		
					Pr >  t			0.7913
		Week 40	n	40	33			
			LS Mean	-7.828	-10.77	2.944		
			SEM	4.198	4.259	3.587		
			95% CI	(-16.1, 0.4)	(-19.2,-2.4)	(-4.1,10.0)		
			Pr >  t			0.4123		
Week 48	n	37	28					
	LS Mean	-10.18	-12.08	1.900				
	SEM	4.234	4.354	3.740				
	95% CI	(-18.5,-1.8)	(-20.6,-3.5)	(-5.4, 9.2)				
			Pr >  t			0.6116		
Week 56	n	33	23					
	LS Mean	-7.659	-9.401	1.742				
	SEM	4.292	4.485	3.956				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-16.1, 0.8)	(-18.2,-0.6)	(-6.0, 9.5)
		Pr >  t			0.6598
	Week 64	n	26	20	
		LS Mean	-7.436	-11.39	3.956
		SEM	4.426	4.592	4.218
		95% CI	(-16.1, 1.3)	(-20.4,-2.4)	(-4.3,12.2)
		Pr >  t			0.3486
	Week 72	n	28	17	
		LS Mean	-6.358	-8.553	2.194
		SEM	4.383	4.728	4.322
		95% CI	(-15.0, 2.3)	(-17.8, 0.7)	(-6.3,10.7)
		Pr >  t			0.6118
	Week 84	n	23	17	
		LS Mean	-5.796	-12.46	6.660
		SEM	4.508	4.730	4.450
		95% CI	(-14.7, 3.1)	(-21.8,-3.2)	(-2.1,15.4)
		Pr >  t			0.1350
	Week 96	n	24	11	
		LS Mean	-5.065	-14.83	9.767
		SEM	4.480	5.192	4.913
		95% CI	(-13.9, 3.7)	(-25.0,-4.6)	( 0.1,19.4)
		Pr >  t			0.0471
	Week 108	n	15	13	
		LS Mean	-5.758	-9.903	4.146
		SEM	4.861	4.997	5.070
		95% CI	(-15.3, 3.8)	(-19.7,-0.1)	(-5.8,14.1)
		Pr >  t			0.4138
	Week 120	n	17	9	
		LS Mean	-6.069	-7.466	1.397
		SEM	4.747	5.463	5.427
		95% CI	(-15.4, 3.3)	(-18.2, 3.3)	(-9.3,12.1)
		Pr >  t			0.7969
	Week 132	n	14	5	
		LS Mean	-5.848	-17.00	11.148
		SEM	4.929	6.505	6.610
		95% CI	(-15.5, 3.8)	(-29.8,-4.2)	(-1.8,24.1)
		Pr >  t			0.0921
	Week 144	n	8	3	
		LS Mean	-0.442	-9.361	8.919
		SEM	5.639	7.813	8.362

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-11.5,10.6)	(-24.7, 6.0)	(-7.5,25.3)
		Pr >  t			0.2865
		n	7	2	
	Week 168	LS Mean	-7.116	-15.19	8.077
		SEM	5.856	9.184	9.784
		95% CI	(-18.6, 4.4)	(-33.2, 2.8)	(-11.1,27.3)
	Week 180	Pr >  t			0.4093
		n	4	2	
		LS Mean	-3.777	-8.193	4.416
	Week 192	SEM	7.017	9.184	10.52
		95% CI	(-17.6,10.0)	(-26.2, 9.8)	(-16.2,25.1)
		Pr >  t			0.6748
	Week 8	n	1	1	
		LS Mean	-8.126	-12.41	4.279
		SEM	12.40	12.40	16.87
	Week 16	95% CI	(-32.5,16.2)	(-36.7,11.9)	(-28.8,37.4)
		Pr >  t			0.7998
		n	1	1	
	Week 24	LS Mean	-10.13	-8.406	-1.721
		SEM	12.40	12.40	16.87
		95% CI	(-34.5,14.2)	(-32.7,15.9)	(-34.8,31.4)
	Week 32	Pr >  t			0.9188
		n	18	17	
		LS Mean	-5.000	-9.972	4.972
Week 8	SEM	3.972	4.134	5.729	
	95% CI	(-12.9, 2.9)	(-18.2,-1.7)	(-6.5,16.4)	
	Pr >  t			0.3885	
Week 16	n	17	11		
	LS Mean	-5.425	-6.468	1.043	
	SEM	4.081	5.037	6.484	
Week 24	95% CI	(-13.5, 2.7)	(-16.5, 3.5)	(-11.8,13.9)	
	Pr >  t			0.8726	
	n	15	5		
Week 32	LS Mean	-8.079	-6.156	-1.924	
	SEM	4.319	7.198	8.430	
	95% CI	(-16.7, 0.5)	(-20.4, 8.1)	(-18.6,14.7)	
Week 8	Pr >  t			0.8198	
	n	13	5		
	LS Mean	-6.171	-1.956	-4.216	
		SEM	4.580	7.198	8.568

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Placebo qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
		95% CI	N=169		N=172					
Week 40		Pr >  t	(-15.3, 2.9)		(-16.2,12.3)		(-21.2,12.7)		0.6235	
	n		11		5					
	LS Mean		1.859		-3.356		5.215			
	SEM		4.900		7.198		8.745			
	95% CI		(-7.8,11.6)		(-17.6,10.9)		(-12.1,22.5)			
Week 48		Pr >  t					0.5519			
	n		11		2					
	LS Mean		-10.10		1.875		-11.98			
	SEM		4.912		10.65		11.76			
	95% CI		(-19.8,-0.4)		(-19.1,22.9)		(-35.2,11.2)			
Week 56		Pr >  t					0.3100			
	n		8		2					
	LS Mean		-0.127		2.375		-2.503			
	SEM		5.565		10.65		12.05			
	95% CI		(-11.1,10.9)		(-18.6,23.4)		(-26.3,21.3)			
Week 64		Pr >  t					0.8357			
	n		7		3					
	LS Mean		-0.032		0.137		-0.169			
	SEM		5.871		8.945		10.73			
	95% CI		(-11.6,11.6)		(-17.5,17.8)		(-21.4,21.0)			
Week 72		Pr >  t					0.9874			
	n		7		3					
	LS Mean		0.522		-1.197		1.718			
	SEM		5.885		8.945		10.74			
	95% CI		(-11.1,12.1)		(-18.9,16.5)		(-19.5,22.9)			
Week 84		Pr >  t					0.8731			
	n		7		2					
	LS Mean		-4.621		3.375		-7.997			
	SEM		5.885		10.65		12.20			
	95% CI		(-16.2, 7.0)		(-17.6,24.4)		(-32.1,16.1)			
Week 96		Pr >  t					0.5130			
	n		6		3					
	LS Mean		-3.552		-35.20		31.644			
	SEM		6.265		8.945		10.95			
	95% CI		(-15.9, 8.8)		(-52.9, -18)		( 10.0,53.3)			
Week 108		Pr >  t					0.0043			
	n		7		2					
	LS Mean		-8.193		-13.61		5.422			
		SEM		5.885		10.63		12.18		

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-19.8, 3.4)	(-34.6, 7.4)	(-18.6,29.5)
		Pr >  t			0.6566
		n	6	1	
	Week 132	LS Mean	-8.385	-3.340	-5.045
		SEM	6.265	14.61	15.91
		95% CI	(-20.8, 4.0)	(-32.2,25.5)	(-36.5,26.4)
	Week 144	Pr >  t			0.7516
		n	4		
		LS Mean	-8.986	NE	NE
	Week 156	SEM	7.438	NE	NE
		95% CI	(-23.7, 5.7)	NE	NE
		Pr >  t			NE
	Week 8	n	5		
		LS Mean	-18.00	NE	NE
		SEM	6.762	NE	NE
	Week 16	95% CI	(-31.3,-4.6)	NE	NE
		Pr >  t			NE
		n	3		
	Week 24	LS Mean	-0.458	NE	NE
		SEM	8.466	NE	NE
		95% CI	(-17.2,16.3)	NE	NE
	Week 32	Pr >  t			NE
		n	59	58	
		LS Mean	-4.065	4.272	-8.337
Week 16	SEM	2.816	2.948	3.049	
	95% CI	(-9.6, 1.5)	(-1.5,10.1)	(-14.3,-2.3)	
	Pr >  t			0.0066	
Week 24	n	47	44		
	LS Mean	1.001	3.282	-2.281	
	SEM	2.978	3.158	3.392	
Week 32	95% CI	(-4.9, 6.9)	(-2.9, 9.5)	(-9.0, 4.4)	
	Pr >  t			0.5017	
	n	39	34		
Week 8	LS Mean	-2.604	2.326	-4.930	
	SEM	3.134	3.399	3.723	
	95% CI	(-8.8, 3.6)	(-4.4, 9.0)	(-12.2, 2.4)	
Week 16	Pr >  t			0.1862	
	n	27	32		
	LS Mean	-2.756	3.892	-6.648	
Week 24	SEM	3.490	3.451	4.048	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-9.6, 4.1)	(-2.9,10.7)	(-14.6, 1.3)	
	Pr >  t			0.1012	
	n	24	24		
	LS Mean	-0.827	1.182	-2.008	
	SEM	3.608	3.736	4.378	
Week 48	95% CI	(-7.9, 6.3)	(-6.2, 8.5)	(-10.6, 6.6)	
	Pr >  t			0.6466	
	n	21	21		
	LS Mean	1.426	5.539	-4.113	
	SEM	3.750	3.879	4.621	
Week 56	95% CI	(-5.9, 8.8)	(-2.1,13.2)	(-13.2, 5.0)	
	Pr >  t			0.3738	
	n	18	20		
	LS Mean	-0.096	3.741	-3.837	
	SEM	3.924	3.935	4.818	
Week 64	95% CI	(-7.8, 7.6)	(-4.0,11.5)	(-13.3, 5.6)	
	Pr >  t			0.4262	
	n	14	19		
	LS Mean	-4.253	0.454	-4.707	
	SEM	4.253	3.995	5.143	
Week 72	95% CI	(-12.6, 4.1)	(-7.4, 8.3)	(-14.8, 5.4)	
	Pr >  t			0.3604	
	n	13	15		
	LS Mean	-5.471	1.200	-6.671	
	SEM	4.364	4.292	5.467	
Week 84	95% CI	(-14.0, 3.1)	(-7.2, 9.6)	(-17.4, 4.1)	
	Pr >  t			0.2229	
	n	10	14		
	LS Mean	0.205	1.758	-1.553	
	SEM	4.829	4.388	5.887	
Week 96	95% CI	(-9.3, 9.7)	(-6.9,10.4)	(-13.1,10.0)	
	Pr >  t			0.7921	
	n	6	10		
	LS Mean	2.060	-0.261	2.322	
	SEM	5.872	4.916	7.149	
Week 108	95% CI	(-9.5,13.6)	(-9.9, 9.4)	(-11.7,16.4)	
	Pr >  t			0.7455	
	n	4	6		
	LS Mean	0.904	-2.636	3.540	
	SEM	7.000	5.961	8.756	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-12.8,14.7)	(-14.3, 9.1)	(-13.7,20.7)
	Pr >  t			0.6862
	n	6	6	
	LS Mean	-5.758	-0.890	-4.869
	SEM	5.876	5.965	7.909
Week 132	95% CI	(-17.3, 5.8)	(-12.6,10.8)	(-20.4,10.7)
	Pr >  t			0.5384
	n	2	3	
	LS Mean	5.307	-1.068	6.376
	SEM	9.542	7.969	12.11
Week 144	95% CI	(-13.4,24.1)	(-16.7,14.6)	(-17.4,30.2)
	Pr >  t			0.5989
	n	2	2	
	LS Mean	-5.738	5.920	-11.66
	SEM	9.505	9.583	13.24
Week 156	95% CI	(-24.4,12.9)	(-12.9,24.7)	(-37.7,14.4)
	Pr >  t			0.3790
	n		1	
	LS Mean	NE	0.341	NE
	SEM	NE	13.23	NE
	95% CI	NE	(-25.7,26.3)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	2.792	NE	NE	
			SEM	23.11	NE	NE	
			95% CI	( -291, 296)	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	11.292	NE	NE	
			SEM	23.11	NE	NE	
			95% CI	( -282, 305)	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	7.542	NE	NE	
			SEM	24.95	NE	NE	
			95% CI	( -309, 325)	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	6.542	NE	NE	
			SEM	24.95	NE	NE	
			95% CI	( -310, 324)	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	11.042	NE	NE	
			SEM	25.39	NE	NE	
			95% CI	( -312, 334)	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	7.042	NE	NE	
			SEM	25.39	NE	NE	
95% CI	( -316, 330)		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	7.042	NE	NE			
			SEM	25.39	NE	NE	

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-316, 330)	NE	NE
		Pr >  t			NE
	Week 72	n	1		
		LS Mean	7.542	NE	NE
		SEM	24.95	NE	NE
		95% CI	(-309, 325)	NE	NE
		Pr >  t			NE
	Week 84	n	1		
		LS Mean	6.542	NE	NE
		SEM	24.95	NE	NE
		95% CI	(-310, 324)	NE	NE
		Pr >  t			NE
	Week 96	n	1		
		LS Mean	2.542	NE	NE
		SEM	24.95	NE	NE
		95% CI	(-314, 320)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	140	141	
		LS Mean	-5.610	-2.319	-3.291
		SEM	2.210	2.239	1.978
		95% CI	(-10.0,-1.3)	(-6.7, 2.1)	(-7.2, 0.6)
		Pr >  t			0.0967
	Week 16	n	123	107	
		LS Mean	-2.696	-1.983	-0.713
		SEM	2.270	2.367	2.146
		95% CI	(-7.2, 1.8)	(-6.6, 2.7)	(-4.9, 3.5)
		Pr >  t			0.7400
	Week 24	n	104	82	
		LS Mean	-5.073	-3.222	-1.851
		SEM	2.335	2.488	2.335
		95% CI	(-9.7,-0.5)	(-8.1, 1.7)	(-6.4, 2.7)
		Pr >  t			0.4280
	Week 32	n	85	73	
		LS Mean	-4.925	-2.366	-2.560
		SEM	2.436	2.551	2.473
		95% CI	(-9.7,-0.1)	(-7.4, 2.6)	(-7.4, 2.3)
		Pr >  t			0.3009
	Week 40	n	74	62	
		LS Mean	-2.635	-4.113	1.478
		SEM	2.497	2.640	2.617

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-7.5, 2.3)	(-9.3, 1.1)	(-3.7, 6.6)
	Pr >  t			0.5723
Week 48	n	68	51	
	LS Mean	-4.957	-2.999	-1.958
	SEM	2.536	2.749	2.763
	95% CI	(-9.9, 0.0)	(-8.4, 2.4)	(-7.4, 3.5)
	Pr >  t			0.4788
Week 56	n	58	45	
	LS Mean	-2.526	-2.218	-0.308
	SEM	2.615	2.827	2.915
	95% CI	(-7.7, 2.6)	(-7.8, 3.3)	(-6.0, 5.4)
	Pr >  t			0.9160
Week 64	n	47	42	
	LS Mean	-3.660	-4.647	0.987
	SEM	2.734	2.874	3.069
	95% CI	(-9.0, 1.7)	(-10.3, 1.0)	(-5.0, 7.0)
	Pr >  t			0.7476
Week 72	n	47	35	
	LS Mean	-3.223	-2.920	-0.303
	SEM	2.736	3.005	3.193
	95% CI	(-8.6, 2.1)	(-8.8, 3.0)	(-6.6, 6.0)
	Pr >  t			0.9244
Week 84	n	39	33	
	LS Mean	-2.130	-4.492	2.362
	SEM	2.869	3.052	3.342
	95% CI	(-7.8, 3.5)	(-10.5, 1.5)	(-4.2, 8.9)
	Pr >  t			0.4799
Week 96	n	35	24	
	LS Mean	-1.007	-10.64	9.632
	SEM	2.944	3.336	3.669
	95% CI	(-6.8, 4.8)	(-17.2, -4.1)	( 2.4, 16.8)
	Pr >  t			0.0087
Week 108	n	26	21	
	LS Mean	-3.163	-5.640	2.477
	SEM	3.205	3.476	3.997
	95% CI	(-9.5, 3.1)	(-12.5, 1.2)	(-5.4, 10.3)
	Pr >  t			0.5356
Week 120	n	29	16	
	LS Mean	-4.463	-3.115	-1.347
	SEM	3.101	3.801	4.210

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-10.5, 1.6)	(-10.6, 4.3)	(-9.6, 6.9)
	Pr >  t			0.7490
Week 132	n	20	8	
	LS Mean	-2.713	-8.992	6.279
	SEM	3.475	4.922	5.470
	95% CI	(-9.5, 4.1)	(-18.6, 0.7)	(-4.5, 17.0)
	Pr >  t			0.2512
Week 144	n	15	5	
	LS Mean	-4.884	-1.529	-3.355
	SEM	3.823	6.002	6.658
	95% CI	(-12.4, 2.6)	(-13.3, 10.2)	(-16.4, 9.7)
	Pr >  t			0.6144
Week 156	n	10	3	
	LS Mean	-2.109	-7.485	5.377
	SEM	4.461	7.534	8.384
	95% CI	(-10.9, 6.6)	(-22.3, 7.3)	(-11.1, 21.8)
	Pr >  t			0.5214
Week 168	n	4	2	
	LS Mean	-0.231	-1.350	1.119
	SEM	6.578	9.097	10.94
	95% CI	(-13.1, 12.7)	(-19.2, 16.5)	(-20.3, 22.6)
	Pr >  t			0.9185
Week 180	n	1	1	
	LS Mean	-4.711	-5.615	0.903
	SEM	12.65	12.66	17.72
	95% CI	(-29.5, 20.1)	(-30.4, 19.2)	(-33.9, 35.7)
	Pr >  t			0.9594
Week 192	n	1	1	
	LS Mean	-6.711	-1.615	-5.097
	SEM	12.65	12.66	17.72
	95% CI	(-31.5, 18.1)	(-26.4, 23.2)	(-39.9, 29.7)
	Pr >  t			0.7736

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-32i**  
**Linear mixed effects model analysis on change from baseline in EQ-5D-5L VAS**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-7.120	-3.164	-3.956
			SEM	2.290	2.375	2.241
			95% CI	(-11.6,-2.6)	(-7.8, 1.5)	(-8.4, 0.4)
		Pr >  t			0.0782	
		Week 16	n	91	75	
			LS Mean	-3.659	-2.887	-0.772
			SEM	2.353	2.505	2.422
			95% CI	(-8.3, 1.0)	(-7.8, 2.0)	(-5.5, 4.0)
		Pr >  t			0.7501	
		Week 24	n	79	62	
			LS Mean	-5.122	-4.189	-0.933
			SEM	2.422	2.618	2.585
			95% CI	(-9.9,-0.4)	(-9.3, 1.0)	(-6.0, 4.1)
		Pr >  t			0.7183	
		Week 32	n	70	56	
			LS Mean	-5.628	-2.938	-2.690
			SEM	2.505	2.685	2.694
			95% CI	(-10.6,-0.7)	(-8.2, 2.3)	(-8.0, 2.6)
		Pr >  t			0.3184	
		Week 40	n	61	46	
			LS Mean	-3.397	-4.465	1.068
			SEM	2.572	2.811	2.871
			95% CI	(-8.5, 1.7)	(-10.0, 1.1)	(-4.6, 6.7)
		Pr >  t			0.7100	
		Week 48	n	56	38	
			LS Mean	-5.464	-2.118	-3.346
			SEM	2.616	2.940	3.036
95% CI	(-10.6,-0.3)		(-7.9, 3.7)	(-9.3, 2.6)		
Pr >  t			0.2707			
Week 56	n	49	33			
	LS Mean	-3.904	-2.338	-1.566		
	SEM	2.689	3.044	3.203		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.2, 1.4)	(-8.3, 3.6)	(-7.9, 4.7)
	Pr >  t			0.6250
	n	37	29	
	LS Mean	-4.438	-3.255	-1.183
	SEM	2.866	3.153	3.454
Week 72	95% CI	(-10.1, 1.2)	(-9.4, 2.9)	(-8.0, 5.6)
	Pr >  t			0.7320
	n	40	25	
	LS Mean	-4.045	-1.961	-2.084
	SEM	2.815	3.283	3.531
Week 84	95% CI	(-9.6, 1.5)	(-8.4, 4.5)	(-9.0, 4.8)
	Pr >  t			0.5552
	n	32	23	
	LS Mean	-3.175	-3.516	0.341
	SEM	2.988	3.364	3.735
Week 96	95% CI	(-9.0, 2.7)	(-10.1, 3.1)	(-7.0, 7.7)
	Pr >  t			0.9272
	n	30	17	
	LS Mean	-2.350	-9.860	7.510
	SEM	3.034	3.694	4.074
Week 108	95% CI	(-8.3, 3.6)	(-17.1,-2.6)	(-0.5,15.5)
	Pr >  t			0.0655
	n	22	15	
	LS Mean	-4.881	-1.539	-3.342
	SEM	3.329	3.852	4.428
Week 120	95% CI	(-11.4, 1.7)	(-9.1, 6.0)	(-12.0, 5.3)
	Pr >  t			0.4505
	n	24	13	
	LS Mean	-8.222	-2.216	-6.006
	SEM	3.237	4.049	4.539
Week 132	95% CI	(-14.6,-1.9)	(-10.2, 5.7)	(-14.9, 2.9)
	Pr >  t			0.1860
	n	17	5	
	LS Mean	-4.903	-7.622	2.720
	SEM	3.614	5.887	6.434
Week 144	95% CI	(-12.0, 2.2)	(-19.2, 3.9)	(-9.9,15.3)
	Pr >  t			0.6726
	n	14	3	
Week 144	LS Mean	-8.840	-1.805	-7.035
	SEM	3.854	7.385	7.947

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.4,-1.3)	(-16.3,12.7)	(-22.6, 8.6)
		Pr >  t			0.3762
	Week 156	n	9	2	
		LS Mean	-2.182	-8.258	6.076
		SEM	4.562	8.892	9.673
		95% CI	(-11.1, 6.8)	(-25.7, 9.2)	(-12.9,25.1)
		Pr >  t			0.5300
	Week 168	n	4	1	
		LS Mean	-1.598	2.919	-4.517
		SEM	6.428	12.37	13.71
		95% CI	(-14.2,11.0)	(-21.3,27.2)	(-31.4,22.4)
		Pr >  t			0.7418
	Week 180	n	1	1	
		LS Mean	-6.037	-5.081	-0.957
		SEM	12.33	12.37	17.28
		95% CI	(-30.2,18.2)	(-29.3,19.2)	(-34.9,32.9)
		Pr >  t			0.9559
	Week 192	n	1	1	
		LS Mean	-8.037	-1.081	-6.957
		SEM	12.33	12.37	17.28
		95% CI	(-32.2,16.2)	(-25.3,23.2)	(-40.9,26.9)
		Pr >  t			0.6873
>= 3	Week 8	n	37	46	
		LS Mean	6.494	8.261	-1.767
		SEM	7.142	7.118	4.034
		95% CI	(-7.6,20.6)	(-5.8,22.3)	(-9.7, 6.2)
		Pr >  t			0.6618
	Week 16	n	34	32	
		LS Mean	8.417	8.819	-0.402
		SEM	7.325	7.410	4.401
		95% CI	(-6.0,22.9)	(-5.8,23.4)	(-9.1, 8.3)
		Pr >  t			0.9273
	Week 24	n	26	20	
		LS Mean	3.131	7.636	-4.505
		SEM	7.460	7.700	5.081
		95% CI	(-11.6,17.8)	(-7.5,22.8)	(-14.5, 5.5)
		Pr >  t			0.3760
	Week 32	n	16	17	
		LS Mean	4.710	7.246	-2.536
		SEM	7.786	7.827	5.732



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-10.6,20.1)	(-8.2,22.7)	(-13.8, 8.7)
	Pr >  t			0.6585
	n	14	16	
	LS Mean	7.172	4.901	2.271
	SEM	7.903	7.871	5.952
Week 48	95% CI	(-8.4,22.7)	(-10.6,20.4)	(-9.4,14.0)
	Pr >  t			0.7031
	n	13	13	
	LS Mean	3.698	2.464	1.234
	SEM	7.964	8.053	6.267
Week 56	95% CI	(-12.0,19.4)	(-13.4,18.3)	(-11.1,13.6)
	Pr >  t			0.8440
	n	10	12	
	LS Mean	9.759	6.240	3.519
	SEM	8.243	8.132	6.701
Week 64	95% CI	(-6.5,26.0)	(-9.8,22.3)	(-9.7,16.7)
	Pr >  t			0.5998
	n	10	13	
	LS Mean	6.177	0.744	5.433
	SEM	8.241	8.058	6.618
Week 72	95% CI	(-10.1,22.4)	(-15.1,16.6)	(-7.6,18.4)
	Pr >  t			0.4123
	n	8	10	
	LS Mean	6.845	2.997	3.847
	SEM	8.511	8.325	7.266
Week 84	95% CI	(-9.9,23.6)	(-13.4,19.4)	(-10.4,18.1)
	Pr >  t			0.5968
	n	8	10	
	LS Mean	8.875	1.709	7.166
	SEM	8.518	8.325	7.270
Week 96	95% CI	(-7.9,25.6)	(-14.7,18.1)	(-7.1,21.5)
	Pr >  t			0.3249
	n	6	7	
	LS Mean	10.678	-3.899	14.577
	SEM	8.962	8.797	8.277
Week 108	95% CI	(-7.0,28.3)	(-21.2,13.4)	(-1.7,30.9)
	Pr >  t			0.0790
	n	4	6	
Week 108	LS Mean	11.509	-7.312	18.821
	SEM	9.759	9.033	9.382

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-7.7,30.7)	(-25.1,10.5)	( 0.4,37.3)
	Pr >  t			0.0456
	n	5	3	
	LS Mean	19.346	2.314	17.032
	SEM	9.284	10.57	10.44
Week 132	95% CI	( 1.1,37.6)	(-18.5,23.1)	( -3.5,37.6)
	Pr >  t			0.1039
	n	3	3	
	LS Mean	14.468	-3.027	17.495
	SEM	10.50	10.57	11.54
Week 144	95% CI	( -6.2,35.1)	(-23.8,17.8)	( -5.2,40.2)
	Pr >  t			0.1305
	n	1	2	
	LS Mean	45.220	7.002	38.218
	SEM	15.17	11.91	16.83
Week 156	95% CI	( 15.4,75.0)	(-16.4,30.4)	( 5.1,71.3)
	Pr >  t			0.0238
	n	1	1	
	LS Mean	0.220	2.378	-2.158
	SEM	15.17	15.23	19.31
Week 168	95% CI	(-29.6,30.0)	(-27.6,32.3)	(-40.2,35.8)
	Pr >  t			0.9111
	n		1	
	LS Mean	NE	2.378	NE
	SEM	NE	15.23	NE
	95% CI	NE	(-27.6,32.3)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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#### 4.8.4.4 Gesundheitsbezogenen Lebensqualität: EORTC QLQ-C30 – 2. Datenschnitt

Tabelle 4H-53: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Allgemeiner Gesundheitszustand/Lebensqualität“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Presence of Liver Metastases (L)	No	Week 8	n	104	98	
			LS Mean	0.501	0.952	-0.451
			SEM	2.776	2.760	2.381
			95% CI	(-5.0, 6.0)	(-4.5, 6.4)	(-5.1, 4.2)
				Pr >  t	0.8500	
		Week 16	n	92	77	
	LS Mean		0.524	-1.522	2.045	
	SEM		2.816	2.926	2.568	
	95% CI		(-5.0, 6.1)	(-7.3, 4.2)	(-3.0, 7.1)	
				Pr >  t	0.4261	
		Week 24	n	83	66	
	LS Mean		-0.214	0.565	-0.778	
	SEM		2.871	2.995	2.702	
	95% CI		(-5.9, 5.4)	(-5.3, 6.5)	(-6.1, 4.5)	
				Pr >  t	0.7734	
		Week 32	n	72	60	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	-1.786	0.810	-2.595
		SEM	2.943	3.059	2.824
		95% CI	(-7.6, 4.0)	(-5.2, 6.8)	(-8.1, 2.9)
		Pr >  t			0.3584
	Week 40	n	64	51	
		LS Mean	-0.699	-1.278	0.580
		SEM	2.997	3.162	2.978
		95% CI	(-6.6, 5.2)	(-7.5, 4.9)	(-5.3, 6.4)
		Pr >  t			0.8457
	Week 48	n	58	45	
		LS Mean	-2.381	0.062	-2.442
		SEM	3.044	3.237	3.107
		95% CI	(-8.4, 3.6)	(-6.3, 6.4)	(-8.5, 3.7)
		Pr >  t			0.4320
	Week 56	n	49	38	
		LS Mean	-0.216	1.514	-1.729
		SEM	3.133	3.352	3.314
		95% CI	(-6.4, 5.9)	(-5.1, 8.1)	(-8.2, 4.8)
		Pr >  t			0.6019
	Week 64	n	39	37	
		LS Mean	-1.624	-0.926	-0.698
		SEM	3.273	3.371	3.471
		95% CI	(-8.1, 4.8)	(-7.5, 5.7)	(-7.5, 6.1)
		Pr >  t			0.8406
	Week 72	n	41	32	
		LS Mean	-2.104	-1.142	-0.962
		SEM	3.242	3.481	3.547
		95% CI	(-8.5, 4.3)	(-8.0, 5.7)	(-7.9, 6.0)
		Pr >  t			0.7864
	Week 84	n	33	29	
		LS Mean	0.355	0.107	0.248
		SEM	3.412	3.562	3.766
		95% CI	(-6.3, 7.1)	(-6.9, 7.1)	(-7.1, 7.6)
		Pr >  t			0.9475
	Week 96	n	31	21	
		LS Mean	-3.983	-1.265	-2.717
		SEM	3.453	3.872	4.103
		95% CI	(-10.8, 2.8)	(-8.9, 6.3)	(-10.8, 5.3)
		Pr >  t			0.5079
	Week 108	n	23	18	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		LS Mean	-0.645	0.245	-0.890
		SEM	3.734	4.047	4.492
		95% CI	(-8.0, 6.7)	(-7.7, 8.2)	(-9.7, 7.9)
		Pr >  t			0.8429
	Week 120	n	25	15	
		LS Mean	-0.113	-0.555	0.442
		SEM	3.644	4.279	4.639
		95% CI	(-7.3, 7.0)	(-9.0, 7.8)	(-8.7, 9.5)
		Pr >  t			0.9242
	Week 132	n	17	8	
		LS Mean	1.230	-7.304	8.534
		SEM	4.071	5.320	5.895
		95% CI	(-6.8, 9.2)	(-17.7, 3.1)	(-3.0, 20.1)
		Pr >  t			0.1480
	Week 144	n	15	5	
		LS Mean	-5.974	5.804	-11.78
		SEM	4.218	6.422	7.003
		95% CI	(-14.3, 2.3)	(-6.8, 18.4)	(-25.5, 2.0)
		Pr >  t			0.0928
	Week 156	n	10	3	
		LS Mean	0.117	-5.280	5.397
		SEM	4.862	8.000	8.804
		95% CI	(-9.4, 9.7)	(-21.0, 10.4)	(-11.9, 22.7)
		Pr >  t			0.5400
	Week 168	n	4	2	
		LS Mean	-1.393	6.321	-7.714
		SEM	7.018	9.617	11.47
		95% CI	(-15.2, 12.4)	(-12.5, 25.2)	(-30.2, 14.8)
		Pr >  t			0.5015
	Week 180	n	1	1	
		LS Mean	-15.00	3.041	-18.04
		SEM	13.32	13.32	18.56
		95% CI	(-41.1, 11.1)	(-23.1, 29.2)	(-54.5, 18.4)
		Pr >  t			0.3313
	Week 192	n	1	1	
		LS Mean	1.667	3.041	-1.374
		SEM	13.32	13.32	18.56
		95% CI	(-24.5, 27.8)	(-23.1, 29.2)	(-37.8, 35.1)
		Pr >  t			0.9410
Yes	Week 8	n	38	42	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	-7.599	-1.343	-6.256
		SEM	4.189	4.440	4.173
		95% CI	(-15.9, 0.7)	(-10.1, 7.4)	(-14.5, 2.0)
		Pr >  t			0.1360
	Week 16	n	32	30	
		LS Mean	-5.312	-3.254	-2.058
		SEM	4.444	4.668	4.588
		95% CI	(-14.1, 3.5)	(-12.5, 6.0)	(-11.1, 7.0)
		Pr >  t			0.6543
	Week 24	n	22	15	
		LS Mean	-8.959	0.291	-9.250
		SEM	4.731	5.457	5.617
		95% CI	(-18.3, 0.4)	(-10.5, 11.1)	(-20.3, 1.8)
		Pr >  t			0.1008
	Week 32	n	14	13	
		LS Mean	0.114	-3.789	3.904
		SEM	5.342	5.642	6.224
		95% CI	(-10.4, 10.6)	(-14.9, 7.3)	(-8.3, 16.2)
		Pr >  t			0.5311
	Week 40	n	11	11	
		LS Mean	-6.169	0.610	-6.779
		SEM	5.682	5.875	6.719
		95% CI	(-17.4, 5.0)	(-11.0, 12.2)	(-20.0, 6.4)
		Pr >  t			0.3139
	Week 48	n	11	6	
		LS Mean	-2.380	-4.190	1.811
		SEM	5.682	6.962	7.692
		95% CI	(-13.6, 8.8)	(-17.9, 9.5)	(-13.3, 17.0)
		Pr >  t			0.8141
	Week 56	n	10	7	
		LS Mean	-1.294	-0.267	-1.027
		SEM	5.825	6.644	7.513
		95% CI	(-12.8, 10.2)	(-13.3, 12.8)	(-15.8, 13.8)
		Pr >  t			0.8914
	Week 64	n	8	5	
		LS Mean	3.921	-1.052	4.973
		SEM	6.196	7.380	8.444
		95% CI	(-8.3, 16.1)	(-15.6, 13.5)	(-11.6, 21.6)
		Pr >  t			0.5564
	Week 72	n	7	3	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		LS Mean	4.015	6.507	-2.492
		SEM	6.447	8.818	9.878
		95% CI	(-8.7,16.7)	(-10.8,23.9)	(-21.9,17.0)
		Pr >  t			0.8010
	Week 84	n	7	4	
		LS Mean	-0.748	-5.365	4.617
		SEM	6.447	7.956	9.123
		95% CI	(-13.4,11.9)	(-21.0,10.3)	(-13.3,22.6)
		Pr >  t			0.6132
	Week 96	n	4	3	
		LS Mean	8.946	-1.826	10.772
		SEM	7.754	8.818	10.78
		95% CI	(-6.3,24.2)	(-19.2,15.5)	(-10.4,32.0)
		Pr >  t			0.3184
	Week 108	n	3	3	
		LS Mean	-2.059	-8.253	6.194
		SEM	8.626	8.816	11.42
		95% CI	(-19.0,14.9)	(-25.6, 9.1)	(-16.3,28.7)
		Pr >  t			0.5881
	Week 120	n	3	1	
		LS Mean	-14.31	-0.556	-13.76
		SEM	8.624	13.87	15.65
		95% CI	(-31.3, 2.7)	(-27.9,26.8)	(-44.6,17.1)
		Pr >  t			0.3804
	Week 132	n	3		
		LS Mean	-11.73	NE	NE
		SEM	8.629	NE	NE
		95% CI	(-28.7, 5.3)	NE	NE
		Pr >  t			NE

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	-1.575	0.495	-2.070		
			SEM	1.483	1.489	2.099		
			95% CI	(-4.5, 1.3)	(-2.4, 3.4)	(-6.2, 2.1)		
					Pr >  t			0.3244
		Week 16	n	118	104			
			LS Mean	-1.072	-1.533	0.460		
			SEM	1.558	1.650	2.267		
			95% CI	(-4.1, 2.0)	(-4.8, 1.7)	(-4.0, 4.9)		
					Pr >  t			0.8392
		Week 24	n	100	79			
			LS Mean	-1.703	0.612	-2.315		
			SEM	1.660	1.834	2.471		
			95% CI	(-5.0, 1.6)	(-3.0, 4.2)	(-7.2, 2.5)		
					Pr >  t			0.3490
		Week 32	n	84	72			
			LS Mean	-1.918	0.073	-1.991		
			SEM	1.771	1.901	2.595		
			95% CI	(-5.4, 1.6)	(-3.7, 3.8)	(-7.1, 3.1)		
					Pr >  t			0.4431
		Week 40	n	73	62			
			LS Mean	-1.872	-0.832	-1.040		
			SEM	1.868	2.010	2.740		
			95% CI	(-5.5, 1.8)	(-4.8, 3.1)	(-6.4, 4.3)		
					Pr >  t			0.7044
		Week 48	n	67	51			
			LS Mean	-2.590	-0.444	-2.146		
			SEM	1.927	2.165	2.895		
95% CI	(-6.4, 1.2)		(-4.7, 3.8)	(-7.8, 3.5)				
			Pr >  t			0.4587		
Week 56	n	57	45					
	LS Mean	-0.350	1.261	-1.612				
	SEM	2.048	2.274	3.058				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-4.4, 3.7)	(-3.2, 5.7)	(-7.6, 4.4)
	Pr >  t			0.5983
	n	45	42	
	LS Mean	-0.996	-0.950	-0.046
	SEM	2.242	2.337	3.236
Week 72	95% CI	(-5.4, 3.4)	(-5.5, 3.6)	(-6.4, 6.3)
	Pr >  t			0.9886
	n	46	35	
	LS Mean	-1.234	-0.574	-0.661
	SEM	2.225	2.512	3.353
Week 84	95% CI	(-5.6, 3.1)	(-5.5, 4.4)	(-7.2, 5.9)
	Pr >  t			0.8438
	n	40	33	
	LS Mean	-0.056	-0.552	0.496
	SEM	2.349	2.572	3.482
Week 96	95% CI	(-4.7, 4.6)	(-5.6, 4.5)	(-6.3, 7.3)
	Pr >  t			0.8868
	n	34	24	
	LS Mean	-2.100	-1.394	-0.705
	SEM	2.510	2.935	3.860
Week 108	95% CI	(-7.0, 2.8)	(-7.2, 4.4)	(-8.3, 6.9)
	Pr >  t			0.8551
	n	26	21	
	LS Mean	-1.088	-0.923	-0.164
	SEM	2.807	3.109	4.187
Week 120	95% CI	(-6.6, 4.4)	(-7.0, 5.2)	(-8.4, 8.0)
	Pr >  t			0.9687
	n	27	16	
	LS Mean	-2.292	-0.698	-1.595
	SEM	2.766	3.502	4.460
Week 132	95% CI	(-7.7, 3.1)	(-7.6, 6.2)	(-10.3, 7.2)
	Pr >  t			0.7207
	n	20	8	
	LS Mean	-0.972	-7.520	6.548
	SEM	3.142	4.800	5.735
Week 144	95% CI	(-7.1, 5.2)	(-16.9, 1.9)	(-4.7, 17.8)
	Pr >  t			0.2538
	n	14	5	
	LS Mean	-6.878	5.601	-12.48
	SEM	3.685	6.002	7.041

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.1, 0.3)	(-6.2,17.4)	(-26.3, 1.3)
		Pr >  t			0.0765
	Week 156	n	10	3	
		LS Mean	-0.478	-5.528	5.050
		SEM	4.300	7.673	8.795
		95% CI	(-8.9, 8.0)	(-20.6, 9.5)	(-12.2,22.3)
		Pr >  t			0.5659
	Week 168	n	4	2	
		LS Mean	-1.980	6.036	-8.017
		SEM	6.650	9.354	11.48
		95% CI	(-15.0,11.1)	(-12.3,24.4)	(-30.5,14.5)
		Pr >  t			0.4850
	Week 180	n	1	1	
		LS Mean	-15.54	2.802	-18.34
		SEM	13.15	13.15	18.59
		95% CI	(-41.3,10.3)	(-23.0,28.6)	(-54.8,18.1)
		Pr >  t			0.3241
	Week 192	n	1	1	
		LS Mean	1.133	2.802	-1.669
		SEM	13.15	13.15	18.59
		95% CI	(-24.7,26.9)	(-23.0,28.6)	(-38.1,34.8)
		Pr >  t			0.9285
Prior use	Week 8	n	8	6	
		LS Mean	-1.848	0.124	-1.972
		SEM	7.728	8.735	11.68
		95% CI	(-18.9,15.2)	(-18.8,19.1)	(-27.5,23.5)
		Pr >  t			0.8688
	Week 16	n	6	3	
		LS Mean	0.457	-16.65	17.109
		SEM	8.404	11.27	13.98
		95% CI	(-17.6,18.5)	(-40.0, 6.7)	(-12.2,46.4)
		Pr >  t			0.2365
	Week 24	n	5	2	
		LS Mean	-11.46	-4.752	-6.712
		SEM	8.778	12.41	15.12
		95% CI	(-30.0, 7.1)	(-30.2,20.7)	(-37.9,24.5)
		Pr >  t			0.6610
	Week 32	n	2	1	
		LS Mean	0.656	-5.333	5.989
		SEM	11.49	15.67	19.39

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-22.9,24.2)	(-37.5,26.8)	(-33.7,45.7)
		Pr >  t			0.7597
	Week 40	n	2		
		LS Mean	-3.509	NE	NE
		SEM	11.49	NE	NE
		95% CI	(-27.1,20.0)	NE	NE
		Pr >  t			NE
	Week 48	n	2		
		LS Mean	-7.674	NE	NE
		SEM	11.49	NE	NE
		95% CI	(-31.2,15.9)	NE	NE
		Pr >  t			NE
	Week 56	n	2		
		LS Mean	-11.84	NE	NE
		SEM	11.49	NE	NE
		95% CI	(-35.4,11.7)	NE	NE
		Pr >  t			NE
	Week 64	n	2		
		LS Mean	-3.509	NE	NE
		SEM	11.49	NE	NE
		95% CI	(-27.1,20.0)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	-11.84	NE	NE
		SEM	11.49	NE	NE
		95% CI	(-35.4,11.7)	NE	NE
		Pr >  t			NE
	Week 96	n	1		
		LS Mean	-31.80	NE	NE
		SEM	14.43	NE	NE
		95% CI	(-61.4,-2.2)	NE	NE
		Pr >  t			NE
	Week 120	n	1		
		LS Mean	1.529	NE	NE
		SEM	14.43	NE	NE
		95% CI	(-28.1,31.2)	NE	NE
		Pr >  t			NE
	Week 144	n	1		
		LS Mean	-6.801	NE	NE
		SEM	14.43	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-36.4,22.8)	NE	NE
	Pr >  t			NE

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-2.444	-0.475	-1.969		
			SEM	2.330	2.378	2.200		
					95% CI	(-7.0, 2.1)	(-5.2, 4.2)	(-6.3, 2.4)
					Pr >  t			0.3710
				Week 16	n	111	91	
					LS Mean	-2.324	-1.776	-0.548
					SEM	2.395	2.535	2.391
					95% CI	(-7.0, 2.4)	(-6.8, 3.2)	(-5.2, 4.1)
					Pr >  t			0.8187
				Week 24	n	96	70	
					LS Mean	-3.088	-0.722	-2.367
					SEM	2.461	2.679	2.592
					95% CI	(-7.9, 1.7)	(-6.0, 4.5)	(-7.5, 2.7)
					Pr >  t			0.3614
				Week 32	n	77	61	
					LS Mean	-2.807	-3.102	0.294
					SEM	2.585	2.765	2.767
					95% CI	(-7.9, 2.3)	(-8.5, 2.3)	(-5.1, 5.7)
					Pr >  t			0.9153
				Week 40	n	69	52	
					LS Mean	-2.728	-1.887	-0.841
					SEM	2.640	2.873	2.916
					95% CI	(-7.9, 2.5)	(-7.5, 3.8)	(-6.6, 4.9)
			Pr >  t			0.7731		
		Week 48	n	62	41			
			LS Mean	-2.505	-1.590	-0.915		
			SEM	2.696	3.035	3.125		
			95% CI	(-7.8, 2.8)	(-7.5, 4.4)	(-7.0, 5.2)		
			Pr >  t			0.7697		
		Week 56	n	53	35			
			LS Mean	-2.523	-0.327	-2.196		
			SEM	2.785	3.159	3.323		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.0, 2.9)	(-6.5, 5.9)	(-8.7, 4.3)
		Pr >  t			0.5089
	Week 64	n	44	33	
		LS Mean	-1.793	0.352	-2.145
		SEM	2.902	3.210	3.472
		95% CI	(-7.5, 3.9)	(-5.9, 6.7)	(-9.0, 4.7)
		Pr >  t			0.5368
	Week 72	n	45	28	
		LS Mean	-2.986	-0.675	-2.311
		SEM	2.889	3.357	3.597
		95% CI	(-8.7, 2.7)	(-7.3, 5.9)	(-9.4, 4.7)
		Pr >  t			0.5206
	Week 84	n	39	27	
		LS Mean	-1.166	-2.810	1.644
		SEM	3.001	3.392	3.711
		95% CI	(-7.1, 4.7)	(-9.5, 3.8)	(-5.6, 8.9)
		Pr >  t			0.6578
	Week 96	n	34	19	
		LS Mean	-4.240	-2.291	-1.950
		SEM	3.105	3.777	4.148
		95% CI	(-10.3, 1.9)	(-9.7, 5.1)	(-10.1, 6.2)
		Pr >  t			0.6384
	Week 108	n	26	17	
		LS Mean	-2.221	-2.077	-0.144
		SEM	3.357	3.920	4.459
		95% CI	(-8.8, 4.4)	(-9.8, 5.6)	(-8.9, 8.6)
		Pr >  t			0.9742
	Week 120	n	27	11	
		LS Mean	-3.023	0.379	-3.403
		SEM	3.315	4.582	5.027
		95% CI	(-9.5, 3.5)	(-8.6, 9.4)	(-13.3, 6.5)
		Pr >  t			0.4986
	Week 132	n	20	6	
		LS Mean	-2.118	-8.188	6.071
		SEM	3.643	5.843	6.377
		95% CI	(-9.3, 5.0)	(-19.7, 3.3)	(-6.4, 18.6)
		Pr >  t			0.3413
	Week 144	n	15	4	
		LS Mean	-7.656	4.837	-12.49
		SEM	4.011	6.978	7.623

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.5, 0.2)	(-8.9, 18.5)	(-27.4, 2.5)
		Pr >  t			0.1015
	Week 156	n	10	2	
		LS Mean	-1.609	-7.520	5.911
		SEM	4.684	9.586	10.35
		95% CI	(-10.8, 7.6)	(-26.3, 11.3)	(-14.4, 26.2)
		Pr >  t			0.5680
	Week 168	n	4	2	
		LS Mean	-3.133	4.980	-8.113
		SEM	6.915	9.586	11.53
		95% CI	(-16.7, 10.4)	(-13.8, 23.8)	(-30.7, 14.5)
		Pr >  t			0.4819
	Week 180	n	1	1	
		LS Mean	-16.64	1.787	-18.43
		SEM	13.31	13.33	18.66
		95% CI	(-42.8, 9.5)	(-24.4, 27.9)	(-55.0, 18.2)
		Pr >  t			0.3236
	Week 192	n	1	1	
		LS Mean	0.029	1.787	-1.758
		SEM	13.31	13.33	18.66
		95% CI	(-26.1, 26.1)	(-24.4, 27.9)	(-38.4, 34.9)
		Pr >  t			0.9250
>= 75 Years	Week 8	n	17	19	
		LS Mean	-0.051	1.278	-1.329
		SEM	4.418	3.953	5.929
		95% CI	(-8.9, 8.8)	(-6.6, 9.2)	(-13.2, 10.5)
		Pr >  t			0.8234
	Week 16	n	13	16	
		LS Mean	5.170	-6.908	12.078
		SEM	4.857	4.242	6.450
		95% CI	(-4.5, 14.8)	(-15.3, 1.5)	(-0.8, 24.9)
		Pr >  t			0.0648
	Week 24	n	9	11	
		LS Mean	0.313	3.126	-2.813
		SEM	5.485	4.836	7.309
		95% CI	(-10.6, 11.2)	(-6.5, 12.7)	(-17.3, 11.7)
		Pr >  t			0.7011
	Week 32	n	9	12	
		LS Mean	0.450	11.330	-10.88
		SEM	5.481	4.720	7.225

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.4,11.3)	(-2.0,20.7)	(-25.2, 3.4)
		Pr >  t			0.1351
	Week 40	n	6	10	
		LS Mean	-1.297	-0.509	-0.789
		SEM	6.293	4.996	8.029
		95% CI	(-13.7,11.1)	(-10.4, 9.4)	(-16.7,15.1)
		Pr >  t			0.9219
	Week 48	n	7	10	
		LS Mean	-10.79	0.273	-11.06
		SEM	5.971	5.007	7.778
		95% CI	(-22.6, 1.0)	(-9.6,10.2)	(-26.5, 4.3)
		Pr >  t			0.1574
	Week 56	n	6	10	
		LS Mean	9.102	3.679	5.422
		SEM	6.282	5.010	8.012
		95% CI	(-3.3,21.5)	(-6.2,13.6)	(-10.4,21.3)
		Pr >  t			0.4997
	Week 64	n	3	9	
		LS Mean	-1.201	-9.052	7.851
		SEM	8.142	5.190	9.637
		95% CI	(-17.3,14.9)	(-19.3, 1.2)	(-11.2,26.9)
		Pr >  t			0.4164
	Week 72	n	3	7	
		LS Mean	7.132	-3.673	10.806
		SEM	8.142	5.661	9.890
		95% CI	(-8.9,23.2)	(-14.9, 7.5)	(-8.7,30.3)
		Pr >  t			0.2762
	Week 84	n	1	6	
		LS Mean	1.526	5.581	-4.055
		SEM	13.08	5.977	14.36
		95% CI	(-24.3,27.4)	(-6.2,17.4)	(-32.4,24.3)
		Pr >  t			0.7780
	Week 96	n	1	5	
		LS Mean	9.856	-1.415	11.272
		SEM	13.08	6.403	14.55
		95% CI	(-16.0,35.7)	(-14.1,11.2)	(-17.4,40.0)
		Pr >  t			0.4395
	Week 108	n		4	
		LS Mean	NE	0.193	NE
		SEM	NE	6.986	NE



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	NE	(-13.6,14.0)	NE
		Pr >  t			NE
	Week 120	n	1	5	
		LS Mean	-1.116	-4.747	3.631
		SEM	13.11	6.403	14.58
		95% CI	(-27.0,24.8)	(-17.4, 7.9)	(-25.2,32.4)
		Pr >  t			0.8036
	Week 132	n		2	
		LS Mean	NE	-8.128	NE
		SEM	NE	9.302	NE
		95% CI	NE	(-26.5,10.2)	NE
		Pr >  t			NE
	Week 144	n		1	
		LS Mean	NE	4.988	NE
		SEM	NE	12.74	NE
		95% CI	NE	(-20.2,30.1)	NE
		Pr >  t			NE
	Week 156	n		1	
		LS Mean	NE	-3.342	NE
		SEM	NE	12.74	NE
		95% CI	NE	(-28.5,21.8)	NE
		Pr >  t			NE

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73		
			LS Mean	-5.868	-4.210	-1.658	
			SEM	7.098	7.287	2.822	
			95% CI	(-19.9, 8.2)	(-18.6,10.2)	(-7.2, 3.9)	
					Pr >  t		0.5571
		Week 16	n	69	55		
			LS Mean	-4.345	-5.880	1.536	
			SEM	7.107	7.357	3.033	
			95% CI	(-18.4, 9.7)	(-20.4, 8.7)	(-4.4, 7.5)	
					Pr >  t		0.6130
		Week 24	n	54	46		
			LS Mean	-4.008	-5.323	1.314	
			SEM	7.142	7.404	3.280	
			95% CI	(-18.1,10.1)	(-19.9, 9.3)	(-5.1, 7.8)	
					Pr >  t		0.6888
		Week 32	n	49	41		
			LS Mean	-6.238	-5.255	-0.983	
			SEM	7.236	7.437	3.412	
			95% CI	(-20.5, 8.1)	(-19.9, 9.4)	(-7.7, 5.7)	
					Pr >  t		0.7734
		Week 40	n	40	33		
			LS Mean	-4.254	-3.532	-0.722	
			SEM	7.296	7.508	3.687	
			95% CI	(-18.7,10.2)	(-18.4,11.3)	(-8.0, 6.5)	
					Pr >  t		0.8448
		Week 48	n	38	28		
			LS Mean	-5.337	-2.613	-2.724	
			SEM	7.312	7.572	3.849	
95% CI	(-19.8, 9.1)		(-17.6,12.3)	(-10.3, 4.8)			
			Pr >  t		0.4793		
Week 56	n	32	28				
	LS Mean	-3.446	-1.483	-1.963			
	SEM	7.373	7.573	3.962			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-18.0,11.1)	(-16.4,13.5)	(-9.7, 5.8)
	Pr >  t			0.6205
	n	23	26	
	LS Mean	-6.394	-3.329	-3.065
	SEM	7.515	7.604	4.277
Week 72	95% CI	(-21.2, 8.4)	(-18.3,11.7)	(-11.5, 5.3)
	Pr >  t			0.4739
	n	27	25	
	LS Mean	-3.498	-4.644	1.146
	SEM	7.441	7.621	4.179
Week 84	95% CI	(-18.2,11.2)	(-19.7,10.4)	(-7.1, 9.4)
	Pr >  t			0.7840
	n	23	22	
	LS Mean	-3.667	-4.061	0.394
	SEM	7.514	7.681	4.417
Week 96	95% CI	(-18.5,11.2)	(-19.2,11.1)	(-8.3, 9.1)
	Pr >  t			0.9290
	n	20	16	
	LS Mean	-8.958	-2.641	-6.317
	SEM	7.588	7.870	4.852
Week 108	95% CI	(-23.9, 6.0)	(-18.2,12.9)	(-15.8, 3.2)
	Pr >  t			0.1932
	n	20	14	
	LS Mean	-2.667	-3.348	0.681
	SEM	7.589	7.965	5.008
Week 120	95% CI	(-17.6,12.3)	(-19.0,12.4)	(-9.1,10.5)
	Pr >  t			0.8919
	n	17	11	
	LS Mean	-3.887	-5.698	1.811
	SEM	7.686	8.167	5.464
Week 132	95% CI	(-19.0,11.3)	(-21.8,10.4)	(-8.9,12.5)
	Pr >  t			0.7404
	n	13	6	
	LS Mean	-0.807	-13.68	12.871
	SEM	7.881	8.907	6.748
Week 144	95% CI	(-16.3,14.7)	(-31.2, 3.8)	(-0.4,26.1)
	Pr >  t			0.0568
	n	10	5	
	LS Mean	-12.22	1.735	-13.96
	SEM	8.121	9.218	7.418

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-28.2, 3.8)	(-16.4,19.9)	(-28.5, 0.6)
		Pr >  t			0.0602
	Week 156	n	7	3	
		LS Mean	-5.295	-9.358	4.063
		SEM	8.550	10.35	9.184
		95% CI	(-22.1,11.5)	(-29.7,11.0)	(-14.0,22.1)
		Pr >  t			0.6583
	Week 168	n	3	2	
		LS Mean	-6.474	2.269	-8.743
		SEM	10.23	11.62	11.99
		95% CI	(-26.6,13.6)	(-20.5,25.1)	(-32.3,14.8)
		Pr >  t			0.4661
	Week 180	n		1	
		LS Mean	NE	-1.104	NE
		SEM	NE	14.76	NE
		95% CI	NE	(-30.1,27.9)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-1.104	NE
		SEM	NE	14.76	NE
		95% CI	NE	(-30.1,27.9)	NE
		Pr >  t			NE
Second Line	Week 8	n	66	67	
		LS Mean	-1.431	1.481	-2.911
		SEM	2.757	2.771	3.041
		95% CI	(-6.9, 4.0)	(-4.0, 6.9)	(-8.9, 3.1)
		Pr >  t			0.3391
	Week 16	n	54	52	
		LS Mean	-1.406	-1.341	-0.065
		SEM	2.922	3.009	3.344
		95% CI	(-7.2, 4.3)	(-7.3, 4.6)	(-6.6, 6.5)
		Pr >  t			0.9845
	Week 24	n	49	35	
		LS Mean	-4.852	3.453	-8.305
		SEM	3.010	3.347	3.705
		95% CI	(-10.8, 1.1)	(-3.1,10.0)	(-15.6,-1.0)
		Pr >  t			0.0255
	Week 32	n	36	32	
		LS Mean	-1.631	1.995	-3.626
		SEM	3.277	3.443	3.978

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-8.1, 4.8)	(-4.8, 8.8)	(-11.4, 4.2)
	Pr >  t			0.3625
	n	33	29	
	LS Mean	-3.972	-2.168	-1.804
	SEM	3.352	3.559	4.126
Week 48	95% CI	(-10.6, 2.6)	(-9.2, 4.8)	(-9.9, 6.3)
	Pr >  t			0.6621
	n	29	23	
	LS Mean	-3.996	-2.532	-1.465
	SEM	3.471	3.799	4.429
Week 56	95% CI	(-10.8, 2.8)	(-10.0, 4.9)	(-10.2, 7.2)
	Pr >  t			0.7410
	n	25	17	
	LS Mean	-1.893	-0.825	-1.068
	SEM	3.615	4.170	4.868
Week 64	95% CI	(-9.0, 5.2)	(-9.0, 7.4)	(-10.6, 8.5)
	Pr >  t			0.8265
	n	22	16	
	LS Mean	-0.110	-3.548	3.438
	SEM	3.752	4.256	5.044
Week 72	95% CI	(-7.5, 7.3)	(-11.9, 4.8)	(-6.5, 13.3)
	Pr >  t			0.4957
	n	20	10	
	LS Mean	-4.104	-0.376	-3.729
	SEM	3.864	5.020	5.779
Week 84	95% CI	(-11.7, 3.5)	(-10.2, 9.5)	(-15.1, 7.6)
	Pr >  t			0.5191
	n	16	11	
	LS Mean	-0.360	-1.555	1.195
	SEM	4.172	4.848	5.835
Week 96	95% CI	(-8.6, 7.8)	(-11.1, 8.0)	(-10.3, 12.7)
	Pr >  t			0.8378
	n	15	8	
	LS Mean	-0.135	-6.985	6.850
	SEM	4.255	5.461	6.414
Week 108	95% CI	(-8.5, 8.2)	(-17.7, 3.7)	(-5.7, 19.4)
	Pr >  t			0.2859
	n	6	7	
	LS Mean	-8.355	-3.995	-4.361
	SEM	6.049	5.755	7.926

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-20.2, 3.5)	(-15.3, 7.3)	(-19.9,11.2)
	Pr >  t			0.5824
	n	11	5	
	LS Mean	-5.324	1.467	-6.791
	SEM	4.761	6.608	7.717
Week 132	95% CI	(-14.7, 4.0)	(-11.5,14.4)	(-21.9, 8.4)
	Pr >  t			0.3792
	n	7	2	
	LS Mean	-8.659	-0.770	-7.889
	SEM	5.677	9.933	11.14
Week 144	95% CI	(-19.8, 2.5)	(-20.3,18.7)	(-29.8,14.0)
	Pr >  t			0.4789
	n	5		
	LS Mean	-2.835	NE	NE
	SEM	6.515	NE	NE
Week 156	95% CI	(-15.6,10.0)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	2.047	NE	NE
	SEM	8.189	NE	NE
Week 168	95% CI	(-14.0,18.1)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	0.603	NE	NE
	SEM	13.73	NE	NE
Week 180	95% CI	(-26.4,27.6)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-16.07	NE	NE
	SEM	13.73	NE	NE
Week 192	95% CI	(-43.0,10.9)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	0.603	NE	NE
	SEM	13.73	NE	NE
Week 192	95% CI	(-26.4,27.6)	NE	NE
	Pr >  t			NE
	Pr >  t			NE

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66		
			LS Mean	-5.872	-3.199	-2.673	
			SEM	4.057	3.966	3.051	
			95% CI	(-13.9, 2.1)	(-11.0, 4.6)	(-8.7, 3.3)	
					Pr >  t		0.3816
		Week 16	n	60	51		
			LS Mean	-3.376	-4.564	1.189	
			SEM	4.135	4.177	3.261	
			95% CI	(-11.5, 4.8)	(-12.8, 3.7)	(-5.2, 7.6)	
					Pr >  t		0.7156
		Week 24	n	51	42		
			LS Mean	-3.572	-4.325	0.753	
			SEM	4.198	4.266	3.465	
			95% CI	(-11.8, 4.7)	(-12.7, 4.1)	(-6.1, 7.6)	
					Pr >  t		0.8280
		Week 32	n	46	36		
			LS Mean	-5.284	-7.860	2.576	
			SEM	4.275	4.385	3.627	
			95% CI	(-13.7, 3.1)	(-16.5, 0.8)	(-4.6, 9.7)	
					Pr >  t		0.4779
		Week 40	n	40	33		
			LS Mean	-5.988	-7.790	1.801	
			SEM	4.347	4.438	3.770	
			95% CI	(-14.5, 2.6)	(-16.5, 0.9)	(-5.6, 9.2)	
			Pr >  t		0.6330		
Week 48	n	37	28				
	LS Mean	-5.324	-8.059	2.735			
	SEM	4.386	4.544	3.938			
	95% CI	(-14.0, 3.3)	(-17.0, 0.9)	(-5.0, 10.5)			
			Pr >  t		0.4875		
Week 56	n	33	23				
	LS Mean	-2.659	-4.836	2.178			
	SEM	4.451	4.688	4.174			



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-11.4, 6.1)	(-14.1, 4.4)	(-6.0,10.4)
		Pr >  t			0.6020
		n	26	20	
		LS Mean	-2.110	-4.862	2.752
		SEM	4.601	4.806	4.462
Week 72		95% CI	(-11.2, 6.9)	(-14.3, 4.6)	(-6.0,11.5)
		Pr >  t			0.5376
		n	28	17	
		LS Mean	-3.580	-1.705	-1.875
		SEM	4.553	4.955	4.573
Week 84		95% CI	(-12.5, 5.4)	(-11.4, 8.0)	(-10.9, 7.1)
		Pr >  t			0.6819
		n	23	17	
		LS Mean	-1.846	-1.399	-0.447
		SEM	4.690	4.958	4.714
Week 96		95% CI	(-11.1, 7.4)	(-11.1, 8.3)	(-9.7, 8.8)
		Pr >  t			0.9244
		n	23	11	
		LS Mean	-3.610	-1.539	-2.072
		SEM	4.692	5.466	5.247
Week 108		95% CI	(-12.8, 5.6)	(-12.3, 9.2)	(-12.4, 8.2)
		Pr >  t			0.6930
		n	15	13	
		LS Mean	-4.392	-2.409	-1.983
		SEM	5.083	5.252	5.389
Week 120		95% CI	(-14.4, 5.6)	(-12.7, 7.9)	(-12.6, 8.6)
		Pr >  t			0.7129
		n	16	9	
		LS Mean	-0.337	-3.916	3.579
		SEM	5.019	5.762	5.829
Week 132		95% CI	(-10.2, 9.5)	(-15.2, 7.4)	(-7.9,15.0)
		Pr >  t			0.5394
		n	14	5	
		LS Mean	-4.351	-12.70	8.349
		SEM	5.158	6.900	7.058
Week 144		95% CI	(-14.5, 5.8)	(-26.2, 0.8)	(-5.5,22.2)
		Pr >  t			0.2372
		n	8	3	
		LS Mean	-1.158	-1.405	0.247
		SEM	5.942	8.321	8.952

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-12.8,10.5)	(-17.7,14.9)	(-17.3,17.8)
		Pr >  t			0.9780
		n	7	2	
	Week 168	LS Mean	-1.319	-10.95	9.633
		SEM	6.178	9.807	10.49
		95% CI	(-13.4,10.8)	(-30.2, 8.3)	(-11.0,30.2)
	Week 180	Pr >  t			0.3586
		n	4	2	
		LS Mean	-3.913	1.548	-5.461
	Week 192	SEM	7.446	9.807	11.28
		95% CI	(-18.5,10.7)	(-17.7,20.8)	(-27.6,16.7)
		Pr >  t			0.6284
	Week 8	n	1	1	
		LS Mean	-17.20	-1.833	-15.37
		SEM	13.28	13.28	18.12
	Week 16	95% CI	(-43.3, 8.9)	(-27.9,24.2)	(-50.9,20.2)
		Pr >  t			0.3967
		n	1	1	
	Week 24	LS Mean	-0.528	-1.833	1.305
		SEM	13.28	13.28	18.12
		95% CI	(-26.6,25.5)	(-27.9,24.2)	(-34.3,36.9)
	Week 32	Pr >  t			0.9426
		n	18	17	
		LS Mean	-1.719	-7.669	5.950
Week 8	SEM	4.016	4.303	5.848	
	95% CI	(-9.7, 6.3)	(-16.2, 0.9)	(-5.7,17.6)	
	Pr >  t			0.3117	
Week 16	n	17	11		
	LS Mean	-8.329	-13.31	4.977	
	SEM	4.119	5.123	6.539	
Week 24	95% CI	(-16.5,-0.2)	(-23.5,-3.1)	(-8.0,17.9)	
	Pr >  t			0.4483	
	n	15	5		
Week 32	LS Mean	-2.349	0.203	-2.553	
	SEM	4.337	7.163	8.373	
	95% CI	(-10.9, 6.2)	(-13.9,14.4)	(-19.1,14.0)	
Week 8	Pr >  t			0.7609	
	n	13	5		
	LS Mean	-3.460	-1.465	-1.995	
		SEM	4.604	7.163	8.522

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-12.6, 5.7)	(-15.6,12.7)	(-18.8,14.8)
		Pr >  t			0.8152
		n	11	5	
		LS Mean	-3.995	3.535	-7.531
		SEM	4.920	7.163	8.697
Week 48		95% CI	(-13.7, 5.7)	(-10.6,17.7)	(-24.7, 9.7)
		Pr >  t			0.3879
		n	11	2	
		LS Mean	-9.588	2.108	-11.70
		SEM	4.923	10.60	11.70
Week 56		95% CI	(-19.3, 0.1)	(-18.8,23.0)	(-34.8,11.4)
		Pr >  t			0.3187
		n	8	2	
		LS Mean	-3.339	-6.227	2.888
		SEM	5.573	10.60	11.98
Week 64		95% CI	(-14.3, 7.7)	(-27.1,14.7)	(-20.8,26.5)
		Pr >  t			0.8099
		n	7	3	
		LS Mean	-8.822	4.727	-13.55
		SEM	5.876	8.899	10.67
Week 72		95% CI	(-20.4, 2.8)	(-12.8,22.3)	(-34.6, 7.5)
		Pr >  t			0.2058
		n	7	3	
		LS Mean	-4.098	-6.386	2.288
		SEM	5.892	8.899	10.68
Week 84		95% CI	(-15.7, 7.5)	(-23.9,11.2)	(-18.8,23.4)
		Pr >  t			0.8306
		n	7	2	
		LS Mean	-6.481	-2.062	-4.419
		SEM	5.892	10.60	12.14
Week 96		95% CI	(-18.1, 5.2)	(-23.0,18.9)	(-28.4,19.5)
		Pr >  t			0.7162
		n	6	3	
		LS Mean	-7.769	-3.609	-4.160
		SEM	6.271	8.899	10.89
Week 108		95% CI	(-20.1, 4.6)	(-21.2,14.0)	(-25.7,17.3)
		Pr >  t			0.7030
		n	7	2	
		LS Mean	-4.101	-11.21	7.108
		SEM	5.892	10.58	12.12

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-15.7, 7.5)	(-32.1, 9.7)	(-16.8,31.0)
		Pr >  t			0.5582
		n	6	1	
	Week 132	LS Mean	-10.55	1.625	-12.17
		SEM	6.271	14.55	15.85
		95% CI	(-22.9, 1.8)	(-27.1,30.4)	(-43.5,19.1)
	Week 144	Pr >  t			0.4435
		n	4		
		LS Mean	-4.823	NE	NE
	Week 156	SEM	7.439	NE	NE
		95% CI	(-19.5, 9.9)	NE	NE
		Pr >  t			NE
	Week 8	n	5		
		LS Mean	-25.27	NE	NE
		SEM	6.764	NE	NE
	Week 16	95% CI	(-38.6, -12)	NE	NE
		Pr >  t			NE
		n	3		
	Week 24	LS Mean	-7.956	NE	NE
		SEM	8.457	NE	NE
		95% CI	(-24.6, 8.7)	NE	NE
	Week 32	Pr >  t			NE
		n	59	57	
		LS Mean	-0.297	3.652	-3.948
Week 16	SEM	3.022	3.172	3.255	
	95% CI	(-6.3, 5.7)	(-2.6, 9.9)	(-10.4, 2.5)	
	Pr >  t			0.2262	
Week 24	n	47	44		
	LS Mean	0.574	0.884	-0.310	
	SEM	3.185	3.378	3.598	
Week 32	95% CI	(-5.7, 6.9)	(-5.8, 7.5)	(-7.4, 6.8)	
	Pr >  t			0.9314	
	n	39	34		
Week 8	LS Mean	-4.694	3.762	-8.456	
	SEM	3.342	3.622	3.932	
	95% CI	(-11.3, 1.9)	(-3.4,10.9)	(-16.2,-0.7)	
Week 16	Pr >  t			0.0321	
	n	27	32		
	LS Mean	-1.097	6.581	-7.678	
Week 24	SEM	3.701	3.674	4.262	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-8.4, 6.2)	(-0.7,13.8)	(-16.1, 0.7)	
	Pr >  t			0.0723	
	n	24	24		
	LS Mean	0.324	3.666	-3.342	
	SEM	3.819	3.961	4.598	
Week 48	95% CI	(-7.2, 7.8)	(-4.1,11.5)	(-12.4, 5.7)	
	Pr >  t			0.4678	
	n	21	21		
	LS Mean	-0.719	5.863	-6.581	
	SEM	3.963	4.106	4.846	
Week 56	95% CI	(-8.5, 7.1)	(-2.2,13.9)	(-16.1, 2.9)	
	Pr >  t			0.1750	
	n	18	20		
	LS Mean	-2.181	6.346	-8.527	
	SEM	4.140	4.162	5.047	
Week 64	95% CI	(-10.3, 6.0)	(-1.8,14.5)	(-18.4, 1.4)	
	Pr >  t			0.0917	
	n	14	19		
	LS Mean	-1.372	0.004	-1.376	
	SEM	4.473	4.223	5.378	
Week 72	95% CI	(-10.2, 7.4)	(-8.3, 8.3)	(-11.9, 9.2)	
	Pr >  t			0.7982	
	n	13	15		
	LS Mean	-3.274	-1.038	-2.236	
	SEM	4.584	4.523	5.707	
Week 84	95% CI	(-12.3, 5.7)	(-9.9, 7.9)	(-13.4, 9.0)	
	Pr >  t			0.6953	
	n	10	14		
	LS Mean	-0.429	-2.434	2.004	
	SEM	5.056	4.618	6.136	
Week 96	95% CI	(-10.4, 9.5)	(-11.5, 6.6)	(-10.0,14.1)	
	Pr >  t			0.7440	
	n	6	10		
	LS Mean	-8.797	-3.539	-5.258	
	SEM	6.119	5.152	7.425	
Week 108	95% CI	(-20.8, 3.2)	(-13.7, 6.6)	(-19.8, 9.3)	
	Pr >  t			0.4791	
	n	4	6		
	LS Mean	-0.668	-2.051	1.383	
	SEM	7.269	6.216	9.071	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-14.9,13.6)	(-14.3,10.2)	(-16.4,19.2)
	Pr >  t			0.8788
	n	6	6	
	LS Mean	-8.509	-0.721	-7.788
	SEM	6.121	6.219	8.200
Week 132	95% CI	(-20.5, 3.5)	(-12.9,11.5)	(-23.9, 8.3)
	Pr >  t			0.3427
	n	2	3	
	LS Mean	5.118	-4.042	9.161
	SEM	9.876	8.269	12.52
Week 144	95% CI	(-14.3,24.5)	(-20.3,12.2)	(-15.4,33.8)
	Pr >  t			0.4647
	n	2	2	
	LS Mean	-1.035	11.718	-12.75
	SEM	9.841	9.925	13.68
Week 156	95% CI	(-20.4,18.3)	(-7.8,31.2)	(-39.6,14.1)
	Pr >  t			0.3517
	n		1	
	LS Mean	NE	-1.113	NE
	SEM	NE	13.67	NE
	95% CI	NE	(-28.0,25.8)	NE
	Pr >  t			NE

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	6.252	NE	NE	
			SEM	5.931	NE	NE	
			95% CI	(-69.1,81.6)	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	14.582	NE	NE	
			SEM	5.931	NE	NE	
			95% CI	(-60.8,89.9)	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	10.417	NE	NE	
			SEM	9.024	NE	NE	
			95% CI	( -104, 125)	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	-6.253	NE	NE	
			SEM	9.024	NE	NE	
			95% CI	( -121, 108)	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	2.087	NE	NE	
			SEM	9.644	NE	NE	
			95% CI	( -120, 125)	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	18.747	NE	NE	
			SEM	9.644	NE	NE	
95% CI	( -104, 141)		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	2.087	NE	NE			
	SEM	9.644	NE	NE			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-120, 125)	NE
		Pr >  t		NE
	Week 72	n	1	
		LS Mean	10.417	NE
		SEM	9.024	NE
		95% CI	(-104, 125)	NE
		Pr >  t		NE
	Week 84	n	1	
		LS Mean	-6.253	NE
		SEM	9.024	NE
		95% CI	(-121, 108)	NE
		Pr >  t		NE
	Week 96	n	1	
		LS Mean	2.087	NE
		SEM	9.024	NE
		95% CI	(-113, 117)	NE
		Pr >  t		NE
Positive	Week 8	n	140	140
		LS Mean	-2.576	-0.330
		SEM	2.298	2.332
		95% CI	(-7.1, 1.9)	(-4.9, 4.3)
		Pr >  t		(-6.3, 1.8) 0.2771
	Week 16	n	122	107
		LS Mean	-2.017	-2.630
		SEM	2.364	2.465
		95% CI	(-6.7, 2.6)	(-7.5, 2.2)
		Pr >  t		(-3.8, 5.0) 0.7847
	Week 24	n	104	81
		LS Mean	-3.153	-0.276
		SEM	2.429	2.598
		95% CI	(-7.9, 1.6)	(-5.4, 4.8)
		Pr >  t		(-7.7, 1.9) 0.2393
	Week 32	n	85	73
		LS Mean	-2.724	-0.822
		SEM	2.537	2.659
		95% CI	(-7.7, 2.3)	(-6.0, 4.4)
		Pr >  t		(-7.0, 3.2) 0.4619
	Week 40	n	74	62
		LS Mean	-2.830	-1.784
		SEM	2.601	2.753



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-7.9, 2.3)	(-7.2, 3.6)	(-6.4, 4.3)
	Pr >  t			0.7022
Week 48	n	68	51	
	LS Mean	-3.901	-1.397	-2.505
	SEM	2.642	2.868	2.890
	95% CI	(-9.1, 1.3)	(-7.0, 4.2)	(-8.2, 3.2)
	Pr >  t			0.3863
Week 56	n	58	45	
	LS Mean	-1.597	0.317	-1.914
	SEM	2.726	2.951	3.051
	95% CI	(-7.0, 3.8)	(-5.5, 6.1)	(-7.9, 4.1)
	Pr >  t			0.5305
Week 64	n	47	42	
	LS Mean	-2.005	-1.905	-0.100
	SEM	2.852	3.001	3.212
	95% CI	(-7.6, 3.6)	(-7.8, 4.0)	(-6.4, 6.2)
	Pr >  t			0.9752
Week 72	n	47	35	
	LS Mean	-2.741	-1.530	-1.211
	SEM	2.854	3.139	3.343
	95% CI	(-8.3, 2.9)	(-7.7, 4.6)	(-7.8, 5.3)
	Pr >  t			0.7172
Week 84	n	39	33	
	LS Mean	-0.902	-1.511	0.608
	SEM	2.995	3.187	3.500
	95% CI	(-6.8, 5.0)	(-7.8, 4.7)	(-6.3, 7.5)
	Pr >  t			0.8620
Week 96	n	34	24	
	LS Mean	-3.940	-2.352	-1.588
	SEM	3.098	3.488	3.863
	95% CI	(-10.0, 2.1)	(-9.2, 4.5)	(-9.2, 6.0)
	Pr >  t			0.6810
Week 108	n	26	21	
	LS Mean	-2.207	-1.883	-0.324
	SEM	3.350	3.635	4.189
	95% CI	(-8.8, 4.4)	(-9.0, 5.2)	(-8.5, 7.9)
	Pr >  t			0.9384
Week 120	n	28	16	
	LS Mean	-3.082	-1.667	-1.415
	SEM	3.273	3.978	4.437

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-9.5, 3.3)	(-9.5, 6.1)	(-10.1, 7.3)
	Pr >  t			0.7498
Week 132	n	20	8	
	LS Mean	-2.095	-8.492	6.397
	SEM	3.635	5.158	5.739
	95% CI	(-9.2, 5.0)	(-18.6, 1.6)	(-4.9, 17.7)
	Pr >  t			0.2652
Week 144	n	15	5	
	LS Mean	-7.642	4.615	-12.26
	SEM	4.002	6.295	6.988
	95% CI	(-15.5, 0.2)	(-7.7, 17.0)	(-26.0, 1.5)
	Pr >  t			0.0796
Week 156	n	10	3	
	LS Mean	-1.585	-6.505	4.920
	SEM	4.674	7.907	8.802
	95% CI	(-10.8, 7.6)	(-22.0, 9.0)	(-12.3, 22.2)
	Pr >  t			0.5762
Week 168	n	4	2	
	LS Mean	-3.097	5.072	-8.170
	SEM	6.901	9.549	11.49
	95% CI	(-16.6, 10.4)	(-13.7, 23.8)	(-30.7, 14.4)
	Pr >  t			0.4770
Week 180	n	1	1	
	LS Mean	-16.65	1.812	-18.47
	SEM	13.28	13.29	18.61
	95% CI	(-42.7, 9.4)	(-24.3, 27.9)	(-55.0, 18.0)
	Pr >  t			0.3212
Week 192	n	1	1	
	LS Mean	0.016	1.812	-1.795
	SEM	13.28	13.29	18.61
	95% CI	(-26.0, 26.1)	(-24.3, 27.9)	(-38.3, 34.7)
	Pr >  t			0.9232

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-2.415	-1.783	-0.632
			SEM	2.351	2.441	2.303
			95% CI	(-7.0, 2.2)	(-6.6, 3.0)	(-5.2, 3.9)
		Pr >  t			0.7838	
		Week 16	n	90	75	
			LS Mean	-3.026	-4.680	1.654
			SEM	2.418	2.572	2.498
			95% CI	(-7.8, 1.7)	(-9.7, 0.4)	(-3.3, 6.6)
		Pr >  t			0.5081	
		Week 24	n	79	62	
			LS Mean	-1.409	-1.132	-0.277
			SEM	2.485	2.693	2.666
			95% CI	(-6.3, 3.5)	(-6.4, 4.2)	(-5.5, 5.0)
		Pr >  t			0.9172	
		Week 32	n	70	56	
			LS Mean	-3.102	-2.287	-0.815
			SEM	2.573	2.763	2.780
			95% CI	(-8.2, 2.0)	(-7.7, 3.1)	(-6.3, 4.6)
		Pr >  t			0.7695	
		Week 40	n	61	46	
			LS Mean	-3.703	-2.994	-0.709
			SEM	2.645	2.895	2.967
			95% CI	(-8.9, 1.5)	(-8.7, 2.7)	(-6.5, 5.1)
Pr >  t			0.8113			
Week 48	n	56	38			
	LS Mean	-3.950	-3.735	-0.215		
	SEM	2.691	3.031	3.140		
	95% CI	(-9.2, 1.3)	(-9.7, 2.2)	(-6.4, 5.9)		
Pr >  t			0.9453			
Week 56	n	49	33			
	LS Mean	-2.614	-0.364	-2.249		
	SEM	2.769	3.142	3.316		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.1, 2.8)	(-6.5, 5.8)	(-8.8, 4.3)
	Pr >  t			0.4977
	n	37	29	
	LS Mean	-2.886	0.184	-3.070
	SEM	2.955	3.255	3.580
Week 72	95% CI	(-8.7, 2.9)	(-6.2, 6.6)	(-10.1, 4.0)
	Pr >  t			0.3914
	n	40	25	
	LS Mean	-3.776	-2.850	-0.927
	SEM	2.901	3.392	3.662
Week 84	95% CI	(-9.5, 1.9)	(-9.5, 3.8)	(-8.1, 6.3)
	Pr >  t			0.8003
	n	32	23	
	LS Mean	-1.902	-3.780	1.879
	SEM	3.084	3.478	3.875
Week 96	95% CI	(-8.0, 4.2)	(-10.6, 3.0)	(-5.7, 9.5)
	Pr >  t			0.6279
	n	29	17	
	LS Mean	-4.361	-1.795	-2.566
	SEM	3.163	3.826	4.254
Week 108	95% CI	(-10.6, 1.8)	(-9.3, 5.7)	(-10.9, 5.8)
	Pr >  t			0.5465
	n	22	15	
	LS Mean	-3.576	1.728	-5.304
	SEM	3.444	3.992	4.603
Week 120	95% CI	(-10.3, 3.2)	(-6.1, 9.6)	(-14.3, 3.7)
	Pr >  t			0.2494
	n	23	13	
	LS Mean	-5.276	-1.899	-3.378
	SEM	3.391	4.200	4.752
Week 132	95% CI	(-11.9, 1.4)	(-10.1, 6.3)	(-12.7, 5.9)
	Pr >  t			0.4773
	n	17	5	
	LS Mean	-4.186	-10.79	6.605
	SEM	3.744	6.129	6.706
Week 144	95% CI	(-11.5, 3.2)	(-22.8, 1.2)	(-6.6, 19.8)
	Pr >  t			0.3249
	n	14	3	
Week 144	LS Mean	-12.49	5.511	-18.00
	SEM	3.997	7.698	8.289

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.3,-4.7)	(-9.6,20.6)	(-34.3,-1.7)
		Pr >  t			0.0301
	Week 156	n	9	2	
		LS Mean	-3.218	-6.260	3.041
		SEM	4.742	9.275	10.09
		95% CI	(-12.5, 6.1)	(-24.5,11.9)	(-16.8,22.8)
		Pr >  t			0.7633
	Week 168	n	4	1	
		LS Mean	-4.127	1.116	-5.243
		SEM	6.697	12.91	14.31
		95% CI	(-17.3, 9.0)	(-24.2,26.4)	(-33.3,22.8)
		Pr >  t			0.7142
	Week 180	n	1	1	
		LS Mean	-17.70	1.116	-18.82
		SEM	12.87	12.91	18.04
		95% CI	(-43.0, 7.6)	(-24.2,26.4)	(-54.2,16.6)
		Pr >  t			0.2973
	Week 192	n	1	1	
		LS Mean	-1.030	1.116	-2.146
		SEM	12.87	12.91	18.04
		95% CI	(-26.3,24.2)	(-24.2,26.4)	(-37.6,33.3)
		Pr >  t			0.9054
>= 3	Week 8	n	37	45	
		LS Mean	0.620	6.568	-5.949
		SEM	7.638	7.537	4.291
		95% CI	(-14.5,15.7)	(-8.3,21.5)	(-14.4, 2.5)
		Pr >  t			0.1674
	Week 16	n	34	32	
		LS Mean	4.917	5.439	-0.522
		SEM	7.826	7.826	4.666
		95% CI	(-10.5,20.4)	(-10.0,20.9)	(-9.7, 8.7)
		Pr >  t			0.9111
	Week 24	n	26	19	
		LS Mean	-5.015	4.440	-9.455
		SEM	7.957	8.151	5.407
		95% CI	(-20.7,10.7)	(-11.6,20.5)	(-20.1, 1.2)
		Pr >  t			0.0815
	Week 32	n	16	17	
		LS Mean	0.834	5.779	-4.946
		SEM	8.283	8.250	6.024

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-15.5,17.2)	(-10.5,22.0)	(-16.8, 6.9)
		Pr >  t			0.4123
	Week 40	n	14	16	
		LS Mean	3.213	3.843	-0.630
		SEM	8.404	8.295	6.254
		95% CI	(-13.4,19.8)	(-12.5,20.2)	(-12.9,11.7)
		Pr >  t			0.9198
	Week 48	n	13	13	
		LS Mean	-0.044	7.623	-7.666
		SEM	8.469	8.484	6.579
		95% CI	(-16.7,16.7)	(-9.1,24.3)	(-20.6, 5.3)
		Pr >  t			0.2447
	Week 56	n	10	12	
		LS Mean	4.878	4.734	0.144
		SEM	8.755	8.570	7.032
		95% CI	(-12.4,22.1)	(-12.2,21.6)	(-13.7,14.0)
		Pr >  t			0.9837
	Week 64	n	10	13	
		LS Mean	3.909	-3.449	7.358
		SEM	8.754	8.489	6.942
		95% CI	(-13.3,21.2)	(-20.2,13.3)	(-6.3,21.0)
		Pr >  t			0.2899
	Week 72	n	8	10	
		LS Mean	5.431	4.774	0.657
		SEM	9.034	8.777	7.615
		95% CI	(-12.4,23.2)	(-12.5,22.1)	(-14.3,15.6)
		Pr >  t			0.9313
	Week 84	n	8	10	
		LS Mean	4.214	6.777	-2.563
		SEM	9.039	8.766	7.615
		95% CI	(-13.6,22.0)	(-10.5,24.0)	(-17.5,12.4)
		Pr >  t			0.7366
	Week 96	n	6	7	
		LS Mean	-0.153	-0.389	0.235
		SEM	9.491	9.254	8.663
		95% CI	(-18.8,18.5)	(-18.6,17.8)	(-16.8,17.3)
		Pr >  t			0.9783
	Week 108	n	4	6	
		LS Mean	6.855	-7.568	14.424
		SEM	10.32	9.501	9.813

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.4,27.2)	(-26.3,11.1)	(-4.9,33.7)
		Pr >  t			0.1425
	Week 120	n	5	3	
		LS Mean	9.037	1.518	7.518
		SEM	9.827	11.09	10.92
		95% CI	(-10.3,28.4)	(-20.3,23.3)	(-14.0,29.0)
		Pr >  t			0.4917
	Week 132	n	3	3	
		LS Mean	10.950	-1.026	11.976
		SEM	11.08	11.10	12.07
		95% CI	(-10.8,32.7)	(-22.9,20.8)	(-11.8,35.7)
		Pr >  t			0.3218
	Week 144	n	1	2	
		LS Mean	54.638	7.327	47.311
		SEM	15.92	12.50	17.60
		95% CI	(23.3,85.9)	(-17.3,31.9)	(12.7,81.9)
		Pr >  t			0.0076
	Week 156	n	1	1	
		LS Mean	12.978	-3.388	16.366
		SEM	15.92	15.96	20.20
		95% CI	(-18.3,44.3)	(-34.8,28.0)	(-23.4,56.1)
		Pr >  t			0.4183
	Week 168	n		1	
		LS Mean	NE	13.282	NE
		SEM	NE	15.96	NE
		95% CI	NE	(-18.1,44.7)	NE
		Pr >  t			NE

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-15i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Global health status/QOL scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60			
			LS Mean	0.282	2.118	-1.836		
			SEM	5.374	5.561	2.799		
			95% CI	(-10.4,10.9)	(-8.9,13.2)	(-7.3, 3.7)		
					Pr >  t			0.5122
		Week 16	n	59	49			
			LS Mean	0.378	-3.332	3.710		
			SEM	5.411	5.633	3.031		
			95% CI	(-10.4,11.1)	(-14.5, 7.8)	(-2.2, 9.7)		
					Pr >  t			0.2215
		Week 24	n	54	41			
			LS Mean	1.296	3.090	-1.794		
			SEM	5.432	5.707	3.217		
			95% CI	(-9.5,12.1)	(-8.2,14.4)	(-8.1, 4.5)		
					Pr >  t			0.5772
		Week 32	n	48	37			
			LS Mean	-1.140	-0.525	-0.615		
			SEM	5.465	5.750	3.364		
			95% CI	(-12.0, 9.7)	(-11.9,10.9)	(-7.2, 6.0)		
					Pr >  t			0.8551
		Week 40	n	43	33			
			LS Mean	0.222	0.781	-0.560		
			SEM	5.500	5.803	3.520		
			95% CI	(-10.7,11.1)	(-10.7,12.3)	(-7.5, 6.4)		
					Pr >  t			0.8737
		Week 48	n	41	28			
			LS Mean	-1.585	-0.612	-0.973		
			SEM	5.516	5.887	3.688		
95% CI	(-12.5, 9.3)		(-12.3,11.0)	(-8.2, 6.3)				
			Pr >  t			0.7920		
Week 56	n	35	22					
	LS Mean	-1.577	0.981	-2.558				
	SEM	5.576	6.038	4.021				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.6, 9.5)	(-11.0,12.9)	(-10.5, 5.3)
		Pr >  t			0.5249
	Week 64	n	26	23	
		LS Mean	-2.181	3.653	-5.834
		SEM	5.716	6.009	4.193
		95% CI	(-13.5, 9.1)	( -8.2,15.5)	(-14.1, 2.4)
		Pr >  t			0.1645
	Week 72	n	28	18	
		LS Mean	-3.107	-2.814	-0.293
		SEM	5.678	6.186	4.389
		95% CI	(-14.3, 8.1)	(-15.0, 9.4)	( -8.9, 8.3)
		Pr >  t			0.9468
	Week 84	n	22	18	
		LS Mean	-0.392	-0.095	-0.297
		SEM	5.865	6.186	4.578
		95% CI	(-12.0,11.2)	(-12.3,12.1)	( -9.3, 8.7)
		Pr >  t			0.9482
	Week 96	n	21	13	
		LS Mean	-5.558	2.507	-8.065
		SEM	5.842	6.483	5.014
		95% CI	(-17.1, 6.0)	(-10.3,15.3)	(-17.9, 1.8)
		Pr >  t			0.1081
	Week 108	n	17	12	
		LS Mean	0.397	1.067	-0.670
		SEM	6.062	6.570	5.311
		95% CI	(-11.6,12.4)	(-11.9,14.0)	(-11.1, 9.8)
		Pr >  t			0.8996
	Week 120	n	18	11	
		LS Mean	-4.799	1.677	-6.476
		SEM	5.950	6.670	5.384
		95% CI	(-16.6, 7.0)	(-11.5,14.8)	(-17.0, 4.1)
		Pr >  t			0.2294
	Week 132	n	13	5	
		LS Mean	-0.394	-7.878	7.484
		SEM	6.311	7.960	7.180
		95% CI	(-12.8,12.1)	(-23.5, 7.8)	( -6.6,21.6)
		Pr >  t			0.2975
	Week 144	n	12	3	
		LS Mean	-8.701	8.510	-17.21
		SEM	6.312	9.303	8.711

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-21.2, 3.8)	(-9.8, 26.8)	(-34.3, -0.1)
		Pr >  t			0.0485
	Week 156	n	7	2	
		LS Mean	-2.794	-3.166	0.372
		SEM	7.156	10.73	10.71
		95% CI	(-16.9, 11.3)	(-24.2, 17.9)	(-20.7, 21.4)
		Pr >  t			0.9723
	Week 168	n	3	1	
		LS Mean	-1.230	4.265	-5.495
		SEM	9.158	14.19	15.28
		95% CI	(-19.2, 16.8)	(-23.6, 32.1)	(-35.5, 24.5)
		Pr >  t			0.7192
	Week 180	n	1	1	
		LS Mean	-15.88	4.265	-20.14
		SEM	14.10	14.19	18.66
		95% CI	(-43.5, 11.8)	(-23.6, 32.1)	(-56.8, 16.5)
		Pr >  t			0.2808
	Week 192	n	1	1	
		LS Mean	0.793	4.265	-3.472
		SEM	14.10	14.19	18.66
		95% CI	(-26.9, 28.5)	(-23.6, 32.1)	(-40.1, 33.2)
		Pr >  t			0.8525
Yes	Week 8	n	73	80	
		LS Mean	-7.375	-5.555	-1.821
		SEM	3.904	3.937	2.970
		95% CI	(-15.1, 0.3)	(-13.3, 2.2)	(-7.7, 4.0)
		Pr >  t			0.5404
	Week 16	n	65	58	
		LS Mean	-6.355	-5.213	-1.142
		SEM	4.011	4.118	3.220
		95% CI	(-14.3, 1.5)	(-13.3, 2.9)	(-7.5, 5.2)
		Pr >  t			0.7231
	Week 24	n	51	40	
		LS Mean	-9.704	-6.886	-2.818
		SEM	4.101	4.346	3.590
		95% CI	(-17.8, -1.6)	(-15.4, 1.7)	(-9.9, 4.2)
		Pr >  t			0.4329
	Week 32	n	38	36	
		LS Mean	-6.467	-4.277	-2.189
		SEM	4.308	4.416	3.845

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.9, 2.0)	(-13.0, 4.4)	(-9.7, 5.4)
		Pr >  t			0.5693
	Week 40	n	32	29	
		LS Mean	-8.504	-7.591	-0.913
		SEM	4.425	4.560	4.126
		95% CI	(-17.2, 0.2)	(-16.6, 1.4)	(-9.0, 7.2)
		Pr >  t			0.8249
	Week 48	n	28	23	
		LS Mean	-8.174	-5.180	-2.994
		SEM	4.514	4.743	4.413
		95% CI	(-17.1, 0.7)	(-14.5, 4.1)	(-11.7, 5.7)
		Pr >  t			0.4978
	Week 56	n	24	23	
		LS Mean	-3.330	-3.551	0.221
		SEM	4.636	4.742	4.534
		95% CI	(-12.4, 5.8)	(-12.9, 5.8)	(-8.7, 9.1)
		Pr >  t			0.9612
	Week 64	n	21	19	
		LS Mean	-3.603	-11.40	7.796
		SEM	4.753	4.911	4.823
		95% CI	(-12.9, 5.7)	(-21.1,-1.7)	(-1.7,17.3)
		Pr >  t			0.1065
	Week 72	n	20	17	
		LS Mean	-3.285	-3.116	-0.169
		SEM	4.801	5.020	4.979
		95% CI	(-12.7, 6.2)	(-13.0, 6.7)	(-9.9, 9.6)
		Pr >  t			0.9729
	Week 84	n	18	15	
		LS Mean	-3.817	-6.032	2.215
		SEM	4.890	5.158	5.204
		95% CI	(-13.4, 5.8)	(-16.2, 4.1)	(-8.0,12.4)
		Pr >  t			0.6706
	Week 96	n	14	11	
		LS Mean	-2.765	-10.80	8.036
		SEM	5.170	5.552	5.834
		95% CI	(-12.9, 7.4)	(-21.7, 0.1)	(-3.4,19.5)
		Pr >  t			0.1688
	Week 108	n	9	9	
		LS Mean	-7.705	-8.132	0.427
		SEM	5.786	5.853	6.655

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.1, 3.7)	(-19.6, 3.4)	(-12.6,13.5)
		Pr >  t			0.9488
	Week 120	n	10	5	
		LS Mean	-0.779	-9.419	8.640
		SEM	5.639	7.033	7.604
		95% CI	(-11.9,10.3)	(-23.2, 4.4)	( -6.3,23.6)
		Pr >  t			0.2562
	Week 132	n	7	3	
		LS Mean	-5.893	-11.00	5.104
		SEM	6.235	8.473	9.347
		95% CI	(-18.1, 6.3)	(-27.6, 5.6)	(-13.2,23.5)
		Pr >  t			0.5852
	Week 144	n	3	2	
		LS Mean	-1.592	-2.767	1.175
		SEM	8.420	9.999	12.15
		95% CI	(-18.1,14.9)	(-22.4,16.9)	(-22.7,25.0)
		Pr >  t			0.9230
	Week 156	n	3	1	
		LS Mean	1.109	-13.37	14.480
		SEM	8.430	13.58	15.23
		95% CI	(-15.4,17.7)	(-40.0,13.3)	(-15.4,44.4)
		Pr >  t			0.3422
	Week 168	n	1	1	
		LS Mean	-9.231	3.299	-12.53
		SEM	13.58	13.58	18.59
		95% CI	(-35.9,17.4)	(-23.4,30.0)	(-49.0,24.0)
		Pr >  t			0.5004

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-54: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Körperliche Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73	
			LS Mean	-3.142	-0.382	-2.760
			SEM	2.645	2.668	2.323
			95% CI	(-8.4, 2.1)	(-5.6, 4.9)	(-7.3, 1.8)
				Pr >  t		0.2358
		Week 16	n	67	56	
	LS Mean		-1.450	-2.289	0.839	
	SEM		2.679	2.790	2.482	
	95% CI		(-6.7, 3.8)	(-7.8, 3.2)	(-4.0, 5.7)	
			Pr >  t		0.7355	
		Week 24	n	61	46	
	LS Mean		-4.029	-1.441	-2.588	
	SEM		2.718	2.858	2.598	
	95% CI		(-9.4, 1.3)	(-7.1, 4.2)	(-7.7, 2.5)	
			Pr >  t		0.3199	
		Week 32	n	52	41	
	LS Mean		-2.857	-3.553	0.696	
	SEM		2.788	2.913	2.699	
	95% CI		(-8.4, 2.6)	(-9.3, 2.2)	(-4.6, 6.0)	
			Pr >  t		0.7967	
		Week 40	n	45	36	
	LS Mean		0.046	-2.063	2.109	
	SEM		2.837	2.977	2.808	
	95% CI		(-5.5, 5.6)	(-7.9, 3.8)	(-3.4, 7.6)	
		Pr >  t		0.4529		
	Week 48	n	42	30		
LS Mean		-3.691	-1.907	-1.784		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	SEM	2.863	3.060	2.922
	95% CI	(-9.3, 1.9)	(-7.9, 4.1)	(-7.5, 4.0)
	Pr >  t			0.5419
	n	35	24	
	LS Mean	-2.916	-2.722	-0.194
Week 64	SEM	2.934	3.179	3.117
	95% CI	(-8.7, 2.9)	(-9.0, 3.5)	(-6.3, 5.9)
	Pr >  t			0.9505
	n	25	25	
	LS Mean	-3.377	-0.371	-3.006
Week 72	SEM	3.094	3.157	3.249
	95% CI	(-9.5, 2.7)	(-6.6, 5.8)	(-9.4, 3.4)
	Pr >  t			0.3551
	n	27	20	
	LS Mean	-3.677	-0.912	-2.764
Week 84	SEM	3.055	3.291	3.343
	95% CI	(-9.7, 2.3)	(-7.4, 5.6)	(-9.3, 3.8)
	Pr >  t			0.4085
	n	23	19	
	LS Mean	-5.306	-1.387	-3.920
Week 96	SEM	3.150	3.326	3.457
	95% CI	(-11.5, 0.9)	(-7.9, 5.2)	(-10.7, 2.9)
	Pr >  t			0.2572
	n	20	13	
	LS Mean	-3.467	-4.789	1.322
Week 108	SEM	3.238	3.623	3.818
	95% CI	(-9.8, 2.9)	(-11.9, 2.3)	(-6.2, 8.8)
	Pr >  t			0.7293
	n	17	13	
	LS Mean	-3.535	-5.605	2.070
Week 120	SEM	3.352	3.624	3.915
	95% CI	(-10.1, 3.1)	(-12.7, 1.5)	(-5.6, 9.8)
	Pr >  t			0.5972
	n	17	12	
	LS Mean	-2.470	0.212	-2.682
Week 132	SEM	3.352	3.698	3.984
	95% CI	(-9.1, 4.1)	(-7.1, 7.5)	(-10.5, 5.1)
	Pr >  t			0.5009
Week 132	n	13	6	
	LS Mean	-6.225	-6.808	0.583

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 144	SEM	3.571	4.542	4.934
		95% CI	(-13.2, 0.8)	(-15.7, 2.1)	(-9.1,10.3)
		Pr >  t			0.9060
	Week 156	n	11	4	
		LS Mean	-8.687	-1.912	-6.775
		SEM	3.731	5.257	5.703
	Week 168	95% CI	(-16.0,-1.4)	(-12.2, 8.4)	(-18.0, 4.4)
		Pr >  t			0.2352
		n	7	2	
	Week 180	LS Mean	-3.231	-2.029	-1.202
		SEM	4.271	6.954	7.587
		95% CI	(-11.6, 5.2)	(-15.7,11.6)	(-16.1,13.7)
	Week 192	Pr >  t			0.8741
		n	3	1	
		LS Mean	-0.228	3.335	-3.563
	Week 8	SEM	5.831	9.480	10.72
		95% CI	(-11.7,11.2)	(-15.3,21.9)	(-24.6,17.5)
		Pr >  t			0.7396
	Week 16	n	1	1	
		LS Mean	-6.860	-3.335	-3.525
		SEM	9.453	9.480	13.05
	Week 24	95% CI	(-25.4,11.7)	(-21.9,15.3)	(-29.1,22.1)
		Pr >  t			0.7871
		n	1	1	
Week 8	LS Mean	-20.20	-3.335	-16.86	
	SEM	9.453	9.480	13.05	
	95% CI	(-38.8,-1.6)	(-21.9,15.3)	(-42.5, 8.7)	
Week 16	Pr >  t			0.1965	
	n	65	67		
	LS Mean	-2.727	-4.308	1.581	
Week 24	SEM	3.316	3.403	2.801	
	95% CI	(-9.3, 3.8)	(-11.0, 2.4)	(-3.9, 7.1)	
	Pr >  t			0.5731	
Week 8	n	57	51		
	LS Mean	-3.888	-3.113	-0.775	
	SEM	3.415	3.529	2.989	
Week 16	95% CI	(-10.6, 2.8)	(-10.1, 3.8)	(-6.7, 5.1)	
	Pr >  t			0.7957	
	n	44	35		
Week 24	LS Mean	-2.843	-8.137	5.294	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	3.505	3.725	3.295
		95% CI	(-9.8, 4.1)	(-15.5,-0.8)	(-1.2,11.8)
		Pr >  t			0.1091
	Week 32	n	34	32	
		LS Mean	-0.820	-4.739	3.919
		SEM	3.634	3.775	3.474
		95% CI	(-8.0, 6.3)	(-12.2, 2.7)	(-2.9,10.7)
		Pr >  t			0.2600
	Week 40	n	30	26	
		LS Mean	-2.346	-8.297	5.951
		SEM	3.699	3.888	3.664
		95% CI	(-9.6, 4.9)	(-16.0,-0.6)	(-1.3,13.2)
		Pr >  t			0.1051
	Week 48	n	27	21	
		LS Mean	-4.679	-9.518	4.840
		SEM	3.750	4.024	3.860
		95% CI	(-12.1, 2.7)	(-17.4,-1.6)	(-2.7,12.4)
		Pr >  t			0.2105
	Week 56	n	24	21	
		LS Mean	-1.246	-5.447	4.200
		SEM	3.820	4.024	3.928
		95% CI	(-8.8, 6.3)	(-13.4, 2.5)	(-3.5,11.9)
		Pr >  t			0.2855
	Week 64	n	22	17	
		LS Mean	-2.995	-6.742	3.747
		SEM	3.874	4.179	4.139
		95% CI	(-10.6, 4.6)	(-15.0, 1.5)	(-4.4,11.9)
		Pr >  t			0.3657
	Week 72	n	21	15	
		LS Mean	-1.644	-6.030	4.386
		SEM	3.906	4.282	4.272
		95% CI	(-9.3, 6.0)	(-14.4, 2.4)	(-4.0,12.8)
		Pr >  t			0.3051
	Week 84	n	17	14	
		LS Mean	-2.600	-4.607	2.007
		SEM	4.065	4.341	4.468
		95% CI	(-10.6, 5.4)	(-13.1, 3.9)	(-6.8,10.8)
		Pr >  t			0.6535
	Week 96	n	15	11	
		LS Mean	-2.715	-6.450	3.735

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 108	SEM	4.157	4.580	4.792
	95% CI	(-10.9, 5.5)	(-15.5, 2.6)	(-5.7,13.1)
	Pr >  t			0.4360
	n	9	8	
	LS Mean	-4.663	-7.192	2.529
Week 120	SEM	4.704	4.968	5.604
	95% CI	(-13.9, 4.6)	(-17.0, 2.6)	(-8.5,13.5)
	Pr >  t			0.6519
	n	11	4	
	LS Mean	-6.138	-5.580	-0.558
Week 132	SEM	4.466	6.179	6.546
	95% CI	(-14.9, 2.6)	(-17.7, 6.6)	(-13.4,12.3)
	Pr >  t			0.9320
	n	7	2	
	LS Mean	-8.061	-2.207	-5.855
Week 144	SEM	5.050	8.034	8.640
	95% CI	(-18.0, 1.9)	(-18.0,13.6)	(-22.8,11.1)
	Pr >  t			0.4983
	n	4	1	
	LS Mean	-7.607	-1.135	-6.472
Week 156	SEM	6.039	10.85	11.80
	95% CI	(-19.5, 4.2)	(-22.4,20.2)	(-29.7,16.7)
	Pr >  t			0.5836
	n	3	1	
	LS Mean	-6.857	-1.135	-5.722
Week 168	SEM	6.760	10.85	12.17
	95% CI	(-20.1, 6.4)	(-22.4,20.2)	(-29.6,18.2)
	Pr >  t			0.6384
	n	1	1	
	LS Mean	-2.865	-1.135	-1.730
Week 168	SEM	10.81	10.85	14.81
	95% CI	(-24.1,18.4)	(-22.4,20.2)	(-30.8,27.4)
	Pr >  t			0.9070

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Presence of Liver Metastases (L)	No	Week 8	n	104	98	
			LS Mean	-1.981	-1.075	-0.906
			SEM	2.462	2.441	1.999
			95% CI	(-6.8, 2.9)	(-5.9, 3.7)	(-4.8, 3.0)
		Pr >  t			0.6507	
		Week 16	n	92	77	
			LS Mean	-1.529	-2.503	0.975
			SEM	2.487	2.546	2.123
			95% CI	(-6.4, 3.4)	(-7.5, 2.5)	(-3.2, 5.1)
		Pr >  t			0.6463	
		Week 24	n	83	66	
			LS Mean	-2.985	-3.573	0.589
			SEM	2.519	2.588	2.208
			95% CI	(-7.9, 2.0)	(-8.7, 1.5)	(-3.7, 4.9)
		Pr >  t			0.7899	
		Week 32	n	72	60	
			LS Mean	-2.170	-3.667	1.497
			SEM	2.561	2.626	2.284
			95% CI	(-7.2, 2.9)	(-8.8, 1.5)	(-3.0, 6.0)
		Pr >  t			0.5125	
		Week 40	n	64	51	
			LS Mean	-0.327	-3.982	3.655
			SEM	2.592	2.685	2.380
			95% CI	(-5.4, 4.8)	(-9.3, 1.3)	(-1.0, 8.3)
		Pr >  t			0.1252	
		Week 48	n	58	45	
			LS Mean	-3.393	-3.092	-0.302
			SEM	2.619	2.730	2.461
95% CI	(-8.5, 1.8)		(-8.5, 2.3)	(-5.1, 4.5)		
Pr >  t			0.9025			
Week 56	n	49	38			
	LS Mean	-1.822	-3.135	1.313		
	SEM	2.671	2.798	2.592		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.1, 3.4)	(-8.6, 2.4)	(-3.8, 6.4)
	Pr >  t			0.6127
	n	39	37	
	LS Mean	-2.589	-2.188	-0.400
	SEM	2.753	2.810	2.692
Week 72	95% CI	(-8.0, 2.8)	(-7.7, 3.3)	(-5.7, 4.9)
	Pr >  t			0.8818
	n	41	32	
	LS Mean	-2.498	-2.662	0.165
	SEM	2.735	2.875	2.741
Week 84	95% CI	(-7.9, 2.9)	(-8.3, 3.0)	(-5.2, 5.5)
	Pr >  t			0.9521
	n	33	29	
	LS Mean	-3.848	-3.513	-0.335
	SEM	2.835	2.924	2.882
Week 96	95% CI	(-9.4, 1.7)	(-9.3, 2.2)	(-6.0, 5.3)
	Pr >  t			0.9075
	n	31	21	
	LS Mean	-3.134	-5.101	1.968
	SEM	2.860	3.113	3.101
Week 108	95% CI	(-8.8, 2.5)	(-11.2, 1.0)	(-4.1, 8.1)
	Pr >  t			0.5259
	n	23	18	
	LS Mean	-3.723	-7.161	3.438
	SEM	3.029	3.221	3.357
Week 120	95% CI	(-9.7, 2.2)	(-13.5,-0.8)	(-3.1,10.0)
	Pr >  t			0.3061
	n	25	15	
	LS Mean	-2.807	-0.990	-1.816
	SEM	2.975	3.366	3.455
Week 132	95% CI	(-8.7, 3.0)	(-7.6, 5.6)	(-8.6, 5.0)
	Pr >  t			0.5993
	n	17	8	
	LS Mean	-5.316	-5.857	0.541
	SEM	3.236	4.033	4.297
Week 144	95% CI	(-11.7, 1.0)	(-13.8, 2.1)	(-7.9, 9.0)
	Pr >  t			0.8998
	n	15	5	
Week 144	LS Mean	-7.856	-2.155	-5.701
	SEM	3.329	4.760	5.052

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.4,-1.3)	(-11.5, 7.2)	(-15.6, 4.2)
		Pr >  t			0.2593
	Week 156	n	10	3	
		LS Mean	-3.725	-1.687	-2.038
		SEM	3.736	5.821	6.291
		95% CI	(-11.1, 3.6)	(-13.1, 9.7)	(-14.4,10.3)
		Pr >  t			0.7460
	Week 168	n	4	2	
		LS Mean	-0.278	1.610	-1.888
		SEM	5.158	6.925	8.142
		95% CI	(-10.4, 9.8)	(-12.0,15.2)	(-17.9,14.1)
		Pr >  t			0.8167
	Week 180	n	1	1	
		LS Mean	-6.438	-4.207	-2.231
		SEM	9.476	9.482	13.09
		95% CI	(-25.0,12.2)	(-22.8,14.4)	(-27.9,23.5)
		Pr >  t			0.8647
	Week 192	n	1	1	
		LS Mean	-19.78	-4.207	-15.57
		SEM	9.476	9.482	13.09
		95% CI	(-38.4,-1.2)	(-22.8,14.4)	(-41.3,10.1)
		Pr >  t			0.2346
Yes	Week 8	n	38	42	
		LS Mean	-4.465	-4.112	-0.354
		SEM	4.009	4.280	3.961
		95% CI	(-12.4, 3.5)	(-12.6, 4.4)	( -8.2, 7.5)
		Pr >  t			0.9290
	Week 16	n	32	30	
		LS Mean	-4.078	-2.056	-2.022
		SEM	4.226	4.475	4.331
		95% CI	(-12.4, 4.3)	(-10.9, 6.8)	(-10.6, 6.5)
		Pr >  t			0.6412
	Week 24	n	22	15	
		LS Mean	-3.690	-5.995	2.305
		SEM	4.462	5.134	5.202
		95% CI	(-12.5, 5.1)	(-16.1, 4.1)	( -7.9,12.6)
		Pr >  t			0.6581
	Week 32	n	14	13	
		LS Mean	1.487	-3.996	5.484
		SEM	4.964	5.284	5.711

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.3,11.3)	(-14.4, 6.4)	(-5.8,16.7)
		Pr >  t			0.3378
	Week 40	n	11	11	
		LS Mean	-1.040	-6.335	5.295
		SEM	5.251	5.477	6.131
		95% CI	(-11.4, 9.3)	(-17.1, 4.5)	(-6.8,17.4)
		Pr >  t			0.3885
	Week 48	n	11	6	
		LS Mean	-4.676	-16.87	12.192
		SEM	5.251	6.389	6.960
		95% CI	(-15.0, 5.7)	(-29.4,-4.3)	(-1.5,25.9)
		Pr >  t			0.0809
	Week 56	n	10	7	
		LS Mean	-1.456	-5.797	4.341
		SEM	5.372	6.125	6.813
		95% CI	(-12.0, 9.1)	(-17.9, 6.3)	(-9.1,17.8)
		Pr >  t			0.5245
	Week 64	n	8	5	
		LS Mean	-3.328	-5.880	2.552
		SEM	5.682	6.736	7.595
		95% CI	(-14.5, 7.9)	(-19.1, 7.4)	(-12.4,17.5)
		Pr >  t			0.7371
	Week 72	n	7	3	
		LS Mean	-1.056	-2.412	1.356
		SEM	5.893	7.961	8.838
		95% CI	(-12.7,10.5)	(-18.1,13.3)	(-16.0,18.8)
		Pr >  t			0.8781
	Week 84	n	7	4	
		LS Mean	-2.962	6.176	-9.138
		SEM	5.893	7.221	8.177
		95% CI	(-14.6, 8.6)	(-8.0,20.4)	(-25.2, 7.0)
		Pr >  t			0.2648
	Week 96	n	4	3	
		LS Mean	0.941	-4.636	5.577
		SEM	7.003	7.961	9.613
		95% CI	(-12.8,14.7)	(-20.3,11.0)	(-13.4,24.5)
		Pr >  t			0.5623
	Week 108	n	3	3	
		LS Mean	-0.912	0.505	-1.417
		SEM	7.747	7.962	10.17

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.2,14.3)	(-15.2,16.2)	(-21.4,18.6)
		Pr >  t			0.8893
	Week 120	n	3	1	
		LS Mean	-8.030	-8.028	-0.002
		SEM	7.748	12.31	13.84
		95% CI	(-23.3, 7.2)	(-32.3,16.2)	(-27.3,27.3)
		Pr >  t			0.9999
	Week 132	n	3		
		LS Mean	-12.18	NE	NE
		SEM	7.749	NE	NE
		95% CI	(-27.4, 3.1)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	-2.993	-2.561	-0.432		
			SEM	1.313	1.317	1.857		
					95% CI	(-5.6,-0.4)	(-5.1, 0.0)	(-4.1, 3.2)
					Pr >  t			0.8161
				Week 16	n	118	104	
					LS Mean	-2.725	-2.732	0.007
					SEM	1.363	1.427	1.972
					95% CI	(-5.4,-0.0)	(-5.5, 0.1)	(-3.9, 3.9)
					Pr >  t			0.9973
				Week 24	n	100	79	
					LS Mean	-4.121	-4.396	0.276
					SEM	1.430	1.549	2.105
					95% CI	(-6.9,-1.3)	(-7.4,-1.4)	(-3.9, 4.4)
					Pr >  t			0.8959
				Week 32	n	84	72	
					LS Mean	-2.371	-4.346	1.974
					SEM	1.501	1.593	2.187
					95% CI	(-5.3, 0.6)	(-7.5,-1.2)	(-2.3, 6.3)
					Pr >  t			0.3669
				Week 40	n	73	62	
					LS Mean	-1.201	-4.965	3.764
					SEM	1.564	1.664	2.281
					95% CI	(-4.3, 1.9)	(-8.2,-1.7)	(-0.7, 8.2)
			Pr >  t			0.0993		
		Week 48	n	67	51			
			LS Mean	-4.349	-5.355	1.005		
			SEM	1.603	1.766	2.383		
			95% CI	(-7.5,-1.2)	(-8.8,-1.9)	(-3.7, 5.7)		
			Pr >  t			0.6731		
		Week 56	n	57	45			
			LS Mean	-2.557	-4.068	1.511		
			SEM	1.681	1.838	2.489		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-5.9, 0.7)	(-7.7, -0.5)	(-3.4, 6.4)
	Pr >  t			0.5439
Week 64	n	45	42	
	LS Mean	-3.574	-3.265	-0.308
	SEM	1.809	1.881	2.608
	95% CI	(-7.1, -0.0)	(-7.0, 0.4)	(-5.4, 4.8)
	Pr >  t			0.9059
Week 72	n	46	35	
	LS Mean	-3.422	-3.324	-0.098
	SEM	1.798	1.998	2.687
	95% CI	(-7.0, 0.1)	(-7.2, 0.6)	(-5.4, 5.2)
	Pr >  t			0.9708
Week 84	n	40	33	
	LS Mean	-4.533	-2.993	-1.540
	SEM	1.881	2.039	2.773
	95% CI	(-8.2, -0.8)	(-7.0, 1.0)	(-7.0, 3.9)
	Pr >  t			0.5788
Week 96	n	34	24	
	LS Mean	-3.585	-5.649	2.063
	SEM	1.989	2.287	3.030
	95% CI	(-7.5, 0.3)	(-10.1, -1.2)	(-3.9, 8.0)
	Pr >  t			0.4960
Week 108	n	26	21	
	LS Mean	-4.260	-6.611	2.351
	SEM	2.192	2.407	3.254
	95% CI	(-8.6, 0.0)	(-11.3, -1.9)	(-4.0, 8.7)
	Pr >  t			0.4701
Week 120	n	27	16	
	LS Mean	-4.116	-2.079	-2.037
	SEM	2.164	2.681	3.443
	95% CI	(-8.4, 0.1)	(-7.3, 3.2)	(-8.8, 4.7)
	Pr >  t			0.5542
Week 132	n	20	8	
	LS Mean	-7.217	-6.599	-0.618
	SEM	2.423	3.599	4.338
	95% CI	(-12.0, -2.5)	(-13.7, 0.5)	(-9.1, 7.9)
	Pr >  t			0.8867
Week 144	n	14	5	
	LS Mean	-9.356	-2.902	-6.454
	SEM	2.803	4.462	5.268

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.9,-3.9)	(-11.7, 5.9)	(-16.8, 3.9)
		Pr >  t			0.2207
	Week 156	n	10	3	
		LS Mean	-4.666	-2.437	-2.229
		SEM	3.238	5.670	6.528
		95% CI	(-11.0, 1.7)	(-13.6, 8.7)	(-15.0,10.6)
		Pr >  t			0.7329
	Week 168	n	4	2	
		LS Mean	-1.230	0.849	-2.079
		SEM	4.926	6.890	8.469
		95% CI	(-10.9, 8.4)	(-12.7,14.4)	(-18.7,14.5)
		Pr >  t			0.8061
	Week 180	n	1	1	
		LS Mean	-7.390	-4.987	-2.403
		SEM	9.648	9.652	13.65
		95% CI	(-26.3,11.5)	(-23.9,13.9)	(-29.2,24.4)
		Pr >  t			0.8603
	Week 192	n	1	1	
		LS Mean	-20.73	-4.987	-15.74
		SEM	9.648	9.652	13.65
		95% CI	(-39.7,-1.8)	(-23.9,13.9)	(-42.5,11.0)
		Pr >  t			0.2489
Prior use	Week 8	n	8	6	
		LS Mean	-4.851	0.993	-5.845
		SEM	4.384	4.960	6.635
		95% CI	(-14.2, 4.5)	( -9.4,11.4)	(-19.9, 8.2)
		Pr >  t			0.3913
	Week 16	n	6	3	
		LS Mean	-2.789	-8.329	5.540
		SEM	5.001	6.993	8.507
		95% CI	(-13.3, 7.7)	(-22.8, 6.1)	(-12.1,23.2)
		Pr >  t			0.5217
	Week 24	n	5	2	
		LS Mean	3.722	-12.50	16.218
		SEM	5.300	8.407	9.817
		95% CI	( -7.3,14.7)	(-29.7, 4.7)	( -3.9,36.4)
		Pr >  t			0.1100
	Week 32	n	2	1	
		LS Mean	0.351	-0.635	0.986
		SEM	7.876	11.30	13.76

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-15.8,16.5)	(-23.9,22.6)	(-27.3,29.2)
	Pr >  t			0.9434
Week 40	n	2		
	LS Mean	0.351	NE	NE
	SEM	7.876	NE	NE
	95% CI	(-15.8,16.5)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	-2.984	NE	NE
	SEM	7.876	NE	NE
	95% CI	(-19.1,13.2)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	0.346	NE	NE
	SEM	7.876	NE	NE
	95% CI	(-15.8,16.5)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	0.351	NE	NE
	SEM	7.876	NE	NE
	95% CI	(-15.8,16.5)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	7.016	NE	NE
	SEM	7.876	NE	NE
	95% CI	(-9.1,23.2)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	3.291	NE	NE
	SEM	10.45	NE	NE
	95% CI	(-18.3,24.9)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	-3.379	NE	NE
	SEM	10.45	NE	NE
	95% CI	(-25.0,18.2)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	3.291	NE	NE
	SEM	10.45	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-18.3,24.9)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-2.633	-2.702	0.069		
			SEM	2.129	2.166	1.922		
			95% CI	(-6.8, 1.6)	(-7.0, 1.6)	(-3.7, 3.8)		
					Pr >  t			0.9713
		Week 16	n	111	91			
			LS Mean	-2.456	-2.460	0.004		
			SEM	2.169	2.265	2.047		
			95% CI	(-6.7, 1.8)	(-6.9, 2.0)	(-4.0, 4.0)		
					Pr >  t			0.9985
		Week 24	n	96	70			
			LS Mean	-3.419	-4.125	0.706		
			SEM	2.207	2.352	2.174		
			95% CI	(-7.8, 0.9)	(-8.7, 0.5)	(-3.6, 5.0)		
					Pr >  t			0.7455
		Week 32	n	77	61			
			LS Mean	-1.742	-3.384	1.641		
			SEM	2.279	2.403	2.283		
			95% CI	(-6.2, 2.7)	(-8.1, 1.3)	(-2.8, 6.1)		
					Pr >  t			0.4724
		Week 40	n	69	52			
			LS Mean	-0.719	-4.342	3.623		
			SEM	2.312	2.466	2.377		
			95% CI	(-5.3, 3.8)	(-9.2, 0.5)	(-1.0, 8.3)		
			Pr >  t			0.1280		
Week 48	n	62	41					
	LS Mean	-3.678	-4.486	0.808				
	SEM	2.344	2.563	2.508				
	95% CI	(-8.3, 0.9)	(-9.5, 0.5)	(-4.1, 5.7)				
			Pr >  t			0.7475		
Week 56	n	53	35					
	LS Mean	-2.276	-2.607	0.331				
	SEM	2.396	2.638	2.634				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.0, 2.4)	(-7.8, 2.6)	(-4.8, 5.5)
		Pr >  t			0.9000
	Week 64	n	44	33	
		LS Mean	-3.100	-2.983	-0.117
		SEM	2.466	2.668	2.729
		95% CI	(-7.9, 1.7)	(-8.2, 2.3)	(-5.5, 5.2)
		Pr >  t			0.9659
	Week 72	n	45	28	
		LS Mean	-3.406	-2.404	-1.003
		SEM	2.458	2.758	2.810
		95% CI	(-8.2, 1.4)	(-7.8, 3.0)	(-6.5, 4.5)
		Pr >  t			0.7213
	Week 84	n	39	27	
		LS Mean	-4.429	-2.176	-2.253
		SEM	2.523	2.780	2.884
		95% CI	(-9.4, 0.5)	(-7.6, 3.3)	(-7.9, 3.4)
		Pr >  t			0.4348
	Week 96	n	34	19	
		LS Mean	-3.417	-4.931	1.514
		SEM	2.587	3.020	3.170
		95% CI	(-8.5, 1.7)	(-10.9, 1.0)	(-4.7, 7.7)
		Pr >  t			0.6330
	Week 108	n	26	17	
		LS Mean	-3.908	-5.482	1.574
		SEM	2.741	3.110	3.376
		95% CI	(-9.3, 1.5)	(-11.6, 0.6)	(-5.0, 8.2)
		Pr >  t			0.6411
	Week 120	n	27	11	
		LS Mean	-4.508	-2.747	-1.761
		SEM	2.716	3.536	3.757
		95% CI	(-9.8, 0.8)	(-9.7, 4.2)	(-9.1, 5.6)
		Pr >  t			0.6393
	Week 132	n	20	6	
		LS Mean	-6.864	-8.728	1.865
		SEM	2.918	4.373	4.675
		95% CI	(-12.6,-1.1)	(-17.3,-0.2)	(-7.3,11.0)
		Pr >  t			0.6901
	Week 144	n	15	4	
		LS Mean	-8.427	-0.719	-7.709
		SEM	3.153	5.143	5.536

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.6,-2.2)	(-10.8, 9.4)	(-18.6, 3.2)
		Pr >  t			0.1640
	Week 156	n	10	2	
		LS Mean	-4.292	1.568	-5.860
		SEM	3.588	6.941	7.435
		95% CI	(-11.3, 2.7)	(-12.0,15.2)	(-20.4, 8.7)
		Pr >  t			0.4307
	Week 168	n	4	2	
		LS Mean	-0.867	1.568	-2.435
		SEM	5.089	6.941	8.264
		95% CI	(-10.8, 9.1)	(-12.0,15.2)	(-18.6,13.8)
		Pr >  t			0.7683
	Week 180	n	1	1	
		LS Mean	-6.978	-4.304	-2.674
		SEM	9.536	9.558	13.29
		95% CI	(-25.7,11.7)	(-23.1,14.4)	(-28.7,23.4)
		Pr >  t			0.8405
	Week 192	n	1	1	
		LS Mean	-20.32	-4.304	-16.01
		SEM	9.536	9.558	13.29
		95% CI	(-39.0,-1.6)	(-23.1,14.4)	(-42.1,10.1)
		Pr >  t			0.2283
>= 75 Years	Week 8	n	17	19	
		LS Mean	-2.878	2.613	-5.491
		SEM	3.876	3.674	5.269
		95% CI	(-10.6, 4.8)	( -4.7, 9.9)	(-16.0, 5.0)
		Pr >  t			0.3007
	Week 16	n	13	16	
		LS Mean	-0.705	-2.660	1.955
		SEM	4.293	3.895	5.782
		95% CI	( -9.2, 7.8)	(-10.4, 5.1)	( -9.5,13.4)
		Pr >  t			0.7361
	Week 24	n	9	11	
		LS Mean	-2.305	-4.919	2.613
		SEM	4.901	4.420	6.581
		95% CI	(-12.0, 7.4)	(-13.7, 3.8)	(-10.4,15.6)
		Pr >  t			0.6920
	Week 32	n	9	12	
		LS Mean	-2.879	-6.742	3.863
		SEM	4.901	4.307	6.503



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.6, 6.8)	(-15.3, 1.8)	(-9.0,16.7)
		Pr >  t			0.5537
	Week 40	n	6	10	
		LS Mean	-1.069	-5.791	4.722
		SEM	5.690	4.569	7.276
		95% CI	(-12.3,10.2)	(-14.8, 3.3)	(-9.7,19.1)
		Pr >  t			0.5175
	Week 48	n	7	10	
		LS Mean	-5.415	-7.009	1.594
		SEM	5.378	4.577	7.031
		95% CI	(-16.0, 5.2)	(-16.1, 2.1)	(-12.3,15.5)
		Pr >  t			0.8210
	Week 56	n	6	10	
		LS Mean	0.096	-7.726	7.822
		SEM	5.681	4.576	7.256
		95% CI	(-11.1,11.3)	(-16.8, 1.3)	(-6.5,22.2)
		Pr >  t			0.2829
	Week 64	n	3	9	
		LS Mean	-1.638	-2.699	1.061
		SEM	7.472	4.739	8.809
		95% CI	(-16.4,13.1)	(-12.1, 6.7)	(-16.3,18.5)
		Pr >  t			0.9042
	Week 72	n	3	7	
		LS Mean	9.472	-5.311	14.783
		SEM	7.472	5.197	9.061
		95% CI	(-5.3,24.2)	(-15.6, 5.0)	(-3.1,32.7)
		Pr >  t			0.1047
	Week 84	n	1	6	
		LS Mean	9.499	-4.571	14.070
		SEM	12.16	5.499	13.32
		95% CI	(-14.5,33.5)	(-15.4, 6.3)	(-12.2,40.4)
		Pr >  t			0.2922
	Week 96	n	1	5	
		LS Mean	9.499	-6.497	15.996
		SEM	12.16	5.901	13.49
		95% CI	(-14.5,33.5)	(-18.1, 5.2)	(-10.6,42.6)
		Pr >  t			0.2374
	Week 108	n		4	
		LS Mean	NE	-9.444	NE
		SEM	NE	6.452	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-22.2, 3.3)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	15.173	0.167
		SEM	12.19	5.901
		95% CI	(-8.9,39.2)	(-11.5,11.8)
		Pr >  t		0.2683
	Week 132	n		2
		LS Mean	NE	0.935
		SEM	NE	8.643
		95% CI	NE	(-16.1,18.0)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	-10.09
		SEM	NE	11.89
		95% CI	NE	(-33.6,13.4)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	-10.09
		SEM	NE	11.89
		95% CI	NE	(-33.6,13.4)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Line of Advanced Anti-Cancer Trt (L)	First Line	Week 8	n	74	73			
			LS Mean	-0.529	-3.583	3.053		
			SEM	7.203	7.401	2.602		
			95% CI	(-14.8,13.7)	(-18.2,11.0)	(-2.1, 8.2)		
					Pr >  t			0.2418
		Week 16	n	69	55			
			LS Mean	-1.662	-2.960	1.298		
			SEM	7.208	7.443	2.744		
			95% CI	(-15.9,12.6)	(-17.7,11.8)	(-4.1, 6.7)		
					Pr >  t			0.6365
		Week 24	n	54	46			
			LS Mean	-3.718	-6.429	2.710		
			SEM	7.227	7.469	2.901		
			95% CI	(-18.0,10.6)	(-21.2, 8.3)	(-3.0, 8.4)		
					Pr >  t			0.3508
		Week 32	n	49	41			
			LS Mean	-2.580	-4.994	2.413		
			SEM	7.278	7.487	2.985		
			95% CI	(-17.0,11.8)	(-19.8, 9.8)	(-3.5, 8.3)		
					Pr >  t			0.4193
		Week 40	n	40	33			
			LS Mean	-0.610	-4.691	4.080		
			SEM	7.311	7.525	3.157		
			95% CI	(-15.1,13.8)	(-19.6,10.2)	(-2.1,10.3)		
					Pr >  t			0.1970
		Week 48	n	38	28			
			LS Mean	-5.091	-7.002	1.911		
			SEM	7.320	7.560	3.261		
95% CI	(-19.6, 9.4)		(-21.9, 7.9)	(-4.5, 8.3)				
			Pr >  t			0.5582		
Week 56	n	32	28					
	LS Mean	-1.914	-3.250	1.336				
	SEM	7.353	7.561	3.334				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-16.4,12.6)	(-18.2,11.7)	(-5.2, 7.9)
	Pr >  t			0.6889
Week 64	n	23	26	
	LS Mean	-3.871	-2.185	-1.685
	SEM	7.430	7.578	3.538
	95% CI	(-18.5,10.8)	(-17.2,12.8)	(-8.6, 5.3)
	Pr >  t			0.6340
Week 72	n	27	25	
	LS Mean	-2.598	-4.389	1.790
	SEM	7.390	7.586	3.474
	95% CI	(-17.2,12.0)	(-19.4,10.6)	(-5.0, 8.6)
	Pr >  t			0.6065
Week 84	n	23	22	
	LS Mean	-6.461	-5.553	-0.908
	SEM	7.430	7.619	3.629
	95% CI	(-21.1, 8.2)	(-20.6, 9.5)	(-8.0, 6.2)
	Pr >  t			0.8025
Week 96	n	20	16	
	LS Mean	-6.079	-5.940	-0.140
	SEM	7.470	7.722	3.917
	95% CI	(-20.8, 8.7)	(-21.2, 9.3)	(-7.8, 7.5)
	Pr >  t			0.9716
Week 108	n	20	14	
	LS Mean	-2.620	-7.371	4.751
	SEM	7.471	7.774	4.021
	95% CI	(-17.4,12.1)	(-22.7, 8.0)	(-3.1,12.6)
	Pr >  t			0.2378
Week 120	n	17	11	
	LS Mean	-5.416	-3.175	-2.240
	SEM	7.524	7.887	4.329
	95% CI	(-20.3, 9.4)	(-18.7,12.4)	(-10.7, 6.3)
	Pr >  t			0.6050
Week 132	n	13	6	
	LS Mean	-4.464	-8.907	4.443
	SEM	7.632	8.306	5.211
	95% CI	(-19.5,10.6)	(-25.3, 7.5)	(-5.8,14.7)
	Pr >  t			0.3942
Week 144	n	10	5	
	LS Mean	-8.722	-3.735	-4.987
	SEM	7.766	8.486	5.680

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-24.0, 6.6)	(-20.5,13.0)	(-16.1, 6.2)
		Pr >  t			0.3802
	Week 156	n	7	3	
		LS Mean	-3.813	-3.276	-0.537
		SEM	8.010	9.162	6.929
		95% CI	(-19.6,12.0)	(-21.3,14.8)	(-14.1,13.1)
		Pr >  t			0.9383
	Week 168	n	3	2	
		LS Mean	-3.441	-0.002	-3.439
		SEM	9.010	9.944	8.941
		95% CI	(-21.2,14.3)	(-19.5,19.5)	(-21.0,14.1)
		Pr >  t			0.7006
	Week 180	n		1	
		LS Mean	NE	-5.852	NE
		SEM	NE	11.97	NE
		95% CI	NE	(-29.4,17.7)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-5.852	NE
		SEM	NE	11.97	NE
		95% CI	NE	(-29.4,17.7)	NE
		Pr >  t			NE
Second Line	Week 8	n	66	67	
		LS Mean	-5.893	-0.391	-5.502
		SEM	2.291	2.297	2.471
		95% CI	(-10.4,-1.4)	( -4.9, 4.1)	(-10.4,-0.6)
		Pr >  t			0.0269
	Week 16	n	54	52	
		LS Mean	-3.543	-2.063	-1.480
		SEM	2.402	2.457	2.678
		95% CI	( -8.3, 1.2)	( -6.9, 2.8)	( -6.8, 3.8)
		Pr >  t			0.5810
	Week 24	n	49	35	
		LS Mean	-3.447	-1.638	-1.810
		SEM	2.459	2.681	2.921
		95% CI	( -8.3, 1.4)	( -6.9, 3.6)	( -7.6, 3.9)
		Pr >  t			0.5359
	Week 32	n	36	32	
		LS Mean	-1.024	-2.811	1.787
		SEM	2.632	2.744	3.105

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-6.2, 4.2)	(-8.2, 2.6)	(-4.3, 7.9)
	Pr >  t			0.5651
	n	33	29	
	LS Mean	-0.111	-4.566	4.456
	SEM	2.681	2.819	3.203
Week 48	95% CI	(-5.4, 5.2)	(-10.1, 1.0)	(-1.8, 10.8)
	Pr >  t			0.1649
	n	29	23	
	LS Mean	-2.813	-2.695	-0.118
	SEM	2.758	2.977	3.406
Week 56	95% CI	(-8.2, 2.6)	(-8.5, 3.2)	(-6.8, 6.6)
	Pr >  t			0.9724
	n	25	17	
	LS Mean	-2.684	-5.130	2.446
	SEM	2.851	3.223	3.701
Week 64	95% CI	(-8.3, 2.9)	(-11.5, 1.2)	(-4.8, 9.7)
	Pr >  t			0.5089
	n	22	16	
	LS Mean	-2.676	-4.772	2.096
	SEM	2.942	3.280	3.821
Week 72	95% CI	(-8.5, 3.1)	(-11.2, 1.7)	(-5.4, 9.6)
	Pr >  t			0.5834
	n	20	10	
	LS Mean	-2.945	-0.845	-2.100
	SEM	3.017	3.798	4.327
Week 84	95% CI	(-8.9, 3.0)	(-8.3, 6.6)	(-10.6, 6.4)
	Pr >  t			0.6277
	n	16	11	
	LS Mean	-0.944	2.225	-3.168
	SEM	3.219	3.680	4.363
Week 96	95% CI	(-7.3, 5.4)	(-5.0, 9.5)	(-11.7, 5.4)
	Pr >  t			0.4680
	n	15	8	
	LS Mean	0.777	-4.990	5.767
	SEM	3.275	4.100	4.766
Week 108	95% CI	(-5.7, 7.2)	(-13.0, 3.1)	(-3.6, 15.1)
	Pr >  t			0.2267
	n	6	7	
	LS Mean	-8.766	-4.903	-3.864
	SEM	4.499	4.302	5.821

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-17.6, 0.1)	(-13.4, 3.5)	(-15.3, 7.6)
	Pr >  t			0.5071
Week 120	n	11	5	
	LS Mean	-1.430	0.344	-1.775
	SEM	3.620	4.893	5.677
	95% CI	(-8.5, 5.7)	(-9.3, 10.0)	(-12.9, 9.4)
	Pr >  t			0.7546
Week 132	n	7	2	
	LS Mean	-11.39	-0.168	-11.23
	SEM	4.242	7.229	8.086
	95% CI	(-19.7, -3.1)	(-14.4, 14.0)	(-27.1, 4.7)
	Pr >  t			0.1656
Week 144	n	5		
	LS Mean	-7.769	NE	NE
	SEM	4.825	NE	NE
	95% CI	(-17.2, 1.7)	NE	NE
	Pr >  t			NE
Week 156	n	3		
	LS Mean	-5.360	NE	NE
	SEM	5.995	NE	NE
	95% CI	(-17.1, 6.4)	NE	NE
	Pr >  t			NE
Week 168	n	1		
	LS Mean	6.768	NE	NE
	SEM	9.926	NE	NE
	95% CI	(-12.7, 26.3)	NE	NE
	Pr >  t			NE
Week 180	n	1		
	LS Mean	-6.562	NE	NE
	SEM	9.926	NE	NE
	95% CI	(-26.1, 12.9)	NE	NE
	Pr >  t			NE
Week 192	n	1		
	LS Mean	-19.90	NE	NE
	SEM	9.926	NE	NE
	95% CI	(-39.4, -0.4)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	-4.023	-3.145	-0.879
			SEM	3.178	3.475	3.338
			95% CI	(-10.3, 2.3)	(-10.0, 3.8)	(-7.5, 5.7)
		Pr >  t			0.7928	
		Week 16	n	35	22	
			LS Mean	-2.353	-0.492	-1.861
			SEM	3.316	3.925	3.785
			95% CI	(-8.9, 4.2)	(-8.3, 7.3)	(-9.3, 5.6)
		Pr >  t			0.6234	
		Week 24	n	28	16	
			LS Mean	-5.852	-7.055	1.203
			SEM	3.443	4.200	4.195
			95% CI	(-12.7, 1.0)	(-15.3, 1.2)	(-7.1, 9.5)
		Pr >  t			0.7745	
		Week 32	n	22	16	
			LS Mean	0.564	-5.912	6.476
			SEM	3.653	4.213	4.334
			95% CI	(-6.7, 7.8)	(-14.2, 2.4)	(-2.1, 15.0)
		Pr >  t			0.1364	
		Week 40	n	19	12	
			LS Mean	-0.195	-4.931	4.737
			SEM	3.766	4.490	4.701
			95% CI	(-7.6, 7.2)	(-13.8, 3.9)	(-4.5, 14.0)
		Pr >  t			0.3146	
		Week 48	n	16	10	
			LS Mean	-8.350	-4.180	-4.171
			SEM	3.912	4.703	5.016
95% CI	(-16.1, -0.6)		(-13.4, 5.1)	(-14.0, 5.7)		
Pr >  t			0.4064			
Week 56	n	14	7			
	LS Mean	-2.430	-2.854	0.424		
	SEM	4.039	5.199	5.579		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-10.4, 5.5)	(-13.1, 7.4)	(-10.6,11.4)
		Pr >  t			0.9395
	Week 64	n	8	7	
		LS Mean	-1.911	-2.960	1.049
		SEM	4.679	5.197	6.069
		95% CI	(-11.1, 7.3)	(-13.2, 7.3)	(-10.9,13.0)
		Pr >  t			0.8628
	Week 72	n	12	6	
		LS Mean	-5.299	-2.497	-2.802
		SEM	4.194	5.449	5.926
		95% CI	(-13.6, 3.0)	(-13.2, 8.2)	(-14.5, 8.9)
		Pr >  t			0.6366
	Week 84	n	8	5	
		LS Mean	-3.836	-7.017	3.180
		SEM	4.712	5.774	6.574
		95% CI	(-13.1, 5.4)	(-18.4, 4.3)	(-9.7,16.1)
		Pr >  t			0.6288
	Week 96	n	5	5	
		LS Mean	-4.624	-0.351	-4.273
		SEM	5.488	5.774	7.152
		95% CI	(-15.4, 6.2)	(-11.7,11.0)	(-18.3, 9.8)
		Pr >  t			0.5506
	Week 108	n	7	5	
		LS Mean	-4.252	-0.351	-3.901
		SEM	4.913	5.774	6.719
		95% CI	(-13.9, 5.4)	(-11.7,11.0)	(-17.1, 9.3)
		Pr >  t			0.5619
	Week 120	n	5	3	
		LS Mean	-10.34	-0.873	-9.465
		SEM	5.496	6.902	8.094
		95% CI	(-21.1, 0.5)	(-14.4,12.7)	(-25.4, 6.5)
		Pr >  t			0.2431
	Week 132	n	2	2	
		LS Mean	-7.903	1.235	-9.138
		SEM	7.851	8.036	10.67
		95% CI	(-23.3, 7.5)	(-14.6,17.0)	(-30.1,11.9)
		Pr >  t			0.3924
	Week 144	n	2		
		LS Mean	-19.40	NE	NE
		SEM	7.858	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-34.9,-3.9)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	2.722	NE	NE
		SEM	7.868	NE	NE
		95% CI	(-12.8,18.2)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-2.442	NE	NE
		SEM	10.69	NE	NE
		95% CI	(-23.5,18.6)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	98	104	
		LS Mean	-1.575	-0.859	-0.716
		SEM	2.767	2.748	2.176
		95% CI	(-7.0, 3.9)	(-6.3, 4.6)	(-5.0, 3.6)
		Pr >  t			0.7424
	Week 16	n	87	84	
		LS Mean	-1.859	-2.108	0.250
		SEM	2.809	2.804	2.283
		95% CI	(-7.4, 3.7)	(-7.6, 3.4)	(-4.2, 4.7)
		Pr >  t			0.9130
	Week 24	n	76	65	
		LS Mean	-1.871	-2.663	0.791
		SEM	2.851	2.885	2.412
		95% CI	(-7.5, 3.7)	(-8.3, 3.0)	(-3.9, 5.5)
		Pr >  t			0.7430
	Week 32	n	62	57	
		LS Mean	-2.184	-2.496	0.312
		SEM	2.911	2.931	2.523
		95% CI	(-7.9, 3.5)	(-8.3, 3.3)	(-4.6, 5.3)
		Pr >  t			0.9015
	Week 40	n	54	50	
		LS Mean	0.047	-3.643	3.690
		SEM	2.953	2.979	2.618
		95% CI	(-5.8, 5.9)	(-9.5, 2.2)	(-1.5, 8.8)
		Pr >  t			0.1592
	Week 48	n	52	41	
		LS Mean	-1.825	-4.294	2.469
		SEM	2.964	3.049	2.711

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-7.7, 4.0)	(-10.3, 1.7)	(-2.9, 7.8)
		Pr >  t			0.3627
	Week 56	n	44	38	
		LS Mean	-1.173	-2.917	1.744
		SEM	3.018	3.080	2.805
		95% CI	(-7.1, 4.8)	(-9.0, 3.1)	(-3.8, 7.3)
		Pr >  t			0.5342
	Week 64	n	39	35	
		LS Mean	-2.342	-1.968	-0.373
		SEM	3.062	3.114	2.891
		95% CI	(-8.4, 3.7)	(-8.1, 4.2)	(-6.0, 5.3)
		Pr >  t			0.8973
	Week 72	n	36	29	
		LS Mean	-0.976	-2.121	1.145
		SEM	3.095	3.200	3.017
		95% CI	(-7.1, 5.1)	(-8.4, 4.2)	(-4.8, 7.1)
		Pr >  t			0.7046
	Week 84	n	32	28	
		LS Mean	-3.266	-0.899	-2.367
		SEM	3.148	3.218	3.087
		95% CI	(-9.5, 2.9)	(-7.2, 5.4)	(-8.4, 3.7)
		Pr >  t			0.4435
	Week 96	n	30	19	
		LS Mean	-1.791	-5.662	3.871
		SEM	3.174	3.450	3.357
		95% CI	(-8.0, 4.4)	(-12.4, 1.1)	(-2.7, 10.5)
		Pr >  t			0.2492
	Week 108	n	18	16	
		LS Mean	-2.437	-7.201	4.764
		SEM	3.480	3.578	3.764
		95% CI	(-9.3, 4.4)	(-14.2, -0.2)	(-2.6, 12.1)
		Pr >  t			0.2059
	Week 120	n	23	13	
		LS Mean	-1.386	-1.031	-0.355
		SEM	3.318	3.755	3.795
		95% CI	(-7.9, 5.1)	(-8.4, 6.3)	(-7.8, 7.1)
		Pr >  t			0.9255
	Week 132	n	18	6	
		LS Mean	-5.525	-7.835	2.310
		SEM	3.480	4.705	4.849

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.4, 1.3)	(-17.1, 1.4)	(-7.2,11.8)
		Pr >  t			0.6339
	Week 144	n	13	5	
		LS Mean	-5.597	-1.955	-3.642
		SEM	3.736	5.014	5.332
		95% CI	(-12.9, 1.7)	(-11.8, 7.9)	(-14.1, 6.8)
		Pr >  t			0.4947
	Week 156	n	8	3	
		LS Mean	-4.834	-1.523	-3.311
		SEM	4.277	6.081	6.674
		95% CI	(-13.2, 3.6)	(-13.5,10.4)	(-16.4, 9.8)
		Pr >  t			0.6199
	Week 168	n	3	2	
		LS Mean	1.002	1.749	-0.747
		SEM	6.064	7.198	8.822
		95% CI	(-10.9,12.9)	(-12.4,15.9)	(-18.1,16.6)
		Pr >  t			0.9325
	Week 180	n	1	1	
		LS Mean	-5.647	-4.087	-1.560
		SEM	9.801	9.800	13.47
		95% CI	(-24.9,13.6)	(-23.3,15.1)	(-28.0,24.9)
		Pr >  t			0.9078
	Week 192	n	1	1	
		LS Mean	-18.99	-4.087	-14.90
		SEM	9.801	9.800	13.47
		95% CI	(-38.2, 0.2)	(-23.3,15.1)	(-41.3,11.5)
		Pr >  t			0.2688

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
ER and PR Status (L)	Both positive	Week 8	n	96	104			
			LS Mean	-1.611	-0.827	-0.785		
			SEM	2.780	2.754	2.192		
			95% CI	(-7.1, 3.9)	(-6.3, 4.6)	(-5.1, 3.5)		
					Pr >  t			0.7205
		Week 16	n	85	84			
			LS Mean	-2.061	-2.071	0.011		
			SEM	2.823	2.810	2.301		
			95% CI	(-7.6, 3.5)	(-7.6, 3.5)	(-4.5, 4.5)		
					Pr >  t			0.9963
		Week 24	n	75	65			
			LS Mean	-2.108	-2.629	0.521		
			SEM	2.864	2.891	2.427		
			95% CI	(-7.7, 3.5)	(-8.3, 3.1)	(-4.2, 5.3)		
					Pr >  t			0.8303
		Week 32	n	61	57			
			LS Mean	-2.449	-2.463	0.014		
			SEM	2.926	2.938	2.540		
			95% CI	(-8.2, 3.3)	(-8.2, 3.3)	(-5.0, 5.0)		
					Pr >  t			0.9957
		Week 40	n	53	50			
			LS Mean	-0.252	-3.609	3.357		
			SEM	2.969	2.985	2.637		
			95% CI	(-6.1, 5.6)	(-9.5, 2.3)	(-1.8, 8.5)		
					Pr >  t			0.2036
		Week 48	n	51	41			
			LS Mean	-2.034	-4.260	2.226		
			SEM	2.981	3.056	2.731		
95% CI	(-7.9, 3.8)		(-10.3, 1.8)	(-3.1, 7.6)				
			Pr >  t			0.4152		
Week 56	n	43	38					
	LS Mean	-1.678	-2.883	1.204				
	SEM	3.037	3.087	2.827				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.7, 4.3)	(-9.0, 3.2)	(-4.3, 6.8)
	Pr >  t			0.6703
	n	39	35	
	LS Mean	-2.576	-1.935	-0.641
	SEM	3.074	3.122	2.905
Week 72	95% CI	(-8.6, 3.5)	(-8.1, 4.2)	(-6.3, 5.1)
	Pr >  t			0.8254
	n	35	29	
	LS Mean	-1.259	-2.087	0.828
	SEM	3.118	3.208	3.043
Week 84	95% CI	(-7.4, 4.9)	(-8.4, 4.2)	(-5.1, 6.8)
	Pr >  t			0.7857
	n	31	28	
	LS Mean	-3.630	-0.865	-2.765
	SEM	3.175	3.226	3.116
Week 96	95% CI	(-9.9, 2.6)	(-7.2, 5.5)	(-8.9, 3.4)
	Pr >  t			0.3752
	n	29	19	
	LS Mean	-1.881	-5.628	3.747
	SEM	3.202	3.458	3.387
Week 108	95% CI	(-8.2, 4.4)	(-12.4, 1.2)	(-2.9, 10.4)
	Pr >  t			0.2688
	n	18	16	
	LS Mean	-2.671	-7.169	4.498
	SEM	3.492	3.587	3.779
Week 120	95% CI	(-9.5, 4.2)	(-14.2, -0.1)	(-2.9, 11.9)
	Pr >  t			0.2342
	n	23	13	
	LS Mean	-1.619	-0.999	-0.619
	SEM	3.330	3.764	3.810
Week 132	95% CI	(-8.2, 4.9)	(-8.4, 6.4)	(-8.1, 6.9)
	Pr >  t			0.8709
	n	18	6	
	LS Mean	-5.761	-7.803	2.042
	SEM	3.493	4.718	4.866
Week 144	95% CI	(-12.6, 1.1)	(-17.1, 1.5)	(-7.5, 11.6)
	Pr >  t			0.6748
	n	13	5	
	LS Mean	-5.832	-1.922	-3.909
	SEM	3.749	5.028	5.351

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	(-13.2, 1.5)	(-11.8, 7.9)	(-14.4, 6.6)
		Pr >  t			0.4652
		n	8	3	
		LS Mean	-5.070	-1.489	-3.581
		SEM	4.292	6.099	6.696
	Week 168	95% CI	(-13.5, 3.4)	(-13.5,10.5)	(-16.7, 9.6)
		Pr >  t			0.5929
		n	3	2	
		LS Mean	0.766	1.784	-1.019
		SEM	6.083	7.219	8.850
	Week 180	95% CI	(-11.2,12.7)	(-12.4,15.9)	(-18.4,16.3)
		Pr >  t			0.9084
		n	1	1	
		LS Mean	-5.878	-4.055	-1.823
		SEM	9.831	9.828	13.51
	Week 192	95% CI	(-25.2,13.4)	(-23.3,15.2)	(-28.3,24.7)
		Pr >  t			0.8927
		n	1	1	
		LS Mean	-19.22	-4.055	-15.16
		SEM	9.831	9.828	13.51
	Week 8	95% CI	(-38.5, 0.1)	(-23.3,15.2)	(-41.7,11.3)
		Pr >  t			0.2619
		n	42	35	
		LS Mean	-4.023	-3.145	-0.879
SEM		3.178	3.475	3.338	
Week 16	95% CI	(-10.3, 2.3)	(-10.0, 3.8)	(-7.5, 5.7)	
	Pr >  t			0.7928	
	n	35	22		
	LS Mean	-2.353	-0.492	-1.861	
	SEM	3.316	3.925	3.785	
Week 24	95% CI	(-8.9, 4.2)	(-8.3, 7.3)	(-9.3, 5.6)	
	Pr >  t			0.6234	
	n	28	16		
	LS Mean	-5.852	-7.055	1.203	
	SEM	3.443	4.200	4.195	
Week 32	95% CI	(-12.7, 1.0)	(-15.3, 1.2)	(-7.1, 9.5)	
	Pr >  t			0.7745	
	n	22	16		
	LS Mean	0.564	-5.912	6.476	
	SEM	3.653	4.213	4.334	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-6.7, 7.8)	(-14.2, 2.4)	(-2.1,15.0)
	Pr >  t			0.1364
	n	19	12	
	LS Mean	-0.195	-4.931	4.737
	SEM	3.766	4.490	4.701
Week 48	95% CI	(-7.6, 7.2)	(-13.8, 3.9)	(-4.5,14.0)
	Pr >  t			0.3146
	n	16	10	
	LS Mean	-8.350	-4.180	-4.171
	SEM	3.912	4.703	5.016
Week 56	95% CI	(-16.1,-0.6)	(-13.4, 5.1)	(-14.0, 5.7)
	Pr >  t			0.4064
	n	14	7	
	LS Mean	-2.430	-2.854	0.424
	SEM	4.039	5.199	5.579
Week 64	95% CI	(-10.4, 5.5)	(-13.1, 7.4)	(-10.6,11.4)
	Pr >  t			0.9395
	n	8	7	
	LS Mean	-1.911	-2.960	1.049
	SEM	4.679	5.197	6.069
Week 72	95% CI	(-11.1, 7.3)	(-13.2, 7.3)	(-10.9,13.0)
	Pr >  t			0.8628
	n	12	6	
	LS Mean	-5.299	-2.497	-2.802
	SEM	4.194	5.449	5.926
Week 84	95% CI	(-13.6, 3.0)	(-13.2, 8.2)	(-14.5, 8.9)
	Pr >  t			0.6366
	n	8	5	
	LS Mean	-3.836	-7.017	3.180
	SEM	4.712	5.774	6.574
Week 96	95% CI	(-13.1, 5.4)	(-18.4, 4.3)	(-9.7,16.1)
	Pr >  t			0.6288
	n	5	5	
	LS Mean	-4.624	-0.351	-4.273
	SEM	5.488	5.774	7.152
Week 108	95% CI	(-15.4, 6.2)	(-11.7,11.0)	(-18.3, 9.8)
	Pr >  t			0.5506
	n	7	5	
	LS Mean	-4.252	-0.351	-3.901
	SEM	4.913	5.774	6.719

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-13.9, 5.4)	(-11.7,11.0)	(-17.1, 9.3)
	Pr >  t			0.5619
	n	5	3	
	LS Mean	-10.34	-0.873	-9.465
	SEM	5.496	6.902	8.094
Week 132	95% CI	(-21.1, 0.5)	(-14.4,12.7)	(-25.4, 6.5)
	Pr >  t			0.2431
	n	2	2	
	LS Mean	-7.903	1.235	-9.138
	SEM	7.851	8.036	10.67
Week 144	95% CI	(-23.3, 7.5)	(-14.6,17.0)	(-30.1,11.9)
	Pr >  t			0.3924
	n	2		
	LS Mean	-19.40	NE	NE
	SEM	7.858	NE	NE
Week 156	95% CI	(-34.9,-3.9)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	2.722	NE	NE
	SEM	7.868	NE	NE
Week 168	95% CI	(-12.8,18.2)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-2.442	NE	NE
	SEM	10.69	NE	NE
	95% CI	(-23.5,18.6)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-4.503	-1.849	-2.654
			SEM	2.192	2.263	2.031
			95% CI	(-8.8, -0.2)	(-6.3, 2.6)	(-6.6, 1.3)
		Pr >  t			0.1923	
		Week 16	n	90	75	
			LS Mean	-2.571	-3.125	0.554
			SEM	2.231	2.342	2.151
			95% CI	(-7.0, 1.8)	(-7.7, 1.5)	(-3.7, 4.8)
		Pr >  t			0.7968	
		Week 24	n	79	62	
			LS Mean	-2.228	-3.977	1.750
			SEM	2.268	2.410	2.250
			95% CI	(-6.7, 2.2)	(-8.7, 0.8)	(-2.7, 6.2)
		Pr >  t			0.4372	
		Week 32	n	70	56	
			LS Mean	-2.230	-4.820	2.590
			SEM	2.314	2.449	2.317
			95% CI	(-6.8, 2.3)	(-9.6, -0.0)	(-2.0, 7.1)
		Pr >  t			0.2641	
		Week 40	n	61	46	
			LS Mean	-0.669	-5.200	4.530
			SEM	2.353	2.520	2.425
			95% CI	(-5.3, 4.0)	(-10.2, -0.2)	(-0.2, 9.3)
		Pr >  t			0.0622	
		Week 48	n	56	38	
			LS Mean	-2.894	-4.155	1.261
			SEM	2.378	2.595	2.527
95% CI	(-7.6, 1.8)		(-9.3, 0.9)	(-3.7, 6.2)		
Pr >  t			0.6178			
Week 56	n	49	33			
	LS Mean	-2.523	-4.629	2.106		
	SEM	2.420	2.656	2.631		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-7.3, 2.2)	(-9.8, 0.6)	(-3.1, 7.3)
	Pr >  t			0.4237
	n	37	29	
	LS Mean	-3.313	-1.772	-1.540
	SEM	2.522	2.720	2.789
Week 72	95% CI	(-8.3, 1.6)	(-7.1, 3.6)	(-7.0, 3.9)
	Pr >  t			0.5808
	n	40	25	
	LS Mean	-2.199	-3.804	1.604
	SEM	2.492	2.798	2.839
Week 84	95% CI	(-7.1, 2.7)	(-9.3, 1.7)	(-4.0, 7.2)
	Pr >  t			0.5721
	n	32	23	
	LS Mean	-4.010	-4.560	0.550
	SEM	2.592	2.848	2.969
Week 96	95% CI	(-9.1, 1.1)	(-10.2, 1.0)	(-5.3, 6.4)
	Pr >  t			0.8531
	n	29	17	
	LS Mean	-2.455	-6.465	4.010
	SEM	2.637	3.050	3.204
Week 108	95% CI	(-7.6, 2.7)	(-12.5,-0.5)	(-2.3,10.3)
	Pr >  t			0.2110
	n	22	15	
	LS Mean	-4.278	-3.840	-0.438
	SEM	2.797	3.148	3.423
Week 120	95% CI	(-9.8, 1.2)	(-10.0, 2.3)	(-7.2, 6.3)
	Pr >  t			0.8982
	n	23	13	
	LS Mean	-3.248	-1.518	-1.730
	SEM	2.768	3.273	3.517
Week 132	95% CI	(-8.7, 2.2)	(-7.9, 4.9)	(-8.6, 5.2)
	Pr >  t			0.6229
	n	17	5	
	LS Mean	-7.105	-9.574	2.469
	SEM	2.972	4.477	4.780
Week 144	95% CI	(-12.9,-1.3)	(-18.4,-0.8)	(-6.9,11.8)
	Pr >  t			0.6056
	n	14	3	
Week 144	LS Mean	-10.29	-3.758	-6.530
	SEM	3.123	5.496	5.829

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.4,-4.2)	(-14.5, 7.0)	(-18.0, 4.9)
		Pr >  t			0.2628
	Week 156	n	9	2	
		LS Mean	-4.490	-3.807	-0.683
		SEM	3.577	6.537	7.036
		95% CI	(-11.5, 2.5)	(-16.6, 9.0)	(-14.5,13.1)
		Pr >  t			0.9227
	Week 168	n	4	1	
		LS Mean	-0.859	1.552	-2.411
		SEM	4.824	8.970	9.885
		95% CI	(-10.3, 8.6)	(-16.0,19.2)	(-21.8,17.0)
		Pr >  t			0.8074
	Week 180	n	1	1	
		LS Mean	-6.953	-5.118	-1.835
		SEM	8.932	8.970	12.42
		95% CI	(-24.5,10.6)	(-22.7,12.5)	(-26.2,22.5)
		Pr >  t			0.8826
	Week 192	n	1	1	
		LS Mean	-20.29	-5.118	-15.17
		SEM	8.932	8.970	12.42
		95% CI	(-37.8,-2.8)	(-22.7,12.5)	(-39.5, 9.2)
		Pr >  t			0.2220
>= 3	Week 8	n	37	45	
		LS Mean	3.156	-0.698	3.854
		SEM	6.595	6.543	3.737
		95% CI	(-9.9,16.2)	(-13.7,12.3)	(-3.5,11.2)
		Pr >  t			0.3043
	Week 16	n	34	32	
		LS Mean	-0.715	0.494	-1.209
		SEM	6.764	6.810	4.055
		95% CI	(-14.1,12.7)	(-13.0,14.0)	(-9.2, 6.8)
		Pr >  t			0.7660
	Week 24	n	26	19	
		LS Mean	-6.098	-3.472	-2.626
		SEM	6.890	7.090	4.694
		95% CI	(-19.7, 7.5)	(-17.5,10.5)	(-11.9, 6.6)
		Pr >  t			0.5764
	Week 32	n	16	17	
		LS Mean	-0.457	0.655	-1.112
		SEM	7.179	7.177	5.225

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-14.6,13.7)	(-13.5,14.8)	(-11.4, 9.2)
		Pr >  t			0.8315
		n	14	16	
		LS Mean	-1.038	-1.113	0.074
		SEM	7.284	7.215	5.420
Week 48		95% CI	(-15.4,13.3)	(-15.4,13.1)	(-10.6,10.7)
		Pr >  t			0.9891
		n	13	13	
		LS Mean	-8.056	-5.667	-2.389
		SEM	7.336	7.373	5.697
Week 56		95% CI	(-22.5, 6.4)	(-20.2, 8.9)	(-13.6, 8.8)
		Pr >  t			0.6753
		n	10	12	
		LS Mean	0.395	0.637	-0.242
		SEM	7.584	7.445	6.083
Week 64		95% CI	(-14.6,15.4)	(-14.1,15.3)	(-12.2,11.7)
		Pr >  t			0.9682
		n	10	13	
		LS Mean	-1.652	-3.419	1.767
		SEM	7.585	7.381	6.007
Week 72		95% CI	(-16.6,13.3)	(-18.0,11.1)	(-10.0,13.6)
		Pr >  t			0.7688
		n	8	10	
		LS Mean	-4.408	1.081	-5.489
		SEM	7.820	7.615	6.581
Week 84		95% CI	(-19.8,11.0)	(-13.9,16.1)	(-18.4, 7.5)
		Pr >  t			0.4047
		n	8	10	
		LS Mean	-3.655	3.804	-7.459
		SEM	7.827	7.610	6.581
Week 96		95% CI	(-19.1,11.8)	(-11.2,18.8)	(-20.4, 5.5)
		Pr >  t			0.2578
		n	6	7	
		LS Mean	-5.142	-0.369	-4.773
		SEM	8.216	8.020	7.474
Week 108		95% CI	(-21.3,11.0)	(-16.2,15.4)	(-19.5, 9.9)
		Pr >  t			0.5235
		n	4	6	
	LS Mean	-0.398	-10.29	9.896	
	SEM	8.917	8.227	8.456	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-17.9,17.2)	(-26.5, 5.9)	( -6.7,26.5)
	Pr >  t			0.2427
	n	5	3	
	LS Mean	-5.544	-1.362	-4.182
	SEM	8.499	9.589	9.406
Week 132	95% CI	(-22.3,11.2)	(-20.2,17.5)	(-22.7,14.3)
	Pr >  t			0.6568
	n	3	3	
	LS Mean	-3.860	1.538	-5.398
	SEM	9.564	9.593	10.39
Week 144	95% CI	(-22.7,15.0)	(-17.3,20.4)	(-25.8,15.0)
	Pr >  t			0.6037
	n	1	2	
	LS Mean	20.026	1.600	18.426
	SEM	13.70	10.78	15.12
Week 156	95% CI	( -6.9,47.0)	(-19.6,22.8)	(-11.3,48.2)
	Pr >  t			0.2240
	n	1	1	
	LS Mean	0.026	3.628	-3.603
	SEM	13.70	13.74	17.35
Week 168	95% CI	(-26.9,27.0)	(-23.4,30.6)	(-37.7,30.5)
	Pr >  t			0.8356
	n		1	
	LS Mean	NE	3.628	NE
	SEM	NE	13.74	NE
	95% CI	NE	(-23.4,30.6)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-16i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Physical Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>	<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Visceral Disease (L)	No	Week 8	n	69	60	
		LS Mean	1.531	5.277	-3.746	
	SEM	5.976	6.164	2.478		
	95% CI	(-10.3,13.4)	(-6.9,17.5)	(-8.6, 1.1)		
	Pr >  t			0.1320		
	Week 16	n	59	49		
		LS Mean	2.336	2.555	-0.219	
		SEM	5.991	6.201	2.616	
		95% CI	(-9.5,14.2)	(-9.7,14.8)	(-5.4, 4.9)	
	Week 24	n	54	41		
		LS Mean	1.779	3.937	-2.158	
		SEM	6.000	6.233	2.722	
		95% CI	(-10.1,13.7)	(-8.4,16.3)	(-7.5, 3.2)	
	Week 32	n	48	37		
		LS Mean	2.760	1.690	1.069	
		SEM	6.013	6.251	2.802	
		95% CI	(-9.2,14.7)	(-10.7,14.1)	(-4.4, 6.6)	
	Week 40	n	43	33		
		LS Mean	5.241	2.974	2.268	
		SEM	6.027	6.274	2.887	
		95% CI	(-6.7,17.2)	(-9.5,15.4)	(-3.4, 7.9)	
	Week 48	n	41	28		
		LS Mean	1.437	3.358	-1.921	
		SEM	6.034	6.309	2.980	
95% CI		(-10.5,13.4)	(-9.1,15.9)	(-7.8, 3.9)		
Week 56	n	35	22			
	LS Mean	2.207	2.197	0.010		
	SEM	6.058	6.372	3.165		



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-9.8,14.2)	(-10.4,14.8)	(-6.2, 6.2)
		Pr >  t			0.9974
	Week 64	n	26	23	
		LS Mean	1.801	5.060	-3.258
		SEM	6.115	6.360	3.262
		95% CI	(-10.3,13.9)	(-7.5,17.7)	(-9.7, 3.1)
		Pr >  t			0.3183
	Week 72	n	28	18	
		LS Mean	1.513	4.517	-3.004
		SEM	6.099	6.434	3.373
		95% CI	(-10.6,13.6)	(-8.2,17.2)	(-9.6, 3.6)
		Pr >  t			0.3736
	Week 84	n	22	18	
		LS Mean	-0.039	3.802	-3.841
		SEM	6.177	6.434	3.483
		95% CI	(-12.3,12.2)	(-8.9,16.5)	(-10.7, 3.0)
		Pr >  t			0.2706
	Week 96	n	21	13	
		LS Mean	1.749	0.383	1.366
		SEM	6.167	6.562	3.737
		95% CI	(-10.5,14.0)	(-12.6,13.4)	(-6.0, 8.7)
		Pr >  t			0.7148
	Week 108	n	17	12	
		LS Mean	1.561	-0.767	2.329
		SEM	6.260	6.600	3.913
		95% CI	(-10.8,13.9)	(-13.8,12.3)	(-5.4,10.0)
		Pr >  t			0.5520
	Week 120	n	18	11	
		LS Mean	2.325	5.550	-3.225
		SEM	6.212	6.644	3.957
		95% CI	(-10.0,14.6)	(-7.6,18.7)	(-11.0, 4.5)
		Pr >  t			0.4153
	Week 132	n	13	5	
		LS Mean	-1.112	-2.702	1.589
		SEM	6.366	7.239	5.054
		95% CI	(-13.7,11.5)	(-17.0,11.6)	(-8.3,11.5)
		Pr >  t			0.7532
	Week 144	n	12	3	
		LS Mean	-2.930	3.118	-6.048
		SEM	6.367	7.911	6.018

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.5, 9.7)	(-12.5,18.7)	(-17.9, 5.8)
		Pr >  t			0.3152
	Week 156	n	7	2	
		LS Mean	1.905	3.055	-1.150
		SEM	6.747	8.666	7.294
		95% CI	(-11.4,15.2)	(-14.0,20.1)	(-15.5,13.2)
		Pr >  t			0.8748
	Week 168	n	3	1	
		LS Mean	4.919	8.385	-3.466
		SEM	7.733	10.62	10.26
		95% CI	(-10.3,20.1)	(-12.5,29.2)	(-23.6,16.7)
		Pr >  t			0.7355
	Week 180	n	1	1	
		LS Mean	-1.698	1.715	-3.414
		SEM	10.49	10.62	12.47
		95% CI	(-22.3,18.9)	(-19.1,22.6)	(-27.9,21.1)
		Pr >  t			0.7843
	Week 192	n	1	1	
		LS Mean	-15.04	1.715	-16.75
		SEM	10.49	10.62	12.47
		95% CI	(-35.6, 5.6)	(-19.1,22.6)	(-41.2, 7.7)
		Pr >  t			0.1795
Yes	Week 8	n	73	80	
		LS Mean	-4.658	-6.303	1.645
		SEM	3.468	3.501	2.601
		95% CI	(-11.5, 2.2)	(-13.2, 0.6)	( -3.5, 6.8)
		Pr >  t			0.5277
	Week 16	n	65	58	
		LS Mean	-4.710	-4.848	0.138
		SEM	3.552	3.644	2.801
		95% CI	(-11.7, 2.3)	(-12.0, 2.3)	( -5.4, 5.6)
		Pr >  t			0.9608
	Week 24	n	51	40	
		LS Mean	-6.141	-9.567	3.426
		SEM	3.623	3.819	3.096
		95% CI	(-13.3, 1.0)	(-17.1,-2.0)	( -2.7, 9.5)
		Pr >  t			0.2692
	Week 32	n	38	36	
		LS Mean	-4.115	-6.681	2.565
		SEM	3.781	3.874	3.299

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.6, 3.3)	(-14.3, 0.9)	(-3.9, 9.0)
		Pr >  t			0.4373
	Week 40	n	32	29	
		LS Mean	-4.793	-9.476	4.684
		SEM	3.873	3.985	3.523
		95% CI	(-12.4, 2.8)	(-17.3,-1.6)	(-2.2,11.6)
		Pr >  t			0.1842
	Week 48	n	28	23	
		LS Mean	-7.121	-10.88	3.758
		SEM	3.941	4.127	3.751
		95% CI	(-14.9, 0.6)	(-19.0,-2.8)	(-3.6,11.1)
		Pr >  t			0.3168
	Week 56	n	24	23	
		LS Mean	-3.739	-6.889	3.150
		SEM	4.037	4.127	3.847
		95% CI	(-11.7, 4.2)	(-15.0, 1.2)	(-4.4,10.7)
		Pr >  t			0.4132
	Week 64	n	21	19	
		LS Mean	-5.558	-8.366	2.808
		SEM	4.127	4.258	4.078
		95% CI	(-13.7, 2.6)	(-16.7, 0.0)	(-5.2,10.8)
		Pr >  t			0.4913
	Week 72	n	20	17	
		LS Mean	-4.142	-7.731	3.589
		SEM	4.165	4.344	4.204
		95% CI	(-12.3, 4.0)	(-16.3, 0.8)	(-4.7,11.8)
		Pr >  t			0.3936
	Week 84	n	18	15	
		LS Mean	-5.406	-6.234	0.828
		SEM	4.233	4.451	4.383
		95% CI	(-13.7, 2.9)	(-15.0, 2.5)	(-7.8, 9.4)
		Pr >  t			0.8502
	Week 96	n	14	11	
		LS Mean	-5.334	-8.021	2.687
		SEM	4.452	4.761	4.891
		95% CI	(-14.1, 3.4)	(-17.4, 1.3)	(-6.9,12.3)
		Pr >  t			0.5828
	Week 108	n	9	9	
		LS Mean	-7.132	-8.512	1.381
		SEM	4.939	4.999	5.554

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.8, 2.6)	(-18.3, 1.3)	(-9.5,12.3)
		Pr >  t			0.8037
	Week 120	n	10	5	
		LS Mean	-8.500	-7.056	-1.444
		SEM	4.825	5.938	6.325
		95% CI	(-18.0, 1.0)	(-18.7, 4.6)	(-13.9,11.0)
		Pr >  t			0.8194
	Week 132	n	7	3	
		LS Mean	-10.56	-4.794	-5.771
		SEM	5.294	7.095	7.741
		95% CI	(-21.0,-0.2)	(-18.7, 9.1)	(-21.0, 9.4)
		Pr >  t			0.4562
	Week 144	n	3	2	
		LS Mean	-12.57	-4.736	-7.836
		SEM	7.047	8.329	10.03
		95% CI	(-26.4, 1.3)	(-21.1,11.6)	(-27.5,11.9)
		Pr >  t			0.4350
	Week 156	n	3	1	
		LS Mean	-9.387	-2.856	-6.531
		SEM	7.056	11.24	12.56
		95% CI	(-23.2, 4.5)	(-24.9,19.2)	(-31.2,18.1)
		Pr >  t			0.6031
	Week 168	n	1	1	
		LS Mean	-5.193	-2.856	-2.337
		SEM	11.24	11.24	15.30
		95% CI	(-27.3,16.9)	(-24.9,19.2)	(-32.4,27.7)
		Pr >  t			0.8787

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-55: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Rollenfunktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134			
			LS Mean	-3.867	-2.744	-1.124		
			SEM	1.863	1.867	2.632		
			95% CI	(-7.5,-0.2)	(-6.4, 0.9)	(-6.3, 4.0)		
					Pr >  t			0.6696
		Week 16	n	118	104			
			LS Mean	-3.054	-4.506	1.452		
			SEM	1.941	2.039	2.812		
			95% CI	(-6.9, 0.8)	(-8.5,-0.5)	(-4.1, 7.0)		
					Pr >  t			0.6056
		Week 24	n	100	79			
			LS Mean	-3.758	-2.561	-1.196		
			SEM	2.047	2.233	3.025		
			95% CI	(-7.8, 0.3)	(-6.9, 1.8)	(-7.1, 4.7)		
					Pr >  t			0.6926
		Week 32	n	84	72			
			LS Mean	-2.667	-4.636	1.969		
			SEM	2.162	2.303	3.154		
			95% CI	(-6.9, 1.6)	(-9.2,-0.1)	(-4.2, 8.2)		
					Pr >  t			0.5326
		Week 40	n	73	62			
			LS Mean	-2.280	-5.541	3.261		
			SEM	2.261	2.415	3.304		
			95% CI	(-6.7, 2.2)	(-10.3,-0.8)	(-3.2, 9.7)		
					Pr >  t			0.3239
		Week 48	n	67	51			
			LS Mean	-4.322	-4.220	-0.101		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	2.323	2.577	3.465
	95% CI	(-8.9, 0.2)	(-9.3, 0.8)	(-6.9, 6.7)
	Pr >  t			0.9766
Week 56	n	57	45	
	LS Mean	-4.215	-5.129	0.914
	SEM	2.448	2.691	3.634
	95% CI	(-9.0, 0.6)	(-10.4, 0.2)	(-6.2, 8.0)
	Pr >  t			0.8015
Week 64	n	45	42	
	LS Mean	-3.599	-3.882	0.283
	SEM	2.650	2.757	3.821
	95% CI	(-8.8, 1.6)	(-9.3, 1.5)	(-7.2, 7.8)
	Pr >  t			0.9410
Week 72	n	46	35	
	LS Mean	-4.079	-3.163	-0.915
	SEM	2.632	2.942	3.945
	95% CI	(-9.2, 1.1)	(-8.9, 2.6)	(-8.7, 6.8)
	Pr >  t			0.8165
Week 84	n	40	33	
	LS Mean	-6.477	-3.208	-3.269
	SEM	2.762	3.006	4.080
	95% CI	(-11.9, -1.1)	(-9.1, 2.7)	(-11.3, 4.7)
	Pr >  t			0.4231
Week 96	n	34	24	
	LS Mean	-3.768	-4.818	1.050
	SEM	2.932	3.393	4.482
	95% CI	(-9.5, 2.0)	(-11.5, 1.8)	(-7.7, 9.8)
	Pr >  t			0.8147
Week 108	n	26	21	
	LS Mean	-5.620	-6.452	0.832
	SEM	3.249	3.579	4.831
	95% CI	(-12.0, 0.8)	(-13.5, 0.6)	(-8.6, 10.3)
	Pr >  t			0.8633
Week 120	n	27	16	
	LS Mean	-5.281	-3.846	-1.435
	SEM	3.205	4.003	5.125
	95% CI	(-11.6, 1.0)	(-11.7, 4.0)	(-11.5, 8.6)
	Pr >  t			0.7795
Week 132	n	20	8	
	LS Mean	-8.363	-8.435	0.072

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	3.608	5.416	6.506
		95% CI	(-15.4,-1.3)	(-19.1, 2.2)	(-12.7,12.8)
		Pr >  t			0.9912
	Week 144	n	14	5	
		LS Mean	-11.28	-0.709	-10.57
		SEM	4.195	6.738	7.935
		95% CI	(-19.5,-3.1)	(-13.9,12.5)	(-26.1, 5.0)
		Pr >  t			0.1830
	Week 156	n	10	3	
		LS Mean	-4.932	-10.38	5.452
		SEM	4.865	8.582	9.863
		95% CI	(-14.5, 4.6)	(-27.2, 6.5)	(-13.9,24.8)
		Pr >  t			0.5805
	Week 168	n	4	2	
		LS Mean	-3.533	3.098	-6.631
		SEM	7.448	10.44	12.82
		95% CI	(-18.1,11.1)	(-17.4,23.6)	(-31.8,18.5)
		Pr >  t			0.6052
	Week 180	n	1	1	
		LS Mean	-20.31	-24.38	4.078
		SEM	14.64	14.65	20.71
		95% CI	(-49.0, 8.4)	(-53.1, 4.3)	(-36.5,44.7)
		Pr >  t			0.8439
	Week 192	n	1	1	
		LS Mean	13.025	8.947	4.078
		SEM	14.64	14.65	20.71
		95% CI	(-15.7,41.7)	(-19.8,37.7)	(-36.5,44.7)
		Pr >  t			0.8439
Prior use	Week 8	n	8	6	
		LS Mean	-6.506	-8.998	2.492
		SEM	9.708	10.44	14.52
		95% CI	(-27.9,14.9)	(-31.6,13.6)	(-29.3,34.2)
		Pr >  t			0.8667
	Week 16	n	6	3	
		LS Mean	-0.332	-29.82	29.489
		SEM	10.50	13.76	17.35
		95% CI	(-22.9,22.2)	(-58.4,-1.2)	( -7.0,66.0)
		Pr >  t			0.1069
	Week 24	n	5	2	
		LS Mean	-9.018	-41.83	32.809

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	10.91	15.41	18.79
	95% CI	(-32.2,14.2)	(-73.4, -10)	( -6.0,71.6)
	Pr >  t			0.0939
Week 32	n	2	1	
	LS Mean	0.749	-22.94	23.684
	SEM	14.46	19.86	24.58
	95% CI	(-28.9,30.4)	(-63.7,17.9)	(-26.7,74.0)
	Pr >  t			0.3435
Week 40	n	2		
	LS Mean	0.749	NE	NE
	SEM	14.46	NE	NE
	95% CI	(-28.9,30.4)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	0.749	NE	NE
	SEM	14.46	NE	NE
	95% CI	(-28.9,30.4)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	0.749	NE	NE
	SEM	14.46	NE	NE
	95% CI	(-28.9,30.4)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	0.749	NE	NE
	SEM	14.46	NE	NE
	95% CI	(-28.9,30.4)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	-15.92	NE	NE
	SEM	14.46	NE	NE
	95% CI	(-45.6,13.7)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	-2.495	NE	NE
	SEM	18.38	NE	NE
	95% CI	(-40.3,35.3)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	-2.495	NE	NE



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	18.38	NE	NE
	95% CI	(-40.3,35.3)	NE	NE
	Pr >  t			NE
	Week 144			
	n	1		
	LS Mean	-2.495	NE	NE
	SEM	18.38	NE	NE
	95% CI	(-40.3,35.3)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
 -The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-5.558	-4.493	-1.065		
			SEM	3.015	3.076	2.681		
			95% CI	(-11.5, 0.4)	(-10.5, 1.6)	(-6.3, 4.2)		
					Pr >  t			0.6914
		Week 16	n	119	97			
			LS Mean	-4.702	-6.428	1.726		
			SEM	3.084	3.232	2.890		
			95% CI	(-10.8, 1.4)	(-12.8,-0.1)	(-4.0, 7.4)		
					Pr >  t			0.5506
		Week 24	n	100	75			
			LS Mean	-6.045	-6.113	0.068		
			SEM	3.156	3.367	3.101		
			95% CI	(-12.3, 0.2)	(-12.7, 0.5)	(-6.0, 6.2)		
					Pr >  t			0.9826
		Week 32	n	82	69			
			LS Mean	-4.631	-6.062	1.431		
			SEM	3.262	3.421	3.236		
			95% CI	(-11.0, 1.8)	(-12.8, 0.7)	(-4.9, 7.8)		
					Pr >  t			0.6584
		Week 40	n	73	58			
			LS Mean	-4.166	-7.879	3.713		
			SEM	3.317	3.522	3.391		
			95% CI	(-10.7, 2.4)	(-14.8,-1.0)	(-2.9,10.4)		
			Pr >  t			0.2739		
Week 48	n	66	48					
	LS Mean	-6.822	-5.342	-1.479				
	SEM	3.365	3.639	3.559				
	95% CI	(-13.4,-0.2)	(-12.5, 1.8)	(-8.5, 5.5)				
			Pr >  t			0.6778		
Week 56	n	56	43					
	LS Mean	-6.508	-6.753	0.245				
		SEM	3.453	3.715	3.721			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-13.3, 0.3)	(-14.0, 0.5)	(-7.1, 7.5)
		Pr >  t			0.9475
	Week 64	n	45	41	
		LS Mean	-5.405	-6.165	0.760
		SEM	3.587	3.750	3.882
		95% CI	(-12.4, 1.6)	(-13.5, 1.2)	(-6.9, 8.4)
		Pr >  t			0.8448
	Week 72	n	46	34	
		LS Mean	-6.579	-5.487	-1.092
		SEM	3.575	3.896	4.011
		95% CI	(-13.6, 0.4)	(-13.1, 2.2)	(-9.0, 6.8)
		Pr >  t			0.7855
	Week 84	n	37	32	
		LS Mean	-8.887	-5.548	-3.339
		SEM	3.740	3.947	4.199
		95% CI	(-16.2,-1.5)	(-13.3, 2.2)	(-11.6, 4.9)
		Pr >  t			0.4267
	Week 96	n	33	23	
		LS Mean	-6.763	-7.327	0.564
		SEM	3.829	4.271	4.585
		95% CI	(-14.3, 0.8)	(-15.7, 1.1)	(-8.4, 9.6)
		Pr >  t			0.9021
	Week 108	n	24	20	
		LS Mean	-8.565	-7.417	-1.148
		SEM	4.143	4.435	4.989
		95% CI	(-16.7,-0.4)	(-16.1, 1.3)	(-10.9, 8.6)
		Pr >  t			0.8181
	Week 120	n	25	16	
		LS Mean	-5.543	-5.886	0.342
		SEM	4.096	4.730	5.222
		95% CI	(-13.6, 2.5)	(-15.2, 3.4)	(-9.9,10.6)
		Pr >  t			0.9478
	Week 132	n	19	8	
		LS Mean	-11.23	-10.46	-0.769
		SEM	4.415	5.973	6.576
		95% CI	(-19.9,-2.6)	(-22.2, 1.3)	(-13.7,12.1)
		Pr >  t			0.9070
	Week 144	n	14	5	
		LS Mean	-14.05	-2.756	-11.30
		SEM	4.838	7.193	7.957

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-23.5,-4.6)	(-16.9,11.4)	(-26.9, 4.3)
		Pr >  t			0.1559
	Week 156	n	10	3	
		LS Mean	-7.092	-12.42	5.333
		SEM	5.439	8.942	9.880
		95% CI	(-17.8, 3.6)	(-30.0, 5.1)	(-14.0,24.7)
		Pr >  t			0.5895
	Week 168	n	4	2	
		LS Mean	-5.669	1.067	-6.737
		SEM	7.834	10.74	12.84
		95% CI	(-21.0, 9.7)	(-20.0,22.1)	(-31.9,18.4)
		Pr >  t			0.5998
	Week 180	n	1	1	
		LS Mean	-22.42	-26.41	3.990
		SEM	14.84	14.86	20.71
		95% CI	(-51.5, 6.7)	(-55.6, 2.7)	(-36.6,44.6)
		Pr >  t			0.8473
	Week 192	n	1	1	
		LS Mean	10.909	6.919	3.990
		SEM	14.84	14.86	20.71
		95% CI	(-18.2,40.0)	(-22.2,36.1)	(-36.6,44.6)
		Pr >  t			0.8473
Yes	Week 8	n	5	9	
		LS Mean	-4.300	-5.254	0.955
		SEM	7.706	5.475	9.486
		95% CI	(-20.3,11.7)	(-16.5, 6.0)	(-18.7,20.6)
		Pr >  t			0.9207
	Week 16	n	5	9	
		LS Mean	2.366	-12.09	14.460
		SEM	7.706	5.706	9.673
		95% CI	(-13.7,18.4)	(-23.8,-0.4)	( -5.6,34.5)
		Pr >  t			0.1487
	Week 24	n	5	5	
		LS Mean	5.700	8.001	-2.301
		SEM	7.706	7.272	10.70
		95% CI	(-10.3,21.7)	( -6.7,22.7)	(-24.2,19.6)
		Pr >  t			0.8312
	Week 32	n	4	3	
		LS Mean	5.837	-14.10	19.936
		SEM	8.297	8.791	12.21

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.2,22.9)	(-31.8, 3.6)	(-4.8,44.6)
		Pr >  t			0.1105
	Week 40	n	2	3	
		LS Mean	3.773	-0.924	4.697
		SEM	10.55	8.777	13.72
		95% CI	(-17.5,25.0)	(-18.6,16.7)	(-22.9,32.3)
		Pr >  t			0.7336
	Week 48	n	3	2	
		LS Mean	17.478	-14.85	32.331
		SEM	9.158	10.43	13.80
		95% CI	(-1.1,36.1)	(-35.8, 6.1)	( 4.5,60.1)
		Pr >  t			0.0236
	Week 56	n	3	1	
		LS Mean	11.921	-39.74	51.657
		SEM	9.158	14.05	16.89
		95% CI	(-6.7,30.5)	(-68.0, -11)	( 17.7,85.6)
		Pr >  t			0.0035
	Week 64	n	2		
		LS Mean	3.773	NE	NE
		SEM	10.55	NE	NE
		95% CI	(-17.5,25.0)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	1.111	NE	NE
		SEM	10.54	NE	NE
		95% CI	(-20.1,22.3)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	6.365	NE	NE
		SEM	9.158	NE	NE
		95% CI	(-12.3,25.0)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	20.443	NE	NE
		SEM	10.55	NE	NE
		95% CI	(-0.8,41.7)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	14.210	NE	NE
		SEM	10.59	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-7.1,35.5)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	-10.30	NE	NE
	SEM	9.158	NE	NE
	95% CI	(-28.9, 8.3)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	16.873	NE	NE
	SEM	13.95	NE	NE
	95% CI	(-11.1,44.9)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	16.873	NE	NE
	SEM	13.95	NE	NE
	95% CI	(-11.1,44.9)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-5.883	-4.815	-1.068		
			SEM	2.990	3.044	2.751		
			95% CI	(-11.8,-0.0)	(-10.8, 1.2)	( -6.5, 4.3)		
					Pr >  t			0.6980
		Week 16	n	111	91			
			LS Mean	-4.829	-7.396	2.568		
			SEM	3.058	3.212	2.959		
			95% CI	(-10.8, 1.2)	(-13.7,-1.1)	( -3.2, 8.4)		
					Pr >  t			0.3859
		Week 24	n	96	70			
			LS Mean	-6.295	-5.306	-0.989		
			SEM	3.126	3.363	3.174		
			95% CI	(-12.4,-0.1)	(-11.9, 1.3)	( -7.2, 5.2)		
					Pr >  t			0.7554
		Week 32	n	77	61			
			LS Mean	-4.254	-7.986	3.731		
			SEM	3.252	3.452	3.359		
			95% CI	(-10.6, 2.1)	(-14.8,-1.2)	( -2.9,10.3)		
					Pr >  t			0.2670
		Week 40	n	69	52			
			LS Mean	-4.409	-8.441	4.032		
			SEM	3.309	3.563	3.518		
			95% CI	(-10.9, 2.1)	(-15.4,-1.4)	( -2.9,10.9)		
			Pr >  t			0.2521		
Week 48	n	62	41					
	LS Mean	-5.777	-6.872	1.095				
	SEM	3.365	3.730	3.739				
	95% CI	(-12.4, 0.8)	(-14.2, 0.5)	( -6.2, 8.4)				
			Pr >  t			0.7698		
Week 56	n	53	35					
	LS Mean	-6.489	-7.373	0.884				
	SEM	3.456	3.859	3.951				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.3, 0.3)	(-14.9, 0.2)	(-6.9, 8.6)
		Pr >  t			0.8230
	Week 64	n	44	33	
		LS Mean	-4.756	-4.607	-0.148
		SEM	3.577	3.912	4.110
		95% CI	(-11.8, 2.3)	(-12.3, 3.1)	(-8.2, 7.9)
		Pr >  t			0.9712
	Week 72	n	45	28	
		LS Mean	-7.146	-5.843	-1.304
		SEM	3.563	4.066	4.244
		95% CI	(-14.1,-0.1)	(-13.8, 2.1)	(-9.6, 7.0)
		Pr >  t			0.7587
	Week 84	n	39	27	
		LS Mean	-8.587	-4.864	-3.723
		SEM	3.678	4.103	4.368
		95% CI	(-15.8,-1.4)	(-12.9, 3.2)	(-12.3, 4.8)
		Pr >  t			0.3942
	Week 96	n	34	19	
		LS Mean	-5.815	-7.435	1.620
		SEM	3.786	4.509	4.840
		95% CI	(-13.2, 1.6)	(-16.3, 1.4)	(-7.9,11.1)
		Pr >  t			0.7379
	Week 108	n	26	17	
		LS Mean	-7.668	-10.03	2.366
		SEM	4.050	4.661	5.180
		95% CI	(-15.6, 0.3)	(-19.2,-0.9)	(-7.8,12.5)
		Pr >  t			0.6479
	Week 120	n	27	11	
		LS Mean	-7.833	-7.712	-0.122
		SEM	4.006	5.372	5.801
		95% CI	(-15.7, 0.0)	(-18.2, 2.8)	(-11.5,11.3)
		Pr >  t			0.9833
	Week 132	n	20	6	
		LS Mean	-10.39	-13.65	3.257
		SEM	4.351	6.747	7.291
		95% CI	(-18.9,-1.9)	(-26.9,-0.4)	(-11.0,17.6)
		Pr >  t			0.6551
	Week 144	n	15	4	
		LS Mean	-12.78	-2.623	-10.15
		SEM	4.744	7.998	8.676



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.1,-3.5)	(-18.3,13.1)	(-27.2, 6.9)
		Pr >  t			0.2421
	Week 156	n	10	2	
		LS Mean	-6.958	-16.41	9.454
		SEM	5.469	10.89	11.72
		95% CI	(-17.7, 3.8)	(-37.8, 5.0)	(-13.5,32.4)
		Pr >  t			0.4199
	Week 168	n	4	2	
		LS Mean	-5.569	0.253	-5.822
		SEM	7.918	10.89	13.04
		95% CI	(-21.1,10.0)	(-21.1,21.6)	(-31.4,19.8)
		Pr >  t			0.6554
	Week 180	n	1	1	
		LS Mean	-22.36	-27.24	4.881
		SEM	15.05	15.08	21.04
		95% CI	(-51.9, 7.2)	(-56.8, 2.4)	(-36.4,46.2)
		Pr >  t			0.8166
	Week 192	n	1	1	
		LS Mean	10.974	6.093	4.881
		SEM	15.05	15.08	21.04
		95% CI	(-18.6,40.5)	(-23.5,35.7)	(-36.4,46.2)
		Pr >  t			0.8166
>= 75 Years	Week 8	n	17	19	
		LS Mean	-0.860	-0.525	-0.334
		SEM	5.756	5.151	7.630
		95% CI	(-12.4,10.7)	(-10.9, 9.8)	(-15.7,15.0)
		Pr >  t			0.9652
	Week 16	n	13	16	
		LS Mean	0.305	-1.381	1.686
		SEM	6.181	5.444	8.157
		95% CI	(-12.1,12.7)	(-12.3, 9.5)	(-14.6,18.0)
		Pr >  t			0.8369
	Week 24	n	9	11	
		LS Mean	4.096	-2.540	6.636
		SEM	6.776	6.007	8.981
		95% CI	(-9.4,17.6)	(-14.5, 9.4)	(-11.2,24.5)
		Pr >  t			0.4621
	Week 32	n	9	12	
		LS Mean	-1.088	1.686	-2.774
		SEM	6.776	5.900	8.907

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.6,12.4)	(-10.1,13.4)	(-20.5,15.0)
		Pr >  t			0.7563
	Week 40	n	6	10	
		LS Mean	4.390	-1.679	6.069
		SEM	7.558	6.156	9.672
		95% CI	(-10.6,19.4)	(-13.9,10.6)	(-13.1,25.3)
		Pr >  t			0.5317
	Week 48	n	7	10	
		LS Mean	-3.315	-1.941	-1.374
		SEM	7.250	6.175	9.443
		95% CI	(-17.7,11.1)	(-14.2,10.3)	(-20.1,17.4)
		Pr >  t			0.8846
	Week 56	n	6	10	
		LS Mean	4.242	-4.051	8.293
		SEM	7.554	6.174	9.670
		95% CI	(-10.7,19.2)	(-16.3, 8.2)	(-10.9,27.5)
		Pr >  t			0.3931
	Week 64	n	3	9	
		LS Mean	-7.895	-8.551	0.656
		SEM	9.405	6.345	11.28
		95% CI	(-26.5,10.7)	(-21.1, 4.0)	(-21.6,22.9)
		Pr >  t			0.9537
	Week 72	n	3	7	
		LS Mean	8.768	-0.436	9.205
		SEM	9.405	6.802	11.54
		95% CI	(-9.8,27.3)	(-13.9,13.0)	(-13.6,32.0)
		Pr >  t			0.4262
	Week 84	n	1	6	
		LS Mean	1.460	-4.988	6.449
		SEM	14.51	7.112	16.11
		95% CI	(-27.2,30.1)	(-19.1, 9.1)	(-25.3,38.2)
		Pr >  t			0.6894
	Week 96	n	1	5	
		LS Mean	1.460	-2.477	3.938
		SEM	14.51	7.531	16.30
		95% CI	(-27.2,30.1)	(-17.4,12.4)	(-28.2,36.1)
		Pr >  t			0.8094
	Week 108	n		4	
		LS Mean	NE	-0.076	NE
		SEM	NE	8.110	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-16.1,15.9)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	17.115	0.855
		SEM	14.55	7.531
		95% CI	(-11.6,45.8)	(-14.0,15.7)
		Pr >  t		0.3209
	Week 132	n		2
		LS Mean	NE	1.541
		SEM	NE	10.47
		95% CI	NE	(-19.1,22.2)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	-1.343
		SEM	NE	14.06
		95% CI	NE	(-29.1,26.4)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	-1.343
		SEM	NE	14.06
		95% CI	NE	(-29.1,26.4)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Race Group 1 (L)	Asian	Week 8	n	32	36			
			LS Mean	-8.618	3.011	-11.63		
			SEM	5.779	5.414	4.805		
			95% CI	(-20.1, 2.9)	(-7.8,13.8)	(-21.1,-2.1)		
					Pr >  t			0.0169
		Week 16	n	30	30			
			LS Mean	-5.273	-0.338	-4.935		
			SEM	5.818	5.650	5.016		
			95% CI	(-16.9, 6.3)	(-11.6,10.9)	(-14.8, 5.0)		
					Pr >  t			0.3268
		Week 24	n	21	26			
			LS Mean	-7.842	1.437	-9.279		
			SEM	6.079	5.744	5.450		
			95% CI	(-19.9, 4.2)	(-10.0,12.8)	(-20.0, 1.5)		
					Pr >  t			0.0904
		Week 32	n	19	24			
			LS Mean	-7.824	-1.802	-6.022		
			SEM	6.158	5.808	5.623		
			95% CI	(-20.0, 4.4)	(-13.3, 9.7)	(-17.1, 5.1)		
					Pr >  t			0.2856
		Week 40	n	16	19			
			LS Mean	0.536	-4.131	4.667		
			SEM	6.318	6.066	6.020		
			95% CI	(-12.0,13.1)	(-16.1, 7.9)	(-7.2,16.5)		
					Pr >  t			0.4390
		Week 48	n	16	18			
			LS Mean	0.535	-3.521	4.057		
			SEM	6.318	6.116	6.073		
95% CI	(-12.0,13.1)		(-15.6, 8.6)	(-7.9,16.0)				
			Pr >  t			0.5048		
Week 56	n	12	14					
	LS Mean	-5.408	-3.309	-2.099				
	SEM	6.635	6.379	6.677				

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.5, 7.7)	(-15.9, 9.3)	(-15.2,11.0)
		Pr >  t			0.7535
	Week 64	n	12	11	
		LS Mean	-5.408	-9.238	3.830
		SEM	6.635	6.690	6.972
		95% CI	(-18.5, 7.7)	(-22.5, 4.0)	(-9.9,17.5)
		Pr >  t			0.5832
	Week 72	n	10	9	
		LS Mean	-8.209	-5.516	-2.692
		SEM	6.878	6.997	7.485
		95% CI	(-21.8, 5.4)	(-19.3, 8.3)	(-17.4,12.0)
		Pr >  t			0.7193
	Week 84	n	8	8	
		LS Mean	0.044	-4.038	4.082
		SEM	7.290	7.199	7.996
		95% CI	(-14.3,14.4)	(-18.2,10.2)	(-11.6,19.8)
		Pr >  t			0.6100
	Week 96	n	6	6	
		LS Mean	-6.071	-16.64	10.570
		SEM	7.837	7.760	8.980
		95% CI	(-21.5, 9.4)	(-31.9,-1.4)	(-7.1,28.2)
		Pr >  t			0.2399
	Week 108	n	4	5	
		LS Mean	-11.71	-7.107	-4.603
		SEM	8.823	8.181	10.19
		95% CI	(-29.1, 5.7)	(-23.2, 9.0)	(-24.6,15.4)
		Pr >  t			0.6517
	Week 120	n	4	4	
		LS Mean	-11.71	-13.13	1.424
		SEM	8.823	8.771	10.67
		95% CI	(-29.1, 5.7)	(-30.4, 4.1)	(-19.6,22.4)
		Pr >  t			0.8939
	Week 132	n	3	2	
		LS Mean	-8.346	-1.108	-7.238
		SEM	9.701	11.20	13.36
		95% CI	(-27.4,10.7)	(-23.1,20.9)	(-33.5,19.0)
		Pr >  t			0.5884
	Week 144	n	3	1	
		LS Mean	-30.57	-3.781	-26.78
		SEM	9.701	14.93	16.62

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	Pr >  t		
Other	Week 156	n	2	1	
		LS Mean	-16.77	-3.781	-12.99
		SEM	11.25	14.93	17.56
	Week 168	95% CI	(-38.9, 5.3)	(-33.1,25.6)	(-47.5,21.6)
		Pr >  t			0.4600
		n	1		
	Week 8	LS Mean	-17.24	NE	NE
		SEM	14.94	NE	NE
		95% CI	(-46.6,12.1)	NE	NE
	Week 16	Pr >  t			NE
		n	16	17	
		LS Mean	4.950	-2.013	6.964
Week 24	SEM	12.42	11.94	7.678	
	95% CI	(-20.0,29.9)	(-25.9,21.8)	(-8.4,22.4)	
	Pr >  t			0.3685	
Week 32	n	15	14		
	LS Mean	4.438	-0.444	4.883	
	SEM	12.52	11.25	8.233	
Week 40	95% CI	(-20.7,29.5)	(-23.0,22.1)	(-11.6,21.3)	
	Pr >  t			0.5553	
	n	12	11		
Week 48	LS Mean	4.474	-4.225	8.699	
	SEM	12.75	12.31	8.939	
	95% CI	(-21.1,30.0)	(-28.8,20.3)	(-9.1,26.5)	
Week 8	Pr >  t			0.3335	
	n	8	9		
	LS Mean	6.084	-7.746	13.830	
Week 16	SEM	13.26	12.59	9.998	
	95% CI	(-20.4,32.6)	(-32.8,17.3)	(-6.0,33.7)	
	Pr >  t			0.1697	
Week 24	n	6	7		
	LS Mean	2.812	-10.38	13.195	
	SEM	13.75	12.95	11.02	
Week 32	95% CI	(-24.6,30.2)	(-36.1,15.4)	(-8.6,35.0)	
	Pr >  t			0.2335	
	n	4	6		
Week 40	LS Mean	3.192	5.491	-2.299	
	SEM	14.64	13.21	12.40	
	95% CI				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 56	95% CI	(-25.9,32.3)	(-20.8,31.8)	(-26.8,22.2)	
	Pr >  t			0.8531	
	n	4	6		
	LS Mean	7.015	-4.138	11.153	
	SEM	14.64	13.24	12.39	
Week 64	95% CI	(-22.1,36.1)	(-30.5,22.2)	(-13.3,35.7)	
	Pr >  t			0.3695	
	n	4	4		
	LS Mean	14.612	0.521	14.090	
	SEM	14.65	14.11	13.31	
Week 72	95% CI	(-14.5,43.7)	(-27.5,28.5)	(-12.2,40.4)	
	Pr >  t			0.2915	
	n	4	4		
	LS Mean	6.279	4.689	1.590	
	SEM	14.65	14.11	13.31	
Week 84	95% CI	(-22.9,35.4)	(-23.3,32.7)	(-24.7,27.9)	
	Pr >  t			0.9050	
	n	4	4		
	LS Mean	-0.973	-3.644	2.670	
	SEM	14.64	14.11	13.32	
Week 96	95% CI	(-30.1,28.1)	(-31.6,24.3)	(-23.7,29.0)	
	Pr >  t			0.8414	
	n	3	2		
	LS Mean	-1.687	4.667	-6.354	
	SEM	15.44	16.42	16.45	
Week 108	95% CI	(-32.3,28.9)	(-27.8,37.1)	(-38.9,26.2)	
	Pr >  t			0.6999	
	n	3	3		
	LS Mean	-1.687	5.537	-7.224	
	SEM	15.44	14.93	14.99	
Week 120	95% CI	(-32.3,28.9)	(-24.0,35.1)	(-36.8,22.4)	
	Pr >  t			0.6305	
	n	2	1		
	LS Mean	6.747	8.988	-2.241	
	SEM	16.89	20.21	21.35	
Week 132	95% CI	(-26.7,40.2)	(-30.9,48.9)	(-44.5,40.0)	
	Pr >  t			0.9166	
	n	2	1		
	LS Mean	-14.58	8.988	-23.57	
	SEM	16.88	20.21	21.36	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-48.0,18.8)	(-30.9,48.9)	(-65.8,18.7)
		Pr >  t			0.2719
	Week 156	n	1		
		LS Mean	6.054	NE	NE
		SEM	20.63	NE	NE
		95% CI	(-34.7,46.8)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	6.054	NE	NE
		SEM	20.63	NE	NE
		95% CI	(-34.7,46.8)	NE	NE
		Pr >  t			NE
White	Week 8	n	93	85	
		LS Mean	-5.850	-7.861	2.011
		SEM	3.661	3.852	3.382
		95% CI	(-13.1, 1.4)	(-15.5,-0.3)	( -4.6, 8.7)
		Pr >  t			0.5527
	Week 16	n	79	61	
		LS Mean	-5.292	-10.56	5.264
		SEM	3.765	4.103	3.686
		95% CI	(-12.7, 2.1)	(-18.6,-2.5)	( -2.0,12.5)
		Pr >  t			0.1541
	Week 24	n	71	43	
		LS Mean	-6.398	-7.805	1.407
		SEM	3.825	4.316	3.978
		95% CI	(-13.9, 1.1)	(-16.3, 0.7)	( -6.4, 9.2)
		Pr >  t			0.7236
	Week 32	n	59	39	
		LS Mean	-4.286	-8.189	3.902
		SEM	3.952	4.403	4.141
		95% CI	(-12.1, 3.5)	(-16.8, 0.5)	( -4.2,12.0)
		Pr >  t			0.3465
	Week 40	n	52	35	
		LS Mean	-5.034	-8.372	3.339
		SEM	4.022	4.483	4.293
		95% CI	(-12.9, 2.9)	(-17.2, 0.4)	( -5.1,11.8)
		Pr >  t			0.4370
	Week 48	n	48	26	
		LS Mean	-9.099	-9.491	0.392
		SEM	4.066	4.729	4.588



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.1,-1.1)	(-18.8,-0.2)	(-8.6, 9.4)
		Pr >  t			0.9320
	Week 56	n	42	24	
		LS Mean	-7.742	-9.358	1.616
		SEM	4.145	4.805	4.739
		95% CI	(-15.9, 0.4)	(-18.8, 0.1)	(-7.7,10.9)
		Pr >  t			0.7332
	Week 64	n	30	26	
		LS Mean	-7.501	-5.586	-1.914
		SEM	4.385	4.731	4.882
		95% CI	(-16.1, 1.1)	(-14.9, 3.7)	(-11.5, 7.7)
		Pr >  t			0.6951
	Week 72	n	34	21	
		LS Mean	-7.120	-6.813	-0.307
		SEM	4.291	4.940	5.002
		95% CI	(-15.6, 1.3)	(-16.5, 2.9)	(-10.1, 9.5)
		Pr >  t			0.9511
	Week 84	n	28	20	
		LS Mean	-11.30	-6.018	-5.284
		SEM	4.451	4.990	5.184
		95% CI	(-20.0,-2.6)	(-15.8, 3.8)	(-15.5, 4.9)
		Pr >  t			0.3084
	Week 96	n	26	15	
		LS Mean	-5.719	-4.814	-0.905
		SEM	4.509	5.339	5.574
		95% CI	(-14.6, 3.1)	(-15.3, 5.7)	(-11.8,10.0)
		Pr >  t			0.8710
	Week 108	n	19	12	
		LS Mean	-6.894	-13.95	7.057
		SEM	4.843	5.666	6.141
		95% CI	(-16.4, 2.6)	(-25.1,-2.8)	(-5.0,19.1)
		Pr >  t			0.2507
	Week 120	n	22	10	
		LS Mean	-7.401	-6.725	-0.676
		SEM	4.677	5.973	6.307
		95% CI	(-16.6, 1.8)	(-18.4, 5.0)	(-13.1,11.7)
		Pr >  t			0.9147
	Week 132	n	15	4	
		LS Mean	-9.692	-11.88	2.192
		SEM	5.139	8.218	8.724

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.8, 0.4)	(-28.0, 4.2)	(-14.9,19.3)
		Pr >  t			0.8017
	Week 144	n	12	4	
		LS Mean	-8.888	-3.960	-4.928
		SEM	5.460	8.223	8.930
		95% CI	(-19.6, 1.8)	(-20.1,12.2)	(-22.5,12.6)
		Pr >  t			0.5812
	Week 156	n	7	2	
		LS Mean	-5.084	-17.72	12.632
		SEM	6.521	10.97	12.04
		95% CI	(-17.9, 7.7)	(-39.2, 3.8)	(-11.0,36.3)
		Pr >  t			0.2944
	Week 168	n	2	2	
		LS Mean	-1.102	-1.052	-0.051
		SEM	10.84	10.97	14.83
		95% CI	(-22.4,20.2)	(-22.6,20.5)	(-29.2,29.1)
		Pr >  t			0.9973
	Week 180	n	1	1	
		LS Mean	-22.14	-28.50	6.359
		SEM	14.93	15.00	20.74
		95% CI	(-51.5, 7.2)	(-57.9, 0.9)	(-34.3,47.1)
		Pr >  t			0.7592
	Week 192	n	1	1	
		LS Mean	11.186	4.826	6.359
		SEM	14.93	15.00	20.74
		95% CI	(-18.1,40.5)	(-24.6,34.3)	(-34.3,47.1)
		Pr >  t			0.7592

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-10.08	-6.134	-3.941		
			SEM	4.711	4.594	3.537		
			95% CI	(-19.4,-0.8)	(-15.2, 2.9)	(-10.9, 3.0)		
					Pr >  t			0.2661
		Week 16	n	60	51			
			LS Mean	-8.107	-13.60	5.492		
			SEM	4.801	4.834	3.771		
			95% CI	(-17.6, 1.4)	(-23.1,-4.1)	(-1.9,12.9)		
					Pr >  t			0.1463
		Week 24	n	51	42			
			LS Mean	-10.47	-10.61	0.147		
			SEM	4.873	4.938	4.010		
			95% CI	(-20.1,-0.9)	(-20.3,-0.9)	(-7.7, 8.0)		
					Pr >  t			0.9708
		Week 32	n	46	36			
			LS Mean	-7.900	-11.37	3.473		
			SEM	4.960	5.076	4.197		
			95% CI	(-17.7, 1.9)	(-21.4,-1.4)	(-4.8,11.7)		
					Pr >  t			0.4084
		Week 40	n	40	33			
			LS Mean	-10.41	-12.56	2.144		
			SEM	5.042	5.137	4.360		
			95% CI	(-20.3,-0.5)	(-22.7,-2.4)	(-6.4,10.7)		
			Pr >  t			0.6232		
Week 48	n	37	28					
	LS Mean	-9.761	-12.95	3.191				
	SEM	5.087	5.259	4.555				
	95% CI	(-19.8, 0.3)	(-23.3,-2.6)	(-5.8,12.1)				
			Pr >  t			0.4838		
Week 56	n	33	23					
	LS Mean	-9.351	-13.06	3.707				
	SEM	5.163	5.424	4.828				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Placebo qd + Fulv	Treatment difference
		N=169	N=172	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-19.5, 0.8)	(-23.7,-2.4)	(-5.8,13.2)	
	Pr >  t			0.4429	
	n	26	20		
	LS Mean	-9.174	-10.28	1.103	
	SEM	5.334	5.559	5.156	
Week 72	95% CI	(-19.7, 1.3)	(-21.2, 0.7)	(-9.0,11.2)	
	Pr >  t			0.8306	
	n	28	17		
	LS Mean	-9.896	-12.02	2.126	
	SEM	5.278	5.731	5.282	
Week 84	95% CI	(-20.3, 0.5)	(-23.3,-0.8)	(-8.2,12.5)	
	Pr >  t			0.6875	
	n	23	17		
	LS Mean	-13.17	-8.480	-4.691	
	SEM	5.435	5.733	5.443	
Week 96	95% CI	(-23.9,-2.5)	(-19.8, 2.8)	(-15.4, 6.0)	
	Pr >  t			0.3890	
	n	23	11		
	LS Mean	-9.081	-9.569	0.489	
	SEM	5.437	6.317	6.056	
Week 108	95% CI	(-19.8, 1.6)	(-22.0, 2.8)	(-11.4,12.4)	
	Pr >  t			0.9357	
	n	15	13		
	LS Mean	-12.00	-12.80	0.800	
	SEM	5.885	6.071	6.220	
Week 120	95% CI	(-23.6,-0.4)	(-24.7,-0.9)	(-11.4,13.0)	
	Pr >  t			0.8977	
	n	16	9		
	LS Mean	-6.250	-14.32	8.065	
	SEM	5.810	6.656	6.725	
Week 132	95% CI	(-17.7, 5.2)	(-27.4,-1.2)	(-5.1,21.3)	
	Pr >  t			0.2308	
	n	14	5		
	LS Mean	-16.04	-21.42	5.380	
	SEM	5.970	7.964	8.140	
Week 144	95% CI	(-27.8,-4.3)	(-37.1,-5.8)	(-10.6,21.4)	
	Pr >  t			0.5088	
	n	8	3		
	LS Mean	-10.47	-6.154	-4.316	
	SEM	6.868	9.598	10.32	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Neoadjuvant	Week 156	95% CI	(-24.0, 3.0)	(-25.0,12.7)	(-24.6,15.9)
		Pr >  t			0.6758
		n	7	2	
	Week 168	LS Mean	-11.09	-20.91	9.821
		SEM	7.139	11.31	12.08
		95% CI	(-25.1, 2.9)	(-43.1, 1.3)	(-13.9,33.5)
	Week 180	Pr >  t			0.4166
		n	4	2	
		LS Mean	-9.132	-4.249	-4.882
	Week 192	SEM	8.595	11.31	13.00
		95% CI	(-26.0, 7.7)	(-26.4,17.9)	(-30.4,20.6)
		Pr >  t			0.7073
	Week 8	n	1	1	
		LS Mean	-25.83	-31.75	5.916
		SEM	15.30	15.31	20.87
	Week 16	95% CI	(-55.9, 4.2)	(-61.8,-1.7)	(-35.1,46.9)
		Pr >  t			0.7769
		n	1	1	
	Week 24	LS Mean	7.497	1.581	5.916
		SEM	15.30	15.31	20.87
		95% CI	(-22.5,37.5)	(-28.5,31.6)	(-35.1,46.9)
	Week 32	Pr >  t			0.7769
		n	18	17	
		LS Mean	-5.213	-17.71	12.502
Week 8	SEM	5.893	6.245	8.586	
	95% CI	(-17.1, 6.7)	(-30.4,-5.1)	(-4.9,29.9)	
	Pr >  t			0.1534	
Week 16	n	17	11		
	LS Mean	-8.745	-18.66	9.916	
	SEM	5.983	7.016	9.247	
Week 24	95% CI	(-20.8, 3.3)	(-32.7,-4.6)	(-8.7,28.5)	
	Pr >  t			0.2887	
	n	15	5		
Week 32	LS Mean	-8.987	-23.58	14.593	
	SEM	6.160	8.782	10.76	
	95% CI	(-21.4, 3.4)	(-41.0,-6.2)	(-6.8,36.0)	
Week 8	Pr >  t			0.1788	
	n	13	5		
	LS Mean	-6.959	-23.58	16.621	
		SEM	6.352	8.782	10.87

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-19.7, 5.8)	(-41.0,-6.2)	(-5.0,38.2)
	Pr >  t			0.1301
	n	11	5	
	LS Mean	-1.177	-16.91	15.737
	SEM	6.585	8.782	11.01
Week 48	95% CI	(-14.3,12.0)	(-34.3, 0.5)	(-6.1,37.6)
	Pr >  t			0.1565
	n	11	2	
	LS Mean	-14.32	-30.37	16.047
	SEM	6.586	11.75	13.49
Week 56	95% CI	(-27.5,-1.2)	(-53.6,-7.2)	(-10.6,42.7)
	Pr >  t			0.2364
	n	8	2	
	LS Mean	-8.598	-13.71	5.108
	SEM	7.082	11.75	13.74
Week 64	95% CI	(-22.7, 5.5)	(-36.9, 9.5)	(-22.1,32.3)
	Pr >  t			0.7107
	n	7	3	
	LS Mean	-6.358	-15.40	9.047
	SEM	7.318	10.25	12.62
Week 72	95% CI	(-20.9, 8.2)	(-35.7, 4.9)	(-15.9,34.0)
	Pr >  t			0.4750
	n	7	3	
	LS Mean	-4.763	-15.40	10.642
	SEM	7.335	10.25	12.64
Week 84	95% CI	(-19.3, 9.8)	(-35.7, 4.9)	(-14.4,35.7)
	Pr >  t			0.4013
	n	7	2	
	LS Mean	-7.144	-13.71	6.563
	SEM	7.335	11.75	13.88
Week 96	95% CI	(-21.7, 7.4)	(-36.9, 9.5)	(-20.9,34.0)
	Pr >  t			0.6369
	n	6	3	
	LS Mean	-8.135	-15.40	7.270
	SEM	7.641	10.25	12.82
Week 108	95% CI	(-23.3, 7.0)	(-35.7, 4.9)	(-18.1,32.6)
	Pr >  t			0.5716
	n	7	2	
	LS Mean	-11.90	-30.80	18.900
	SEM	7.335	11.73	13.86

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
No Prior Use	Week 120	95% CI	(-26.5, 2.7)	(-54.0,-7.7)	(-8.5,46.3)
		Pr >  t			0.1747
		n	6	1	
	Week 132	LS Mean	-19.24	-18.80	-0.443
		SEM	7.641	15.37	17.19
		95% CI	(-34.4,-4.1)	(-49.1,11.5)	(-34.4,33.5)
	Week 144	Pr >  t			0.9795
		n	4		
		LS Mean	-11.97	NE	NE
	Week 156	SEM	8.613	NE	NE
		95% CI	(-29.0, 5.1)	NE	NE
		Pr >  t			NE
	Week 8	n	5		
		LS Mean	-29.82	NE	NE
		SEM	8.043	NE	NE
	Week 16	95% CI	(-45.8, -14)	NE	NE
		Pr >  t			NE
		n	3		
	Week 24	LS Mean	-8.597	NE	NE
		SEM	9.486	NE	NE
		95% CI	(-27.3,10.1)	NE	NE
	Week 32	Pr >  t			NE
		n	59	57	
		LS Mean	-3.404	-1.217	-2.186
Week 16	SEM	3.986	4.183	4.179	
	95% CI	(-11.3, 4.5)	(-9.5, 7.1)	(-10.4, 6.1)	
	Pr >  t			0.6015	
Week 24	n	47	44		
	LS Mean	-1.903	0.932	-2.835	
	SEM	4.153	4.398	4.544	
Week 32	95% CI	(-10.1, 6.3)	(-7.8, 9.6)	(-11.8, 6.1)	
	Pr >  t			0.5333	
	n	39	34		
Week 8	LS Mean	-1.809	2.248	-4.057	
	SEM	4.312	4.645	4.894	
	95% CI	(-10.3, 6.7)	(-6.9,11.4)	(-13.7, 5.6)	
Week 16	Pr >  t			0.4078	
	n	27	32		
	LS Mean	-2.496	-0.475	-2.021	
Week 24	SEM	4.668	4.697	5.233	

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-11.7, 6.7)	(-9.7, 8.8)	(-12.3, 8.3)
		Pr >  t			0.6996
		n	24	24	
		LS Mean	0.313	-2.614	2.927
		SEM	4.788	4.980	5.581
Week 48		95% CI	(-9.1, 9.7)	(-12.4, 7.2)	(-8.0, 13.9)
		Pr >  t			0.6003
		n	21	21	
		LS Mean	-0.900	2.884	-3.784
		SEM	4.933	5.125	5.837
Week 56		95% CI	(-10.6, 8.8)	(-7.2, 13.0)	(-15.3, 7.7)
		Pr >  t			0.5171
		n	18	20	
		LS Mean	-4.354	-0.888	-3.466
		SEM	5.112	5.183	6.047
Week 64		95% CI	(-14.4, 5.7)	(-11.1, 9.3)	(-15.3, 8.4)
		Pr >  t			0.5668
		n	14	19	
		LS Mean	-3.684	-1.279	-2.405
		SEM	5.450	5.244	6.392
Week 72		95% CI	(-14.4, 7.0)	(-11.6, 9.0)	(-15.0, 10.2)
		Pr >  t			0.7069
		n	13	15	
		LS Mean	-7.264	2.184	-9.447
		SEM	5.565	5.548	6.739
Week 84		95% CI	(-18.2, 3.7)	(-8.7, 13.1)	(-22.7, 3.8)
		Pr >  t			0.1615
		n	10	14	
		LS Mean	-6.305	-2.133	-4.172
		SEM	6.049	5.643	7.191
Week 96		95% CI	(-18.2, 5.6)	(-13.2, 9.0)	(-18.3, 10.0)
		Pr >  t			0.5621
		n	6	10	
		LS Mean	-4.711	-4.803	0.091
		SEM	7.169	6.192	8.569
Week 108		95% CI	(-18.8, 9.4)	(-17.0, 7.4)	(-16.7, 16.9)
		Pr >  t			0.9915
		n	4	6	
		LS Mean	0.493	-1.101	1.594
		SEM	8.395	7.307	10.35



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.0,17.0)	(-15.5,13.3)	(-18.7,21.9)
		Pr >  t			0.8777
	Week 120	n	6	6	
		LS Mean	-6.530	5.050	-11.58
		SEM	7.170	7.310	9.407
		95% CI	(-20.6, 7.6)	(-9.3,19.4)	(-30.1, 6.9)
		Pr >  t			0.2188
	Week 132	n	2	3	
		LS Mean	4.684	5.424	-0.739
		SEM	11.22	9.503	14.13
		95% CI	(-17.4,26.7)	(-13.2,24.1)	(-28.5,27.0)
		Pr >  t			0.9583
	Week 144	n	2	2	
		LS Mean	2.816	0.870	1.946
		SEM	11.19	11.30	15.41
		95% CI	(-19.2,24.8)	(-21.3,23.1)	(-28.3,32.2)
		Pr >  t			0.8996
	Week 156	n		1	
		LS Mean	NE	0.954	NE
		SEM	NE	15.41	NE
		95% CI	NE	(-29.3,31.2)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	-10.47	-10.38	-0.086
			SEM	5.195	5.658	5.362
			95% CI	(-20.8,-0.1)	(-21.6, 0.9)	(-10.7,10.5)
		Pr >  t			0.9873	
		Week 16	n	35	22	
			LS Mean	-6.549	-7.056	0.507
			SEM	5.384	6.272	5.986
			95% CI	(-17.2, 4.1)	(-19.5, 5.4)	(-11.3,12.3)
		Pr >  t			0.9326	
		Week 24	n	28	16	
			LS Mean	-9.740	-12.16	2.417
			SEM	5.549	6.643	6.550
			95% CI	(-20.7, 1.3)	(-25.3, 1.0)	(-10.5,15.3)
		Pr >  t			0.7125	
		Week 32	n	22	16	
			LS Mean	-6.730	-13.38	6.646
			SEM	5.827	6.660	6.742
			95% CI	(-18.3, 4.8)	(-26.5,-0.2)	( -6.7,19.9)
		Pr >  t			0.3255	
		Week 40	n	19	12	
			LS Mean	-4.459	-13.14	8.678
			SEM	5.977	7.040	7.247
			95% CI	(-16.3, 7.4)	(-27.0, 0.8)	( -5.6,23.0)
		Pr >  t			0.2323	
		Week 48	n	16	10	
			LS Mean	-11.36	-8.635	-2.721
			SEM	6.170	7.328	7.684
95% CI	(-23.5, 0.8)		(-23.1, 5.8)	(-17.9,12.4)		
Pr >  t			0.7235			
Week 56	n	14	7			
	LS Mean	-11.05	-6.526	-4.524		
	SEM	6.341	8.003	8.464		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-23.6, 1.5)	(-22.3, 9.2)	(-21.2,12.1)
	Pr >  t			0.5934
	n	8	7	
	LS Mean	-4.243	-9.352	5.109
	SEM	7.211	8.006	9.149
Week 72	95% CI	(-18.5,10.0)	(-25.1, 6.4)	(-12.9,23.1)
	Pr >  t			0.5770
	n	12	6	
	LS Mean	-11.00	-8.568	-2.434
	SEM	6.550	8.350	8.949
Week 84	95% CI	(-23.9, 1.9)	(-25.0, 7.9)	(-20.0,15.2)
	Pr >  t			0.7858
	n	8	5	
	LS Mean	-11.32	-12.28	0.953
	SEM	7.256	8.802	9.858
Week 96	95% CI	(-25.6, 3.0)	(-29.6, 5.0)	(-18.4,20.3)
	Pr >  t			0.9231
	n	5	5	
	LS Mean	-16.12	-8.943	-7.180
	SEM	8.327	8.802	10.67
Week 108	95% CI	(-32.5, 0.3)	(-26.3, 8.4)	(-28.2,13.8)
	Pr >  t			0.5015
	n	7	5	
	LS Mean	-10.82	-12.28	1.458
	SEM	7.532	8.802	10.06
Week 120	95% CI	(-25.7, 4.0)	(-29.6, 5.0)	(-18.3,21.3)
	Pr >  t			0.8849
	n	5	3	
	LS Mean	-26.36	-4.254	-22.11
	SEM	8.337	10.38	12.01
Week 132	95% CI	(-42.8, -10)	(-24.7,16.2)	(-45.7, 1.5)
	Pr >  t			0.0665
	n	2	2	
	LS Mean	-20.27	-1.787	-18.48
	SEM	11.65	11.97	15.69
Week 144	95% CI	(-43.2, 2.7)	(-25.3,21.8)	(-49.3,12.4)
	Pr >  t			0.2396
	n	2		
	LS Mean	-33.63	NE	NE
	SEM	11.66	NE	NE

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive	Week 156	95% CI	(-56.6, -11)	NE	NE
		Pr >  t			NE
		n	2		
		LS Mean	-5.593	NE	NE
		SEM	11.67	NE	NE
	Week 168	95% CI	(-28.6,17.4)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-8.903	NE	NE
		SEM	15.71	NE	NE
	Week 8	95% CI	(-39.8,22.0)	NE	NE
		Pr >  t			NE
		n	98	104	
		LS Mean	-3.175	-2.155	-1.020
		SEM	3.748	3.704	3.010
	Week 16	95% CI	(-10.6, 4.2)	(-9.4, 5.1)	(-6.9, 4.9)
		Pr >  t			0.7348
		n	87	84	
		LS Mean	-3.509	-6.054	2.545
		SEM	3.816	3.800	3.188
	Week 24	95% CI	(-11.0, 4.0)	(-13.5, 1.4)	(-3.7, 8.8)
		Pr >  t			0.4252
		n	76	65	
		LS Mean	-3.580	-2.733	-0.847
		SEM	3.888	3.939	3.401
	Week 32	95% CI	(-11.2, 4.1)	(-10.5, 5.0)	(-7.5, 5.8)
		Pr >  t			0.8034
		n	62	57	
LS Mean		-3.004	-4.299	1.294	
SEM		3.993	4.020	3.585	
Week 40	95% CI	(-10.9, 4.9)	(-12.2, 3.6)	(-5.7, 8.3)	
	Pr >  t			0.7182	
	n	54	50		
	LS Mean	-2.915	-5.648	2.733	
	SEM	4.064	4.104	3.745	
Week 48	95% CI	(-10.9, 5.1)	(-13.7, 2.4)	(-4.6,10.1)	
	Pr >  t			0.4658	
	n	52	41		
	LS Mean	-3.126	-5.072	1.946	
	SEM	4.083	4.226	3.898	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-11.2, 4.9)	(-13.4, 3.2)	(-5.7, 9.6)
	Pr >  t			0.6177
	n	44	38	
	LS Mean	-3.029	-6.405	3.376
	SEM	4.175	4.278	4.053
Week 64	95% CI	(-11.2, 5.2)	(-14.8, 2.0)	(-4.6, 11.3)
	Pr >  t			0.4051
	n	39	35	
	LS Mean	-4.006	-4.432	0.426
	SEM	4.251	4.337	4.194
Week 72	95% CI	(-12.4, 4.4)	(-13.0, 4.1)	(-7.8, 8.7)
	Pr >  t			0.9191
	n	36	29	
	LS Mean	-4.003	-3.713	-0.290
	SEM	4.306	4.484	4.401
Week 84	95% CI	(-12.5, 4.5)	(-12.5, 5.1)	(-8.9, 8.3)
	Pr >  t			0.9475
	n	32	28	
	LS Mean	-6.368	-3.090	-3.278
	SEM	4.398	4.514	4.514
Week 96	95% CI	(-15.0, 2.3)	(-12.0, 5.8)	(-12.1, 5.6)
	Pr >  t			0.4679
	n	30	19	
	LS Mean	-2.310	-5.719	3.409
	SEM	4.441	4.904	4.951
Week 108	95% CI	(-11.0, 6.4)	(-15.3, 3.9)	(-6.3, 13.1)
	Pr >  t			0.4912
	n	18	16	
	LS Mean	-5.023	-6.946	1.923
	SEM	4.955	5.117	5.604
Week 120	95% CI	(-14.8, 4.7)	(-17.0, 3.1)	(-9.1, 12.9)
	Pr >  t			0.7315
	n	23	13	
	LS Mean	-1.524	-5.566	4.042
	SEM	4.683	5.411	5.653
Week 132	95% CI	(-10.7, 7.7)	(-16.2, 5.1)	(-7.0, 15.1)
	Pr >  t			0.4748
	n	18	6	
	LS Mean	-7.241	-13.05	5.806
	SEM	4.956	6.957	7.323

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 144	95% CI	(-17.0, 2.5)	(-26.7, 0.6)	( -8.6,20.2)
	Pr >  t			0.4280
	n	13	5	
	LS Mean	-7.647	-1.503	-6.144
	SEM	5.379	7.453	8.082
Week 156	95% CI	(-18.2, 2.9)	(-16.1,13.1)	(-22.0, 9.7)
	Pr >  t			0.4472
	n	8	3	
	LS Mean	-5.744	-11.20	5.453
	SEM	6.267	9.149	10.18
Week 168	95% CI	(-18.0, 6.6)	(-29.1, 6.8)	(-14.5,25.4)
	Pr >  t			0.5923
	n	3	2	
	LS Mean	-3.368	2.302	-5.670
	SEM	9.121	10.91	13.52
Week 180	95% CI	(-21.3,14.5)	(-19.1,23.7)	(-32.2,20.9)
	Pr >  t			0.6750
	n	1	1	
	LS Mean	-19.68	-25.23	5.545
	SEM	14.97	14.97	20.71
Week 192	95% CI	(-49.1, 9.7)	(-54.6, 4.1)	(-35.1,46.2)
	Pr >  t			0.7890
	n	1	1	
	LS Mean	13.647	8.102	5.545
	SEM	14.97	14.97	20.71
	95% CI	(-15.7,43.0)	(-21.3,37.5)	(-35.1,46.2)
	Pr >  t			0.7890

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
ER and PR Status (L)	Both positive	Week 8	n	96	104		
			LS Mean	-3.438	-2.076	-1.363	
			SEM	3.757	3.703	3.028	
			95% CI	(-10.8, 4.0)	(-9.4, 5.2)	(-7.3, 4.6)	
					Pr >  t		0.6529
		Week 16	n	85	84		
			LS Mean	-3.788	-5.963	2.176	
			SEM	3.827	3.800	3.209	
			95% CI	(-11.3, 3.7)	(-13.4, 1.5)	(-4.1, 8.5)	
					Pr >  t		0.4982
		Week 24	n	75	65		
			LS Mean	-3.831	-2.640	-1.192	
			SEM	3.898	3.941	3.420	
			95% CI	(-11.5, 3.8)	(-10.4, 5.1)	(-7.9, 5.5)	
					Pr >  t		0.7277
		Week 32	n	61	57		
			LS Mean	-3.258	-4.205	0.948	
			SEM	4.007	4.023	3.608	
			95% CI	(-11.1, 4.6)	(-12.1, 3.7)	(-6.1, 8.0)	
					Pr >  t		0.7930
		Week 40	n	53	50		
			LS Mean	-3.226	-5.555	2.329	
			SEM	4.081	4.108	3.771	
			95% CI	(-11.3, 4.8)	(-13.6, 2.5)	(-5.1, 9.7)	
					Pr >  t		0.5370
		Week 48	n	51	41		
			LS Mean	-3.447	-4.979	1.531	
			SEM	4.101	4.230	3.925	
95% CI	(-11.5, 4.6)		(-13.3, 3.3)	(-6.2, 9.2)			
			Pr >  t		0.6966		
Week 56	n	43	38				
	LS Mean	-3.362	-6.310	2.948			
	SEM	4.197	4.283	4.085			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-11.6, 4.9)	(-14.7, 2.1)	(-5.1,11.0)
	Pr >  t			0.4707
Week 64	n	39	35	
	LS Mean	-4.271	-4.339	0.068
	SEM	4.260	4.342	4.212
	95% CI	(-12.6, 4.1)	(-12.9, 4.2)	(-8.2, 8.3)
	Pr >  t			0.9871
Week 72	n	35	29	
	LS Mean	-4.303	-3.619	-0.684
	SEM	4.336	4.490	4.440
	95% CI	(-12.8, 4.2)	(-12.4, 5.2)	(-9.4, 8.0)
	Pr >  t			0.8775
Week 84	n	31	28	
	LS Mean	-6.749	-2.995	-3.753
	SEM	4.434	4.521	4.559
	95% CI	(-15.5, 2.0)	(-11.9, 5.9)	(-12.7, 5.2)
	Pr >  t			0.4105
Week 96	n	29	19	
	LS Mean	-2.563	-5.625	3.062
	SEM	4.480	4.913	4.998
	95% CI	(-11.4, 6.2)	(-15.3, 4.0)	(-6.7,12.9)
	Pr >  t			0.5402
Week 108	n	18	16	
	LS Mean	-5.295	-6.855	1.560
	SEM	4.970	5.129	5.630
	95% CI	(-15.1, 4.5)	(-16.9, 3.2)	(-9.5,12.6)
	Pr >  t			0.7818
Week 120	n	23	13	
	LS Mean	-1.788	-5.476	3.689
	SEM	4.695	5.425	5.679
	95% CI	(-11.0, 7.4)	(-16.1, 5.2)	(-7.5,14.8)
	Pr >  t			0.5161
Week 132	n	18	6	
	LS Mean	-7.512	-12.96	5.444
	SEM	4.971	6.981	7.357
	95% CI	(-17.3, 2.2)	(-26.7, 0.7)	(-9.0,19.9)
	Pr >  t			0.4595
Week 144	n	13	5	
	LS Mean	-7.918	-1.408	-6.510
	SEM	5.397	7.480	8.120



Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive Negative	Week 156	95% CI	(-18.5, 2.7)	(-16.1,13.3)	(-22.4, 9.4)
		Pr >  t			0.4229
		n	8	3	
		LS Mean	-6.019	-11.10	5.080
		SEM	6.290	9.186	10.23
	Week 168	95% CI	(-18.4, 6.3)	(-29.1, 6.9)	(-15.0,25.2)
		Pr >  t			0.6195
		n	3	2	
		LS Mean	-3.648	2.403	-6.051
		SEM	9.161	10.95	13.59
	Week 180	95% CI	(-21.6,14.3)	(-19.1,23.9)	(-32.7,20.6)
		Pr >  t			0.6561
		n	1	1	
		LS Mean	-19.96	-25.13	5.174
		SEM	15.04	15.04	20.81
	Week 192	95% CI	(-49.5, 9.6)	(-54.6, 4.4)	(-35.7,46.0)
		Pr >  t			0.8037
		n	1	1	
		LS Mean	13.371	8.197	5.174
		SEM	15.04	15.04	20.81
	Week 8	95% CI	(-16.1,42.9)	(-21.3,37.7)	(-35.7,46.0)
		Pr >  t			0.8037
		n	42	35	
		LS Mean	-10.47	-10.38	-0.086
SEM		5.195	5.658	5.362	
Week 16	95% CI	(-20.8,-0.1)	(-21.6, 0.9)	(-10.7,10.5)	
	Pr >  t			0.9873	
	n	35	22		
	LS Mean	-6.549	-7.056	0.507	
	SEM	5.384	6.272	5.986	
Week 24	95% CI	(-17.2, 4.1)	(-19.5, 5.4)	(-11.3,12.3)	
	Pr >  t			0.9326	
	n	28	16		
	LS Mean	-9.740	-12.16	2.417	
	SEM	5.549	6.643	6.550	
Week 32	95% CI	(-20.7, 1.3)	(-25.3, 1.0)	(-10.5,15.3)	
	Pr >  t			0.7125	
	n	22	16		
	LS Mean	-6.730	-13.38	6.646	
	SEM	5.827	6.660	6.742	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-18.3, 4.8)	(-26.5,-0.2)	(-6.7,19.9)
	Pr >  t			0.3255
Week 40	n	19	12	
	LS Mean	-4.459	-13.14	8.678
	SEM	5.977	7.040	7.247
	95% CI	(-16.3, 7.4)	(-27.0, 0.8)	(-5.6,23.0)
	Pr >  t			0.2323
Week 48	n	16	10	
	LS Mean	-11.36	-8.635	-2.721
	SEM	6.170	7.328	7.684
	95% CI	(-23.5, 0.8)	(-23.1, 5.8)	(-17.9,12.4)
	Pr >  t			0.7235
Week 56	n	14	7	
	LS Mean	-11.05	-6.526	-4.524
	SEM	6.341	8.003	8.464
	95% CI	(-23.6, 1.5)	(-22.3, 9.2)	(-21.2,12.1)
	Pr >  t			0.5934
Week 64	n	8	7	
	LS Mean	-4.243	-9.352	5.109
	SEM	7.211	8.006	9.149
	95% CI	(-18.5,10.0)	(-25.1, 6.4)	(-12.9,23.1)
	Pr >  t			0.5770
Week 72	n	12	6	
	LS Mean	-11.00	-8.568	-2.434
	SEM	6.550	8.350	8.949
	95% CI	(-23.9, 1.9)	(-25.0, 7.9)	(-20.0,15.2)
	Pr >  t			0.7858
Week 84	n	8	5	
	LS Mean	-11.32	-12.28	0.953
	SEM	7.256	8.802	9.858
	95% CI	(-25.6, 3.0)	(-29.6, 5.0)	(-18.4,20.3)
	Pr >  t			0.9231
Week 96	n	5	5	
	LS Mean	-16.12	-8.943	-7.180
	SEM	8.327	8.802	10.67
	95% CI	(-32.5, 0.3)	(-26.3, 8.4)	(-28.2,13.8)
	Pr >  t			0.5015
Week 108	n	7	5	
	LS Mean	-10.82	-12.28	1.458
	SEM	7.532	8.802	10.06

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-25.7, 4.0)	(-29.6, 5.0)	(-18.3,21.3)
	Pr >  t			0.8849
	n	5	3	
	LS Mean	-26.36	-4.254	-22.11
	SEM	8.337	10.38	12.01
Week 132	95% CI	(-42.8, -10)	(-24.7,16.2)	(-45.7, 1.5)
	Pr >  t			0.0665
	n	2	2	
	LS Mean	-20.27	-1.787	-18.48
	SEM	11.65	11.97	15.69
Week 144	95% CI	(-43.2, 2.7)	(-25.3,21.8)	(-49.3,12.4)
	Pr >  t			0.2396
	n	2		
	LS Mean	-33.63	NE	NE
	SEM	11.66	NE	NE
Week 156	95% CI	(-56.6, -11)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	-5.593	NE	NE
	SEM	11.67	NE	NE
Week 168	95% CI	(-28.6,17.4)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-8.903	NE	NE
	SEM	15.71	NE	NE
	95% CI	(-39.8,22.0)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-19i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Role Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64		
			LS Mean	-5.753	-4.100	-1.653	
			SEM	3.653	3.773	3.527	
			95% CI	(-13.0, 1.5)	(-11.5, 3.3)	(-8.6, 5.3)	
					Pr >  t		0.6398
		Week 16	n	70	52		
			LS Mean	-4.624	-5.581	0.958	
			SEM	3.738	3.952	3.743	
			95% CI	(-12.0, 2.7)	(-13.4, 2.2)	(-6.4, 8.3)	
					Pr >  t		0.7982
		Week 24	n	54	40		
			LS Mean	-5.239	-3.691	-1.548	
			SEM	3.873	4.153	4.059	
			95% CI	(-12.9, 2.4)	(-11.9, 4.5)	(-9.5, 6.4)	
					Pr >  t		0.7031
		Week 32	n	50	36		
			LS Mean	-2.730	-4.303	1.572	
			SEM	3.929	4.226	4.174	
			95% CI	(-10.5, 5.0)	(-12.6, 4.0)	(-6.6, 9.8)	
					Pr >  t		0.7066
		Week 40	n	42	28		
			LS Mean	-1.293	-3.092	1.799	
			SEM	4.028	4.437	4.463	
			95% CI	(-9.2, 6.6)	(-11.8, 5.6)	(-7.0, 10.6)	
			Pr >  t		0.6870		
Week 48	n	38	24				
	LS Mean	-7.131	0.942	-8.073			
	SEM	4.090	4.572	4.654			
	95% CI	(-15.2, 0.9)	(-8.0, 9.9)	(-17.2, 1.1)			
			Pr >  t		0.0834		
Week 56	n	33	24				
	LS Mean	-5.756	-4.247	-1.509			
		SEM	4.185	4.575	4.745		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.0, 2.5)	(-13.2, 4.7)	(-10.8, 7.8)
		Pr >  t			0.7506
	Week 64	n	27	19	
		LS Mean	-5.338	0.553	-5.892
		SEM	4.337	4.812	5.104
		95% CI	(-13.9, 3.2)	(-8.9, 10.0)	(-15.9, 4.1)
		Pr >  t			0.2488
	Week 72	n	26	17	
		LS Mean	-7.003	0.575	-7.578
		SEM	4.369	4.936	5.247
		95% CI	(-15.6, 1.6)	(-9.1, 10.3)	(-17.9, 2.7)
		Pr >  t			0.1491
	Week 84	n	18	16	
		LS Mean	-6.902	-0.230	-6.672
		SEM	4.750	5.009	5.620
		95% CI	(-16.2, 2.4)	(-10.1, 9.6)	(-17.7, 4.4)
		Pr >  t			0.2355
	Week 96	n	20	10	
		LS Mean	-2.688	-2.879	0.191
		SEM	4.630	5.689	6.150
		95% CI	(-11.8, 6.4)	(-14.1, 8.3)	(-11.9, 12.3)
		Pr >  t			0.9753
	Week 108	n	14	10	
		LS Mean	-6.397	-4.946	-1.450
		SEM	5.069	5.689	6.480
		95% CI	(-16.4, 3.6)	(-16.1, 6.2)	(-14.2, 11.3)
		Pr >  t			0.8230
	Week 120	n	14	7	
		LS Mean	2.382	3.232	-0.849
		SEM	5.053	6.373	7.086
		95% CI	(-7.5, 12.3)	(-9.3, 15.7)	(-14.8, 13.1)
		Pr >  t			0.9046
	Week 132	n	12	5	
		LS Mean	-2.776	-0.337	-2.439
		SEM	5.285	7.181	7.964
		95% CI	(-13.2, 7.6)	(-14.4, 13.8)	(-18.1, 13.2)
		Pr >  t			0.7594
	Week 144	n	11	4	
		LS Mean	-9.938	2.148	-12.09
		SEM	5.404	7.817	8.626

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	(-20.6, 0.7)	(-13.2,17.5)	(-29.0, 4.8)
		Pr >  t			0.1616
		n	8	3	
		LS Mean	-6.148	-8.217	2.068
	Week 168	SEM	5.986	8.771	9.834
		95% CI	(-17.9, 5.6)	(-25.4, 9.0)	(-17.2,21.4)
		Pr >  t			0.8335
		n	4	2	
	Week 180	LS Mean	-3.528	5.213	-8.741
		SEM	7.719	10.42	12.33
		95% CI	(-18.7,11.6)	(-15.2,25.7)	(-33.0,15.5)
		Pr >  t			0.4787
Week 192	n	1	1		
	LS Mean	-20.28	-22.22	1.937	
	SEM	14.21	14.25	19.72	
	95% CI	(-48.2, 7.6)	(-50.2, 5.7)	(-36.8,40.6)	
Week 8	Pr >  t			0.9218	
	n	1	1		
	LS Mean	13.047	11.110	1.937	
	SEM	14.21	14.25	19.72	
Week 16	95% CI	(-14.8,40.9)	(-16.9,39.1)	(-36.8,40.6)	
	Pr >  t			0.9218	
	n	53	64		
	LS Mean	-4.084	-3.239	-0.845	
Week 24	SEM	6.147	6.587	4.155	
	95% CI	(-16.3, 8.1)	(-16.3, 9.8)	( -9.0, 7.3)	
	Pr >  t			0.8391	
	n	48	48		
Week 32	LS Mean	-2.016	-3.860	1.844	
	SEM	6.274	6.713	4.435	
	95% CI	(-14.4,10.4)	(-17.1, 9.4)	( -6.9,10.6)	
	Pr >  t			0.6780	
Week 32	n	46	36		
	LS Mean	-4.750	-2.960	-1.790	
	SEM	6.295	6.860	4.700	
	95% CI	(-17.2, 7.7)	(-16.5,10.6)	(-11.0, 7.5)	
Week 32	Pr >  t			0.7035	
	n	31	33		
Week 32	LS Mean	-4.894	-6.955	2.061	
	SEM	6.617	6.917	5.071	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-18.0, 8.2)	(-20.6, 6.7)	(-7.9,12.0)
		Pr >  t			0.6847
	Week 40	n	28	30	
		LS Mean	-4.587	-10.03	5.438
		SEM	6.689	6.977	5.239
		95% CI	(-17.8, 8.6)	(-23.8, 3.8)	(-4.9,15.7)
		Pr >  t			0.3000
	Week 48	n	26	23	
		LS Mean	-2.436	-11.79	9.358
		SEM	6.729	7.167	5.549
		95% CI	(-15.7,10.8)	(-25.9, 2.4)	(-1.5,20.3)
		Pr >  t			0.0924
	Week 56	n	22	17	
		LS Mean	-3.596	-7.690	4.094
		SEM	6.853	7.436	6.039
		95% CI	(-17.1, 9.9)	(-22.4, 7.0)	(-7.8,16.0)
		Pr >  t			0.4981
	Week 64	n	17	19	
		LS Mean	-2.785	-9.680	6.895
		SEM	7.089	7.328	6.181
		95% CI	(-16.8,11.2)	(-24.1, 4.8)	(-5.2,19.0)
		Pr >  t			0.2651
	Week 72	n	20	14	
		LS Mean	-3.469	-8.670	5.202
		SEM	6.944	7.644	6.391
		95% CI	(-17.2,10.2)	(-23.7, 6.4)	(-7.4,17.8)
		Pr >  t			0.4160
	Week 84	n	19	13	
		LS Mean	-6.689	-9.010	2.321
		SEM	6.979	7.731	6.541
		95% CI	(-20.5, 7.1)	(-24.2, 6.2)	(-10.5,15.2)
		Pr >  t			0.7228
	Week 96	n	12	12	
		LS Mean	-8.279	-7.954	-0.325
		SEM	7.495	7.834	7.200
		95% CI	(-23.0, 6.5)	(-23.4, 7.5)	(-14.5,13.8)
		Pr >  t			0.9640
	Week 108	n	9	9	
		LS Mean	-5.730	-9.712	3.982
		SEM	7.928	8.253	8.082

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-21.3, 9.9)	(-26.0, 6.5)	(-11.9,19.9)
	Pr >  t			0.6224
Week 120	n	12	7	
	LS Mean	-15.74	-7.111	-8.633
	SEM	7.518	8.710	8.157
	95% CI	(-30.6,-0.9)	(-24.2,10.0)	(-24.7, 7.4)
	Pr >  t			0.2903
Week 132	n	5	2	
	LS Mean	-21.75	-22.32	0.568
	SEM	9.168	12.69	13.39
	95% CI	(-39.8,-3.7)	(-47.2, 2.6)	(-25.7,26.9)
	Pr >  t			0.9662
Week 144	n	3	1	
	LS Mean	-20.91	-6.948	-13.96
	SEM	10.78	16.79	18.24
	95% CI	(-42.1, 0.3)	(-39.9,26.0)	(-49.8,21.9)
	Pr >  t			0.4444
Week 156	n	2		
	LS Mean	-1.559	NE	NE
	SEM	12.51	NE	NE
	95% CI	(-26.1,23.0)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Tabelle 4H-56: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Emotionale Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	1.095	0.729	0.367		
			SEM	2.940	2.918	2.438		
			95% CI	(-4.7, 6.9)	(-5.0, 6.5)	(-4.4, 5.2)		
					Pr >  t			0.8805
		Week 16	n	92	77			
			LS Mean	1.171	-1.461	2.632		
			SEM	2.973	3.063	2.600		
			95% CI	(-4.7, 7.0)	(-7.5, 4.6)	(-2.5, 7.7)		
					Pr >  t			0.3118
		Week 24	n	83	66			
			LS Mean	-1.443	1.511	-2.954		
			SEM	3.018	3.120	2.715		
			95% CI	(-7.4, 4.5)	(-4.6, 7.6)	(-8.3, 2.4)		
					Pr >  t			0.2771
		Week 32	n	72	60			
			LS Mean	2.029	-1.009	3.038		
			SEM	3.077	3.174	2.819		
			95% CI	(-4.0, 8.1)	(-7.3, 5.2)	(-2.5, 8.6)		
					Pr >  t			0.2816
		Week 40	n	64	51			
			LS Mean	0.553	-1.562	2.115		
			SEM	3.121	3.258	2.950		
			95% CI	(-5.6, 6.7)	(-8.0, 4.8)	(-3.7, 7.9)		
			Pr >  t			0.4738		
Week 48	n	58	45					
	LS Mean	-3.775	0.615	-4.390				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	3.160	3.320	3.061
	95% CI	(-10.0, 2.4)	(-5.9, 7.1)	(-10.4, 1.6)
	Pr >  t			0.1520
Week 56	n	49	38	
	LS Mean	0.310	1.832	-1.522
	SEM	3.233	3.415	3.240
	95% CI	(-6.0, 6.7)	(-4.9, 8.5)	(-7.9, 4.8)
	Pr >  t			0.6386
Week 64	n	39	37	
	LS Mean	-1.391	-2.481	1.091
	SEM	3.348	3.431	3.375
	95% CI	(-8.0, 5.2)	(-9.2, 4.3)	(-5.5, 7.7)
	Pr >  t			0.7466
Week 72	n	41	32	
	LS Mean	-1.962	-2.753	0.791
	SEM	3.322	3.522	3.442
	95% CI	(-8.5, 4.6)	(-9.7, 4.2)	(-6.0, 7.5)
	Pr >  t			0.8183
Week 84	n	33	29	
	LS Mean	-0.903	-2.943	2.040
	SEM	3.462	3.590	3.632
	95% CI	(-7.7, 5.9)	(-10.0, 4.1)	(-5.1, 9.2)
	Pr >  t			0.5745
Week 96	n	31	21	
	LS Mean	-1.138	-2.617	1.479
	SEM	3.497	3.851	3.927
	95% CI	(-8.0, 5.7)	(-10.2, 4.9)	(-6.2, 9.2)
	Pr >  t			0.7065
Week 108	n	23	18	
	LS Mean	2.945	-2.790	5.734
	SEM	3.731	4.000	4.270
	95% CI	(-4.4, 10.3)	(-10.6, 5.1)	(-2.6, 14.1)
	Pr >  t			0.1796
Week 120	n	25	15	
	LS Mean	-0.145	0.290	-0.435
	SEM	3.656	4.198	4.400
	95% CI	(-7.3, 7.0)	(-7.9, 8.5)	(-9.1, 8.2)
	Pr >  t			0.9213
Week 132	n	17	8	
	LS Mean	-3.094	0.074	-3.167

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	4.016	5.101	5.521
		95% CI	(-11.0, 4.8)	(-9.9,10.1)	(-14.0, 7.7)
		Pr >  t			0.5663
	Week 144	n	15	5	
		LS Mean	-3.271	3.245	-6.516
		SEM	4.143	6.074	6.518
		95% CI	(-11.4, 4.9)	(-8.7,15.2)	(-19.3, 6.3)
		Pr >  t			0.3176
	Week 156	n	10	3	
		LS Mean	6.472	2.120	4.351
		SEM	4.697	7.484	8.148
		95% CI	(-2.7,15.7)	(-12.6,16.8)	(-11.6,20.3)
		Pr >  t			0.5934
	Week 168	n	4	2	
		LS Mean	-3.673	2.418	-6.090
		SEM	6.602	8.941	10.58
		95% CI	(-16.6, 9.3)	(-15.1,20.0)	(-26.8,14.7)
		Pr >  t			0.5648
	Week 180	n	1	1	
		LS Mean	-10.48	2.701	-13.19
		SEM	12.29	12.30	17.05
		95% CI	(-34.6,13.6)	(-21.4,26.8)	(-46.6,20.3)
		Pr >  t			0.4395
	Week 192	n	1	1	
		LS Mean	-2.145	2.701	-4.846
		SEM	12.29	12.30	17.05
		95% CI	(-26.3,22.0)	(-21.4,26.8)	(-38.3,28.6)
		Pr >  t			0.7763
Yes	Week 8	n	38	42	
		LS Mean	-3.119	-0.177	-2.942
		SEM	4.072	4.426	4.097
		95% CI	(-11.2, 5.0)	(-9.0, 8.6)	(-11.0, 5.2)
		Pr >  t			0.4740
	Week 16	n	32	30	
		LS Mean	-4.449	-5.051	0.602
		SEM	4.334	4.631	4.474
		95% CI	(-13.0, 4.1)	(-14.2, 4.1)	(-8.2, 9.4)
		Pr >  t			0.8931
	Week 24	n	22	15	
		LS Mean	-9.133	-1.075	-8.058

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	4.618	5.447	5.532
	95% CI	(-18.3,-0.0)	(-11.8, 9.7)	(-19.0, 2.8)
	Pr >  t			0.1466
Week 32	n	14	13	
	LS Mean	1.372	-8.367	9.740
	SEM	5.237	5.639	6.156
	95% CI	(-9.0,11.7)	(-19.5, 2.8)	(-2.4,21.9)
	Pr >  t			0.1148
Week 40	n	11	11	
	LS Mean	-0.609	-2.497	1.888
	SEM	5.589	5.868	6.662
	95% CI	(-11.6,10.4)	(-14.1, 9.1)	(-11.2,15.0)
	Pr >  t			0.7771
Week 48	n	11	6	
	LS Mean	-1.367	-13.13	11.759
	SEM	5.589	6.969	7.647
	95% CI	(-12.4, 9.6)	(-26.8, 0.6)	(-3.3,26.8)
	Pr >  t			0.1252
Week 56	n	10	7	
	LS Mean	3.283	-9.184	12.467
	SEM	5.736	6.648	7.472
	95% CI	(-8.0,14.6)	(-22.3, 3.9)	(-2.2,27.2)
	Pr >  t			0.0963
Week 64	n	8	5	
	LS Mean	5.016	-2.514	7.530
	SEM	6.112	7.384	8.403
	95% CI	(-7.0,17.1)	(-17.0,12.0)	(-9.0,24.1)
	Pr >  t			0.3709
Week 72	n	7	3	
	LS Mean	6.914	3.137	3.777
	SEM	6.367	8.816	9.850
	95% CI	(-5.6,19.4)	(-14.2,20.5)	(-15.6,23.2)
	Pr >  t			0.7017
Week 84	n	7	4	
	LS Mean	2.152	-1.737	3.889
	SEM	6.367	7.950	9.082
	95% CI	(-10.4,14.7)	(-17.4,13.9)	(-14.0,21.8)
	Pr >  t			0.6688
Week 96	n	4	3	
	LS Mean	12.383	-7.973	20.356

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	7.693	8.816	10.75
	95% CI	(-2.8,27.5)	(-25.3, 9.4)	(-0.8,41.5)
	Pr >  t			0.0595
Week 108	n	3	3	
	LS Mean	9.225	3.637	5.588
	SEM	8.571	8.820	11.40
	95% CI	(-7.6,26.1)	(-13.7,21.0)	(-16.9,28.1)
	Pr >  t			0.6246
Week 120	n	3	1	
	LS Mean	-2.711	1.506	-4.217
	SEM	8.574	13.88	15.64
	95% CI	(-19.6,14.2)	(-25.8,28.8)	(-35.1,26.6)
	Pr >  t			0.7878
Week 132	n	3		
	LS Mean	6.047	NE	NE
	SEM	8.573	NE	NE
	95% CI	(-10.8,22.9)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134	
			LS Mean	1.762	2.095	-0.333
		SEM	1.508	1.517	2.139	
		95% CI	(-1.2, 4.7)	(-0.9, 5.1)	(-4.5, 3.9)	
		Pr >  t			0.8763	
		Week 16	n	118	104	
			LS Mean	1.544	-0.568	2.112
			SEM	1.575	1.660	2.287
			95% CI	(-1.5, 4.6)	(-3.8, 2.7)	(-2.4, 6.6)
			Pr >  t			0.3560
		Week 24	n	100	79	
			LS Mean	-1.169	2.894	-4.063
			SEM	1.665	1.825	2.469
			95% CI	(-4.4, 2.1)	(-0.7, 6.5)	(-8.9, 0.8)
			Pr >  t			0.1002
		Week 32	n	84	72	
			LS Mean	3.573	-0.886	4.459
			SEM	1.763	1.886	2.580
			95% CI	( 0.1, 7.0)	(-4.6, 2.8)	(-0.6, 9.5)
			Pr >  t			0.0843
		Week 40	n	73	62	
			LS Mean	2.158	-0.145	2.303
			SEM	1.848	1.982	2.708
			95% CI	(-1.5, 5.8)	(-4.0, 3.7)	(-3.0, 7.6)
			Pr >  t			0.3953
		Week 48	n	67	51	
			LS Mean	-1.801	0.384	-2.185
			SEM	1.902	2.120	2.846
95% CI	(-5.5, 1.9)		(-3.8, 4.5)	(-7.8, 3.4)		
Pr >  t				0.4428		
Week 56	n	57	45			
	LS Mean	2.587	1.649	0.938		
	SEM	2.009	2.217	2.990		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-1.4, 6.5)	(-2.7, 6.0)	(-4.9, 6.8)
	Pr >  t			0.7538
	n	45	42	
	LS Mean	1.231	-1.123	2.354
	SEM	2.181	2.274	3.150
Week 72	95% CI	(-3.0, 5.5)	(-5.6, 3.3)	(-3.8, 8.5)
	Pr >  t			0.4550
	n	46	35	
	LS Mean	1.209	-0.984	2.193
	SEM	2.166	2.431	3.255
Week 84	95% CI	(-3.0, 5.5)	(-5.8, 3.8)	(-4.2, 8.6)
	Pr >  t			0.5006
	n	40	33	
	LS Mean	1.155	-1.449	2.604
	SEM	2.277	2.485	3.370
Week 96	95% CI	(-3.3, 5.6)	(-6.3, 3.4)	(-4.0, 9.2)
	Pr >  t			0.4397
	n	34	24	
	LS Mean	1.841	-1.891	3.733
	SEM	2.422	2.813	3.711
Week 108	95% CI	(-2.9, 6.6)	(-7.4, 3.6)	(-3.5, 11.0)
	Pr >  t			0.3147
	n	26	21	
	LS Mean	5.263	-0.382	5.646
	SEM	2.691	2.971	4.007
Week 120	95% CI	(-0.0, 10.5)	(-6.2, 5.4)	(-2.2, 13.5)
	Pr >  t			0.1591
	n	27	16	
	LS Mean	0.966	1.633	-0.667
	SEM	2.653	3.329	4.255
Week 132	95% CI	(-4.2, 6.2)	(-4.9, 8.2)	(-9.0, 7.7)
	Pr >  t			0.8754
	n	20	8	
	LS Mean	-0.205	1.185	-1.390
	SEM	2.995	4.521	5.422
Week 144	95% CI	(-6.1, 5.7)	(-7.7, 10.1)	(-12.0, 9.2)
	Pr >  t			0.7977
	n	14	5	
	LS Mean	-2.028	4.363	-6.391
	SEM	3.491	5.632	6.625

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.9, 4.8)	(-6.7, 15.4)	(-19.4, 6.6)
		Pr >  t			0.3348
	Week 156	n	10	3	
		LS Mean	8.236	3.201	5.035
		SEM	4.056	7.181	8.246
		95% CI	( 0.3, 16.2)	(-10.9, 17.3)	(-11.1, 21.2)
		Pr >  t			0.5416
	Week 168	n	4	2	
		LS Mean	-1.886	3.472	-5.358
		SEM	6.229	8.741	10.73
		95% CI	(-14.1, 10.3)	(-13.7, 20.6)	(-26.4, 15.7)
		Pr >  t			0.6177
	Week 180	n	1	1	
		LS Mean	-8.719	3.816	-12.53
		SEM	12.27	12.27	17.35
		95% CI	(-32.8, 15.3)	(-20.3, 27.9)	(-46.6, 21.5)
		Pr >  t			0.4701
	Week 192	n	1	1	
		LS Mean	-0.379	3.816	-4.195
		SEM	12.27	12.27	17.35
		95% CI	(-24.4, 23.7)	(-20.3, 27.9)	(-38.2, 29.8)
		Pr >  t			0.8090
Prior use	Week 8	n	8	6	
		LS Mean	1.936	4.459	-2.523
		SEM	5.859	6.599	8.613
		95% CI	(-10.4, 14.3)	(-9.3, 18.3)	(-20.6, 15.5)
		Pr >  t			0.7728
	Week 16	n	6	3	
		LS Mean	-1.299	-2.579	1.280
		SEM	6.415	9.481	11.16
		95% CI	(-14.7, 12.1)	(-22.0, 16.9)	(-21.7, 24.2)
		Pr >  t			0.9096
	Week 24	n	5	2	
		LS Mean	-7.956	-6.938	-1.018
		SEM	6.860	11.05	12.71
		95% CI	(-22.2, 6.2)	(-29.6, 15.7)	(-27.0, 25.0)
		Pr >  t			0.9367
	Week 32	n	2	1	
		LS Mean	-7.380	10.743	-18.12
		SEM	9.846	14.38	17.30



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-27.6,12.8)	(-18.8,40.3)	(-53.7,17.4)
	Pr >  t			0.3044
Week 40	n	2		
	LS Mean	-15.72	NE	NE
	SEM	9.846	NE	NE
	95% CI	(-35.9, 4.5)	NE	NE
	Pr >  t			NE
Week 48	n	2		
	LS Mean	-11.55	NE	NE
	SEM	9.846	NE	NE
	95% CI	(-31.7, 8.6)	NE	NE
	Pr >  t			NE
Week 56	n	2		
	LS Mean	-11.55	NE	NE
	SEM	9.846	NE	NE
	95% CI	(-31.7, 8.6)	NE	NE
	Pr >  t			NE
Week 64	n	2		
	LS Mean	-7.380	NE	NE
	SEM	9.846	NE	NE
	95% CI	(-27.6,12.8)	NE	NE
	Pr >  t			NE
Week 72	n	2		
	LS Mean	-15.71	NE	NE
	SEM	9.846	NE	NE
	95% CI	(-35.9, 4.5)	NE	NE
	Pr >  t			NE
Week 96	n	1		
	LS Mean	-1.307	NE	NE
	SEM	13.01	NE	NE
	95% CI	(-28.1,25.5)	NE	NE
	Pr >  t			NE
Week 120	n	1		
	LS Mean	-1.307	NE	NE
	SEM	13.01	NE	NE
	95% CI	(-28.1,25.5)	NE	NE
	Pr >  t			NE
Week 144	n	1		
	LS Mean	-1.307	NE	NE
	SEM	13.01	NE	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-28.1,25.5)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-0.091	0.017	-0.108		
			SEM	2.475	2.532	2.289		
			95% CI	(-5.0, 4.8)	(-5.0, 5.0)	(-4.6, 4.4)		
					Pr >  t			0.9622
		Week 16	n	111	91			
			LS Mean	-1.070	-3.159	2.090		
			SEM	2.532	2.667	2.457		
			95% CI	(-6.0, 3.9)	(-8.4, 2.1)	(-2.7, 6.9)		
					Pr >  t			0.3954
		Week 24	n	96	70			
			LS Mean	-3.809	0.492	-4.301		
			SEM	2.588	2.792	2.635		
			95% CI	(-8.9, 1.3)	(-5.0, 6.0)	(-9.5, 0.9)		
					Pr >  t			0.1031
		Week 32	n	77	61			
			LS Mean	0.692	-4.023	4.715		
			SEM	2.693	2.866	2.789		
			95% CI	(-4.6, 6.0)	(-9.7, 1.6)	(-0.8, 10.2)		
					Pr >  t			0.0913
		Week 40	n	69	52			
			LS Mean	-0.933	-3.000	2.067		
			SEM	2.740	2.957	2.921		
			95% CI	(-6.3, 4.5)	(-8.8, 2.8)	(-3.7, 7.8)		
			Pr >  t			0.4793		
Week 48	n	62	41					
	LS Mean	-4.012	-2.296	-1.717				
	SEM	2.787	3.096	3.105				
	95% CI	(-9.5, 1.5)	(-8.4, 3.8)	(-7.8, 4.4)				
			Pr >  t			0.5805		
Week 56	n	53	35					
	LS Mean	-0.553	-1.234	0.681				
	SEM	2.863	3.204	3.281				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-6.2, 5.1)	(-7.5, 5.1)	(-5.8, 7.1)
		Pr >  t			0.8357
	Week 64	n	44	33	
		LS Mean	-1.256	-2.451	1.195
		SEM	2.963	3.247	3.412
		95% CI	(-7.1, 4.6)	(-8.8, 3.9)	(-5.5, 7.9)
		Pr >  t			0.7262
	Week 72	n	45	28	
		LS Mean	-2.800	-2.317	-0.482
		SEM	2.952	3.374	3.523
		95% CI	(-8.6, 3.0)	(-8.9, 4.3)	(-7.4, 6.4)
		Pr >  t			0.8911
	Week 84	n	39	27	
		LS Mean	-1.927	-2.766	0.839
		SEM	3.047	3.405	3.626
		95% CI	(-7.9, 4.1)	(-9.5, 3.9)	(-6.3, 8.0)
		Pr >  t			0.8170
	Week 96	n	34	19	
		LS Mean	-0.884	-4.906	4.022
		SEM	3.137	3.742	4.017
		95% CI	(-7.0, 5.3)	(-12.2, 2.4)	(-3.9, 11.9)
		Pr >  t			0.3169
	Week 108	n	26	17	
		LS Mean	2.561	-2.932	5.493
		SEM	3.356	3.868	4.299
		95% CI	(-4.0, 9.1)	(-10.5, 4.7)	(-2.9, 13.9)
		Pr >  t			0.2016
	Week 120	n	27	11	
		LS Mean	-1.486	-3.308	1.822
		SEM	3.320	4.458	4.814
		95% CI	(-8.0, 5.0)	(-12.1, 5.4)	(-7.6, 11.3)
		Pr >  t			0.7052
	Week 132	n	20	6	
		LS Mean	-2.912	0.004	-2.916
		SEM	3.606	5.599	6.051
		95% CI	(-10.0, 4.2)	(-11.0, 11.0)	(-14.8, 9.0)
		Pr >  t			0.6299
	Week 144	n	15	4	
		LS Mean	-4.162	2.349	-6.511
		SEM	3.933	6.636	7.199

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-11.9, 3.6)	(-10.7,15.4)	(-20.6, 7.6)
		Pr >  t			0.3659
	Week 156	n	10	2	
		LS Mean	5.550	1.089	4.461
		SEM	4.534	9.039	9.722
		95% CI	(-3.3,14.4)	(-16.6,18.8)	(-14.6,23.5)
		Pr >  t			0.6464
	Week 168	n	4	2	
		LS Mean	-4.591	1.089	-5.680
		SEM	6.567	9.039	10.82
		95% CI	(-17.5, 8.3)	(-16.6,18.8)	(-26.9,15.5)
		Pr >  t			0.5997
	Week 180	n	1	1	
		LS Mean	-11.34	1.313	-12.66
		SEM	12.49	12.51	17.46
		95% CI	(-35.8,13.2)	(-23.2,25.9)	(-46.9,21.6)
		Pr >  t			0.4685
	Week 192	n	1	1	
		LS Mean	-3.004	1.313	-4.317
		SEM	12.49	12.51	17.46
		95% CI	(-27.5,21.5)	(-23.2,25.9)	(-38.6,29.9)
		Pr >  t			0.8047
>= 75 Years	Week 8	n	17	19	
		LS Mean	0.128	2.193	-2.065
		SEM	3.583	3.260	4.816
		95% CI	(-7.0, 7.3)	(-4.3, 8.7)	(-11.6, 7.5)
		Pr >  t			0.6692
	Week 16	n	13	16	
		LS Mean	5.737	1.352	4.385
		SEM	4.008	3.534	5.309
		95% CI	(-2.2,13.7)	(-5.7, 8.4)	(-6.1,14.9)
		Pr >  t			0.4107
	Week 24	n	9	11	
		LS Mean	1.490	2.379	-0.889
		SEM	4.652	4.148	6.203
		95% CI	(-7.7,10.7)	(-5.8,10.6)	(-13.2,11.4)
		Pr >  t			0.8863
	Week 32	n	9	12	
		LS Mean	7.798	5.134	2.664
		SEM	4.652	4.024	6.118

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-1.4,17.0)	(-2.8,13.1)	(-9.4,14.8)
		Pr >  t			0.6639
	Week 40	n	6	10	
		LS Mean	7.118	3.694	3.423
		SEM	5.494	4.307	6.949
		95% CI	(-3.7,18.0)	(-4.8,12.2)	(-10.3,17.2)
		Pr >  t			0.6230
	Week 48	n	7	10	
		LS Mean	-3.147	3.100	-6.246
		SEM	5.162	4.326	6.704
		95% CI	(-13.3, 7.1)	(-5.5,11.7)	(-19.5, 7.0)
		Pr >  t			0.3530
	Week 56	n	6	10	
		LS Mean	7.683	5.047	2.636
		SEM	5.487	4.331	6.954
		95% CI	(-3.2,18.5)	(-3.5,13.6)	(-11.1,16.4)
		Pr >  t			0.7051
	Week 64	n	3	9	
		LS Mean	1.948	-3.190	5.138
		SEM	7.363	4.516	8.609
		95% CI	(-12.6,16.5)	(-12.1, 5.7)	(-11.9,22.1)
		Pr >  t			0.5514
	Week 72	n	3	7	
		LS Mean	18.611	-3.470	22.080
		SEM	7.363	5.003	8.872
		95% CI	( 4.1,33.1)	(-13.3, 6.4)	( 4.6,39.6)
		Pr >  t			0.0138
	Week 84	n	1	6	
		LS Mean	20.389	-4.355	24.744
		SEM	12.19	5.327	13.28
		95% CI	(-3.7,44.5)	(-14.9, 6.2)	(-1.5,51.0)
		Pr >  t			0.0643
	Week 96	n	1	5	
		LS Mean	12.059	2.168	9.891
		SEM	12.19	5.751	13.46
		95% CI	(-12.0,36.1)	(-9.2,13.5)	(-16.7,36.5)
		Pr >  t			0.4635
	Week 108	n		4	
		LS Mean	NE	1.882	NE
		SEM	NE	6.333	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-10.6,14.4)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	1.939	8.832
		SEM	12.22	5.751
		95% CI	(-22.2,26.1)	(-2.5,20.2)
		Pr >  t		(-33.5,19.8)
	Week 132	n		2
		LS Mean	NE	-1.104
		SEM	NE	8.613
		95% CI	NE	(-18.1,15.9)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	4.031
		SEM	NE	11.95
		95% CI	NE	(-19.6,27.6)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	4.031
		SEM	NE	11.95
		95% CI	NE	(-19.6,27.6)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv		
Geographic Region 1 (L)	Asia	Week 8	n	30	35			
			LS Mean	0.311	1.126	-0.816		
			SEM	4.895	4.542	4.198		
			95% CI	(-9.5,10.1)	(-7.9,10.2)	(-9.1, 7.5)		
					Pr >  t			0.8463
		Week 16	n	28	29			
			LS Mean	-3.672	0.050	-3.722		
			SEM	4.929	4.735	4.388		
			95% CI	(-13.5, 6.2)	(-9.4, 9.5)	(-12.4, 5.0)		
					Pr >  t			0.3981
		Week 24	n	21	25			
			LS Mean	0.734	1.440	-0.706		
			SEM	5.110	4.810	4.694		
			95% CI	(-9.4,10.9)	(-8.1,11.0)	(-10.0, 8.6)		
					Pr >  t			0.8807
		Week 32	n	19	23			
			LS Mean	2.021	-5.585	7.606		
			SEM	5.168	4.864	4.824		
			95% CI	(-8.3,12.3)	(-15.3, 4.1)	(-1.9,17.1)		
					Pr >  t			0.1170
		Week 40	n	16	18			
			LS Mean	1.198	-5.713	6.911		
			SEM	5.291	5.078	5.140		
			95% CI	(-9.3,11.7)	(-15.8, 4.4)	(-3.2,17.1)		
					Pr >  t			0.1804
		Week 48	n	16	17			
			LS Mean	-4.010	-5.514	1.504		
			SEM	5.291	5.121	5.181		
95% CI	(-14.5, 6.5)		(-15.7, 4.6)	(-8.7,11.7)				
			Pr >  t			0.7719		
Week 56	n	12	14					
	LS Mean	-2.525	-4.488	1.963				
	SEM	5.533	5.278	5.592				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-13.5, 8.4)	(-14.9, 6.0)	(-9.1,13.0)
	Pr >  t			0.7259
	n	12	11	
	LS Mean	-2.527	-10.72	8.190
	SEM	5.533	5.516	5.820
Week 72	95% CI	(-13.5, 8.4)	(-21.6, 0.2)	(-3.3,19.7)
	Pr >  t			0.1606
	n	10	8	
	LS Mean	-0.635	-8.544	7.910
	SEM	5.712	5.897	6.334
Week 84	95% CI	(-11.9,10.7)	(-20.2, 3.1)	(-4.6,20.4)
	Pr >  t			0.2128
	n	8	8	
	LS Mean	0.077	-10.63	10.703
	SEM	6.021	5.897	6.577
Week 96	95% CI	(-11.8,12.0)	(-22.3, 1.0)	(-2.2,23.6)
	Pr >  t			0.1047
	n	6	6	
	LS Mean	0.047	-5.261	5.308
	SEM	6.441	6.329	7.337
Week 108	95% CI	(-12.7,12.8)	(-17.7, 7.2)	(-9.1,19.7)
	Pr >  t			0.4699
	n	4	5	
	LS Mean	1.276	-6.363	7.639
	SEM	7.199	6.653	8.268
Week 120	95% CI	(-12.9,15.5)	(-19.5, 6.7)	(-8.6,23.9)
	Pr >  t			0.3562
	n	4	4	
	LS Mean	3.361	-8.728	12.089
	SEM	7.199	7.112	8.644
Week 132	95% CI	(-10.8,17.5)	(-22.7, 5.3)	(-4.9,29.1)
	Pr >  t			0.1628
	n	3	2	
	LS Mean	-12.19	-8.075	-4.114
	SEM	7.875	8.997	10.73
Week 144	95% CI	(-27.7, 3.3)	(-25.8, 9.6)	(-25.2,17.0)
	Pr >  t			0.7017
	n	3	1	
	LS Mean	-14.97	-3.106	-11.86
	SEM	7.875	11.92	13.27

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Europe	Week 156	95% CI	(-30.5, 0.5)	(-26.5, 20.3)	(-38.0, 14.2)
		Pr >  t			0.3721
		n	2	1	
	Week 168	LS Mean	5.457	-3.106	8.563
		SEM	9.068	11.92	14.01
		95% CI	(-12.4, 23.3)	(-26.5, 20.3)	(-19.0, 36.1)
	Week 8	Pr >  t			0.5416
		n	1		
		LS Mean	-5.126	NE	NE
	Week 16	SEM	11.96	NE	NE
		95% CI	(-28.6, 18.4)	NE	NE
		Pr >  t			NE
	Week 8	n	66	68	
		LS Mean	-2.991	-4.643	1.651
		SEM	6.017	6.042	3.190
	Week 24	95% CI	(-14.9, 8.9)	(-16.6, 7.3)	(-4.6, 7.9)
		Pr >  t			0.6051
		n	58	48	
	Week 16	LS Mean	-1.017	-7.337	6.319
		SEM	6.048	6.119	3.462
		95% CI	(-13.0, 10.9)	(-19.4, 4.8)	(-0.5, 13.1)
	Week 40	Pr >  t			0.0690
		n	51	36	
		LS Mean	-8.786	-4.564	-4.222
Week 32	SEM	6.081	6.209	3.718	
	95% CI	(-20.8, 3.2)	(-16.8, 7.7)	(-11.5, 3.1)	
	Pr >  t			0.2570	
Week 48	n	43	30		
	LS Mean	-1.778	-6.209	4.431	
	SEM	6.177	6.339	3.936	
Week 40	95% CI	(-14.0, 10.4)	(-18.7, 6.3)	(-3.3, 12.2)	
	Pr >  t			0.2609	
	n	37	25		
Week 48	LS Mean	-3.767	-4.511	0.743	
	SEM	6.228	6.424	4.152	
	95% CI	(-16.1, 8.5)	(-17.2, 8.2)	(-7.4, 8.9)	
Week 48	Pr >  t			0.8580	
	n	33	21		
	LS Mean	-9.477	-5.460	-4.016	
		SEM	6.269	6.521	4.363

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-21.9, 2.9)	(-18.3, 7.4)	(-12.6, 4.6)
	Pr >  t			0.3577
	n	29	20	
	LS Mean	-1.586	-2.694	1.109
	SEM	6.321	6.553	4.484
Week 64	95% CI	(-14.1,10.9)	(-15.6,10.2)	( -7.7, 9.9)
	Pr >  t			0.8048
	n	23	20	
	LS Mean	-7.735	-1.446	-6.289
	SEM	6.430	6.554	4.638
Week 72	95% CI	(-20.4, 5.0)	(-14.4,11.5)	(-15.4, 2.8)
	Pr >  t			0.1756
	n	25	19	
	LS Mean	-6.648	-5.825	-0.823
	SEM	6.390	6.584	4.625
Week 84	95% CI	(-19.3, 6.0)	(-18.8, 7.2)	( -9.9, 8.3)
	Pr >  t			0.8587
	n	22	17	
	LS Mean	-6.215	-5.810	-0.404
	SEM	6.455	6.657	4.815
Week 96	95% CI	(-19.0, 6.5)	(-18.9, 7.3)	( -9.9, 9.1)
	Pr >  t			0.9331
	n	20	13	
	LS Mean	-7.988	-5.657	-2.331
	SEM	6.510	6.864	5.167
Week 108	95% CI	(-20.8, 4.9)	(-19.2, 7.9)	(-12.5, 7.8)
	Pr >  t			0.6521
	n	15	11	
	LS Mean	-0.935	-5.355	4.420
	SEM	6.705	7.019	5.608
Week 120	95% CI	(-14.2,12.3)	(-19.2, 8.5)	( -6.6,15.4)
	Pr >  t			0.4308
	n	16	8	
	LS Mean	-6.461	-4.555	-1.906
	SEM	6.661	7.382	6.005
Week 132	95% CI	(-19.6, 6.7)	(-19.1,10.0)	(-13.7, 9.9)
	Pr >  t			0.7510
	n	12	3	
	LS Mean	-5.958	-7.101	1.142
	SEM	6.890	9.287	8.422

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-19.5, 7.6)	(-25.3,11.1)	(-15.4,17.7)
		Pr >  t			0.8921
	Week 144	n	7	4	
		LS Mean	-5.686	-0.492	-5.194
		SEM	7.517	8.581	8.205
		95% CI	(-20.5, 9.1)	(-17.4,16.4)	(-21.3,10.9)
		Pr >  t			0.5269
	Week 156	n	5	2	
		LS Mean	3.510	-1.821	5.331
		SEM	8.071	10.56	10.67
		95% CI	(-12.4,19.4)	(-22.5,18.9)	(-15.6,26.3)
		Pr >  t			0.6175
	Week 168	n	2	2	
		LS Mean	-4.516	-1.821	-2.696
		SEM	10.51	10.56	12.62
		95% CI	(-25.2,16.1)	(-22.5,18.9)	(-27.5,22.1)
		Pr >  t			0.8309
	Week 180	n		1	
		LS Mean	NE	-1.564	NE
		SEM	NE	13.66	NE
		95% CI	NE	(-28.4,25.2)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	-1.564	NE
		SEM	NE	13.66	NE
		95% CI	NE	(-28.4,25.2)	NE
		Pr >  t			NE
Latin America	Week 8	n	14	13	
		LS Mean	-2.241	6.131	-8.372
		SEM	5.612	5.717	8.137
		95% CI	(-13.5, 9.1)	(-5.4,17.6)	(-24.8, 8.0)
		Pr >  t			0.3091
	Week 16	n	13	12	
		LS Mean	7.621	-2.129	9.750
		SEM	5.715	5.856	8.273
		95% CI	(-3.9,19.1)	(-13.9, 9.6)	(-6.9,26.4)
		Pr >  t			0.2446
	Week 24	n	12	10	
		LS Mean	-3.574	5.752	-9.326
		SEM	5.824	6.143	8.543

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 32	95% CI	(-15.3, 8.1)	(-6.6,18.1)	(-26.5, 7.8)
	Pr >  t			0.2801
	n	9	10	
	LS Mean	-0.988	6.584	-7.572
	SEM	6.293	6.143	8.877
Week 40	95% CI	(-13.6,11.6)	(-5.7,18.9)	(-25.3,10.2)
	Pr >  t			0.3972
	n	7	10	
	LS Mean	-1.551	4.085	-5.636
	SEM	6.755	6.143	9.226
Week 48	95% CI	(-15.0,11.9)	(-8.2,16.4)	(-24.1,12.8)
	Pr >  t			0.5435
	n	7	7	
	LS Mean	5.592	5.404	0.188
	SEM	6.755	6.746	9.620
Week 56	95% CI	(-7.9,19.0)	(-8.0,18.8)	(-19.0,19.4)
	Pr >  t			0.9845
	n	6	7	
	LS Mean	-3.750	3.453	-7.203
	SEM	7.079	6.744	9.861
Week 64	95% CI	(-17.8,10.3)	(-10.0,16.9)	(-26.8,12.4)
	Pr >  t			0.4673
	n	4	7	
	LS Mean	16.209	-5.834	22.042
	SEM	8.036	6.736	10.55
Week 72	95% CI	( 0.3,32.1)	(-19.3, 7.6)	( 1.1,43.0)
	Pr >  t			0.0393
	n	4	4	
	LS Mean	-2.541	2.618	-5.159
	SEM	8.036	8.007	11.40
Week 84	95% CI	(-18.5,13.4)	(-13.2,18.5)	(-27.7,17.4)
	Pr >  t			0.6517
	n	4	5	
	LS Mean	-0.908	1.484	-2.392
	SEM	8.030	7.452	11.03
Week 96	95% CI	(-16.8,15.0)	(-13.3,16.3)	(-24.3,19.5)
	Pr >  t			0.8287
	n	3	2	
	LS Mean	26.452	5.676	20.775
	SEM	8.888	10.33	13.68

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
North America	Week 108	95% CI	( 8.9,44.0)	(-14.7,26.1)	( -6.3,47.8)
		Pr >  t			0.1310
		n	2	3	
	Week 120	LS Mean	6.550	-1.362	7.912
		SEM	10.38	8.902	13.74
		95% CI	(-14.0,27.1)	(-19.0,16.3)	(-19.3,35.1)
	Week 120	Pr >  t			0.5656
		n	2	2	
		LS Mean	-11.63	18.474	-30.11
	Week 132	SEM	10.36	10.35	14.69
		95% CI	(-32.1, 8.9)	( -2.0,38.9)	(-59.1,-1.1)
		Pr >  t			0.0422
	Week 132	n	1	2	
		LS Mean	10.735	18.474	-7.739
		SEM	13.89	10.35	17.37
	Week 8	95% CI	(-16.7,38.2)	( -2.0,38.9)	(-42.1,26.6)
		Pr >  t			0.6565
		n	16	19	
	Week 8	LS Mean	2.299	0.604	1.696
		SEM	4.445	4.304	5.459
		95% CI	( -6.6,11.2)	( -8.0, 9.2)	( -9.2,12.6)
	Week 16	Pr >  t			0.7570
		n	12	14	
		LS Mean	1.442	-3.348	4.790
Week 16	SEM	4.882	4.761	6.095	
	95% CI	( -8.3,11.2)	(-12.8, 6.1)	( -7.3,16.9)	
	Pr >  t			0.4341	
Week 24	n	12	8		
	LS Mean	6.149	4.967	1.182	
	SEM	4.897	5.724	6.829	
Week 24	95% CI	( -3.6,15.9)	( -6.4,16.3)	(-12.4,14.7)	
	Pr >  t			0.8629	
	n	9	7		
Week 32	LS Mean	8.199	-5.837	14.036	
	SEM	5.345	5.954	7.309	
	95% CI	( -2.4,18.8)	(-17.6, 6.0)	( -0.4,28.5)	
Week 32	Pr >  t			0.0573	
	n	9	7		
	LS Mean	1.061	-4.647	5.708	
Week 40	SEM	5.375	5.954	7.348	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 48	95% CI	(-9.6,11.7)	(-16.4, 7.1)	(-8.8,20.3)
	Pr >  t			0.4388
	n	8	5	
	LS Mean	-4.623	3.964	-8.587
	SEM	5.570	6.623	8.044
Week 56	95% CI	(-15.7, 6.4)	(-9.1,17.1)	(-24.5, 7.3)
	Pr >  t			0.2877
	n	7	3	
	LS Mean	3.308	5.398	-2.090
	SEM	5.790	7.921	9.285
Week 64	95% CI	(-8.2,14.8)	(-10.3,21.1)	(-20.4,16.3)
	Pr >  t			0.8223
	n	5	3	
	LS Mean	-0.541	-0.155	-0.386
	SEM	6.420	7.921	9.691
Week 72	95% CI	(-13.2,12.2)	(-15.8,15.5)	(-19.5,18.8)
	Pr >  t			0.9683
	n	5	3	
	LS Mean	2.435	1.386	1.049
	SEM	6.393	7.912	9.655
Week 84	95% CI	(-10.2,15.1)	(-14.3,17.0)	(-18.0,20.1)
	Pr >  t			0.9136
	n	2	2	
	LS Mean	-0.727	5.453	-6.180
	SEM	9.082	9.259	12.55
Week 96	95% CI	(-18.7,17.2)	(-12.9,23.8)	(-31.0,18.6)
	Pr >  t			0.6232
	n	3	2	
	LS Mean	-0.031	-23.71	23.681
	SEM	7.660	9.259	11.60
Week 108	95% CI	(-15.2,15.1)	(-42.0,-5.4)	( 0.7,46.6)
	Pr >  t			0.0431
	n	1	2	
	LS Mean	3.051	5.453	-2.402
	SEM	12.20	9.259	14.96
Week 120	95% CI	(-21.1,27.2)	(-12.9,23.8)	(-32.0,27.2)
	Pr >  t			0.8727
	n	3	2	
	LS Mean	2.745	1.288	1.457
	SEM	7.660	9.259	11.60

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.4,17.9)	(-17.0,19.6)	(-21.5,24.4)
		Pr >  t			0.9002
	Week 132	n	1	1	
		LS Mean	-1.204	-10.40	9.199
		SEM	12.21	12.35	17.06
		95% CI	(-25.4,22.9)	(-34.8,14.0)	(-24.6,43.0)
		Pr >  t			0.5907
	Week 144	n	2		
		LS Mean	-5.743	NE	NE
		SEM	8.999	NE	NE
		95% CI	(-23.5,12.0)	NE	NE
		Pr >  t			NE
	Week 156	n	1		
		LS Mean	-1.204	NE	NE
		SEM	12.21	NE	NE
		95% CI	(-25.4,22.9)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-9.544	NE	NE
		SEM	12.21	NE	NE
		95% CI	(-33.7,14.6)	NE	NE
		Pr >  t			NE
	Week 180	n	1		
		LS Mean	-9.544	NE	NE
		SEM	12.21	NE	NE
		95% CI	(-33.7,14.6)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	-1.204	NE	NE
		SEM	12.21	NE	NE
		95% CI	(-25.4,22.9)	NE	NE
		Pr >  t			NE
Other	Week 8	n	16	5	
		LS Mean	-5.160	4.066	-9.226
		SEM	5.768	8.413	9.414
		95% CI	(-17.2, 6.9)	(-13.3,21.5)	(-28.7,10.3)
		Pr >  t			0.3375
	Week 16	n	13	4	
		LS Mean	-17.95	1.907	-19.85
		SEM	6.044	9.309	10.10



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 24	95% CI	(-30.5,-5.4)	(-17.1,20.9)	(-40.6, 0.8)
	Pr >  t			0.0594
	n	9	2	
	LS Mean	-14.88	-11.65	-3.227
	SEM	6.568	11.36	12.18
Week 32	95% CI	(-28.3,-1.5)	(-34.4,11.1)	(-27.7,21.3)
	Pr >  t			0.7921
	n	6	3	
	LS Mean	-9.040	3.022	-12.06
	SEM	7.221	10.10	11.43
Week 40	95% CI	(-23.6, 5.5)	(-17.4,23.5)	(-35.2,11.0)
	Pr >  t			0.2974
	n	6	2	
	LS Mean	-1.220	7.110	-8.330
	SEM	7.321	11.36	12.63
Week 48	95% CI	(-16.0,13.5)	(-15.7,29.9)	(-33.7,17.0)
	Pr >  t			0.5125
	n	5	1	
	LS Mean	1.007	7.374	-6.367
	SEM	7.650	14.51	15.76
Week 56	95% CI	(-14.4,16.4)	(-21.5,36.3)	(-37.8,25.0)
	Pr >  t			0.6874
	n	5	1	
	LS Mean	1.007	7.374	-6.367
	SEM	7.650	14.51	15.76
Week 64	95% CI	(-14.4,16.4)	(-21.5,36.3)	(-37.8,25.0)
	Pr >  t			0.6874
	n	3	1	
	LS Mean	11.535	7.374	4.161
	SEM	8.858	14.51	16.38
Week 72	95% CI	( -6.2,29.2)	(-21.5,36.3)	(-28.5,36.8)
	Pr >  t			0.8002
	n	4	1	
	LS Mean	8.222	7.374	0.848
	SEM	8.150	14.51	16.01
Week 84	95% CI	( -8.1,24.5)	(-21.5,36.3)	(-31.0,32.7)
	Pr >  t			0.9579
	n	4	1	
	LS Mean	6.140	7.374	-1.234
	SEM	8.150	14.51	16.01

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 96	95% CI	(-10.2,22.5)	(-21.5,36.3)	(-33.1,30.7)
	Pr >  t			0.9388
	n	3	1	
	LS Mean	3.202	7.374	-4.172
	SEM	8.858	14.51	16.38
Week 108	95% CI	(-14.5,20.9)	(-21.5,36.3)	(-36.8,28.5)
	Pr >  t			0.7996
	n	4		
	LS Mean	6.140	NE	NE
	SEM	8.150	NE	NE
Week 120	95% CI	(-10.2,22.5)	NE	NE
	Pr >  t		NE	NE
	n	3		
	LS Mean	8.755	NE	NE
	SEM	8.858	NE	NE
Week 132	95% CI	(-8.9,26.4)	NE	NE
	Pr >  t		NE	NE
	n	3		
	LS Mean	3.202	NE	NE
	SEM	8.858	NE	NE
Week 144	95% CI	(-14.5,20.9)	NE	NE
	Pr >  t		NE	NE
	n	3		
	LS Mean	5.893	NE	NE
	SEM	8.855	NE	NE
Week 156	95% CI	(-11.8,23.6)	NE	NE
	Pr >  t		NE	NE
	n	2		
	LS Mean	6.889	NE	NE
	SEM	10.07	NE	NE
	95% CI	(-13.2,26.9)	NE	NE
	Pr >  t		NE	NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
ER and PR Status (L)	Both positive	Week 8	n	96	104		
			LS Mean	-1.182	0.256	-1.438	
			SEM	3.096	3.062	2.507	
			95% CI	(-7.3, 4.9)	(-5.8, 6.3)	(-6.4, 3.5)	
					Pr >  t		0.5667
		Week 16	n	85	84		
			LS Mean	0.166	-4.152	4.318	
			SEM	3.154	3.141	2.653	
			95% CI	(-6.0, 6.4)	(-10.3, 2.0)	(-0.9, 9.5)	
					Pr >  t		0.1043
		Week 24	n	75	65		
			LS Mean	-3.522	0.726	-4.249	
			SEM	3.211	3.257	2.828	
			95% CI	(-9.8, 2.8)	(-5.7, 7.1)	(-9.8, 1.3)	
					Pr >  t		0.1335
		Week 32	n	61	57		
			LS Mean	2.041	-2.388	4.428	
			SEM	3.302	3.325	2.984	
			95% CI	(-4.5, 8.5)	(-8.9, 4.2)	(-1.4, 10.3)	
					Pr >  t		0.1383
		Week 40	n	53	50		
			LS Mean	-0.236	-2.059	1.823	
			SEM	3.363	3.395	3.117	
			95% CI	(-6.8, 6.4)	(-8.7, 4.6)	(-4.3, 7.9)	
					Pr >  t		0.5589
		Week 48	n	51	41		
			LS Mean	-2.107	-1.689	-0.418	
			SEM	3.379	3.496	3.246	
95% CI	(-8.8, 4.5)		(-8.6, 5.2)	(-6.8, 6.0)			
			Pr >  t		0.8975		
Week 56	n	43	38				
	LS Mean	1.680	-0.760	2.440			
	SEM	3.460	3.539	3.378			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-5.1, 8.5)	(-7.7, 6.2)	(-4.2, 9.1)
	Pr >  t			0.4703
	n	39	35	
	LS Mean	-0.690	-1.899	1.209
	SEM	3.512	3.589	3.483
Week 72	95% CI	(-7.6, 6.2)	(-9.0, 5.2)	(-5.6, 8.0)
	Pr >  t			0.7286
	n	35	29	
	LS Mean	-0.929	-2.565	1.636
	SEM	3.574	3.711	3.671
Week 84	95% CI	(-8.0, 6.1)	(-9.9, 4.7)	(-5.6, 8.8)
	Pr >  t			0.6559
	n	31	28	
	LS Mean	1.034	-2.853	3.888
	SEM	3.656	3.736	3.769
Week 96	95% CI	(-6.1, 8.2)	(-10.2, 4.5)	(-3.5, 11.3)
	Pr >  t			0.3026
	n	29	19	
	LS Mean	2.055	-4.892	6.947
	SEM	3.695	4.061	4.132
Week 108	95% CI	(-5.2, 9.3)	(-12.9, 3.1)	(-1.2, 15.1)
	Pr >  t			0.0930
	n	18	16	
	LS Mean	3.908	-3.097	7.005
	SEM	4.101	4.239	4.655
Week 120	95% CI	(-4.1, 12.0)	(-11.4, 5.2)	(-2.1, 16.1)
	Pr >  t			0.1326
	n	23	13	
	LS Mean	3.149	-2.494	5.642
	SEM	3.872	4.484	4.695
Week 132	95% CI	(-4.5, 10.8)	(-11.3, 6.3)	(-3.6, 14.9)
	Pr >  t			0.2297
	n	18	6	
	LS Mean	-0.728	0.052	-0.780
	SEM	4.102	5.771	6.083
Week 144	95% CI	(-8.8, 7.3)	(-11.3, 11.4)	(-12.7, 11.2)
	Pr >  t			0.8980
	n	13	5	
	LS Mean	-2.446	2.098	-4.544
	SEM	4.454	6.183	6.714

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive Negative	Week 156	95% CI	(-11.2, 6.3)	(-10.0,14.2)	(-17.7, 8.6)
		Pr >  t			0.4987
		n	8	3	
	Week 168	LS Mean	7.554	0.980	6.574
		SEM	5.194	7.594	8.457
		95% CI	(-2.6,17.7)	(-13.9,15.9)	(-10.0,23.2)
	Week 180	Pr >  t			0.4371
		n	3	2	
		LS Mean	-4.701	1.271	-5.972
	Week 192	SEM	7.570	9.056	11.23
		95% CI	(-19.6,10.1)	(-16.5,19.0)	(-28.0,16.1)
		Pr >  t			0.5951
	Week 8	n	1	1	
		LS Mean	-9.984	1.486	-11.47
		SEM	12.44	12.44	17.21
	Week 16	95% CI	(-34.4,14.4)	(-22.9,25.9)	(-45.2,22.3)
		Pr >  t			0.5052
		n	1	1	
	Week 24	LS Mean	-1.644	1.486	-3.130
		SEM	12.44	12.44	17.21
		95% CI	(-26.0,22.8)	(-22.9,25.9)	(-36.9,30.6)
	Week 32	Pr >  t			0.8557
		n	42	35	
		LS Mean	-0.624	-1.815	1.190
Week 8	SEM	3.659	3.986	3.869	
	95% CI	(-7.9, 6.6)	(-9.7, 6.1)	(-6.5, 8.8)	
	Pr >  t			0.7588	
Week 16	n	35	22		
	LS Mean	-5.019	0.090	-5.109	
	SEM	3.818	4.528	4.419	
Week 24	95% CI	(-12.6, 2.5)	(-8.9, 9.0)	(-13.8, 3.6)	
	Pr >  t			0.2490	
	n	28	16		
Week 32	LS Mean	-5.912	-2.850	-3.062	
	SEM	3.977	4.870	4.926	
	95% CI	(-13.8, 2.0)	(-12.5, 6.8)	(-12.8, 6.6)	
Week 8	Pr >  t			0.5348	
	n	22	16		
	LS Mean	-0.871	-6.897	6.026	
Week 16	SEM	4.243	4.884	5.097	
	95% CI				
	Pr >  t				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-9.2, 7.5)	(-16.5, 2.7)	(-4.0,16.1)
	Pr >  t			0.2382
	n	19	12	
	LS Mean	-1.600	-5.669	4.068
	SEM	4.387	5.238	5.553
Week 48	95% CI	(-10.3, 7.1)	(-16.0, 4.7)	(-6.9,15.0)
	Pr >  t			0.4643
	n	16	10	
	LS Mean	-12.04	-4.572	-7.471
	SEM	4.564	5.505	5.944
Week 56	95% CI	(-21.0,-3.0)	(-15.4, 6.3)	(-19.2, 4.2)
	Pr >  t			0.2097
	n	14	7	
	LS Mean	-6.374	-1.493	-4.881
	SEM	4.724	6.116	6.636
Week 64	95% CI	(-15.7, 2.9)	(-13.5,10.5)	(-17.9, 8.2)
	Pr >  t			0.4625
	n	8	7	
	LS Mean	-3.061	-12.70	9.635
	SEM	5.520	6.116	7.241
Week 72	95% CI	(-13.9, 7.8)	(-24.7,-0.7)	(-4.6,23.9)
	Pr >  t			0.1842
	n	12	6	
	LS Mean	-4.862	-8.491	3.629
	SEM	4.917	6.427	7.063
Week 84	95% CI	(-14.5, 4.8)	(-21.1, 4.2)	(-10.3,17.5)
	Pr >  t			0.6077
	n	8	5	
	LS Mean	-11.37	-10.26	-1.109
	SEM	5.563	6.832	7.859
Week 96	95% CI	(-22.3,-0.4)	(-23.7, 3.2)	(-16.6,14.3)
	Pr >  t			0.8878
	n	5	5	
	LS Mean	-14.24	-3.591	-10.65
	SEM	6.525	6.832	8.567
Week 108	95% CI	(-27.1,-1.4)	(-17.0, 9.8)	(-27.5, 6.2)
	Pr >  t			0.2147
	n	7	5	
	LS Mean	-3.888	-3.591	-0.297
	SEM	5.813	6.832	8.037

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.3, 7.5)	(-16.1,15.5)
		Pr >  t		0.9705
	Week 120	n	5	3
		LS Mean	-21.74	5.293
		SEM	6.535	8.226
		95% CI	(-34.6,-8.9)	(-10.9,21.5)
		Pr >  t		(-46.1,-7.9) 0.0057
	Week 132	n	2	2
		LS Mean	-14.38	-6.370
		SEM	9.423	9.617
		95% CI	(-32.9, 4.2)	(-25.3,12.5)
		Pr >  t		(-33.3,17.3) 0.5340
	Week 144	n	2	
		LS Mean	-10.37	NE
		SEM	9.430	NE
		95% CI	(-28.9, 8.2)	NE
		Pr >  t		NE
	Week 156	n	2	
		LS Mean	-0.886	NE
		SEM	9.441	NE
		95% CI	(-19.5,17.7)	NE
		Pr >  t		NE
	Week 168	n	1	
		LS Mean	-4.889	NE
		SEM	12.89	NE
		95% CI	(-30.2,20.5)	NE
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final



**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-1.322	-0.375	-0.947
			SEM	2.546	2.639	2.439
			95% CI	(-6.3, 3.7)	(-5.6, 4.8)	(-5.7, 3.8)
		Pr >  t			0.6981	
		Week 16	n	90	75	
			LS Mean	-0.921	-3.018	2.097
			SEM	2.609	2.759	2.616
			95% CI	(-6.1, 4.2)	(-8.4, 2.4)	(-3.0, 7.2)
		Pr >  t			0.4232	
		Week 24	n	79	62	
			LS Mean	-2.194	0.177	-2.371
			SEM	2.669	2.867	2.769
			95% CI	(-7.4, 3.1)	(-5.5, 5.8)	(-7.8, 3.1)
		Pr >  t			0.3924	
		Week 32	n	70	56	
			LS Mean	1.764	-4.013	5.777
			SEM	2.745	2.930	2.874
			95% CI	(-3.6, 7.2)	(-9.8, 1.7)	( 0.1, 11.4)
		Pr >  t			0.0448	
		Week 40	n	61	46	
			LS Mean	-1.019	-0.191	-0.829
			SEM	2.808	3.046	3.042
			95% CI	(-6.5, 4.5)	(-6.2, 5.8)	(-6.8, 5.1)
Pr >  t			0.7854			
Week 48	n	56	38			
	LS Mean	-4.085	-0.243	-3.842		
	SEM	2.848	3.166	3.199		
	95% CI	(-9.7, 1.5)	(-6.5, 6.0)	(-10.1, 2.4)		
Pr >  t			0.2302			
Week 56	n	49	33			
	LS Mean	-0.056	-0.998	0.942		
	SEM	2.917	3.264	3.359		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	Placebo qd + Fulv N=172		
		95% CI	(-5.8, 5.7)	(-7.4, 5.4)	(-5.7, 7.5)
		Pr >  t			0.7792
	Week 64	n	37	29	
		LS Mean	-1.526	-2.555	1.029
		SEM	3.081	3.366	3.601
		95% CI	(-7.6, 4.5)	(-9.2, 4.1)	(-6.0, 8.1)
		Pr >  t			0.7752
	Week 72	n	40	25	
		LS Mean	-1.974	-4.215	2.242
		SEM	3.033	3.489	3.676
		95% CI	(-7.9, 4.0)	(-11.1, 2.6)	(-5.0, 9.5)
		Pr >  t			0.5421
	Week 84	n	32	23	
		LS Mean	-1.108	-5.071	3.963
		SEM	3.195	3.566	3.872
		95% CI	(-7.4, 5.2)	(-12.1, 1.9)	(-3.6, 11.6)
		Pr >  t			0.3064
	Week 96	n	29	17	
		LS Mean	-0.173	-5.868	5.694
		SEM	3.265	3.880	4.222
		95% CI	(-6.6, 6.2)	(-13.5, 1.7)	(-2.6, 14.0)
		Pr >  t			0.1777
	Week 108	n	22	15	
		LS Mean	3.131	-2.506	5.637
		SEM	3.516	4.031	4.547
		95% CI	(-3.8, 10.0)	(-10.4, 5.4)	(-3.3, 14.6)
		Pr >  t			0.2153
	Week 120	n	23	13	
		LS Mean	-1.233	-1.790	0.558
		SEM	3.469	4.221	4.685
		95% CI	(-8.0, 5.6)	(-10.1, 6.5)	(-8.6, 9.7)
		Pr >  t			0.9053
	Week 132	n	17	5	
		LS Mean	-3.342	3.074	-6.416
		SEM	3.788	6.010	6.521
		95% CI	(-10.8, 4.1)	(-8.7, 14.9)	(-19.2, 6.4)
		Pr >  t			0.3254
	Week 144	n	14	3	
		LS Mean	-5.910	2.487	-8.397
		SEM	4.019	7.487	8.021

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-13.8, 2.0)	(-12.2,17.2)	(-24.1, 7.3)
		Pr >  t			0.2954
	Week 156	n	9	2	
		LS Mean	3.819	1.151	2.668
		SEM	4.704	8.980	9.737
		95% CI	(-5.4,13.0)	(-16.5,18.8)	(-16.4,21.8)
		Pr >  t			0.7842
	Week 168	n	4	1	
		LS Mean	-4.549	1.788	-6.338
		SEM	6.532	12.44	13.76
		95% CI	(-17.4, 8.3)	(-22.6,26.2)	(-33.3,20.7)
		Pr >  t			0.6452
	Week 180	n	1	1	
		LS Mean	-11.46	1.788	-13.25
		SEM	12.39	12.44	17.33
		95% CI	(-35.8,12.9)	(-22.6,26.2)	(-47.2,20.8)
		Pr >  t			0.4448
	Week 192	n	1	1	
		LS Mean	-3.117	1.788	-4.905
		SEM	12.39	12.44	17.33
		95% CI	(-27.4,21.2)	(-22.6,26.2)	(-38.9,29.1)
		Pr >  t			0.7772
>= 3	Week 8	n	37	45	
		LS Mean	1.930	1.235	0.694
		SEM	7.162	7.115	4.113
		95% CI	(-12.2,16.1)	(-12.8,15.3)	(-7.4, 8.8)
		Pr >  t			0.8662
	Week 16	n	34	32	
		LS Mean	-0.142	-2.364	2.221
		SEM	7.321	7.371	4.419
		95% CI	(-14.6,14.3)	(-16.9,12.2)	(-6.5,10.9)
		Pr >  t			0.6159
	Week 24	n	26	19	
		LS Mean	-8.205	0.670	-8.875
		SEM	7.441	7.631	5.029
		95% CI	(-22.9, 6.5)	(-14.4,15.7)	(-18.8, 1.0)
		Pr >  t			0.0790
	Week 32	n	16	17	
		LS Mean	-2.037	-0.138	-1.899
		SEM	7.721	7.706	5.536

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40		95% CI	(-17.3,13.2)	(-15.4,15.1)	(-12.8, 9.0)
		Pr >  t			0.7318
		n	14	16	
		LS Mean	1.297	-8.986	10.283
		SEM	7.822	7.745	5.730
Week 48		95% CI	(-14.1,16.7)	(-24.3, 6.3)	(-1.0,21.6)
		Pr >  t			0.0737
		n	13	13	
		LS Mean	-5.276	-6.876	1.600
		SEM	7.873	7.895	6.000
Week 56		95% CI	(-20.8,10.3)	(-22.5, 8.7)	(-10.2,13.4)
		Pr >  t			0.7899
		n	10	12	
		LS Mean	-0.216	0.027	-0.242
		SEM	8.108	7.964	6.378
Week 64		95% CI	(-16.2,15.8)	(-15.7,15.7)	(-12.8,12.3)
		Pr >  t			0.9697
		n	10	13	
		LS Mean	-0.304	-5.657	5.353
		SEM	8.111	7.902	6.303
Week 72		95% CI	(-16.3,15.7)	(-21.2, 9.9)	(-7.0,17.8)
		Pr >  t			0.3964
		n	8	10	
		LS Mean	0.266	-1.356	1.622
		SEM	8.339	8.121	6.863
Week 84		95% CI	(-16.2,16.7)	(-17.4,14.7)	(-11.9,15.1)
		Pr >  t			0.8133
		n	8	10	
		LS Mean	-2.228	-1.021	-1.207
		SEM	8.344	8.116	6.860
Week 96		95% CI	(-18.7,14.2)	(-17.0,15.0)	(-14.7,12.3)
		Pr >  t			0.8604
		n	6	7	
		LS Mean	-2.223	-0.420	-1.803
		SEM	8.720	8.510	7.738
Week 108		95% CI	(-19.4,15.0)	(-17.2,16.4)	(-17.0,13.4)
		Pr >  t			0.8159
		n	4	6	
	LS Mean	1.068	-3.380	4.448	
	SEM	9.402	8.713	8.715	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.4,19.6)	(-12.7,21.6)
		Pr >  t		0.6101
	Week 120	n	5	3
		LS Mean	-1.683	3.765
		SEM	8.997	10.04
		95% CI	(-19.4,16.0)	(-16.0,23.5)
		Pr >  t		0.5732
	Week 132	n	3	3
		LS Mean	1.307	-8.302
		SEM	10.04	10.04
		95% CI	(-18.4,21.1)	(-28.1,11.5)
		Pr >  t		0.3671
	Week 144	n	1	2
		LS Mean	24.460	0.885
		SEM	14.12	11.20
		95% CI	(-3.3,52.2)	(-21.2,22.9)
		Pr >  t		0.1263
	Week 156	n	1	1
		LS Mean	24.460	0.201
		SEM	14.12	14.13
		95% CI	(-3.3,52.2)	(-27.6,28.0)
		Pr >  t		0.1695
	Week 168	n		1
		LS Mean	NE	0.201
		SEM	NE	14.13
		95% CI	NE	(-27.6,28.0)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup		Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
PIK3CA mutation	E542K	Week 8	n	16	24	
			LS Mean	2.887	-7.410	10.298
			SEM	6.940	7.522	6.357
			95% CI	(-11.1,16.9)	(-22.6, 7.8)	( -2.4,23.0)
			Pr >  t			0.1110
		Week 16	n	14	17	
			LS Mean	3.883	-13.12	17.002
			SEM	6.994	7.756	6.817
			95% CI	(-10.2,18.0)	(-28.8, 2.5)	( 3.4,30.6)
			Pr >  t			0.0151
		Week 24	n	14	11	
			LS Mean	-7.425	-7.005	-0.420
			SEM	6.994	8.099	7.212
			95% CI	(-21.5, 6.7)	(-23.3, 9.3)	(-14.8,13.9)
			Pr >  t			0.9537
		Week 32	n	10	10	
			LS Mean	-5.297	-4.681	-0.615
			SEM	7.510	8.198	7.585
			95% CI	(-20.3, 9.7)	(-21.1,11.8)	(-15.7,14.4)
			Pr >  t			0.9355
		Week 40	n	8	10	
			LS Mean	-1.037	-8.898	7.862
			SEM	7.746	8.198	7.814
			95% CI	(-16.5,14.4)	(-25.4, 7.6)	( -7.6,23.4)
			Pr >  t			0.3168
		Week 48	n	7	11	
			LS Mean	-1.820	-3.927	2.107
			SEM	7.890	8.121	7.891
95% CI	(-17.6,13.9)		(-20.2,12.4)	(-13.5,17.8)		
	Pr >  t			0.7900		
Week 56	n	6	9			
	LS Mean	-1.542	-2.662	1.120		
	SEM	8.078	8.297	8.259		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.6,14.6)	(-19.3,14.0)	(-15.2,17.5)
		Pr >  t			0.8923
	Week 64	n	5	8	
		LS Mean	0.283	-4.708	4.991
		SEM	8.344	8.415	8.634
		95% CI	(-16.3,16.9)	(-21.6,12.1)	(-12.1,22.1)
		Pr >  t			0.5642
	Week 72	n	7	7	
		LS Mean	-0.229	-7.716	7.487
		SEM	7.875	8.564	8.336
		95% CI	(-15.9,15.5)	(-24.8, 9.4)	(-9.0,24.0)
		Pr >  t			0.3708
	Week 84	n	7	7	
		LS Mean	-6.181	-8.906	2.724
		SEM	7.875	8.564	8.336
		95% CI	(-21.9, 9.5)	(-26.0, 8.2)	(-13.8,19.2)
		Pr >  t			0.7444
	Week 96	n	5	6	
		LS Mean	-1.324	-13.85	12.530
		SEM	8.345	8.752	8.964
		95% CI	(-17.9,15.3)	(-31.3, 3.6)	(-5.2,30.2)
		Pr >  t			0.1643
	Week 108	n	4	6	
		LS Mean	4.004	-6.909	10.914
		SEM	8.736	8.752	9.331
		95% CI	(-13.3,21.3)	(-24.4,10.6)	(-7.5,29.3)
		Pr >  t			0.2439
	Week 120	n	4	4	
		LS Mean	-13.29	-1.889	-11.40
		SEM	8.738	9.375	9.920
		95% CI	(-30.6, 4.1)	(-20.5,16.8)	(-31.0, 8.2)
		Pr >  t			0.2521
	Week 132	n	3	1	
		LS Mean	-5.828	-16.39	10.565
		SEM	9.339	13.62	14.38
		95% CI	(-24.3,12.7)	(-43.3,10.5)	(-17.8,38.9)
		Pr >  t			0.4633
	Week 144	n	1	1	
		LS Mean	-20.13	0.779	-20.91
		SEM	13.20	13.67	17.19

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
E545X	Week 8	95% CI	(-46.2, 5.9)	(-26.2, 27.7)	(-54.8, 13.0)
		Pr >  t			0.2253
		n	35	37	
	Week 16	LS Mean	-24.71	-20.96	-3.745
		SEM	7.897	8.327	3.639
		95% CI	(-40.3, -9.1)	(-37.4, -4.5)	(-10.9, 3.4)
	Week 24	Pr >  t			0.3045
		n	34	30	
		LS Mean	-23.41	-22.32	-1.098
	Week 32	SEM	8.214	8.411	3.816
		95% CI	(-39.6, -7.2)	(-38.9, -5.7)	(-8.6, 6.4)
		Pr >  t			0.7737
	Week 40	n	32	23	
		LS Mean	-30.00	-20.33	-9.671
		SEM	8.233	8.520	4.119
	Week 48	95% CI	(-46.2, -14)	(-37.1, -3.5)	(-17.8, -1.6)
		Pr >  t			0.0196
		n	21	22	
	Week 56	LS Mean	-20.72	-21.67	0.942
		SEM	8.402	8.548	4.536
		95% CI	(-37.3, -4.2)	(-38.5, -4.8)	(-8.0, 9.9)
	Week 64	Pr >  t			0.8356
		n	20	20	
		LS Mean	-22.87	-27.80	4.934
	Week 8	SEM	8.433	8.600	4.679
		95% CI	(-39.5, -6.3)	(-44.7, -11)	(-4.3, 14.1)
		Pr >  t			0.2925
	Week 16	n	19	12	
		LS Mean	-26.14	-25.43	-0.719
		SEM	8.455	8.946	5.334
	Week 24	95% CI	(-42.8, -9.5)	(-43.0, -7.8)	(-11.2, 9.8)
		Pr >  t			0.8929
		n	16	8	
	Week 32	LS Mean	-16.51	-22.73	6.217
		SEM	8.563	9.371	6.142
		95% CI	(-33.4, 0.4)	(-41.2, -4.3)	(-5.9, 18.3)
	Week 40	Pr >  t			0.3121
		n	12	11	
		LS Mean	-21.63	-29.32	7.699
	Week 48	SEM	8.779	9.040	5.943



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72	95% CI	(-38.9,-4.3)	(-47.1, -12)	(-4.0,19.4)
	Pr >  t			0.1959
	n	13	7	
	LS Mean	-18.78	-21.84	3.060
	SEM	8.719	9.544	6.599
Week 84	95% CI	(-35.9,-1.6)	(-40.6,-3.1)	(-9.9,16.0)
	Pr >  t			0.6431
	n	12	6	
	LS Mean	-22.25	-28.29	6.036
	SEM	8.770	9.773	6.990
Week 96	95% CI	(-39.5,-5.0)	(-47.5,-9.1)	(-7.7,19.8)
	Pr >  t			0.3883
	n	7	6	
	LS Mean	-24.17	-26.38	2.209
	SEM	9.344	9.766	7.692
Week 108	95% CI	(-42.6,-5.8)	(-45.6,-7.2)	(-12.9,17.3)
	Pr >  t			0.7741
	n	5	3	
	LS Mean	-22.56	-26.28	3.725
	SEM	9.854	11.14	9.899
Week 120	95% CI	(-41.9,-3.2)	(-48.2,-4.4)	(-15.7,23.2)
	Pr >  t			0.7069
	n	8	3	
	LS Mean	-30.94	-20.73	-10.21
	SEM	9.200	11.14	9.228
Week 132	95% CI	(-49.1, -13)	(-42.6, 1.2)	(-28.4, 7.9)
	Pr >  t			0.2691
	n	2	1	
	LS Mean	-28.64	-32.54	3.900
	SEM	12.19	15.45	16.23
Week 144	95% CI	(-52.6,-4.7)	(-62.9,-2.2)	(-28.0,35.8)
	Pr >  t			0.8102
	n	2		
	LS Mean	-14.45	NE	NE
	SEM	12.20	NE	NE
Week 156	95% CI	(-38.4, 9.5)	NE	NE
	Pr >  t			NE
	n	2		
	LS Mean	-14.45	NE	NE
	SEM	12.20	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
H1047X	Week 8	95% CI	(-38.4, 9.5)	NE	NE
		Pr >  t			NE
		n	81	64	
	Week 16	LS Mean	1.483	2.348	-0.865
		SEM	3.069	3.215	3.015
		95% CI	(-4.6, 7.5)	(-4.0, 8.7)	(-6.8, 5.1)
	Week 24	Pr >  t			0.7745
		n	70	52	
		LS Mean	-0.350	0.251	-0.601
	Week 32	SEM	3.135	3.349	3.174
		95% CI	(-6.5, 5.8)	(-6.3, 6.8)	(-6.8, 5.6)
		Pr >  t			0.8499
	Week 40	n	54	40	
		LS Mean	0.045	1.678	-1.633
		SEM	3.248	3.518	3.436
	Week 48	95% CI	(-6.4, 6.4)	(-5.2, 8.6)	(-8.4, 5.1)
		Pr >  t			0.6348
		n	50	36	
	Week 56	LS Mean	2.619	-3.494	6.113
		SEM	3.294	3.575	3.529
		95% CI	(-3.9, 9.1)	(-10.5, 3.5)	(-0.8, 13.0)
	Week 64	Pr >  t			0.0839
		n	42	28	
		LS Mean	0.459	2.182	-1.722
Week 8	SEM	3.377	3.744	3.765	
	95% CI	(-6.2, 7.1)	(-5.2, 9.5)	(-9.1, 5.7)	
	Pr >  t			0.6475	
Week 16	n	38	24		
	LS Mean	-3.332	-0.844	-2.488	
	SEM	3.428	3.854	3.922	
Week 24	95% CI	(-10.1, 3.4)	(-8.4, 6.7)	(-10.2, 5.2)	
	Pr >  t			0.5261	
	n	33	24		
Week 32	LS Mean	-1.273	0.667	-1.940	
	SEM	3.506	3.856	3.994	
	95% CI	(-8.2, 5.6)	(-6.9, 8.2)	(-9.8, 5.9)	
Week 40	Pr >  t			0.6274	
	n	27	19		
	LS Mean	-0.986	0.094	-1.080	
Week 48	SEM	3.630	4.048	4.288	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.1, 6.2)	(-7.9, 8.1)	(-9.5, 7.3)
		Pr >  t			0.8013
	Week 72	n	26	17	
		LS Mean	-2.608	-3.042	0.434
		SEM	3.657	4.147	4.402
		95% CI	(-9.8, 4.6)	(-11.2, 5.1)	(-8.2, 9.1)
		Pr >  t			0.9215
	Week 84	n	18	16	
		LS Mean	-0.171	-0.499	0.328
		SEM	3.969	4.207	4.706
		95% CI	(-8.0, 7.6)	(-8.8, 7.8)	(-8.9, 9.6)
		Pr >  t			0.9444
	Week 96	n	20	10	
		LS Mean	2.663	-0.057	2.720
		SEM	3.869	4.761	5.138
		95% CI	(-4.9, 10.3)	(-9.4, 9.3)	(-7.4, 12.8)
		Pr >  t			0.5967
	Week 108	n	14	10	
		LS Mean	7.318	2.927	4.391
		SEM	4.230	4.764	5.413
		95% CI	(-1.0, 15.6)	(-6.4, 12.3)	(-6.2, 15.0)
		Pr >  t			0.4174
	Week 120	n	14	7	
		LS Mean	7.719	1.544	6.175
		SEM	4.217	5.322	5.907
		95% CI	(-0.6, 16.0)	(-8.9, 12.0)	(-5.4, 17.8)
		Pr >  t			0.2962
	Week 132	n	12	5	
		LS Mean	1.091	0.023	1.068
		SEM	4.408	5.987	6.632
		95% CI	(-7.6, 9.7)	(-11.7, 11.8)	(-11.9, 14.1)
		Pr >  t			0.8721
	Week 144	n	11	4	
		LS Mean	0.125	3.357	-3.233
		SEM	4.506	6.511	7.177
		95% CI	(-8.7, 9.0)	(-9.4, 16.1)	(-17.3, 10.9)
		Pr >  t			0.6525
	Week 156	n	8	3	
		LS Mean	7.845	3.111	4.734
		SEM	4.985	7.295	8.171

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 168		95% CI	(-1.9,17.6)	(-11.2,17.4)	(-11.3,20.8)
		Pr >  t			0.5625
		n	4	2	
		LS Mean	-2.201	3.395	-5.596
		SEM	6.412	8.655	10.23
Week 180		95% CI	(-14.8,10.4)	(-13.6,20.4)	(-25.7,14.5)
		Pr >  t			0.5847
		n	1	1	
		LS Mean	-8.941	3.729	-12.67
		SEM	11.77	11.82	16.34
Week 192		95% CI	(-32.0,14.2)	(-19.5,26.9)	(-44.7,19.4)
		Pr >  t			0.4383
		n	1	1	
		LS Mean	-0.601	3.729	-4.330
		SEM	11.77	11.82	16.34
	95% CI	(-23.7,22.5)	(-19.5,26.9)	(-36.4,27.7)	
	Pr >  t			0.7911	

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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**Table 11.2-17i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Emotional Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PIK3CA mutation location (L)	Exon 20	Week 8	n	81	64			
			LS Mean	1.483	2.348	-0.865		
			SEM	3.069	3.215	3.015		
			95% CI	(-4.6, 7.5)	(-4.0, 8.7)	(-6.8, 5.1)		
					Pr >  t			0.7745
		Week 16	n	70	52			
			LS Mean	-0.350	0.251	-0.601		
			SEM	3.135	3.349	3.174		
			95% CI	(-6.5, 5.8)	(-6.3, 6.8)	(-6.8, 5.6)		
					Pr >  t			0.8499
		Week 24	n	54	40			
			LS Mean	0.045	1.678	-1.633		
			SEM	3.248	3.518	3.436		
			95% CI	(-6.4, 6.4)	(-5.2, 8.6)	(-8.4, 5.1)		
					Pr >  t			0.6348
		Week 32	n	50	36			
			LS Mean	2.619	-3.494	6.113		
			SEM	3.294	3.575	3.529		
			95% CI	(-3.9, 9.1)	(-10.5, 3.5)	(-0.8, 13.0)		
					Pr >  t			0.0839
		Week 40	n	42	28			
			LS Mean	0.459	2.182	-1.722		
			SEM	3.377	3.744	3.765		
			95% CI	(-6.2, 7.1)	(-5.2, 9.5)	(-9.1, 5.7)		
			Pr >  t			0.6475		
Week 48	n	38	24					
	LS Mean	-3.332	-0.844	-2.488				
	SEM	3.428	3.854	3.922				
	95% CI	(-10.1, 3.4)	(-8.4, 6.7)	(-10.2, 5.2)				
			Pr >  t			0.5261		
Week 56	n	33	24					
	LS Mean	-1.273	0.667	-1.940				
	SEM	3.506	3.856	3.994				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-8.2, 5.6)	(-6.9, 8.2)	(-9.8, 5.9)
	Pr >  t			0.6274
	n	27	19	
	LS Mean	-0.986	0.094	-1.080
	SEM	3.630	4.048	4.288
Week 72	95% CI	(-8.1, 6.2)	(-7.9, 8.1)	(-9.5, 7.3)
	Pr >  t			0.8013
	n	26	17	
	LS Mean	-2.608	-3.042	0.434
	SEM	3.657	4.147	4.402
Week 84	95% CI	(-9.8, 4.6)	(-11.2, 5.1)	(-8.2, 9.1)
	Pr >  t			0.9215
	n	18	16	
	LS Mean	-0.171	-0.499	0.328
	SEM	3.969	4.207	4.706
Week 96	95% CI	(-8.0, 7.6)	(-8.8, 7.8)	(-8.9, 9.6)
	Pr >  t			0.9444
	n	20	10	
	LS Mean	2.663	-0.057	2.720
	SEM	3.869	4.761	5.138
Week 108	95% CI	(-4.9, 10.3)	(-9.4, 9.3)	(-7.4, 12.8)
	Pr >  t			0.5967
	n	14	10	
	LS Mean	7.318	2.927	4.391
	SEM	4.230	4.764	5.413
Week 120	95% CI	(-1.0, 15.6)	(-6.4, 12.3)	(-6.2, 15.0)
	Pr >  t			0.4174
	n	14	7	
	LS Mean	7.719	1.544	6.175
	SEM	4.217	5.322	5.907
Week 132	95% CI	(-0.6, 16.0)	(-8.9, 12.0)	(-5.4, 17.8)
	Pr >  t			0.2962
	n	12	5	
	LS Mean	1.091	0.023	1.068
	SEM	4.408	5.987	6.632
Week 144	95% CI	(-7.6, 9.7)	(-11.7, 11.8)	(-11.9, 14.1)
	Pr >  t			0.8721
	n	11	4	
Week 144	LS Mean	0.125	3.357	-3.233
	SEM	4.506	6.511	7.177

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Exon 9	Week 156	95% CI	(-8.7, 9.0)	(-9.4,16.1)	(-17.3,10.9)
		Pr >  t			0.6525
		n	8	3	
		LS Mean	7.845	3.111	4.734
	Week 168	SEM	4.985	7.295	8.171
		95% CI	(-1.9,17.6)	(-11.2,17.4)	(-11.3,20.8)
		Pr >  t			0.5625
		n	4	2	
	Week 180	LS Mean	-2.201	3.395	-5.596
		SEM	6.412	8.655	10.23
		95% CI	(-14.8,10.4)	(-13.6,20.4)	(-25.7,14.5)
		Pr >  t			0.5847
Week 192	n	1	1		
	LS Mean	-8.941	3.729	-12.67	
	SEM	11.77	11.82	16.34	
	95% CI	(-32.0,14.2)	(-19.5,26.9)	(-44.7,19.4)	
Week 8	Pr >  t			0.4383	
	n	1	1		
	LS Mean	-0.601	3.729	-4.330	
	SEM	11.77	11.82	16.34	
Week 16	95% CI	(-23.7,22.5)	(-19.5,26.9)	(-36.4,27.7)	
	Pr >  t			0.7911	
	n	53	64		
	LS Mean	-6.053	-5.934	-0.120	
Week 24	SEM	4.516	4.836	3.142	
	95% CI	(-15.0, 2.9)	(-15.5, 3.6)	(-6.3, 6.1)	
	Pr >  t			0.9696	
	n	48	48		
Week 32	LS Mean	-3.709	-7.680	3.972	
	SEM	4.623	4.950	3.375	
	95% CI	(-12.8, 5.4)	(-17.5, 2.1)	(-2.7,10.6)	
	Pr >  t			0.2402	
Week 32	n	46	36		
	LS Mean	-11.82	-4.182	-7.637	
	SEM	4.638	5.080	3.598	
	95% CI	(-21.0,-2.6)	(-14.2, 5.9)	(-14.7,-0.6)	
Week 32	Pr >  t			0.0346	
	n	31	33		
	LS Mean	-5.046	-5.517	0.471	
	SEM	4.923	5.130	3.913	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-14.8, 4.7)	(-15.7, 4.6)	(-7.2, 8.2)
	Pr >  t			0.9043
	n	28	30	
	LS Mean	-5.147	-10.46	5.317
	SEM	4.985	5.182	4.055
Week 48	95% CI	(-15.0, 4.7)	(-20.7,-0.2)	(-2.7,13.3)
	Pr >  t			0.1906
	n	26	23	
	LS Mean	-7.589	-6.327	-1.262
	SEM	5.027	5.347	4.320
Week 56	95% CI	(-17.5, 2.3)	(-16.9, 4.2)	(-9.7, 7.2)
	Pr >  t			0.7703
	n	22	17	
	LS Mean	-0.441	-4.304	3.863
	SEM	5.139	5.586	4.734
Week 64	95% CI	(-10.6, 9.7)	(-15.3, 6.7)	(-5.4,13.2)
	Pr >  t			0.4148
	n	17	19	
	LS Mean	-3.694	-9.302	5.609
	SEM	5.346	5.494	4.853
Week 72	95% CI	(-14.2, 6.8)	(-20.1, 1.5)	(-3.9,15.1)
	Pr >  t			0.2483
	n	20	14	
	LS Mean	-2.017	-6.510	4.493
	SEM	5.216	5.771	5.028
Week 84	95% CI	(-12.3, 8.3)	(-17.9, 4.9)	(-5.4,14.4)
	Pr >  t			0.3719
	n	19	13	
	LS Mean	-6.397	-10.16	3.763
	SEM	5.250	5.849	5.155
Week 96	95% CI	(-16.7, 3.9)	(-21.7, 1.4)	(-6.4,13.9)
	Pr >  t			0.4657
	n	12	12	
	LS Mean	-5.481	-11.99	6.514
	SEM	5.701	5.938	5.706
Week 108	95% CI	(-16.7, 5.7)	(-23.7,-0.3)	(-4.7,17.7)
	Pr >  t			0.2541
	n	9	9	
	LS Mean	-2.142	-8.031	5.889
	SEM	6.076	6.301	6.439



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-14.1, 9.8)	(-20.4, 4.4)	(-6.8,18.5)
		Pr >  t			0.3607
	Week 120	n	12	7	
		LS Mean	-14.34	-3.135	-11.20
		SEM	5.714	6.696	6.499
		95% CI	(-25.6,-3.1)	(-16.3,10.0)	(-24.0, 1.6)
		Pr >  t			0.0852
	Week 132	n	5	2	
		LS Mean	-9.896	-16.27	6.371
		SEM	7.138	10.06	10.81
		95% CI	(-23.9, 4.1)	(-36.0, 3.5)	(-14.9,27.6)
		Pr >  t			0.5559
	Week 144	n	3	1	
		LS Mean	-6.007	0.591	-6.599
		SEM	8.497	13.46	14.77
		95% CI	(-22.7,10.7)	(-25.8,27.0)	(-35.6,22.4)
		Pr >  t			0.6552
	Week 156	n	2		
		LS Mean	2.250	NE	NE
		SEM	9.940	NE	NE
		95% CI	(-17.3,21.8)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-57: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Kognitive Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	-2.819	-2.205	-0.614		
			SEM	2.632	2.608	2.185		
			95% CI	(-8.0, 2.4)	(-7.3, 2.9)	(-4.9, 3.7)		
					Pr >  t			0.7788
		Week 16	n	92	77			
			LS Mean	-1.017	-4.976	3.959		
			SEM	2.661	2.743	2.333		
			95% CI	(-6.3, 4.2)	(-10.4, 0.4)	(-0.6, 8.5)		
					Pr >  t			0.0903
		Week 24	n	83	66			
			LS Mean	-2.580	-4.920	2.340		
			SEM	2.703	2.796	2.439		
			95% CI	(-7.9, 2.7)	(-10.4, 0.6)	(-2.4, 7.1)		
					Pr >  t			0.3377
		Week 32	n	72	60			
			LS Mean	-3.881	-2.054	-1.828		
			SEM	2.756	2.844	2.534		
			95% CI	(-9.3, 1.5)	(-7.6, 3.5)	(-6.8, 3.1)		
					Pr >  t			0.4710
		Week 40	n	64	51			
			LS Mean	-1.032	-1.737	0.705		
			SEM	2.797	2.921	2.654		
			95% CI	(-6.5, 4.5)	(-7.5, 4.0)	(-4.5, 5.9)		
			Pr >  t			0.7905		
Week 48	n	58	45					
	LS Mean	-4.942	-3.578	-1.364				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	2.832	2.979	2.754
	95% CI	(-10.5, 0.6)	(-9.4, 2.3)	(-6.8, 4.0)
	Pr >  t			0.6206
Week 56	n	49	38	
	LS Mean	-5.076	-5.326	0.250
	SEM	2.899	3.065	2.917
	95% CI	(-10.8, 0.6)	(-11.3, 0.7)	(-5.5, 6.0)
	Pr >  t			0.9317
Week 64	n	39	37	
	LS Mean	-2.635	-3.587	0.952
	SEM	3.005	3.080	3.041
	95% CI	(-8.5, 3.3)	(-9.6, 2.5)	(-5.0, 6.9)
	Pr >  t			0.7543
Week 72	n	41	32	
	LS Mean	-5.583	-6.536	0.953
	SEM	2.981	3.163	3.101
	95% CI	(-11.4, 0.3)	(-12.8,-0.3)	(-5.1, 7.0)
	Pr >  t			0.7587
Week 84	n	33	29	
	LS Mean	-4.082	-4.476	0.394
	SEM	3.110	3.225	3.275
	95% CI	(-10.2, 2.0)	(-10.8, 1.9)	(-6.0, 6.8)
	Pr >  t			0.9042
Week 96	n	31	21	
	LS Mean	-2.552	-7.470	4.918
	SEM	3.141	3.463	3.543
	95% CI	(-8.7, 3.6)	(-14.3,-0.7)	(-2.0,11.9)
	Pr >  t			0.1654
Week 108	n	23	18	
	LS Mean	-4.231	-6.158	1.927
	SEM	3.355	3.599	3.855
	95% CI	(-10.8, 2.4)	(-13.2, 0.9)	(-5.6, 9.5)
	Pr >  t			0.6173
Week 120	n	25	15	
	LS Mean	-2.481	-5.027	2.546
	SEM	3.286	3.780	3.974
	95% CI	(-8.9, 4.0)	(-12.4, 2.4)	(-5.2,10.3)
	Pr >  t			0.5219
Week 132	n	17	8	
	LS Mean	-4.157	-10.72	6.561

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		SEM	3.615	4.602	4.992
		95% CI	(-11.3, 2.9)	(-19.7,-1.7)	(-3.2,16.4)
		Pr >  t			0.1889
	Week 144	n	15	5	
		LS Mean	-11.50	-3.928	-7.574
		SEM	3.730	5.488	5.896
		95% CI	(-18.8,-4.2)	(-14.7, 6.8)	(-19.1, 4.0)
		Pr >  t			0.1991
	Week 156	n	10	3	
		LS Mean	-2.592	-9.746	7.154
		SEM	4.235	6.768	7.376
		95% CI	(-10.9, 5.7)	(-23.0, 3.5)	(-7.3,21.6)
		Pr >  t			0.3322
	Week 168	n	4	2	
		LS Mean	-10.43	-2.534	-7.898
		SEM	5.967	8.090	9.577
		95% CI	(-22.1, 1.3)	(-18.4,13.3)	(-26.7,10.9)
		Pr >  t			0.4097
	Week 180	n	1	1	
		LS Mean	-46.05	-2.489	-43.56
		SEM	11.13	11.14	15.45
		95% CI	(-67.9, -24)	(-24.3,19.4)	(-73.9, -13)
		Pr >  t			0.0049
	Week 192	n	1	1	
		LS Mean	-62.72	-2.489	-60.23
		SEM	11.13	11.14	15.45
		95% CI	(-84.6, -41)	(-24.3,19.4)	(-90.5, -30)
		Pr >  t			0.0001
Yes	Week 8	n	38	42	
		LS Mean	-3.793	-3.321	-0.472
		SEM	3.521	3.751	3.495
		95% CI	(-10.8, 3.2)	(-10.8, 4.1)	(-7.4, 6.4)
		Pr >  t			0.8927
	Week 16	n	32	30	
		LS Mean	-1.483	-5.120	3.638
		SEM	3.734	3.934	3.832
		95% CI	(-8.9, 5.9)	(-12.9, 2.7)	(-3.9,11.2)
		Pr >  t			0.3440
	Week 24	n	22	15	
		LS Mean	-7.041	-4.853	-2.188

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	3.968	4.584	4.682
	95% CI	(-14.9, 0.8)	(-13.9, 4.2)	(-11.4, 7.0)
	Pr >  t			0.6408
Week 32	n	14	13	
	LS Mean	2.262	-4.995	7.257
	SEM	4.468	4.739	5.186
	95% CI	(-6.5,11.1)	(-14.3, 4.4)	(-3.0,17.5)
	Pr >  t			0.1629
Week 40	n	11	11	
	LS Mean	2.841	-2.791	5.632
	SEM	4.751	4.929	5.598
	95% CI	(-6.5,12.2)	(-12.5, 6.9)	(-5.4,16.7)
	Pr >  t			0.3152
Week 48	n	11	6	
	LS Mean	1.324	-15.72	17.044
	SEM	4.751	5.824	6.401
	95% CI	(-8.0,10.7)	(-27.2,-4.3)	( 4.4,29.6)
	Pr >  t			0.0082
Week 56	n	10	7	
	LS Mean	3.580	-3.080	6.660
	SEM	4.871	5.564	6.260
	95% CI	(-6.0,13.2)	(-14.0, 7.9)	(-5.7,19.0)
	Pr >  t			0.2882
Week 64	n	8	5	
	LS Mean	2.394	-9.879	12.273
	SEM	5.174	6.162	7.013
	95% CI	(-7.8,12.6)	(-22.0, 2.2)	(-1.5,26.1)
	Pr >  t			0.0812
Week 72	n	7	3	
	LS Mean	2.700	1.274	1.427
	SEM	5.382	7.354	8.215
	95% CI	(-7.9,13.3)	(-13.2,15.7)	(-14.7,17.6)
	Pr >  t			0.8623
Week 84	n	7	4	
	LS Mean	0.319	-1.419	1.738
	SEM	5.382	6.638	7.580
	95% CI	(-10.3,10.9)	(-14.5,11.6)	(-13.2,16.7)
	Pr >  t			0.8188
Week 96	n	4	3	
	LS Mean	4.773	-4.283	9.056

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	6.462	7.354	8.960
	95% CI	(-7.9,17.5)	(-18.8,10.2)	(-8.6,26.7)
	Pr >  t			0.3131
Week 108	n	3	3	
	LS Mean	5.555	-4.761	10.316
	SEM	7.181	7.353	9.492
	95% CI	(-8.6,19.7)	(-19.2, 9.7)	(-8.4,29.0)
	Pr >  t			0.2782
Week 120	n	3	1	
	LS Mean	-6.811	2.301	-9.112
	SEM	7.182	11.53	13.00
	95% CI	(-21.0, 7.3)	(-20.4,25.0)	(-34.7,16.5)
	Pr >  t			0.4840
Week 132	n	3		
	LS Mean	-0.358	NE	NE
	SEM	7.183	NE	NE
	95% CI	(-14.5,13.8)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>	<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Baseline ECOG performance status	0 Week 8	n	98	90		
		LS Mean	-4.031	-3.259	-0.772	
		SEM	2.702	2.637	2.126	
		95% CI	(-9.3, 1.3)	(-8.4, 1.9)	(-4.9, 3.4)	
			Pr >  t			0.7166
	Week 16	n	88	71		
		LS Mean	-2.541	-5.343	2.802	
		SEM	2.751	2.807	2.274	
		95% CI	(-8.0, 2.9)	(-10.9, 0.2)	(-1.7, 7.3)	
			Pr >  t			0.2185
	Week 24	n	75	54		
		LS Mean	-4.444	-5.495	1.051	
		SEM	2.795	2.908	2.463	
		95% CI	(-9.9, 1.1)	(-11.2, 0.2)	(-3.8, 5.9)	
			Pr >  t			0.6699
	Week 32	n	62	52		
		LS Mean	-3.609	-1.382	-2.226	
		SEM	2.868	2.925	2.557	
		95% CI	(-9.2, 2.0)	(-7.1, 4.4)	(-7.2, 2.8)	
			Pr >  t			0.3842
	Week 40	n	51	46		
		LS Mean	-1.845	-1.584	-0.261	
		SEM	2.942	2.991	2.700	
		95% CI	(-7.6, 3.9)	(-7.5, 4.3)	(-5.6, 5.0)	
		Pr >  t			0.9230	
Week 48	n	50	37			
	LS Mean	-6.036	-3.792	-2.244		
	SEM	2.949	3.096	2.824		
	95% CI	(-11.8, -0.2)	(-9.9, 2.3)	(-7.8, 3.3)		
		Pr >  t			0.4269	
Week 56	n	43	33			
	LS Mean	-5.854	-4.353	-1.501		
	SEM	3.013	3.159	2.960		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-11.8, 0.1)	(-10.6, 1.9)	(-7.3, 4.3)
	Pr >  t			0.6122
	n	35	33	
	LS Mean	-3.929	-4.133	0.204
	SEM	3.112	3.159	3.063
Week 72	95% CI	(-10.0, 2.2)	(-10.3, 2.1)	(-5.8, 6.2)
	Pr >  t			0.9468
	n	35	31	
	LS Mean	-5.388	-6.169	0.781
	SEM	3.113	3.195	3.099
Week 84	95% CI	(-11.5, 0.7)	(-12.4, 0.1)	(-5.3, 6.9)
	Pr >  t			0.8011
	n	31	29	
	LS Mean	-2.650	-4.143	1.493
	SEM	3.187	3.234	3.207
Week 96	95% CI	(-8.9, 3.6)	(-10.5, 2.2)	(-4.8, 7.8)
	Pr >  t			0.6415
	n	27	22	
	LS Mean	-1.669	-6.911	5.242
	SEM	3.263	3.424	3.477
Week 108	95% CI	(-8.1, 4.7)	(-13.6,-0.2)	(-1.6,12.1)
	Pr >  t			0.1319
	n	19	20	
	LS Mean	-4.619	-6.178	1.559
	SEM	3.531	3.498	3.792
Week 120	95% CI	(-11.6, 2.3)	(-13.0, 0.7)	(-5.9, 9.0)
	Pr >  t			0.6811
	n	20	15	
	LS Mean	-4.077	-4.889	0.812
	SEM	3.476	3.759	3.996
Week 132	95% CI	(-10.9, 2.7)	(-12.3, 2.5)	(-7.0, 8.7)
	Pr >  t			0.8391
	n	15	7	
	LS Mean	-6.965	-9.978	3.013
	SEM	3.746	4.760	5.137
Week 144	95% CI	(-14.3, 0.4)	(-19.3,-0.6)	(-7.1,13.1)
	Pr >  t			0.5576
	n	10	5	
Week 144	LS Mean	-15.73	-3.761	-11.97
	SEM	4.197	5.396	6.046



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-24.0,-7.5)	(-14.3, 6.8)	(-23.8,-0.1)
		Pr >  t			0.0480
	Week 156	n	6	3	
		LS Mean	-5.402	-9.618	4.215
		SEM	5.024	6.630	7.674
		95% CI	(-15.3, 4.5)	(-22.6, 3.4)	(-10.8,19.3)
		Pr >  t			0.5829
	Week 168	n	3	2	
		LS Mean	-14.67	-2.399	-12.27
		SEM	6.622	7.909	9.802
		95% CI	(-27.7,-1.7)	(-17.9,13.1)	(-31.5, 7.0)
		Pr >  t			0.2108
	Week 180	n	1	1	
		LS Mean	-47.76	-2.307	-45.45
		SEM	10.87	10.86	15.03
		95% CI	(-69.1, -26)	(-23.6,19.0)	(-74.9, -16)
		Pr >  t			0.0026
	Week 192	n	1	1	
		LS Mean	-64.43	-2.307	-62.12
		SEM	10.87	10.86	15.03
		95% CI	(-85.7, -43)	(-23.6,19.0)	(-91.6, -33)
		Pr >  t			<.0001
1	Week 8	n	43	50	
		LS Mean	-1.580	-0.449	-1.131
		SEM	3.720	3.888	3.791
		95% CI	( -8.9, 5.8)	( -8.2, 7.3)	( -8.6, 6.4)
		Pr >  t			0.7658
	Week 16	n	35	35	
		LS Mean	1.709	-4.386	6.095
		SEM	3.881	4.017	4.129
		95% CI	( -6.0, 9.4)	(-12.3, 3.6)	( -2.1,14.2)
		Pr >  t			0.1417
	Week 24	n	29	26	
		LS Mean	-2.024	-3.612	1.589
		SEM	4.026	4.284	4.452
		95% CI	(-10.0, 5.9)	(-12.1, 4.8)	( -7.2,10.4)
		Pr >  t			0.7216
	Week 32	n	23	21	
		LS Mean	-2.321	-5.474	3.153
		SEM	4.240	4.493	4.768

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-10.7, 6.0)	(-14.3, 3.4)	(-6.2,12.5)
	Pr >  t			0.5090
	n	23	16	
	LS Mean	1.908	-2.918	4.826
	SEM	4.248	4.739	5.006
Week 48	95% CI	(-6.5,10.3)	(-12.3, 6.4)	(-5.0,14.7)
	Pr >  t			0.3358
	n	18	14	
	LS Mean	0.205	-8.521	8.725
	SEM	4.449	4.882	5.318
Week 56	95% CI	(-8.6, 9.0)	(-18.1, 1.1)	(-1.7,19.2)
	Pr >  t			0.1018
	n	15	12	
	LS Mean	0.903	-6.709	7.611
	SEM	4.634	5.060	5.643
Week 64	95% CI	(-8.2,10.0)	(-16.7, 3.3)	(-3.5,18.7)
	Pr >  t			0.1782
	n	11	9	
	LS Mean	4.187	-5.328	9.516
	SEM	4.989	5.454	6.282
Week 72	95% CI	(-5.6,14.0)	(-16.1, 5.4)	(-2.8,21.9)
	Pr >  t			0.1306
	n	12	4	
	LS Mean	-1.955	-3.895	1.939
	SEM	4.891	7.080	7.669
Week 84	95% CI	(-11.6, 7.7)	(-17.8,10.0)	(-13.1,17.0)
	Pr >  t			0.8005
	n	8	4	
	LS Mean	-7.218	-3.895	-3.323
	SEM	5.487	7.080	8.052
Week 96	95% CI	(-18.0, 3.6)	(-17.8,10.0)	(-19.2,12.5)
	Pr >  t			0.6800
	n	8	2	
	LS Mean	-3.051	-8.753	5.702
	SEM	5.487	9.268	10.03
Week 108	95% CI	(-13.8, 7.7)	(-27.0, 9.5)	(-14.0,25.4)
	Pr >  t			0.5700
	n	6	1	
Week 108	LS Mean	-0.314	0.711	-1.025
	SEM	6.005	12.54	13.33

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-12.1,11.5)	(-23.9,25.4)	(-27.2,25.2)
		Pr >  t			0.9387
	Week 120	n	8	1	
		LS Mean	-0.421	0.711	-1.133
		SEM	5.502	12.54	13.11
		95% CI	(-11.2,10.4)	(-23.9,25.4)	(-26.9,24.6)
		Pr >  t			0.9312
	Week 132	n	5	1	
		LS Mean	5.170	-15.96	21.128
		SEM	6.385	12.54	13.50
		95% CI	(-7.4,17.7)	(-40.6, 8.7)	(-5.4,47.7)
		Pr >  t			0.1185
	Week 144	n	5		
		LS Mean	-1.496	NE	NE
		SEM	6.385	NE	NE
		95% CI	(-14.0,11.1)	NE	NE
		Pr >  t			NE
	Week 156	n	4		
		LS Mean	3.493	NE	NE
		SEM	6.909	NE	NE
		95% CI	(-10.1,17.1)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	2.096	NE	NE
		SEM	12.33	NE	NE
		95% CI	(-22.1,26.3)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Estrogen Receptor Status (L)	Negative	Week 8	n	2		
			LS Mean	-16.66	NE	NE
			SEM	13.18	NE	NE
			95% CI	( -127,94.0)	NE	NE
		Pr >  t			NE	
		Week 16	n	2		
			LS Mean	-8.335	NE	NE
			SEM	13.18	NE	NE
			95% CI	( -119, 102)	NE	NE
		Pr >  t			NE	
		Week 24	n	1		
			LS Mean	-11.11	NE	NE
			SEM	15.46	NE	NE
			95% CI	(-89.9,67.6)	NE	NE
		Pr >  t			NE	
		Week 32	n	1		
			LS Mean	-11.11	NE	NE
			SEM	15.46	NE	NE
			95% CI	(-89.9,67.6)	NE	NE
		Pr >  t			NE	
		Week 40	n	1		
			LS Mean	11.112	NE	NE
			SEM	15.46	NE	NE
			95% CI	(-67.6,89.9)	NE	NE
		Pr >  t			NE	
		Week 48	n	1		
			LS Mean	11.112	NE	NE
			SEM	15.46	NE	NE
95% CI	(-67.6,89.9)		NE	NE		
Pr >  t			NE			
Week 56	n	1				
	LS Mean	11.112	NE	NE		
	SEM	15.46	NE	NE		

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Positive	Week 72	95% CI	(-67.6,89.9)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-11.11	NE	NE
		SEM	15.46	NE	NE
	Week 84	95% CI	(-89.9,67.6)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-11.11	NE	NE
		SEM	15.46	NE	NE
	Week 96	95% CI	(-89.9,67.6)	NE	NE
		Pr >  t			NE
		n	1		
		LS Mean	-11.11	NE	NE
		SEM	15.46	NE	NE
	Week 8	95% CI	(-89.9,67.6)	NE	NE
		Pr >  t			NE
		n	140	140	
		LS Mean	-2.786	-2.342	-0.444
		SEM	2.109	2.134	1.855
	Week 16	95% CI	(-6.9, 1.4)	(-6.5, 1.9)	(-4.1, 3.2)
		Pr >  t			0.8111
		n	122	107	
		LS Mean	-1.012	-4.824	3.812
		SEM	2.161	2.240	1.998
	Week 24	95% CI	(-5.3, 3.2)	(-9.2,-0.4)	(-0.1, 7.7)
		Pr >  t			0.0568
		n	104	81	
LS Mean		-3.427	-4.714	1.288	
SEM		2.212	2.345	2.158	
Week 32	95% CI	(-7.8, 0.9)	(-9.3,-0.1)	(-2.9, 5.5)	
	Pr >  t			0.5510	
	n	85	73		
	LS Mean	-2.904	-2.375	-0.529	
	SEM	2.294	2.392	2.270	
Week 40	95% CI	(-7.4, 1.6)	(-7.1, 2.3)	(-5.0, 3.9)	
	Pr >  t			0.8157	
	n	74	62		
	LS Mean	-0.585	-1.720	1.135	
	SEM	2.343	2.464	2.390	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-5.2, 4.0)	(-6.6, 3.1)	(-3.6, 5.8)
	Pr >  t			0.6348
Week 48	n	68	51	
	LS Mean	-4.149	-4.842	0.693
	SEM	2.375	2.554	2.512
	95% CI	(-8.8, 0.5)	(-9.9, 0.2)	(-4.2, 5.6)
	Pr >  t			0.7829
Week 56	n	58	45	
	LS Mean	-3.862	-4.749	0.887
	SEM	2.440	2.618	2.640
	95% CI	(-8.7, 0.9)	(-9.9, 0.4)	(-4.3, 6.1)
	Pr >  t			0.7370
Week 64	n	47	42	
	LS Mean	-1.863	-4.176	2.313
	SEM	2.537	2.657	2.769
	95% CI	(-6.8, 3.1)	(-9.4, 1.0)	(-3.1, 7.7)
	Pr >  t			0.4037
Week 72	n	47	35	
	LS Mean	-4.445	-5.765	1.320
	SEM	2.538	2.765	2.874
	95% CI	(-9.4, 0.5)	(-11.2, -0.3)	(-4.3, 7.0)
	Pr >  t			0.6459
Week 84	n	39	33	
	LS Mean	-3.443	-3.970	0.527
	SEM	2.648	2.803	2.999
	95% CI	(-8.6, 1.8)	(-9.5, 1.5)	(-5.4, 6.4)
	Pr >  t			0.8605
Week 96	n	34	24	
	LS Mean	-1.577	-6.940	5.362
	SEM	2.728	3.039	3.292
	95% CI	(-6.9, 3.8)	(-12.9, -1.0)	(-1.1, 11.8)
	Pr >  t			0.1035
Week 108	n	26	21	
	LS Mean	-2.972	-5.745	2.774
	SEM	2.925	3.155	3.556
	95% CI	(-8.7, 2.8)	(-11.9, 0.4)	(-4.2, 9.7)
	Pr >  t			0.4355
Week 120	n	28	16	
	LS Mean	-2.812	-4.431	1.619
	SEM	2.865	3.428	3.756

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.4, 2.8)	(-11.2, 2.3)	(-5.7, 9.0)
		Pr >  t			0.6665
	Week 132	n	20	8	
		LS Mean	-3.600	-10.60	7.002
		SEM	3.151	4.377	4.819
		95% CI	(-9.8, 2.6)	(-19.2,-2.0)	(-2.4,16.5)
		Pr >  t			0.1464
	Week 144	n	15	5	
		LS Mean	-10.95	-3.760	-7.190
		SEM	3.443	5.302	5.843
		95% CI	(-17.7,-4.2)	(-14.2, 6.6)	(-18.7, 4.3)
		Pr >  t			0.2186
	Week 156	n	10	3	
		LS Mean	-2.056	-9.606	7.550
		SEM	3.981	6.620	7.335
		95% CI	(-9.9, 5.8)	(-22.6, 3.4)	(-6.8,21.9)
		Pr >  t			0.3035
	Week 168	n	4	2	
		LS Mean	-9.907	-2.422	-7.484
		SEM	5.793	7.970	9.550
		95% CI	(-21.3, 1.5)	(-18.1,13.2)	(-26.2,11.3)
		Pr >  t			0.4334
	Week 180	n	1	1	
		LS Mean	-45.58	-2.328	-43.25
		SEM	11.05	11.06	15.44
		95% CI	(-67.2, -24)	(-24.0,19.4)	(-73.5, -13)
		Pr >  t			0.0052
	Week 192	n	1	1	
		LS Mean	-62.25	-2.328	-59.92
		SEM	11.05	11.06	15.44
		95% CI	(-83.9, -41)	(-24.0,19.4)	(-90.2, -30)
		Pr >  t			0.0001

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final





**Table 11.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	-3.365	-2.745	-0.621
			SEM	3.440	3.742	3.565
			95% CI	(-10.2, 3.5)	(-10.2, 4.7)	(-7.7, 6.4)
			Pr >  t			0.8621
		Week 16	n	35	22	
			LS Mean	1.499	-5.434	6.932
			SEM	3.565	4.170	4.000
			95% CI	(-5.6, 8.6)	(-13.7, 2.8)	(-1.0, 14.8)
			Pr >  t			0.0850
		Week 24	n	28	16	
			LS Mean	-2.464	-1.653	-0.810
			SEM	3.685	4.432	4.394
			95% CI	(-9.8, 4.8)	(-10.4, 7.1)	(-9.5, 7.9)
			Pr >  t			0.8539
		Week 32	n	22	16	
			LS Mean	-1.041	0.562	-1.603
			SEM	3.882	4.444	4.527
			95% CI	(-8.7, 6.6)	(-8.2, 9.3)	(-10.5, 7.3)
			Pr >  t			0.7236
		Week 40	n	19	12	
			LS Mean	1.906	-1.074	2.979
			SEM	3.987	4.709	4.880
			95% CI	(-6.0, 9.8)	(-10.4, 8.2)	(-6.6, 12.6)
Pr >  t				0.5421		
Week 48	n	16	10			
	LS Mean	-4.064	-1.983	-2.080		
	SEM	4.120	4.912	5.185		
	95% CI	(-12.2, 4.1)	(-11.7, 7.7)	(-12.3, 8.1)		
	Pr >  t			0.6885		
Week 56	n	14	7			
	LS Mean	-4.579	-0.290	-4.289		
	SEM	4.241	5.382	5.728		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-12.9, 3.8)	(-10.9,10.3)	(-15.6, 7.0)
	Pr >  t			0.4545
	n	8	7	
	LS Mean	0.700	-2.809	3.508
	SEM	4.853	5.381	6.204
Week 72	95% CI	(-8.9,10.3)	(-13.4, 7.8)	(-8.7,15.7)
	Pr >  t			0.5721
	n	12	6	
	LS Mean	-5.790	-8.536	2.746
	SEM	4.387	5.623	6.065
Week 84	95% CI	(-14.4, 2.9)	(-19.6, 2.5)	(-9.2,14.7)
	Pr >  t			0.6510
	n	8	5	
	LS Mean	-2.149	-10.45	8.300
	SEM	4.883	5.937	6.696
Week 96	95% CI	(-11.8, 7.5)	(-22.1, 1.2)	(-4.9,21.5)
	Pr >  t			0.2160
	n	5	5	
	LS Mean	-0.223	-3.783	3.560
	SEM	5.632	5.937	7.260
Week 108	95% CI	(-11.3,10.9)	(-15.5, 7.9)	(-10.7,17.8)
	Pr >  t			0.6242
	n	7	5	
	LS Mean	-1.757	-3.783	2.026
	SEM	5.076	5.937	6.838
Week 120	95% CI	(-11.7, 8.2)	(-15.5, 7.9)	(-11.4,15.5)
	Pr >  t			0.7672
	n	5	3	
	LS Mean	0.370	0.566	-0.195
	SEM	5.639	7.032	8.185
Week 132	95% CI	(-10.7,11.5)	(-13.3,14.4)	(-16.3,15.9)
	Pr >  t			0.9810
	n	2	2	
	LS Mean	-4.867	-12.98	8.111
	SEM	7.938	8.137	10.72
Week 144	95% CI	(-20.5,10.7)	(-29.0, 3.0)	(-13.0,29.2)
	Pr >  t			0.4499
	n	2		
	LS Mean	-6.528	NE	NE
	SEM	7.941	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-22.1, 9.1)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	-0.500	NE	NE
		SEM	7.952	NE	NE
		95% CI	(-16.1,15.1)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-15.51	NE	NE
		SEM	10.74	NE	NE
		95% CI	(-36.6, 5.6)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	98	104	
		LS Mean	-2.923	-2.732	-0.191
		SEM	2.713	2.675	2.207
		95% CI	(-8.3, 2.4)	(-8.0, 2.5)	(-4.5, 4.1)
		Pr >  t			0.9310
	Week 16	n	87	84	
		LS Mean	-2.273	-5.168	2.896
		SEM	2.765	2.754	2.344
		95% CI	(-7.7, 3.2)	(-10.6, 0.3)	(-1.7, 7.5)
		Pr >  t			0.2173
	Week 24	n	76	65	
		LS Mean	-3.912	-5.948	2.036
		SEM	2.822	2.865	2.513
		95% CI	(-9.5, 1.6)	(-11.6,-0.3)	(-2.9, 7.0)
		Pr >  t			0.4180
	Week 32	n	62	57	
		LS Mean	-3.589	-3.634	0.045
		SEM	2.906	2.930	2.657
		95% CI	(-9.3, 2.1)	(-9.4, 2.1)	(-5.2, 5.3)
		Pr >  t			0.9865
	Week 40	n	54	50	
		LS Mean	-1.538	-2.383	0.846
		SEM	2.963	2.999	2.782
		95% CI	(-7.4, 4.3)	(-8.3, 3.5)	(-4.6, 6.3)
		Pr >  t			0.7613
	Week 48	n	52	41	
		LS Mean	-3.902	-6.040	2.138
		SEM	2.979	3.096	2.903

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	95% CI	(-9.8, 2.0)	(-12.1, 0.0)	(-3.6, 7.8)
	Pr >  t			0.4616
	n	44	38	
Week 64	LS Mean	-3.284	-6.149	2.865
	SEM	3.053	3.137	3.025
	95% CI	(-9.3, 2.7)	(-12.3, 0.0)	(-3.1, 8.8)
Week 72	Pr >  t			0.3438
	n	39	35	
	LS Mean	-2.631	-5.007	2.376
Week 84	SEM	3.114	3.185	3.135
	95% CI	(-8.8, 3.5)	(-11.3, 1.3)	(-3.8, 8.5)
	Pr >  t			0.4487
Week 96	n	36	29	
	LS Mean	-4.063	-5.730	1.667
	SEM	3.158	3.302	3.297
Week 108	95% CI	(-10.3, 2.1)	(-12.2, 0.8)	(-4.8, 8.1)
	Pr >  t			0.6132
	n	32	28	
Week 120	LS Mean	-3.883	-3.404	-0.479
	SEM	3.233	3.326	3.386
	95% CI	(-10.2, 2.5)	(-9.9, 3.1)	(-7.1, 6.2)
Week 132	Pr >  t			0.8875
	n	30	19	
	LS Mean	-2.092	-8.328	6.236
Week 108	SEM	3.267	3.635	3.726
	95% CI	(-8.5, 4.3)	(-15.5,-1.2)	(-1.1,13.5)
	Pr >  t			0.0945
Week 120	n	18	16	
	LS Mean	-3.853	-6.889	3.036
	SEM	3.675	3.804	4.234
Week 132	95% CI	(-11.1, 3.4)	(-14.4, 0.6)	(-5.3,11.3)
	Pr >  t			0.4735
	n	23	13	
Week 108	LS Mean	-3.745	-6.183	2.438
	SEM	3.457	4.036	4.272
	95% CI	(-10.5, 3.0)	(-14.1, 1.7)	(-5.9,10.8)
Week 132	Pr >  t			0.5684
	n	18	6	
	LS Mean	-3.820	-10.28	6.462
	SEM	3.676	5.244	5.565

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-11.0, 3.4)	(-20.6, 0.0)	(-4.5,17.4)
	Pr >  t			0.2457
Week 144	n	13	5	
	LS Mean	-11.90	-4.534	-7.368
	SEM	4.009	5.629	6.149
	95% CI	(-19.8,-4.0)	(-15.6, 6.5)	(-19.4, 4.7)
	Pr >  t			0.2311
Week 156	n	8	3	
	LS Mean	-2.689	-10.37	7.677
	SEM	4.704	6.943	7.765
	95% CI	(-11.9, 6.5)	(-24.0, 3.3)	(-7.6,22.9)
	Pr >  t			0.3230
Week 168	n	3	2	
	LS Mean	-8.269	-3.164	-5.106
	SEM	6.921	8.300	10.33
	95% CI	(-21.8, 5.3)	(-19.4,13.1)	(-25.4,15.2)
	Pr >  t			0.6213
Week 180	n	1	1	
	LS Mean	-46.01	-3.141	-42.86
	SEM	11.43	11.43	15.85
	95% CI	(-68.4, -24)	(-25.6,19.3)	(-74.0, -12)
	Pr >  t			0.0069
Week 192	n	1	1	
	LS Mean	-62.68	-3.141	-59.53
	SEM	11.43	11.43	15.85
	95% CI	(-85.1, -40)	(-25.6,19.3)	(-90.6, -28)
	Pr >  t			0.0002

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
ER and PR Status (L)	Both positive	Week 8	n	96	104		
			LS Mean	-2.665	-2.703	0.038	
			SEM	2.731	2.686	2.226	
			95% CI	(-8.0, 2.7)	(-8.0, 2.6)	(-4.3, 4.4)	
					Pr >  t		0.9865
		Week 16	n	85	84		
			LS Mean	-2.181	-5.142	2.961	
			SEM	2.785	2.766	2.364	
			95% CI	(-7.7, 3.3)	(-10.6, 0.3)	(-1.7, 7.6)	
					Pr >  t		0.2110
		Week 24	n	75	65		
			LS Mean	-3.962	-5.924	1.963	
			SEM	2.840	2.876	2.529	
			95% CI	(-9.5, 1.6)	(-11.6,-0.3)	(-3.0, 6.9)	
					Pr >  t		0.4381
		Week 32	n	61	57		
			LS Mean	-3.661	-3.610	-0.051	
			SEM	2.926	2.941	2.676	
			95% CI	(-9.4, 2.1)	(-9.4, 2.2)	(-5.3, 5.2)	
					Pr >  t		0.9849
		Week 40	n	53	50		
			LS Mean	-1.766	-2.361	0.595	
			SEM	2.985	3.009	2.803	
			95% CI	(-7.6, 4.1)	(-8.3, 3.6)	(-4.9, 6.1)	
					Pr >  t		0.8319
		Week 48	n	51	41		
			LS Mean	-4.186	-6.017	1.831	
			SEM	3.001	3.106	2.923	
95% CI	(-10.1, 1.7)		(-12.1, 0.1)	(-3.9, 7.6)			
			Pr >  t		0.5312		
Week 56	n	43	38				
	LS Mean	-3.594	-6.127	2.533			
	SEM	3.078	3.147	3.048			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.6, 2.5)	(-12.3, 0.1)	(-3.4, 8.5)
	Pr >  t			0.4061
	n	39	35	
	LS Mean	-2.710	-4.985	2.275
	SEM	3.128	3.195	3.147
Week 72	95% CI	(-8.9, 3.4)	(-11.3, 1.3)	(-3.9, 8.5)
	Pr >  t			0.4699
	n	35	29	
	LS Mean	-4.184	-5.709	1.525
	SEM	3.188	3.312	3.324
Week 84	95% CI	(-10.4, 2.1)	(-12.2, 0.8)	(-5.0, 8.0)
	Pr >  t			0.6464
	n	31	28	
	LS Mean	-4.006	-3.382	-0.624
	SEM	3.266	3.336	3.416
Week 96	95% CI	(-10.4, 2.4)	(-9.9, 3.2)	(-7.3, 6.1)
	Pr >  t			0.8550
	n	29	19	
	LS Mean	-2.155	-8.306	6.151
	SEM	3.303	3.645	3.757
Week 108	95% CI	(-8.6, 4.3)	(-15.5, -1.2)	(-1.2, 13.5)
	Pr >  t			0.1019
	n	18	16	
	LS Mean	-3.931	-6.869	2.938
	SEM	3.688	3.813	4.245
Week 120	95% CI	(-11.2, 3.3)	(-14.4, 0.6)	(-5.4, 11.3)
	Pr >  t			0.4890
	n	23	13	
	LS Mean	-3.823	-6.163	2.340
	SEM	3.470	4.045	4.282
Week 132	95% CI	(-10.6, 3.0)	(-14.1, 1.8)	(-6.1, 10.7)
	Pr >  t			0.5849
	n	18	6	
	LS Mean	-3.900	-10.26	6.360
	SEM	3.689	5.253	5.575
Week 144	95% CI	(-11.1, 3.3)	(-20.6, 0.0)	(-4.6, 17.3)
	Pr >  t			0.2542
	n	13	5	
	LS Mean	-11.98	-4.515	-7.467
	SEM	4.021	5.638	6.159

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive Negative	Week 156	95% CI	(-19.9, -4.1)	(-15.6, 6.5)	(-19.6, 4.6)
		Pr >  t			0.2256
		n	8	3	
	Week 168	LS Mean	-2.767	-10.34	7.578
		SEM	4.716	6.953	7.775
		95% CI	(-12.0, 6.5)	(-24.0, 3.3)	(-7.7, 22.8)
	Week 180	Pr >  t			0.3300
		n	3	2	
		LS Mean	-8.346	-3.144	-5.202
	Week 192	SEM	6.932	8.310	10.34
		95% CI	(-21.9, 5.3)	(-19.4, 13.2)	(-25.5, 15.1)
		Pr >  t			0.6151
	Week 8	n	1	1	
		LS Mean	-46.08	-3.122	-42.95
		SEM	11.44	11.44	15.86
	Week 16	95% CI	(-68.5, -24)	(-25.6, 19.3)	(-74.1, -12)
		Pr >  t			0.0069
		n	1	1	
	Week 24	LS Mean	-62.75	-3.122	-59.62
		SEM	11.44	11.44	15.86
		95% CI	(-85.2, -40)	(-25.6, 19.3)	(-90.8, -28)
	Week 32	Pr >  t			0.0002
		n	42	35	
		LS Mean	-3.365	-2.745	-0.621
Week 8	SEM	3.440	3.742	3.565	
	95% CI	(-10.2, 3.5)	(-10.2, 4.7)	(-7.7, 6.4)	
	Pr >  t			0.8621	
Week 16	n	35	22		
	LS Mean	1.499	-5.434	6.932	
	SEM	3.565	4.170	4.000	
Week 24	95% CI	(-5.6, 8.6)	(-13.7, 2.8)	(-1.0, 14.8)	
	Pr >  t			0.0850	
	n	28	16		
Week 32	LS Mean	-2.464	-1.653	-0.810	
	SEM	3.685	4.432	4.394	
	95% CI	(-9.8, 4.8)	(-10.4, 7.1)	(-9.5, 7.9)	
	Pr >  t			0.8539	
	n	22	16		
	LS Mean	-1.041	0.562	-1.603	
	SEM	3.882	4.444	4.527	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-8.7, 6.6)	(-8.2, 9.3)	(-10.5, 7.3)
	Pr >  t			0.7236
	n	19	12	
	LS Mean	1.906	-1.074	2.979
	SEM	3.987	4.709	4.880
Week 48	95% CI	(-6.0, 9.8)	(-10.4, 8.2)	(-6.6,12.6)
	Pr >  t			0.5421
	n	16	10	
	LS Mean	-4.064	-1.983	-2.080
	SEM	4.120	4.912	5.185
Week 56	95% CI	(-12.2, 4.1)	(-11.7, 7.7)	(-12.3, 8.1)
	Pr >  t			0.6885
	n	14	7	
	LS Mean	-4.579	-0.290	-4.289
	SEM	4.241	5.382	5.728
Week 64	95% CI	(-12.9, 3.8)	(-10.9,10.3)	(-15.6, 7.0)
	Pr >  t			0.4545
	n	8	7	
	LS Mean	0.700	-2.809	3.508
	SEM	4.853	5.381	6.204
Week 72	95% CI	(-8.9,10.3)	(-13.4, 7.8)	(-8.7,15.7)
	Pr >  t			0.5721
	n	12	6	
	LS Mean	-5.790	-8.536	2.746
	SEM	4.387	5.623	6.065
Week 84	95% CI	(-14.4, 2.9)	(-19.6, 2.5)	(-9.2,14.7)
	Pr >  t			0.6510
	n	8	5	
	LS Mean	-2.149	-10.45	8.300
	SEM	4.883	5.937	6.696
Week 96	95% CI	(-11.8, 7.5)	(-22.1, 1.2)	(-4.9,21.5)
	Pr >  t			0.2160
	n	5	5	
	LS Mean	-0.223	-3.783	3.560
	SEM	5.632	5.937	7.260
Week 108	95% CI	(-11.3,10.9)	(-15.5, 7.9)	(-10.7,17.8)
	Pr >  t			0.6242
	n	7	5	
	LS Mean	-1.757	-3.783	2.026
	SEM	5.076	5.937	6.838

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.7, 8.2)	(-15.5, 7.9)	(-11.4,15.5)
		Pr >  t			0.7672
	Week 120	n	5	3	
		LS Mean	0.370	0.566	-0.195
		SEM	5.639	7.032	8.185
		95% CI	(-10.7,11.5)	(-13.3,14.4)	(-16.3,15.9)
		Pr >  t			0.9810
	Week 132	n	2	2	
		LS Mean	-4.867	-12.98	8.111
		SEM	7.938	8.137	10.72
		95% CI	(-20.5,10.7)	(-29.0, 3.0)	(-13.0,29.2)
		Pr >  t			0.4499
	Week 144	n	2		
		LS Mean	-6.528	NE	NE
		SEM	7.941	NE	NE
		95% CI	(-22.1, 9.1)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	-0.500	NE	NE
		SEM	7.952	NE	NE
		95% CI	(-16.1,15.1)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-15.51	NE	NE
		SEM	10.74	NE	NE
		95% CI	(-36.6, 5.6)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-20i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Cognitive Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Pooled Number of Metastatic Sites (L)	< 3	Week 8	n	105	95	
			LS Mean	-3.944	-2.818	-1.126
			SEM	2.371	2.441	2.252
			95% CI	(-8.6, 0.7)	(-7.6, 2.0)	(-5.6, 3.3)
		Pr >  t			0.6174	
		Week 16	n	90	75	
			LS Mean	-0.767	-5.276	4.510
			SEM	2.425	2.552	2.409
			95% CI	(-5.5, 4.0)	(-10.3,-0.3)	(-0.2, 9.2)
		Pr >  t			0.0619	
		Week 24	n	79	62	
			LS Mean	-1.207	-5.235	4.028
			SEM	2.478	2.647	2.544
			95% CI	(-6.1, 3.7)	(-10.4,-0.0)	(-1.0, 9.0)
		Pr >  t			0.1139	
		Week 32	n	70	56	
			LS Mean	-2.905	-2.859	-0.046
			SEM	2.544	2.701	2.635
			95% CI	(-7.9, 2.1)	(-8.2, 2.5)	(-5.2, 5.1)
		Pr >  t			0.9861	
		Week 40	n	61	46	
			LS Mean	0.830	-1.665	2.495
			SEM	2.598	2.803	2.782
			95% CI	(-4.3, 5.9)	(-7.2, 3.8)	(-3.0, 8.0)
		Pr >  t			0.3703	
		Week 48	n	56	38	
			LS Mean	-3.141	-4.226	1.084
			SEM	2.633	2.907	2.919
95% CI	(-8.3, 2.0)		(-9.9, 1.5)	(-4.6, 6.8)		
Pr >  t			0.7104			
Week 56	n	49	33			
	LS Mean	-3.460	-5.972	2.511		
SEM	2.692	2.993	3.060			

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.8, 1.8)	(-11.8,-0.1)	(-3.5, 8.5)
		Pr >  t			0.4120
	Week 64	n	37	29	
		LS Mean	-1.497	-2.826	1.329
		SEM	2.835	3.082	3.272
		95% CI	(-7.1, 4.1)	(-8.9, 3.2)	(-5.1, 7.7)
		Pr >  t			0.6848
	Week 72	n	40	25	
		LS Mean	-4.081	-6.443	2.361
		SEM	2.793	3.189	3.338
		95% CI	(-9.6, 1.4)	(-12.7,-0.2)	(-4.2, 8.9)
		Pr >  t			0.4794
	Week 84	n	32	23	
		LS Mean	-1.987	-4.729	2.741
		SEM	2.935	3.256	3.512
		95% CI	(-7.8, 3.8)	(-11.1, 1.7)	(-4.1, 9.6)
		Pr >  t			0.4352
	Week 96	n	29	17	
		LS Mean	-0.208	-6.339	6.131
		SEM	2.996	3.532	3.820
		95% CI	(-6.1, 5.7)	(-13.3, 0.6)	(-1.4,13.6)
		Pr >  t			0.1088
	Week 108	n	22	15	
		LS Mean	-1.490	-5.229	3.739
		SEM	3.215	3.664	4.108
		95% CI	(-7.8, 4.8)	(-12.4, 2.0)	(-4.3,11.8)
		Pr >  t			0.3629
	Week 120	n	23	13	
		LS Mean	-2.238	-5.927	3.689
		SEM	3.173	3.832	4.230
		95% CI	(-8.5, 4.0)	(-13.4, 1.6)	(-4.6,12.0)
		Pr >  t			0.3832
	Week 132	n	17	5	
		LS Mean	-4.067	-13.55	9.484
		SEM	3.453	5.414	5.860
		95% CI	(-10.8, 2.7)	(-24.2,-2.9)	(-2.0,21.0)
		Pr >  t			0.1058
	Week 144	n	14	3	
		LS Mean	-11.34	-4.247	-7.089
		SEM	3.655	6.726	7.194

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.5,-4.2)	(-17.4, 8.9)	(-21.2, 7.0)
		Pr >  t			0.3246
	Week 156	n	9	2	
		LS Mean	-1.962	-4.913	2.951
		SEM	4.258	8.055	8.723
		95% CI	(-10.3, 6.4)	(-20.7,10.9)	(-14.2,20.1)
		Pr >  t			0.7352
	Week 168	n	4	1	
		LS Mean	-9.377	-2.428	-6.949
		SEM	5.877	11.14	12.31
		95% CI	(-20.9, 2.2)	(-24.3,19.4)	(-31.1,17.2)
		Pr >  t			0.5727
	Week 180	n	1	1	
		LS Mean	-45.08	-2.428	-42.65
		SEM	11.10	11.14	15.50
		95% CI	(-66.9, -23)	(-24.3,19.4)	(-73.1, -12)
		Pr >  t			0.0060
	Week 192	n	1	1	
		LS Mean	-61.75	-2.428	-59.32
		SEM	11.10	11.14	15.50
		95% CI	(-83.5, -40)	(-24.3,19.4)	(-89.7, -29)
		Pr >  t			0.0001
>= 3	Week 8	n	37	45	
		LS Mean	-4.391	-5.990	1.599
		SEM	5.601	5.561	3.211
		95% CI	(-15.5, 6.7)	(-17.0, 5.0)	( -4.7, 7.9)
		Pr >  t			0.6191
	Week 16	n	34	32	
		LS Mean	-6.396	-8.347	1.951
		SEM	5.759	5.806	3.498
		95% CI	(-17.8, 5.0)	(-19.8, 3.1)	( -4.9, 8.9)
		Pr >  t			0.5777
	Week 24	n	26	19	
		LS Mean	-14.56	-7.701	-6.857
		SEM	5.876	6.057	4.082
		95% CI	(-26.2,-3.0)	(-19.7, 4.3)	(-14.9, 1.2)
		Pr >  t			0.0942
	Week 32	n	16	17	
		LS Mean	-6.657	-5.506	-1.151
		SEM	6.147	6.131	4.566

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-18.8, 5.5)	(-17.6, 6.6)	(-10.1, 7.8)
		Pr >  t			0.8011
	Week 40	n	14	16	
		LS Mean	-9.769	-6.522	-3.248
		SEM	6.245	6.168	4.743
		95% CI	(-22.1, 2.5)	(-18.7, 5.6)	(-12.6, 6.1)
		Pr >  t			0.4940
	Week 48	n	13	13	
		LS Mean	-11.15	-11.27	0.121
		SEM	6.296	6.314	4.996
		95% CI	(-23.6, 1.3)	(-23.7, 1.2)	(-9.7, 9.9)
		Pr >  t			0.9807
	Week 56	n	10	12	
		LS Mean	-7.780	-6.042	-1.738
		SEM	6.525	6.381	5.347
		95% CI	(-20.6, 5.1)	(-18.6, 6.5)	(-12.3, 8.8)
		Pr >  t			0.7453
	Week 64	n	10	13	
		LS Mean	-7.052	-11.71	4.660
		SEM	6.527	6.320	5.277
		95% CI	(-19.9, 5.8)	(-24.2, 0.7)	(-5.7, 15.0)
		Pr >  t			0.3778
	Week 72	n	8	10	
		LS Mean	-8.864	-8.569	-0.295
		SEM	6.749	6.535	5.798
		95% CI	(-22.2, 4.4)	(-21.4, 4.3)	(-11.7, 11.1)
		Pr >  t			0.9595
	Week 84	n	8	10	
		LS Mean	-12.69	-6.715	-5.972
		SEM	6.753	6.531	5.799
		95% CI	(-26.0, 0.6)	(-19.6, 6.2)	(-17.4, 5.4)
		Pr >  t			0.3038
	Week 96	n	6	7	
		LS Mean	-11.43	-12.97	1.535
		SEM	7.116	6.914	6.610
		95% CI	(-25.4, 2.6)	(-26.6, 0.6)	(-11.5, 14.5)
		Pr >  t			0.8164
	Week 108	n	4	6	
		LS Mean	-13.69	-11.53	-2.162
		SEM	7.766	7.108	7.498

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-29.0, 1.6)	(-25.5, 2.5)	(-16.9,12.6)
		Pr >  t			0.7733
	Week 120	n	5	3	
		LS Mean	-8.691	-2.622	-6.069
		SEM	7.380	8.365	8.356
		95% CI	(-23.2, 5.8)	(-19.1,13.8)	(-22.5,10.4)
		Pr >  t			0.4681
	Week 132	n	3	3	
		LS Mean	-3.480	-9.935	6.454
		SEM	8.364	8.367	9.240
		95% CI	(-19.9,13.0)	(-26.4, 6.5)	(-11.7,24.6)
		Pr >  t			0.4854
	Week 144	n	1	2	
		LS Mean	-3.021	-7.078	4.057
		SEM	12.14	9.454	13.49
		95% CI	(-26.9,20.9)	(-25.7,11.5)	(-22.5,30.6)
		Pr >  t			0.7639
	Week 156	n	1	1	
		LS Mean	-3.021	-23.68	20.660
		SEM	12.14	12.15	15.49
		95% CI	(-26.9,20.9)	(-47.6, 0.2)	( -9.8,51.1)
		Pr >  t			0.1833
	Week 168	n		1	
		LS Mean	NE	-7.011	NE
		SEM	NE	12.15	NE
		95% CI	NE	(-30.9,16.9)	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

Tabelle 4H-58: Ergebnisse für den Endpunkt „Gesundheitsbezogene Lebensqualität (EORTC QLQ-C30): Soziale Funktion“ aus RCT mit dem zu bewertenden Arzneimittel: Subgruppenanalysen bei nicht signifikantem Interaktionstest zu den „Linear mixed effects model“-Analysen

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Stratum 3 - Lung and/or Liver metas (L)	Absent	Week 8	n	77	73			
			LS Mean	-2.481	1.302	-3.783		
			SEM	3.475	3.498	3.061		
			95% CI	(-9.3, 4.4)	(-5.6, 8.2)	(-9.8, 2.2)		
					Pr >  t			0.2177
		Week 16	n	67	56			
			LS Mean	-3.658	0.740	-4.398		
			SEM	3.521	3.670	3.280		
			95% CI	(-10.6, 3.3)	(-6.5, 8.0)	(-10.9, 2.1)		
					Pr >  t			0.1809
		Week 24	n	61	46			
			LS Mean	-5.811	2.963	-8.774		
			SEM	3.574	3.764	3.437		
			95% CI	(-12.9, 1.2)	(-4.5, 10.4)	(-15.5, -2.0)		
					Pr >  t			0.0111
		Week 32	n	52	41			
			LS Mean	-3.715	-0.453	-3.262		
			SEM	3.669	3.838	3.574		
			95% CI	(-10.9, 3.5)	(-8.0, 7.1)	(-10.3, 3.8)		
					Pr >  t			0.3621
		Week 40	n	45	36			
			LS Mean	-1.965	-2.456	0.491		
			SEM	3.736	3.927	3.723		
			95% CI	(-9.3, 5.4)	(-10.2, 5.3)	(-6.8, 7.8)		
			Pr >  t			0.8951		
Week 48	n	42	30					
	LS Mean	-4.429	-0.150	-4.278				



Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 56	SEM	3.772	4.039	3.877
	95% CI	(-11.9, 3.0)	(-8.1, 7.8)	(-11.9, 3.3)
	Pr >  t			0.2703
	n	35	24	
	LS Mean	-4.463	-0.390	-4.073
Week 64	SEM	3.869	4.202	4.139
	95% CI	(-12.1, 3.2)	(-8.7, 7.9)	(-12.2, 4.1)
	Pr >  t			0.3255
	n	25	25	
	LS Mean	-4.566	1.588	-6.154
Week 72	SEM	4.086	4.172	4.317
	95% CI	(-12.6, 3.5)	(-6.6, 9.8)	(-14.6, 2.3)
	Pr >  t			0.1545
	n	27	20	
	LS Mean	-9.001	0.260	-9.261
Week 84	SEM	4.033	4.354	4.444
	95% CI	(-16.9,-1.1)	(-8.3, 8.8)	(-18.0,-0.5)
	Pr >  t			0.0375
	n	23	19	
	LS Mean	-11.45	0.096	-11.54
Week 96	SEM	4.163	4.401	4.598
	95% CI	(-19.6,-3.3)	(-8.6, 8.7)	(-20.6,-2.5)
	Pr >  t			0.0123
	n	20	13	
	LS Mean	-6.661	-6.474	-0.187
Week 108	SEM	4.281	4.804	5.084
	95% CI	(-15.1, 1.8)	(-15.9, 3.0)	(-10.2, 9.8)
	Pr >  t			0.9707
	n	17	13	
	LS Mean	-4.231	-3.494	-0.737
Week 120	SEM	4.436	4.805	5.216
	95% CI	(-13.0, 4.5)	(-12.9, 5.9)	(-11.0, 9.5)
	Pr >  t			0.8877
	n	17	12	
	LS Mean	-10.85	-1.656	-9.193
Week 132	SEM	4.435	4.906	5.309
	95% CI	(-19.6,-2.1)	(-11.3, 8.0)	(-19.6, 1.2)
	Pr >  t			0.0837
	n	13	6	
	LS Mean	-11.59	-3.313	-8.280

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Present	Week 144	SEM	4.732	6.045	6.586
		95% CI	(-20.9,-2.3)	(-15.2, 8.6)	(-21.2, 4.6)
		Pr >  t			0.2090
	Week 156	n	11	4	
		LS Mean	-7.726	0.460	-8.186
		SEM	4.950	7.007	7.618
	Week 168	95% CI	(-17.4, 2.0)	(-13.3,14.2)	(-23.1, 6.8)
		Pr >  t			0.2829
		n	7	2	
	Week 180	LS Mean	-5.258	-7.767	2.510
		SEM	5.678	9.287	10.15
		95% CI	(-16.4, 5.9)	(-26.0,10.5)	(-17.4,22.4)
	Week 192	Pr >  t			0.8047
		n	3	1	
		LS Mean	-8.650	2.072	-10.72
	Week 8	SEM	7.778	12.68	14.34
		95% CI	(-23.9, 6.6)	(-22.8,27.0)	(-38.9,17.4)
		Pr >  t			0.4549
	Week 16	n	1	1	
		LS Mean	6.982	2.072	4.910
		SEM	12.64	12.68	17.46
	Week 24	95% CI	(-17.8,31.8)	(-22.8,27.0)	(-29.4,39.2)
		Pr >  t			0.7787
		n	1	1	
Week 8	LS Mean	-9.678	2.072	-11.75	
	SEM	12.64	12.68	17.46	
	95% CI	(-34.5,15.1)	(-22.8,27.0)	(-46.0,22.5)	
Week 16	Pr >  t			0.5013	
	n	65	67		
	LS Mean	-10.68	0.810	-11.49	
Week 24	SEM	3.845	3.992	3.384	
	95% CI	(-18.3,-3.1)	(-7.1, 8.7)	(-18.2,-4.8)	
	Pr >  t			0.0008	
Week 8	n	57	51		
	LS Mean	-4.415	-2.258	-2.157	
	SEM	4.003	4.194	3.670	
Week 16	95% CI	(-12.3, 3.5)	(-10.5, 6.0)	(-9.4, 5.1)	
	Pr >  t			0.5572	
	n	44	35		
Week 24	LS Mean	-7.709	-2.838	-4.871	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference	
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		SEM	4.151	4.519	4.153
		95% CI	(-15.9, 0.5)	(-11.7, 6.1)	(-13.0, 3.3)
		Pr >  t			0.2414
	Week 32	n	34	32	
		LS Mean	-4.236	-4.463	0.227
		SEM	4.366	4.592	4.431
		95% CI	(-12.8, 4.4)	(-13.5, 4.6)	(-8.5, 8.9)
		Pr >  t			0.9592
	Week 40	n	30	26	
		LS Mean	-4.084	-1.804	-2.280
		SEM	4.472	4.776	4.723
		95% CI	(-12.9, 4.7)	(-11.2, 7.6)	(-11.6, 7.0)
		Pr >  t			0.6294
	Week 48	n	27	21	
		LS Mean	-4.518	-4.488	-0.030
		SEM	4.558	4.995	5.026
		95% CI	(-13.5, 4.4)	(-14.3, 5.3)	(-9.9, 9.8)
		Pr >  t			0.9953
	Week 56	n	24	21	
		LS Mean	-4.203	-2.225	-1.978
		SEM	4.671	4.995	5.132
		95% CI	(-13.4, 5.0)	(-12.0, 7.6)	(-12.1, 8.1)
		Pr >  t			0.7001
	Week 64	n	22	17	
		LS Mean	-5.659	-6.012	0.353
		SEM	4.760	5.240	5.451
		95% CI	(-15.0, 3.7)	(-16.3, 4.3)	(-10.4, 11.1)
		Pr >  t			0.9484
	Week 72	n	21	15	
		LS Mean	-0.213	0.771	-0.983
		SEM	4.812	5.400	5.650
		95% CI	(-9.7, 9.2)	(-9.8, 11.4)	(-12.1, 10.1)
		Pr >  t			0.8619
	Week 84	n	17	14	
		LS Mean	-4.531	-6.336	1.805
		SEM	5.074	5.496	5.950
		95% CI	(-14.5, 5.4)	(-17.1, 4.5)	(-9.9, 13.5)
		Pr >  t			0.7617
	Week 96	n	15	11	
		LS Mean	-2.654	-5.186	2.533

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	5.219	5.875	6.440
	95% CI	(-12.9, 7.6)	(-16.7, 6.4)	(-10.1,15.2)
	Pr >  t			0.6942
Week 108	n	9	8	
	LS Mean	-5.968	0.128	-6.096
	SEM	6.090	6.486	7.655
	95% CI	(-17.9, 6.0)	(-12.6,12.9)	(-21.1, 8.9)
	Pr >  t			0.4261
Week 120	n	11	4	
	LS Mean	2.728	4.510	-1.782
	SEM	5.708	8.325	9.035
	95% CI	( -8.5,13.9)	(-11.8,20.9)	(-19.5,16.0)
	Pr >  t			0.8437
Week 132	n	7	2	
	LS Mean	-9.088	-12.78	3.697
	SEM	6.627	11.08	12.09
	95% CI	(-22.1, 3.9)	(-34.5, 9.0)	(-20.0,27.4)
	Pr >  t			0.7599
Week 144	n	4	1	
	LS Mean	-13.05	-2.974	-10.08
	SEM	8.123	15.18	16.64
	95% CI	(-29.0, 2.9)	(-32.8,26.8)	(-42.8,22.6)
	Pr >  t			0.5452
Week 156	n	3	1	
	LS Mean	-12.27	-2.974	-9.292
	SEM	9.210	15.18	17.17
	95% CI	(-30.3, 5.8)	(-32.8,26.8)	(-43.0,24.4)
	Pr >  t			0.5886
Week 168	n	1	1	
	LS Mean	-4.513	-2.974	-1.539
	SEM	15.13	15.18	20.95
	95% CI	(-34.2,25.2)	(-32.8,26.8)	(-42.7,39.6)
	Pr >  t			0.9415

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.



**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Lung Metastases (L)	No	Week 8	n	98	84			
			LS Mean	-5.265	3.323	-8.587		
			SEM	2.826	2.988	2.763		
			95% CI	(-10.8, 0.3)	(-2.6, 9.2)	(-14.0, -3.2)		
					Pr >  t			0.0020
		Week 16	n	86	68			
			LS Mean	-3.288	1.014	-4.302		
			SEM	2.887	3.106	2.944		
			95% CI	(-9.0, 2.4)	(-5.1, 7.1)	(-10.1, 1.5)		
					Pr >  t			0.1447
		Week 24	n	73	48			
			LS Mean	-5.831	4.417	-10.25		
			SEM	2.963	3.320	3.229		
			95% CI	(-11.7, 0.0)	(-2.1, 10.9)	(-16.6, -3.9)		
					Pr >  t			0.0016
		Week 32	n	60	43			
			LS Mean	-3.152	0.004	-3.156		
			SEM	3.086	3.402	3.388		
			95% CI	(-9.2, 2.9)	(-6.7, 6.7)	(-9.8, 3.5)		
					Pr >  t			0.3520
		Week 40	n	50	38			
			LS Mean	-1.680	0.714	-2.394		
			SEM	3.183	3.495	3.560		
			95% CI	(-7.9, 4.6)	(-6.2, 7.6)	(-9.4, 4.6)		
					Pr >  t			0.5015
		Week 48	n	48	31			
			LS Mean	-4.459	2.318	-6.778		
			SEM	3.208	3.645	3.729		
95% CI	(-10.8, 1.8)		(-4.8, 9.5)	(-14.1, 0.5)				
			Pr >  t			0.0696		
Week 56	n	41	25					
	LS Mean	-3.501	1.613	-5.114				
	SEM	3.302	3.830	3.992				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv	Placebo qd + Fulv	Treatment difference
		N=169	N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.0, 3.0)	(-5.9, 9.1)	(-12.9, 2.7)
	Pr >  t			0.2005
	n	30	24	
	LS Mean	-4.539	3.918	-8.457
	SEM	3.522	3.869	4.216
Week 72	95% CI	(-11.5, 2.4)	(-3.7, 11.5)	(-16.7, -0.2)
	Pr >  t			0.0452
	n	32	19	
	LS Mean	-7.189	1.812	-9.001
	SEM	3.474	4.106	4.395
Week 84	95% CI	(-14.0, -0.4)	(-6.3, 9.9)	(-17.6, -0.4)
	Pr >  t			0.0408
	n	26	19	
	LS Mean	-9.934	1.946	-11.88
	SEM	3.658	4.107	4.533
Week 96	95% CI	(-17.1, -2.7)	(-6.1, 10.0)	(-20.8, -3.0)
	Pr >  t			0.0089
	n	23	14	
	LS Mean	-5.222	-4.128	-1.094
	SEM	3.766	4.480	4.961
Week 108	95% CI	(-12.6, 2.2)	(-12.9, 4.7)	(-10.8, 8.6)
	Pr >  t			0.8255
	n	19	13	
	LS Mean	-3.972	-0.024	-3.947
	SEM	3.974	4.583	5.205
Week 120	95% CI	(-11.8, 3.8)	(-9.0, 9.0)	(-14.2, 6.3)
	Pr >  t			0.4484
	n	19	11	
	LS Mean	-9.096	0.119	-9.214
	SEM	3.964	4.835	5.429
Week 132	95% CI	(-16.9, -1.3)	(-9.4, 9.6)	(-19.9, 1.4)
	Pr >  t			0.0899
	n	15	5	
	LS Mean	-12.37	-2.031	-10.34
	SEM	4.258	6.450	7.074
Week 144	95% CI	(-20.7, -4.0)	(-14.7, 10.6)	(-24.2, 3.5)
	Pr >  t			0.1442
	n	12	3	
	LS Mean	-7.037	2.631	-9.668
	SEM	4.563	8.000	8.674

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.0, 1.9)	(-13.1,18.3)	(-26.7, 7.4)
		Pr >  t			0.2653
	Week 156	n	7	2	
		LS Mean	-4.820	-5.782	0.962
		SEM	5.553	9.569	10.62
		95% CI	(-15.7, 6.1)	(-24.6,13.0)	(-19.9,21.8)
		Pr >  t			0.9279
	Week 168	n	3	1	
		LS Mean	-8.265	4.078	-12.34
		SEM	7.896	13.22	15.08
		95% CI	(-23.8, 7.2)	(-21.9,30.0)	(-41.9,17.2)
		Pr >  t			0.4132
	Week 180	n	1	1	
		LS Mean	7.239	4.078	3.161
		SEM	13.16	13.22	18.39
		95% CI	(-18.6,33.1)	(-21.9,30.0)	(-32.9,39.2)
		Pr >  t			0.8635
	Week 192	n	1	1	
		LS Mean	-9.421	4.078	-13.50
		SEM	13.16	13.22	18.39
		95% CI	(-35.2,16.4)	(-21.9,30.0)	(-49.6,22.6)
		Pr >  t			0.4631
Yes	Week 8	n	44	56	
		LS Mean	-13.11	-6.707	-6.408
		SEM	6.247	5.972	3.942
		95% CI	(-25.4,-0.8)	(-18.5, 5.1)	(-14.2, 1.4)
		Pr >  t			0.1058
	Week 16	n	38	39	
		LS Mean	-10.16	-7.222	-2.942
		SEM	6.437	6.337	4.318
		95% CI	(-22.9, 2.5)	(-19.7, 5.3)	(-11.5, 5.6)
		Pr >  t			0.4963
	Week 24	n	32	33	
		LS Mean	-13.42	-10.06	-3.359
		SEM	6.536	6.420	4.586
		95% CI	(-26.3,-0.5)	(-22.7, 2.6)	(-12.4, 5.7)
		Pr >  t			0.4646
	Week 32	n	26	30	
		LS Mean	-10.90	-10.34	-0.564
		SEM	6.663	6.481	4.845



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 40	95% CI	(-24.0, 2.2)	(-23.1, 2.4)	(-10.1, 9.0)
	Pr >  t			0.9074
	n	25	24	
	LS Mean	-10.55	-11.47	0.914
	SEM	6.692	6.624	5.072
Week 48	95% CI	(-23.7, 2.6)	(-24.5, 1.6)	(-9.1,10.9)
	Pr >  t			0.8570
	n	21	20	
	LS Mean	-9.589	-13.33	3.742
	SEM	6.808	6.762	5.399
Week 56	95% CI	(-23.0, 3.8)	(-26.6,-0.0)	(-6.9,14.4)
	Pr >  t			0.4886
	n	18	20	
	LS Mean	-11.43	-10.07	-1.356
	SEM	6.932	6.762	5.557
Week 64	95% CI	(-25.1, 2.2)	(-23.4, 3.2)	(-12.3, 9.6)
	Pr >  t			0.8074
	n	17	18	
	LS Mean	-11.46	-14.03	2.577
	SEM	6.983	6.850	5.724
Week 72	95% CI	(-25.2, 2.3)	(-27.5,-0.5)	(-8.7,13.8)
	Pr >  t			0.6528
	n	16	16	
	LS Mean	-6.432	-6.806	0.374
	SEM	7.041	6.955	5.916
Week 84	95% CI	(-20.3, 7.4)	(-20.5, 6.9)	(-11.3,12.0)
	Pr >  t			0.9497
	n	14	14	
	LS Mean	-11.21	-14.07	2.868
	SEM	7.166	7.085	6.217
Week 96	95% CI	(-25.3, 2.9)	(-28.0,-0.1)	(-9.3,15.1)
	Pr >  t			0.6448
	n	12	10	
	LS Mean	-9.843	-13.28	3.438
	SEM	7.337	7.489	6.857
Week 108	95% CI	(-24.3, 4.6)	(-28.0, 1.5)	(-10.0,16.9)
	Pr >  t			0.6163
	n	7	8	
	LS Mean	-12.16	-10.34	-1.815
	SEM	8.119	7.825	8.014

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-28.1, 3.8)	(-25.7, 5.0)	(-17.6,13.9)
		Pr >  t			0.8209
	Week 120	n	9	5	
		LS Mean	-3.155	-4.721	1.567
		SEM	7.728	8.748	8.560
		95% CI	(-18.4,12.0)	(-21.9,12.5)	(-15.2,18.4)
		Pr >  t			0.8548
	Week 132	n	5	3	
		LS Mean	-10.55	-16.95	6.408
		SEM	8.800	10.16	10.85
		95% CI	(-27.8, 6.7)	(-36.9, 3.0)	(-14.9,27.7)
		Pr >  t			0.5550
	Week 144	n	3	2	
		LS Mean	-21.93	-10.34	-11.59
		SEM	10.20	11.69	13.34
		95% CI	(-42.0,-1.9)	(-33.3,12.6)	(-37.8,14.6)
		Pr >  t			0.3852
	Week 156	n	3	1	
		LS Mean	-18.03	-10.62	-7.409
		SEM	10.21	15.39	16.68
		95% CI	(-38.1, 2.0)	(-40.9,19.6)	(-40.2,25.4)
		Pr >  t			0.6571
	Week 168	n	1	1	
		LS Mean	-10.39	-10.62	0.229
		SEM	15.46	15.39	20.32
		95% CI	(-40.8,20.0)	(-40.9,19.6)	(-39.7,40.2)
		Pr >  t			0.9910

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Presence of Liver Metastases (L)	No	Week 8	n	104	98			
			LS Mean	-4.920	0.881	-5.801		
			SEM	3.133	3.108	2.592		
			95% CI	(-11.1, 1.3)	(-5.2, 7.0)	(-10.9,-0.7)		
					Pr >  t			0.0258
		Week 16	n	92	77			
			LS Mean	-3.890	0.340	-4.230		
			SEM	3.168	3.263	2.768		
			95% CI	(-10.1, 2.4)	(-6.1, 6.8)	(-9.7, 1.2)		
					Pr >  t			0.1271
		Week 24	n	83	66			
			LS Mean	-6.625	1.407	-8.032		
			SEM	3.217	3.325	2.891		
			95% CI	(-13.0,-0.3)	(-5.1, 8.0)	(-13.7,-2.4)		
					Pr >  t			0.0057
		Week 32	n	72	60			
			LS Mean	-4.912	-1.358	-3.555		
			SEM	3.279	3.381	3.002		
			95% CI	(-11.4, 1.5)	(-8.0, 5.3)	(-9.5, 2.3)		
					Pr >  t			0.2368
		Week 40	n	64	51			
			LS Mean	-3.574	-2.130	-1.444		
			SEM	3.325	3.471	3.141		
			95% CI	(-10.1, 3.0)	(-9.0, 4.7)	(-7.6, 4.7)		
					Pr >  t			0.6459
		Week 48	n	58	45			
			LS Mean	-4.548	-0.164	-4.384		
			SEM	3.366	3.537	3.259		
95% CI	(-11.2, 2.1)		(-7.1, 6.8)	(-10.8, 2.0)				
			Pr >  t			0.1790		
Week 56	n	49	38					
	LS Mean	-5.585	-1.124	-4.461				
	SEM	3.444	3.637	3.448				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-12.4, 1.2)	(-8.3, 6.0)	(-11.2, 2.3)
	Pr >  t			0.1961
	n	39	37	
	LS Mean	-6.241	-0.529	-5.712
	SEM	3.566	3.655	3.592
Week 72	95% CI	(-13.3, 0.8)	(-7.7, 6.7)	(-12.8, 1.3)
	Pr >  t			0.1121
	n	41	32	
	LS Mean	-7.005	0.367	-7.372
	SEM	3.539	3.752	3.663
Week 84	95% CI	(-14.0,-0.0)	(-7.0, 7.7)	(-14.6,-0.2)
	Pr >  t			0.0444
	n	33	29	
	LS Mean	-10.30	-1.655	-8.650
	SEM	3.687	3.824	3.865
Week 96	95% CI	(-17.6,-3.1)	(-9.2, 5.9)	(-16.2,-1.1)
	Pr >  t			0.0254
	n	31	21	
	LS Mean	-6.907	-6.314	-0.592
	SEM	3.724	4.100	4.179
Week 108	95% CI	(-14.2, 0.4)	(-14.4, 1.7)	(-8.8, 7.6)
	Pr >  t			0.8873
	n	23	18	
	LS Mean	-5.535	-2.501	-3.033
	SEM	3.972	4.258	4.543
Week 120	95% CI	(-13.3, 2.3)	(-10.9, 5.9)	(-11.9, 5.9)
	Pr >  t			0.5045
	n	25	15	
	LS Mean	-7.584	-0.369	-7.215
	SEM	3.893	4.469	4.682
Week 132	95% CI	(-15.2, 0.1)	(-9.1, 8.4)	(-16.4, 2.0)
	Pr >  t			0.1235
	n	17	8	
	LS Mean	-10.56	-5.627	-4.932
	SEM	4.276	5.428	5.872
Week 144	95% CI	(-19.0,-2.2)	(-16.3, 5.0)	(-16.5, 6.6)
	Pr >  t			0.4011
	n	15	5	
Week 144	LS Mean	-9.770	-0.224	-9.546
	SEM	4.410	6.462	6.932

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.4,-1.1)	(-12.9,12.5)	(-23.1, 4.1)
		Pr >  t			0.1687
	Week 156	n	10	3	
		LS Mean	-7.989	-5.837	-2.151
		SEM	4.998	7.960	8.665
		95% CI	(-17.8, 1.8)	(-21.5, 9.8)	(-19.2,14.8)
		Pr >  t			0.8040
	Week 168	n	4	2	
		LS Mean	-8.352	0.233	-8.585
		SEM	7.023	9.509	11.25
		95% CI	(-22.1, 5.4)	(-18.4,18.9)	(-30.6,13.5)
		Pr >  t			0.4454
	Week 180	n	1	1	
		LS Mean	6.359	1.737	4.622
		SEM	13.07	13.08	18.13
		95% CI	(-19.3,32.0)	(-23.9,27.4)	(-31.0,40.2)
		Pr >  t			0.7988
	Week 192	n	1	1	
		LS Mean	-10.30	1.737	-12.04
		SEM	13.07	13.08	18.13
		95% CI	(-35.9,15.3)	(-23.9,27.4)	(-47.6,23.5)
		Pr >  t			0.5069
Yes	Week 8	n	38	42	
		LS Mean	-7.347	3.815	-11.16
		SEM	4.554	4.878	4.624
		95% CI	(-16.4, 1.7)	(-5.8,13.5)	(-20.3,-2.0)
		Pr >  t			0.0169
	Week 16	n	32	30	
		LS Mean	-0.896	-0.881	-0.015
		SEM	4.875	5.174	5.147
		95% CI	(-10.5, 8.7)	(-11.1, 9.3)	(-10.2,10.1)
		Pr >  t			0.9977
	Week 24	n	22	15	
		LS Mean	-3.560	-1.725	-1.835
		SEM	5.239	6.209	6.473
		95% CI	(-13.9, 6.8)	(-14.0,10.5)	(-14.6,10.9)
		Pr >  t			0.7770
	Week 32	n	14	13	
		LS Mean	3.940	-4.248	8.188
		SEM	6.036	6.444	7.236

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-8.0,15.8)	(-16.9, 8.4)	(-6.1,22.4)
		Pr >  t			0.2588
	Week 40	n	11	11	
		LS Mean	4.349	-1.058	5.406
		SEM	6.474	6.739	7.854
		95% CI	(-8.4,17.1)	(-14.3,12.2)	(-10.1,20.9)
		Pr >  t			0.4918
	Week 48	n	11	6	
		LS Mean	-0.196	-13.42	13.228
		SEM	6.474	8.112	9.063
		95% CI	(-12.9,12.6)	(-29.4, 2.5)	(-4.6,31.1)
		Pr >  t			0.1455
	Week 56	n	10	7	
		LS Mean	5.634	0.082	5.552
		SEM	6.659	7.714	8.845
		95% CI	(-7.5,18.7)	(-15.1,15.3)	(-11.9,23.0)
		Pr >  t			0.5307
	Week 64	n	8	5	
		LS Mean	4.644	-6.635	11.279
		SEM	7.130	8.616	9.969
		95% CI	(-9.4,18.7)	(-23.6,10.3)	(-8.3,30.9)
		Pr >  t			0.2588
	Week 72	n	7	3	
		LS Mean	8.741	5.842	2.899
		SEM	7.447	10.40	11.74
		95% CI	(-5.9,23.4)	(-14.6,26.3)	(-20.2,26.0)
		Pr >  t			0.8051
	Week 84	n	7	4	
		LS Mean	3.979	-6.987	10.966
		SEM	7.447	9.323	10.80
		95% CI	(-10.7,18.6)	(-25.3,11.4)	(-10.3,32.2)
		Pr >  t			0.3106
	Week 96	n	4	3	
		LS Mean	11.685	0.285	11.400
		SEM	9.092	10.40	12.84
		95% CI	(-6.2,29.6)	(-20.2,20.8)	(-13.9,36.7)
		Pr >  t			0.3756
	Week 108	n	3	3	
		LS Mean	2.503	1.310	1.192
		SEM	10.18	10.42	13.65

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.5,22.5)	(-19.2,21.8)	(-25.7,28.1)
		Pr >  t			0.9305
	Week 120	n	3	1	
		LS Mean	12.989	2.611	10.377
		SEM	10.18	16.61	18.80
		95% CI	( -7.0,33.0)	(-30.1,35.3)	(-26.7,47.4)
		Pr >  t			0.5816
	Week 132	n	3		
		LS Mean	-7.440	NE	NE
		SEM	10.18	NE	NE
		95% CI	(-27.5,12.6)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Stratum 2 - Prior CDK4/6 inhibitor (L)	No prior use	Week 8	n	134	134	
			LS Mean	-6.853	1.255	-8.108
		SEM	1.652	1.661	2.340	
		95% CI	(-10.1,-3.6)	(-2.0, 4.5)	(-12.7,-3.5)	
		Pr >  t			0.0006	
		Week 16	n	118	104	
			LS Mean	-4.632	-0.664	-3.968
		SEM	1.725	1.822	2.507	
		95% CI	(-8.0,-1.2)	(-4.2, 2.9)	(-8.9, 1.0)	
		Pr >  t			0.1140	
		Week 24	n	100	79	
			LS Mean	-7.383	0.115	-7.497
		SEM	1.825	2.002	2.705	
		95% CI	(-11.0,-3.8)	(-3.8, 4.0)	(-12.8,-2.2)	
		Pr >  t			0.0057	
		Week 32	n	84	72	
			LS Mean	-4.914	-2.503	-2.411
		SEM	1.931	2.067	2.826	
		95% CI	(-8.7,-1.1)	(-6.6, 1.6)	(-8.0, 3.1)	
		Pr >  t			0.3939	
		Week 40	n	73	62	
			LS Mean	-3.809	-2.501	-1.308
		SEM	2.025	2.172	2.966	
		95% CI	(-7.8, 0.2)	(-6.8, 1.8)	(-7.1, 4.5)	
		Pr >  t			0.6592	
		Week 48	n	67	51	
			LS Mean	-5.366	-2.276	-3.090
		SEM	2.083	2.322	3.116	
95% CI	(-9.5,-1.3)	(-6.8, 2.3)	(-9.2, 3.0)			
Pr >  t			0.3215			
Week 56	n	57	45			
	LS Mean	-5.249	-1.427	-3.822		
SEM	2.200	2.429	3.274			



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-9.6,-0.9)	(-6.2, 3.3)	(-10.2, 2.6)
	Pr >  t			0.2434
	n	45	42	
	LS Mean	-6.075	-1.789	-4.286
	SEM	2.388	2.490	3.448
Week 72	95% CI	(-10.8,-1.4)	(-6.7, 3.1)	(-11.0, 2.5)
	Pr >  t			0.2141
	n	46	35	
	LS Mean	-5.843	0.193	-6.036
	SEM	2.372	2.661	3.562
Week 84	95% CI	(-10.5,-1.2)	(-5.0, 5.4)	(-13.0, 1.0)
	Pr >  t			0.0904
	n	40	33	
	LS Mean	-9.321	-2.921	-6.399
	SEM	2.493	2.721	3.689
Week 96	95% CI	(-14.2,-4.4)	(-8.3, 2.4)	(-13.6, 0.8)
	Pr >  t			0.0830
	n	34	24	
	LS Mean	-5.827	-6.084	0.257
	SEM	2.651	3.079	4.062
Week 108	95% CI	(-11.0,-0.6)	(-12.1,-0.0)	(-7.7, 8.2)
	Pr >  t			0.9496
	n	26	21	
	LS Mean	-5.670	-2.501	-3.169
	SEM	2.945	3.252	4.385
Week 120	95% CI	(-11.4, 0.1)	(-8.9, 3.9)	(-11.8, 5.4)
	Pr >  t			0.4699
	n	27	16	
	LS Mean	-6.399	-0.753	-5.646
	SEM	2.904	3.643	4.656
Week 132	95% CI	(-12.1,-0.7)	(-7.9, 6.4)	(-14.8, 3.5)
	Pr >  t			0.2255
	n	20	8	
	LS Mean	-11.44	-6.250	-5.194
	SEM	3.278	4.946	5.932
Week 144	95% CI	(-17.9,-5.0)	(-16.0, 3.5)	(-16.8, 6.4)
	Pr >  t			0.3814
	n	14	5	
	LS Mean	-10.15	-0.861	-9.289
	SEM	3.820	6.161	7.248

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-17.6,-2.7)	(-12.9,11.2)	(-23.5, 4.9)
		Pr >  t			0.2002
	Week 156	n	10	3	
		LS Mean	-8.083	-6.475	-1.608
		SEM	4.438	7.855	9.021
		95% CI	(-16.8, 0.6)	(-21.9, 8.9)	(-19.3,16.1)
		Pr >  t			0.8585
	Week 168	n	4	2	
		LS Mean	-8.427	-0.434	-7.994
		SEM	6.814	9.562	11.74
		95% CI	(-21.8, 4.9)	(-19.2,18.3)	(-31.0,15.0)
		Pr >  t			0.4961
	Week 180	n	1	1	
		LS Mean	6.196	1.035	5.161
		SEM	13.42	13.42	18.98
		95% CI	(-20.1,32.5)	(-25.3,27.4)	(-32.1,42.4)
		Pr >  t			0.7857
	Week 192	n	1	1	
		LS Mean	-10.46	1.035	-11.50
		SEM	13.42	13.42	18.98
		95% CI	(-36.8,15.9)	(-25.3,27.4)	(-48.7,25.7)
		Pr >  t			0.5446
Prior use	Week 8	n	8	6	
		LS Mean	-5.664	-8.672	3.009
		SEM	4.891	5.448	7.285
		95% CI	(-15.8, 4.4)	(-19.9, 2.5)	(-12.0,18.0)
		Pr >  t			0.6831
	Week 16	n	6	3	
		LS Mean	-0.798	-1.527	0.730
		SEM	5.671	7.811	9.406
		95% CI	(-12.5,10.9)	(-17.6,14.5)	(-18.6,20.0)
		Pr >  t			0.9388
	Week 24	n	5	2	
		LS Mean	-3.958	1.108	-5.066
		SEM	5.963	9.837	11.40
		95% CI	(-16.2, 8.3)	(-19.0,21.3)	(-28.4,18.3)
		Pr >  t			0.6602
	Week 32	n	2	1	
		LS Mean	3.261	-0.651	3.912
		SEM	9.483	13.80	16.75

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-16.2,22.7)	(-30.4,38.2)
		Pr >  t		0.8170
	Week 40	n	2	
		LS Mean	3.261	NE
		SEM	9.483	NE
		95% CI	(-16.2,22.7)	NE
		Pr >  t		NE
	Week 48	n	2	
		LS Mean	3.261	NE
		SEM	9.483	NE
		95% CI	(-16.2,22.7)	NE
		Pr >  t		NE
	Week 56	n	2	
		LS Mean	3.261	NE
		SEM	9.483	NE
		95% CI	(-16.2,22.7)	NE
		Pr >  t		NE
	Week 64	n	2	
		LS Mean	3.261	NE
		SEM	9.483	NE
		95% CI	(-16.2,22.7)	NE
		Pr >  t		NE
	Week 72	n	2	
		LS Mean	-5.074	NE
		SEM	9.483	NE
		95% CI	(-24.5,14.4)	NE
		Pr >  t		NE
	Week 96	n	1	
		LS Mean	1.972	NE
		SEM	13.09	NE
		95% CI	(-24.9,28.9)	NE
		Pr >  t		NE
	Week 120	n	1	
		LS Mean	1.972	NE
		SEM	13.09	NE
		95% CI	(-24.9,28.9)	NE
		Pr >  t		NE
	Week 144	n	1	
		LS Mean	1.972	NE
		SEM	13.09	NE

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-24.9,28.9)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
PTEN Loss of Expression (L)	No	Week 8	n	137	130			
			LS Mean	-6.160	1.447	-7.607		
			SEM	2.593	2.652	2.328		
			95% CI	(-11.3,-1.1)	(-3.8, 6.7)	(-12.2,-3.0)		
					Pr >  t			0.0012
		Week 16	n	119	97			
			LS Mean	-4.026	0.337	-4.363		
			SEM	2.657	2.795	2.519		
			95% CI	(-9.3, 1.2)	(-5.2, 5.8)	(-9.3, 0.6)		
					Pr >  t			0.0838
		Week 24	n	100	75			
			LS Mean	-7.126	1.099	-8.224		
			SEM	2.724	2.920	2.713		
			95% CI	(-12.5,-1.8)	(-4.6, 6.8)	(-13.6,-2.9)		
					Pr >  t			0.0025
		Week 32	n	82	69			
			LS Mean	-4.526	-1.350	-3.177		
			SEM	2.824	2.970	2.839		
			95% CI	(-10.1, 1.0)	(-7.2, 4.5)	(-8.7, 2.4)		
					Pr >  t			0.2635
		Week 40	n	73	58			
			LS Mean	-3.591	-1.802	-1.789		
			SEM	2.875	3.065	2.981		
			95% CI	(-9.2, 2.1)	(-7.8, 4.2)	(-7.6, 4.1)		
					Pr >  t			0.5486
		Week 48	n	66	48			
			LS Mean	-5.187	-1.912	-3.275		
			SEM	2.921	3.174	3.137		
95% CI	(-10.9, 0.6)		(-8.1, 4.3)	(-9.4, 2.9)				
			Pr >  t			0.2967		
Week 56	n	56	43					
	LS Mean	-5.400	-1.699	-3.701				
	SEM	3.003	3.245	3.286				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.3, 0.5)	(-8.1, 4.7)	(-10.1, 2.7)
		Pr >  t			0.2604
	Week 64	n	45	41	
		LS Mean	-5.549	-1.307	-4.242
		SEM	3.128	3.277	3.434
		95% CI	(-11.7, 0.6)	(-7.7, 5.1)	(-11.0, 2.5)
		Pr >  t			0.2170
	Week 72	n	46	34	
		LS Mean	-6.250	0.706	-6.956
		SEM	3.117	3.412	3.553
		95% CI	(-12.4,-0.1)	(-6.0, 7.4)	(-13.9, 0.0)
		Pr >  t			0.0504
	Week 84	n	37	32	
		LS Mean	-9.774	-2.512	-7.263
		SEM	3.271	3.460	3.726
		95% CI	(-16.2,-3.4)	(-9.3, 4.3)	(-14.6, 0.0)
		Pr >  t			0.0515
	Week 96	n	33	23	
		LS Mean	-6.469	-5.863	-0.606
		SEM	3.354	3.761	4.079
		95% CI	(-13.1, 0.1)	(-13.2, 1.5)	(-8.6, 7.4)
		Pr >  t			0.8820
	Week 108	n	24	20	
		LS Mean	-5.300	-0.449	-4.851
		SEM	3.645	3.912	4.449
		95% CI	(-12.5, 1.9)	(-8.1, 7.2)	(-13.6, 3.9)
		Pr >  t			0.2758
	Week 120	n	25	16	
		LS Mean	-6.744	-0.130	-6.614
		SEM	3.601	4.183	4.660
		95% CI	(-13.8, 0.3)	(-8.3, 8.1)	(-15.8, 2.5)
		Pr >  t			0.1560
	Week 132	n	19	8	
		LS Mean	-10.35	-5.625	-4.721
		SEM	3.897	5.324	5.894
		95% CI	(-18.0,-2.7)	(-16.1, 4.8)	(-16.3, 6.8)
		Pr >  t			0.4233
	Week 144	n	14	5	
		LS Mean	-9.484	-0.237	-9.247
		SEM	4.286	6.437	7.148

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.9,-1.1)	(-12.9,12.4)	(-23.3, 4.8)
		Pr >  t			0.1960
	Week 156	n	10	3	
		LS Mean	-7.872	-5.859	-2.013
		SEM	4.838	8.027	8.891
		95% CI	(-17.4, 1.6)	(-21.6, 9.9)	(-19.5,15.4)
		Pr >  t			0.8209
	Week 168	n	4	2	
		LS Mean	-8.211	0.185	-8.396
		SEM	7.022	9.656	11.57
		95% CI	(-22.0, 5.6)	(-18.8,19.1)	(-31.1,14.3)
		Pr >  t			0.4680
	Week 180	n	1	1	
		LS Mean	6.452	1.655	4.797
		SEM	13.37	13.39	18.68
		95% CI	(-19.8,32.7)	(-24.6,27.9)	(-31.9,41.5)
		Pr >  t			0.7974
	Week 192	n	1	1	
		LS Mean	-10.21	1.655	-11.86
		SEM	13.37	13.39	18.68
		95% CI	(-36.4,16.0)	(-24.6,27.9)	(-48.5,24.8)
		Pr >  t			0.5256
Yes	Week 8	n	5	9	
		LS Mean	-10.90	3.691	-14.59
		SEM	9.211	6.570	11.38
		95% CI	(-29.8, 8.0)	( -9.6,17.0)	(-37.8, 8.6)
		Pr >  t			0.2090
	Week 16	n	5	9	
		LS Mean	-4.234	-5.552	1.318
		SEM	9.211	6.628	11.37
		95% CI	(-23.1,14.6)	(-19.0, 7.9)	(-21.9,24.5)
		Pr >  t			0.9085
	Week 24	n	5	5	
		LS Mean	-0.902	-3.173	2.271
		SEM	9.211	8.777	12.75
		95% CI	(-19.8,18.0)	(-20.8,14.5)	(-23.6,28.1)
		Pr >  t			0.8596
	Week 32	n	4	3	
		LS Mean	2.018	-8.225	10.243
		SEM	10.03	10.99	14.95

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-18.4,22.4)	(-30.3,13.8)	(-19.9,40.3)
		Pr >  t			0.4967
	Week 40	n	2	3	
		LS Mean	7.694	-3.937	11.631
		SEM	13.27	11.02	17.18
		95% CI	(-19.0,34.4)	(-26.1,18.2)	(-22.9,46.1)
		Pr >  t			0.5016
	Week 48	n	3	2	
		LS Mean	7.033	2.056	4.978
		SEM	11.28	13.32	17.29
		95% CI	(-15.7,29.8)	(-24.7,28.8)	(-29.8,39.7)
		Pr >  t			0.7746
	Week 56	n	3	1	
		LS Mean	12.587	34.077	-21.49
		SEM	11.28	18.29	21.61
		95% CI	(-10.2,35.4)	(-2.7,70.9)	(-64.9,21.9)
		Pr >  t			0.3246
	Week 64	n	2		
		LS Mean	-0.641	NE	NE
		SEM	13.27	NE	NE
		95% CI	(-27.3,26.0)	NE	NE
		Pr >  t			NE
	Week 72	n	2		
		LS Mean	12.765	NE	NE
		SEM	13.24	NE	NE
		95% CI	(-13.9,39.4)	NE	NE
		Pr >  t			NE
	Week 84	n	3		
		LS Mean	7.033	NE	NE
		SEM	11.28	NE	NE
		95% CI	(-15.7,29.8)	NE	NE
		Pr >  t			NE
	Week 96	n	2		
		LS Mean	16.024	NE	NE
		SEM	13.27	NE	NE
		95% CI	(-10.6,42.7)	NE	NE
		Pr >  t			NE
	Week 108	n	2		
		LS Mean	0.637	NE	NE
		SEM	13.33	NE	NE



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-26.1,27.4)	NE	NE
	Pr >  t			NE
	n	3		
	LS Mean	7.030	NE	NE
	SEM	11.28	NE	NE
	95% CI	(-15.7,29.8)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-21.10	NE	NE
	SEM	18.02	NE	NE
	95% CI	(-57.3,15.1)	NE	NE
	Pr >  t			NE
	n	1		
	LS Mean	-4.439	NE	NE
	SEM	18.02	NE	NE
	95% CI	(-40.6,31.7)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 1 (L)	< 65 Years	Week 8	n	79	69			
			LS Mean	-7.156	0.044	-7.199		
			SEM	3.298	3.440	3.250		
			95% CI	(-13.7,-0.7)	(-6.7, 6.8)	(-13.6,-0.8)		
					Pr >  t			0.0276
		Week 16	n	70	52			
			LS Mean	-3.728	-2.369	-1.359		
			SEM	3.365	3.678	3.492		
			95% CI	(-10.4, 2.9)	(-9.6, 4.9)	(-8.2, 5.5)		
					Pr >  t			0.6974
		Week 24	n	61	37			
			LS Mean	-7.272	-1.635	-5.636		
			SEM	3.439	3.926	3.784		
			95% CI	(-14.0,-0.5)	(-9.4, 6.1)	(-13.1, 1.8)		
					Pr >  t			0.1372
		Week 32	n	48	33			
			LS Mean	-4.497	0.034	-4.531		
			SEM	3.585	4.007	3.986		
			95% CI	(-11.6, 2.6)	(-7.9, 7.9)	(-12.4, 3.3)		
					Pr >  t			0.2562
		Week 40	n	42	31			
			LS Mean	-3.626	0.060	-3.686		
			SEM	3.662	4.055	4.104		
			95% CI	(-10.8, 3.6)	(-7.9, 8.0)	(-11.8, 4.4)		
			Pr >  t			0.3695		
Week 48	n	40	25					
	LS Mean	-5.124	0.445	-5.569				
	SEM	3.692	4.224	4.298				
	95% CI	(-12.4, 2.1)	(-7.9, 8.8)	(-14.0, 2.9)				
			Pr >  t			0.1956		
Week 56	n	35	20					
	LS Mean	-3.957	-0.144	-3.813				
	SEM	3.775	4.435	4.578				

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-11.4, 3.5)	(-8.9, 8.6)	(-12.8, 5.2)
		Pr >  t			0.4053
	Week 64	n	29	18	
		LS Mean	-5.766	0.973	-6.739
		SEM	3.905	4.547	4.795
		95% CI	(-13.4, 1.9)	(-8.0, 9.9)	(-16.2, 2.7)
		Pr >  t			0.1603
	Week 72	n	28	18	
		LS Mean	-8.159	-1.898	-6.261
		SEM	3.933	4.544	4.816
		95% CI	(-15.9,-0.4)	(-10.8, 7.0)	(-15.7, 3.2)
		Pr >  t			0.1940
	Week 84	n	27	17	
		LS Mean	-9.448	-0.832	-8.616
		SEM	3.978	4.609	4.900
		95% CI	(-17.3,-1.6)	(-9.9, 8.2)	(-18.2, 1.0)
		Pr >  t			0.0791
	Week 96	n	23	14	
		LS Mean	-5.409	-8.129	2.720
		SEM	4.108	4.839	5.226
		95% CI	(-13.5, 2.7)	(-17.6, 1.4)	(-7.5,13.0)
		Pr >  t			0.6029
	Week 108	n	19	12	
		LS Mean	-4.779	-3.163	-1.616
		SEM	4.307	5.050	5.565
		95% CI	(-13.2, 3.7)	(-13.1, 6.8)	(-12.5, 9.3)
		Pr >  t			0.7716
	Week 120	n	18	8	
		LS Mean	-8.037	-5.057	-2.980
		SEM	4.352	5.715	6.214
		95% CI	(-16.6, 0.5)	(-16.3, 6.2)	(-15.2, 9.2)
		Pr >  t			0.6316
	Week 132	n	11	4	
		LS Mean	-11.34	-0.419	-10.92
		SEM	5.006	7.347	8.124
		95% CI	(-21.2,-1.5)	(-14.8,14.0)	(-26.9, 5.0)
		Pr >  t			0.1792
	Week 144	n	11	4	
		LS Mean	-5.708	-0.260	-5.448
		SEM	4.994	7.353	8.129

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-15.5, 4.1)	(-14.7,14.2)	(-21.4,10.5)
		Pr >  t			0.5029
	Week 156	n	5	2	
		LS Mean	-5.028	-8.402	3.373
		SEM	6.604	9.820	11.27
		95% CI	(-18.0, 7.9)	(-27.7,10.9)	(-18.7,25.5)
		Pr >  t			0.7648
	Week 168	n	1	2	
		LS Mean	19.658	-0.067	19.725
		SEM	13.35	9.820	16.17
		95% CI	(-6.5,45.9)	(-19.3,19.2)	(-12.0,51.5)
		Pr >  t			0.2229
	Week 180	n		1	
		LS Mean	NE	1.273	NE
		SEM	NE	13.44	NE
		95% CI	NE	(-25.1,27.7)	NE
		Pr >  t			NE
	Week 192	n		1	
		LS Mean	NE	1.273	NE
		SEM	NE	13.44	NE
		95% CI	NE	(-25.1,27.7)	NE
		Pr >  t			NE
>= 65 Years	Week 8	n	63	71	
		LS Mean	-4.577	3.211	-7.788
		SEM	4.343	4.317	3.164
		95% CI	(-13.2, 4.0)	(-5.3,11.7)	(-14.0,-1.6)
		Pr >  t			0.0144
	Week 16	n	54	55	
		LS Mean	-3.682	2.661	-6.343
		SEM	4.468	4.406	3.422
		95% CI	(-12.5, 5.1)	(-6.0,11.4)	(-13.1, 0.4)
		Pr >  t			0.0647
	Week 24	n	44	44	
		LS Mean	-5.363	3.336	-8.699
		SEM	4.571	4.506	3.707
		95% CI	(-14.4, 3.7)	(-5.6,12.2)	(-16.0,-1.4)
		Pr >  t			0.0194
	Week 32	n	38	40	
		LS Mean	-3.026	-2.949	-0.077
		SEM	4.693	4.595	3.877

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.3, 6.2)	(-12.0, 6.1)	(-7.7, 7.5)
		Pr >  t			0.9842
	Week 40	n	33	31	
		LS Mean	-1.570	-3.583	2.013
		SEM	4.782	4.787	4.166
		95% CI	(-11.0, 7.9)	(-13.0, 5.9)	(-6.2, 10.2)
		Pr >  t			0.6292
	Week 48	n	29	26	
		LS Mean	-3.160	-3.309	0.149
		SEM	4.867	4.920	4.412
		95% CI	(-12.8, 6.4)	(-13.0, 6.4)	(-8.5, 8.8)
		Pr >  t			0.9732
	Week 56	n	24	25	
		LS Mean	-4.589	-0.936	-3.653
		SEM	5.011	4.949	4.605
		95% CI	(-14.5, 5.3)	(-10.7, 8.8)	(-12.7, 5.4)
		Pr >  t			0.4280
	Week 64	n	18	24	
		LS Mean	-3.839	-2.405	-1.434
		SEM	5.273	4.984	4.927
		95% CI	(-14.2, 6.5)	(-12.2, 7.4)	(-11.1, 8.2)
		Pr >  t			0.7710
	Week 72	n	20	17	
		LS Mean	-0.758	4.106	-4.864
		SEM	5.176	5.310	5.154
		95% CI	(-10.9, 9.4)	(-6.3, 14.6)	(-15.0, 5.3)
		Pr >  t			0.3456
	Week 84	n	13	16	
		LS Mean	-6.684	-3.353	-3.330
		SEM	5.644	5.374	5.687
		95% CI	(-17.8, 4.4)	(-13.9, 7.2)	(-14.5, 7.8)
		Pr >  t			0.5583
	Week 96	n	12	10	
		LS Mean	-4.295	-1.356	-2.939
		SEM	5.754	6.006	6.386
		95% CI	(-15.6, 7.0)	(-13.2, 10.4)	(-15.5, 9.6)
		Pr >  t			0.6455
	Week 108	n	7	9	
		LS Mean	-5.502	0.095	-5.597
		SEM	6.652	6.177	7.351

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-18.6, 7.6)	(-12.0,12.2)	(-20.0, 8.8)
		Pr >  t			0.4467
	Week 120	n	10	8	
		LS Mean	-0.958	5.222	-6.180
		SEM	6.036	6.388	6.987
		95% CI	(-12.8,10.9)	(-7.3,17.8)	(-19.9, 7.5)
		Pr >  t			0.3767
	Week 132	n	9	4	
		LS Mean	-9.355	-10.24	0.884
		SEM	6.192	8.005	8.602
		95% CI	(-21.5, 2.8)	(-26.0, 5.5)	(-16.0,17.8)
		Pr >  t			0.9182
	Week 144	n	4	1	
		LS Mean	-18.72	-0.217	-18.50
		SEM	8.011	14.27	15.47
		95% CI	(-34.4,-3.0)	(-28.2,27.8)	(-48.9,11.9)
		Pr >  t			0.2322
	Week 156	n	5	1	
		LS Mean	-9.186	-0.217	-8.969
		SEM	7.414	14.27	15.17
		95% CI	(-23.7, 5.4)	(-28.2,27.8)	(-38.8,20.8)
		Pr >  t			0.5546
	Week 168	n	3		
		LS Mean	-16.06	NE	NE
		SEM	8.934	NE	NE
		95% CI	(-33.6, 1.5)	NE	NE
		Pr >  t			NE
	Week 180	n	1		
		LS Mean	6.852	NE	NE
		SEM	14.27	NE	NE
		95% CI	(-21.2,34.9)	NE	NE
		Pr >  t			NE
	Week 192	n	1		
		LS Mean	-9.808	NE	NE
		SEM	14.27	NE	NE
		95% CI	(-37.8,18.2)	NE	NE
		Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Pooled Age Group 2 (L)	< 75 Years	Week 8	n	125	121			
			LS Mean	-6.198	1.384	-7.582		
			SEM	2.673	2.726	2.468		
			95% CI	(-11.5,-0.9)	(-4.0, 6.7)	(-12.4,-2.7)		
					Pr >  t			0.0023
		Week 16	n	111	91			
			LS Mean	-3.970	-0.094	-3.876		
			SEM	2.735	2.879	2.656		
			95% CI	(-9.3, 1.4)	(-5.8, 5.6)	(-9.1, 1.3)		
					Pr >  t			0.1451
		Week 24	n	96	70			
			LS Mean	-6.809	0.899	-7.708		
			SEM	2.797	3.016	2.852		
			95% CI	(-12.3,-1.3)	(-5.0, 6.8)	(-13.3,-2.1)		
					Pr >  t			0.0070
		Week 32	n	77	61			
			LS Mean	-3.415	-1.886	-1.529		
			SEM	2.912	3.097	3.021		
			95% CI	(-9.1, 2.3)	(-8.0, 4.2)	(-7.5, 4.4)		
					Pr >  t			0.6130
		Week 40	n	69	52			
			LS Mean	-2.546	-1.511	-1.035		
			SEM	2.964	3.197	3.164		
			95% CI	(-8.4, 3.3)	(-7.8, 4.8)	(-7.2, 5.2)		
			Pr >  t			0.7437		
Week 48	n	62	41					
	LS Mean	-3.434	-2.168	-1.267				
	SEM	3.015	3.350	3.366				
	95% CI	(-9.4, 2.5)	(-8.7, 4.4)	(-7.9, 5.3)				
			Pr >  t			0.7068		
Week 56	n	53	35					
	LS Mean	-4.064	-1.598	-2.467				
	SEM	3.099	3.468	3.559				



Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-10.2, 2.0)	(-8.4, 5.2)	(-9.4, 4.5)
		Pr >  t			0.4884
	Week 64	n	44	33	
		LS Mean	-4.191	0.436	-4.627
		SEM	3.209	3.515	3.702
		95% CI	(-10.5, 2.1)	(-6.5, 7.3)	(-11.9, 2.6)
		Pr >  t			0.2117
	Week 72	n	45	28	
		LS Mean	-4.723	-0.136	-4.587
		SEM	3.196	3.655	3.824
		95% CI	(-11.0, 1.6)	(-7.3, 7.0)	(-12.1, 2.9)
		Pr >  t			0.2306
	Week 84	n	39	27	
		LS Mean	-8.263	-2.523	-5.741
		SEM	3.301	3.689	3.937
		95% CI	(-14.7,-1.8)	(-9.8, 4.7)	(-13.5, 2.0)
		Pr >  t			0.1450
	Week 96	n	34	19	
		LS Mean	-4.656	-6.473	1.817
		SEM	3.400	4.058	4.366
		95% CI	(-11.3, 2.0)	(-14.4, 1.5)	(-6.7,10.4)
		Pr >  t			0.6774
	Week 108	n	26	17	
		LS Mean	-4.484	-3.760	-0.723
		SEM	3.640	4.197	4.674
		95% CI	(-11.6, 2.7)	(-12.0, 4.5)	(-9.9, 8.4)
		Pr >  t			0.8771
	Week 120	n	27	11	
		LS Mean	-4.751	-2.324	-2.427
		SEM	3.600	4.842	5.237
		95% CI	(-11.8, 2.3)	(-11.8, 7.2)	(-12.7, 7.8)
		Pr >  t			0.6431
	Week 132	n	20	6	
		LS Mean	-10.24	-4.119	-6.126
		SEM	3.914	6.091	6.588
		95% CI	(-17.9,-2.6)	(-16.1, 7.8)	(-19.1, 6.8)
		Pr >  t			0.3526
	Week 144	n	15	4	
		LS Mean	-8.633	-0.332	-8.301
		SEM	4.272	7.225	7.843

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
>= 75 Years	Week 156	95% CI	(-17.0,-0.3)	(-14.5,13.8)	(-23.7, 7.1)
		Pr >  t			0.2901
		n	10	2	
		LS Mean	-6.891	-8.518	1.627
	Week 168	SEM	4.931	9.849	10.60
		95% CI	(-16.6, 2.8)	(-27.8,10.8)	(-19.2,22.4)
		Pr >  t			0.8780
		n	4	2	
	Week 180	LS Mean	-7.232	-0.183	-7.049
		SEM	7.152	9.849	11.80
		95% CI	(-21.3, 6.8)	(-19.5,19.1)	(-30.2,16.1)
		Pr >  t			0.5503
	Week 192	n	1	1	
		LS Mean	7.424	1.231	6.192
		SEM	13.61	13.64	19.04
		95% CI	(-19.3,34.1)	(-25.5,28.0)	(-31.2,43.5)
	Week 8	Pr >  t			0.7450
		n	1	1	
		LS Mean	-9.236	1.231	-10.47
		SEM	13.61	13.64	19.04
	Week 16	95% CI	(-35.9,17.5)	(-25.5,28.0)	(-47.8,26.9)
		Pr >  t			0.5825
		n	17	19	
		LS Mean	-6.648	1.072	-7.720
Week 24	SEM	4.140	3.799	5.571	
	95% CI	(-14.9, 1.6)	( -6.5, 8.6)	(-18.8, 3.4)	
	Pr >  t			0.1699	
	n	13	16		
Week 32	LS Mean	-2.866	-0.799	-2.067	
	SEM	4.628	4.104	6.163	
	95% CI	(-12.1, 6.3)	( -9.0, 7.4)	(-14.3,10.2)	
	Pr >  t			0.7381	
Week 8	n	9	11		
	LS Mean	-4.491	-0.701	-3.790	
	SEM	5.341	4.757	7.121	
	95% CI	(-15.1, 6.1)	(-10.1, 8.7)	(-17.9,10.3)	
Week 16	Pr >  t			0.5956	
	n	9	12		
	LS Mean	-9.322	-2.599	-6.723	
	SEM	5.341	4.623	7.030	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-19.9, 1.3)	(-20.6, 7.2)
		Pr >  t		0.3409
	Week 40	n	6	10
		LS Mean	-5.846	-4.884
		SEM	6.270	4.936
		95% CI	(-18.2, 6.5)	(-14.7, 4.9)
		Pr >  t		(-16.7,14.7) 0.9038
	Week 48	n	7	10
		LS Mean	-12.91	-0.244
		SEM	5.902	4.952
		95% CI	(-24.6,-1.2)	(-10.0, 9.6)
		Pr >  t		(-27.8, 2.5) 0.1006
	Week 56	n	6	10
		LS Mean	-6.206	1.207
		SEM	6.259	4.962
		95% CI	(-18.6, 6.2)	(-8.6,11.0)
		Pr >  t		(-23.1, 8.3) 0.3523
	Week 64	n	3	9
		LS Mean	-16.61	-7.622
		SEM	8.344	5.162
		95% CI	(-33.1,-0.1)	(-17.8, 2.6)
		Pr >  t		(-28.3,10.3) 0.3590
	Week 72	n	3	7
		LS Mean	-11.06	4.073
		SEM	8.344	5.700
		95% CI	(-27.5, 5.4)	(-7.2,15.3)
		Pr >  t		(-35.0, 4.7) 0.1346
	Week 84	n	1	6
		LS Mean	-6.890	-1.819
		SEM	13.74	6.057
		95% CI	(-34.0,20.2)	(-13.8,10.1)
		Pr >  t		(-34.7,24.5) 0.7355
	Week 96	n	1	5
		LS Mean	-6.890	-2.125
		SEM	13.74	6.529
		95% CI	(-34.0,20.2)	(-15.0,10.8)
		Pr >  t		(-34.8,25.2) 0.7541
	Week 108	n		4
		LS Mean	NE	5.354
		SEM	NE	7.176

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	NE	(-8.8,19.5)
		Pr >  t		NE
	Week 120	n	1	5
		LS Mean	-21.99	4.541
		SEM	13.76	6.529
		95% CI	(-49.2, 5.2)	(-8.3,17.4)
		Pr >  t		(-56.6, 3.5)
	Week 132	n		2
		LS Mean	NE	-10.88
		SEM	NE	9.713
		95% CI	NE	(-30.1, 8.3)
		Pr >  t		NE
	Week 144	n		1
		LS Mean	NE	-0.722
		SEM	NE	13.44
		95% CI	NE	(-27.3,25.8)
		Pr >  t		NE
	Week 156	n		1
		LS Mean	NE	-0.722
		SEM	NE	13.44
		95% CI	NE	(-27.3,25.8)
		Pr >  t		NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>		
Prior Chemotherapy Use (L)	Adjuvant	Week 8	n	65	66			
			LS Mean	-13.07	-1.395	-11.68		
			SEM	4.231	4.122	3.161		
			95% CI	(-21.4,-4.7)	(-9.5, 6.7)	(-17.9,-5.5)		
					Pr >  t			0.0003
		Week 16	n	60	51			
			LS Mean	-7.141	-3.142	-3.999		
			SEM	4.310	4.333	3.376		
			95% CI	(-15.6, 1.4)	(-11.7, 5.4)	(-10.6, 2.6)		
					Pr >  t			0.2371
		Week 24	n	51	42			
			LS Mean	-8.971	-2.388	-6.582		
			SEM	4.372	4.423	3.583		
			95% CI	(-17.6,-0.4)	(-11.1, 6.3)	(-13.6, 0.5)		
					Pr >  t			0.0669
		Week 32	n	46	36			
			LS Mean	-7.500	-6.145	-1.356		
			SEM	4.449	4.542	3.747		
			95% CI	(-16.3, 1.3)	(-15.1, 2.8)	(-8.7, 6.0)		
					Pr >  t			0.7176
		Week 40	n	40	33			
			LS Mean	-7.332	-6.408	-0.923		
			SEM	4.518	4.595	3.887		
			95% CI	(-16.2, 1.6)	(-15.5, 2.6)	(-8.6, 6.7)		
			Pr >  t			0.8123		
Week 48	n	37	28					
	LS Mean	-5.747	-7.394	1.647				
	SEM	4.556	4.699	4.054				
	95% CI	(-14.7, 3.2)	(-16.6, 1.9)	(-6.3, 9.6)				
			Pr >  t			0.6846		
Week 56	n	33	23					
	LS Mean	-7.858	-5.780	-2.078				
	SEM	4.621	4.842	4.290				

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64		95% CI	(-17.0, 1.2)	(-15.3, 3.7)	(-10.5, 6.3)
		Pr >  t			0.6283
		n	26	20	
		LS Mean	-10.74	-4.801	-5.941
		SEM	4.768	4.959	4.575
Week 72		95% CI	(-20.1,-1.4)	(-14.6, 5.0)	(-14.9, 3.0)
		Pr >  t			0.1945
		n	28	17	
		LS Mean	-8.394	-2.025	-6.369
		SEM	4.721	5.107	4.685
Week 84		95% CI	(-17.7, 0.9)	(-12.1, 8.0)	(-15.6, 2.8)
		Pr >  t			0.1744
		n	23	17	
		LS Mean	-11.38	-3.851	-7.533
		SEM	4.857	5.110	4.826
Week 96		95% CI	(-20.9,-1.8)	(-13.9, 6.2)	(-17.0, 1.9)
		Pr >  t			0.1190
		n	23	11	
		LS Mean	-8.699	-9.085	0.386
		SEM	4.859	5.615	5.359
Week 108		95% CI	(-18.3, 0.9)	(-20.1, 1.9)	(-10.1,10.9)
		Pr >  t			0.9426
		n	15	13	
		LS Mean	-7.588	-4.228	-3.359
		SEM	5.245	5.402	5.503
Week 120		95% CI	(-17.9, 2.7)	(-14.8, 6.4)	(-14.2, 7.4)
		Pr >  t			0.5417
		n	16	9	
		LS Mean	-3.299	-5.158	1.859
		SEM	5.181	5.910	5.944
Week 132		95% CI	(-13.5, 6.9)	(-16.8, 6.4)	(-9.8,13.5)
		Pr >  t			0.7546
		n	14	5	
		LS Mean	-12.70	-8.114	-4.585
		SEM	5.320	7.048	7.179
Week 144		95% CI	(-23.2,-2.2)	(-22.0, 5.7)	(-18.7, 9.5)
		Pr >  t			0.5232
		n	8	3	
		LS Mean	-8.370	-3.833	-4.537
		SEM	6.098	8.474	9.085

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-20.3, 3.6)	(-20.5,12.8)	(-22.4,13.3)
		Pr >  t			0.6176
	Week 156	n	7	2	
		LS Mean	-13.97	-11.89	-2.078
		SEM	6.334	9.967	10.63
		95% CI	(-26.4,-1.5)	(-31.5, 7.7)	(-22.9,18.8)
		Pr >  t			0.8451
	Week 168	n	4	2	
		LS Mean	-10.92	-3.552	-7.363
		SEM	7.602	9.967	11.43
		95% CI	(-25.8, 4.0)	(-23.1,16.0)	(-29.8,15.1)
		Pr >  t			0.5197
	Week 180	n	1	1	
		LS Mean	3.693	-2.181	5.874
		SEM	13.47	13.47	18.34
		95% CI	(-22.7,30.1)	(-28.6,24.3)	(-30.1,41.9)
		Pr >  t			0.7488
	Week 192	n	1	1	
		LS Mean	-12.97	-2.181	-10.79
		SEM	13.47	13.47	18.34
		95% CI	(-39.4,13.5)	(-28.6,24.3)	(-46.8,25.2)
		Pr >  t			0.5566
Neoadjuvant	Week 8	n	18	17	
		LS Mean	-8.601	-3.404	-5.197
		SEM	5.011	5.372	7.372
		95% CI	(-18.6, 1.4)	(-14.2, 7.4)	(-20.0, 9.6)
		Pr >  t			0.4838
	Week 16	n	17	11	
		LS Mean	-8.768	-5.992	-2.776
		SEM	5.101	6.216	8.044
		95% CI	(-19.0, 1.4)	(-18.4, 6.4)	(-18.8,13.3)
		Pr >  t			0.7311
	Week 24	n	15	5	
		LS Mean	-5.526	-3.654	-1.872
		SEM	5.305	8.237	9.806
		95% CI	(-16.1, 5.1)	(-19.9,12.6)	(-21.3,17.6)
		Pr >  t			0.8489
	Week 32	n	13	5	
		LS Mean	-7.149	-6.988	-0.160
		SEM	5.548	8.237	9.952

Subgroup	Time Window	Alpelisib 300mg qd + Fulv			Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172		
Week 40	95% CI	(-18.2, 3.9)	(-23.3, 9.3)	(-19.9,19.6)	
	Pr >  t			0.9872	
	n	11	5		
	LS Mean	-6.148	-0.320	-5.828	
	SEM	5.828	8.237	10.11	
Week 48	95% CI	(-17.7, 5.4)	(-16.6,16.0)	(-25.8,14.2)	
	Pr >  t			0.5653	
	n	11	2		
	LS Mean	-14.40	-0.886	-13.51	
	SEM	5.832	11.51	12.91	
Week 56	95% CI	(-26.0,-2.8)	(-23.6,21.8)	(-39.0,12.0)	
	Pr >  t			0.2968	
	n	8	2		
	LS Mean	-6.300	-0.886	-5.415	
	SEM	6.424	11.51	13.19	
Week 64	95% CI	(-19.0, 6.4)	(-23.6,21.8)	(-31.4,20.6)	
	Pr >  t			0.6819	
	n	7	3		
	LS Mean	-0.790	-2.016	1.225	
	SEM	6.706	9.861	11.94	
Week 72	95% CI	(-14.1,12.5)	(-21.5,17.5)	(-22.4,24.8)	
	Pr >  t			0.9184	
	n	7	3		
	LS Mean	-7.145	-2.016	-5.130	
	SEM	6.720	9.861	11.94	
Week 84	95% CI	(-20.4, 6.2)	(-21.5,17.5)	(-28.7,18.5)	
	Pr >  t			0.6680	
	n	7	2		
	LS Mean	-16.67	-0.886	-15.78	
	SEM	6.720	11.51	13.33	
Week 96	95% CI	(-30.0,-3.4)	(-23.6,21.8)	(-42.1,10.5)	
	Pr >  t			0.2381	
	n	6	3		
	LS Mean	-8.172	-2.016	-6.156	
	SEM	7.075	9.861	12.14	
Week 108	95% CI	(-22.2, 5.8)	(-21.5,17.5)	(-30.1,17.8)	
	Pr >  t			0.6129	
	n	7	2		
Week 108	LS Mean	-7.147	-18.57	11.420	
	SEM	6.720	11.49	13.31	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169		Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	Pr >  t		
No Prior Use	Week 120	n	6	1	
		LS Mean	-19.28	-4.275	-15.01
		SEM	7.075	15.43	16.98
	Week 132	95% CI	(-33.3,-5.3)	(-34.7,26.2)	(-48.5,18.5)
		Pr >  t			0.3778
		n	4		
	Week 144	LS Mean	-15.71	NE	NE
		SEM	8.190	NE	NE
		95% CI	(-31.9, 0.5)	NE	NE
	Week 156	Pr >  t			NE
		n	5		
		LS Mean	-19.43	NE	NE
	Week 8	SEM	7.543	NE	NE
		95% CI	(-34.3,-4.5)	NE	NE
		Pr >  t			NE
	Week 16	n	3		
LS Mean		-2.924	NE	NE	
SEM		9.171	NE	NE	
Week 24	95% CI	(-21.0,15.2)	NE	NE	
	Pr >  t			NE	
	n	59	57		
Week 32	LS Mean	-0.738	2.993	-3.731	
	SEM	3.505	3.677	3.691	
	95% CI	(-7.7, 6.2)	(-4.3,10.3)	(-11.0, 3.6)	
Week 16	Pr >  t			0.3134	
	n	47	44		
	LS Mean	-1.982	1.667	-3.649	
Week 24	SEM	3.663	3.875	4.034	
	95% CI	(-9.2, 5.3)	(-6.0, 9.3)	(-11.6, 4.3)	
	Pr >  t			0.3666	
Week 32	n	39	34		
	LS Mean	-8.606	2.166	-10.77	
	SEM	3.816	4.110	4.366	
Week 16	95% CI	(-16.1,-1.1)	(-5.9,10.3)	(-19.4,-2.2)	
	Pr >  t			0.0142	
	n	27	32		
Week 32	LS Mean	-3.035	0.751	-3.786	
	SEM	4.156	4.159	4.688	

Subgroup	Time Window	Alpelisib 300mg qd + Fulv		Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		N=169	N=172	
Week 40	95% CI	(-11.2, 5.2)	(-7.5, 9.0)	(-13.0, 5.4)
	Pr >  t			0.4199
	n	24	24	
	LS Mean	-0.194	-0.173	-0.022
	SEM	4.271	4.431	5.018
Week 48	95% CI	(-8.6, 8.2)	(-8.9, 8.6)	(-9.9, 9.8)
	Pr >  t			0.9966
	n	21	21	
	LS Mean	-3.857	2.350	-6.207
	SEM	4.409	4.570	5.262
Week 56	95% CI	(-12.5, 4.8)	(-6.6, 11.3)	(-16.5, 4.1)
	Pr >  t			0.2388
	n	18	20	
	LS Mean	-3.793	2.097	-5.890
	SEM	4.578	4.625	5.458
Week 64	95% CI	(-12.8, 5.2)	(-7.0, 11.2)	(-16.6, 4.8)
	Pr >  t			0.2811
	n	14	19	
	LS Mean	-3.655	0.168	-3.824
	SEM	4.899	4.683	5.785
Week 72	95% CI	(-13.3, 6.0)	(-9.0, 9.4)	(-15.2, 7.5)
	Pr >  t			0.5089
	n	13	15	
	LS Mean	-5.622	1.497	-7.119
	SEM	5.008	4.972	6.112
Week 84	95% CI	(-15.5, 4.2)	(-8.3, 11.3)	(-19.1, 4.9)
	Pr >  t			0.2446
	n	10	14	
	LS Mean	-5.584	-3.755	-1.828
	SEM	5.466	5.063	6.538
Week 96	95% CI	(-16.3, 5.2)	(-13.7, 6.2)	(-14.7, 11.0)
	Pr >  t			0.7799
	n	6	10	
	LS Mean	-3.674	-5.774	2.100
	SEM	6.522	5.585	7.830
Week 108	95% CI	(-16.5, 9.1)	(-16.7, 5.2)	(-13.3, 17.5)
	Pr >  t			0.7887
	n	4	6	
	LS Mean	-9.447	1.327	-10.77
	SEM	7.671	6.635	9.494

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 120	95% CI	(-24.5, 5.6)	(-11.7,14.4)	(-29.4, 7.9)
	Pr >  t			0.2569
	n	6	6	
	LS Mean	-9.649	3.545	-13.19
	SEM	6.523	6.638	8.613
Week 132	95% CI	(-22.5, 3.2)	(-9.5,16.6)	(-30.1, 3.7)
	Pr >  t			0.1261
	n	2	3	
	LS Mean	-16.05	-5.984	-10.07
	SEM	10.31	8.694	13.01
Week 144	95% CI	(-36.3, 4.2)	(-23.1,11.1)	(-35.6,15.5)
	Pr >  t			0.4392
	n	2	2	
	LS Mean	-7.414	1.461	-8.875
	SEM	10.28	10.37	14.20
Week 156	95% CI	(-27.6,12.8)	(-18.9,21.8)	(-36.8,19.0)
	Pr >  t			0.5321
	n		1	
	LS Mean	NE	0.698	NE
	SEM	NE	14.19	NE
	95% CI	NE	(-27.2,28.6)	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>	
Estrogen Receptor Status (L)	Negative	Week 8	n	2			
			LS Mean	-16.67	NE	NE	
			SEM	11.78	NE	NE	
			95% CI	(-67.4,34.0)	NE	NE	
					Pr >  t		NE
		Week 16	n	2			
			LS Mean	0.000	NE	NE	
			SEM	11.78	NE	NE	
			95% CI	(-50.7,50.7)	NE	NE	
					Pr >  t		NE
		Week 24	n	1			
			LS Mean	-0.000	NE	NE	
			SEM	28.86	NE	NE	
			95% CI	( -124, 124)	NE	NE	
					Pr >  t		NE
		Week 32	n	1			
			LS Mean	-0.000	NE	NE	
			SEM	28.86	NE	NE	
			95% CI	( -124, 124)	NE	NE	
					Pr >  t		NE
		Week 40	n	1			
			LS Mean	-16.67	NE	NE	
			SEM	28.86	NE	NE	
			95% CI	( -141, 108)	NE	NE	
					Pr >  t		NE
		Week 48	n	1			
			LS Mean	0.000	NE	NE	
			SEM	28.86	NE	NE	
95% CI	( -124, 124)		NE	NE			
			Pr >  t		NE		
Week 56	n	1					
	LS Mean	0.000	NE	NE			
	SEM	28.86	NE	NE			

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-124, 124)	NE	NE
		Pr >  t			NE
	Week 72	n	1		
		LS Mean	-0.000	NE	NE
		SEM	28.86	NE	NE
		95% CI	(-124, 124)	NE	NE
		Pr >  t			NE
	Week 84	n	1		
		LS Mean	-0.000	NE	NE
		SEM	28.86	NE	NE
		95% CI	(-124, 124)	NE	NE
		Pr >  t			NE
	Week 96	n	1		
		LS Mean	-0.000	NE	NE
		SEM	28.86	NE	NE
		95% CI	(-124, 124)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	140	140	
		LS Mean	-6.094	1.478	-7.571
		SEM	2.572	2.609	2.266
		95% CI	(-11.2,-1.0)	(-3.7, 6.6)	(-12.0,-3.1)
		Pr >  t			0.0009
	Week 16	n	122	107	
		LS Mean	-3.999	-0.065	-3.935
		SEM	2.636	2.739	2.443
		95% CI	(-9.2, 1.2)	(-5.4, 5.3)	(-8.7, 0.9)
		Pr >  t			0.1077
	Week 24	n	104	81	
		LS Mean	-6.728	0.793	-7.521
		SEM	2.698	2.867	2.639
		95% CI	(-12.0,-1.4)	(-4.8, 6.4)	(-12.7,-2.3)
		Pr >  t			0.0045
	Week 32	n	85	73	
		LS Mean	-4.114	-1.909	-2.206
		SEM	2.799	2.924	2.776
		95% CI	(-9.6, 1.4)	(-7.7, 3.8)	(-7.7, 3.2)
		Pr >  t			0.4270
	Week 40	n	74	62	
		LS Mean	-2.917	-1.942	-0.975
		SEM	2.860	3.013	2.923

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-8.5, 2.7)	(-7.9, 4.0)	(-6.7, 4.8)
	Pr >  t			0.7387
Week 48	n	68	51	
	LS Mean	-4.684	-1.717	-2.966
	SEM	2.899	3.123	3.073
	95% CI	(-10.4, 1.0)	(-7.8, 4.4)	(-9.0, 3.1)
	Pr >  t			0.3346
Week 56	n	58	45	
	LS Mean	-4.575	-0.866	-3.709
	SEM	2.978	3.202	3.230
	95% CI	(-10.4, 1.3)	(-7.2, 5.4)	(-10.0, 2.6)
	Pr >  t			0.2511
Week 64	n	47	42	
	LS Mean	-5.163	-1.232	-3.931
	SEM	3.098	3.249	3.388
	95% CI	(-11.2, 0.9)	(-7.6, 5.1)	(-10.6, 2.7)
	Pr >  t			0.2462
Week 72	n	47	35	
	LS Mean	-5.314	0.753	-6.066
	SEM	3.100	3.381	3.516
	95% CI	(-11.4, 0.8)	(-5.9, 7.4)	(-13.0, 0.8)
	Pr >  t			0.0847
Week 84	n	39	33	
	LS Mean	-8.696	-2.362	-6.334
	SEM	3.233	3.428	3.671
	95% CI	(-15.0, -2.3)	(-9.1, 4.4)	(-13.5, 0.9)
	Pr >  t			0.0846
Week 96	n	34	24	
	LS Mean	-5.104	-5.524	0.421
	SEM	3.333	3.718	4.029
	95% CI	(-11.6, 1.4)	(-12.8, 1.8)	(-7.5, 8.3)
	Pr >  t			0.9169
Week 108	n	26	21	
	LS Mean	-4.945	-1.938	-3.007
	SEM	3.575	3.861	4.353
	95% CI	(-12.0, 2.1)	(-9.5, 5.6)	(-11.5, 5.5)
	Pr >  t			0.4898
Week 120	n	28	16	
	LS Mean	-5.638	-0.197	-5.440
	SEM	3.501	4.195	4.600

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-12.5, 1.2)	(-8.4, 8.0)	(-14.5, 3.6)
		Pr >  t			0.2371
	Week 132	n	20	8	
		LS Mean	-10.71	-5.694	-5.016
		SEM	3.852	5.360	5.902
		95% CI	(-18.3,-3.2)	(-16.2, 4.8)	(-16.6, 6.6)
		Pr >  t			0.3955
	Week 144	n	15	5	
		LS Mean	-9.100	-0.295	-8.805
		SEM	4.211	6.493	7.158
		95% CI	(-17.4,-0.8)	(-13.0,12.4)	(-22.8, 5.2)
		Pr >  t			0.2189
	Week 156	n	10	3	
		LS Mean	-7.349	-5.907	-1.442
		SEM	4.872	8.111	8.988
		95% CI	(-16.9, 2.2)	(-21.8,10.0)	(-19.1,16.2)
		Pr >  t			0.8725
	Week 168	n	4	2	
		LS Mean	-7.693	0.142	-7.834
		SEM	7.095	9.765	11.70
		95% CI	(-21.6, 6.2)	(-19.0,19.3)	(-30.8,15.1)
		Pr >  t			0.5033
	Week 180	n	1	1	
		LS Mean	6.920	1.612	5.308
		SEM	13.54	13.55	18.92
		95% CI	(-19.6,33.5)	(-25.0,28.2)	(-31.8,42.4)
		Pr >  t			0.7792
	Week 192	n	1	1	
		LS Mean	-9.740	1.612	-11.35
		SEM	13.54	13.55	18.92
		95% CI	(-36.3,16.8)	(-25.0,28.2)	(-48.5,25.8)
		Pr >  t			0.5487

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final





**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
Progesterone Receptor Status (L)	Negative	Week 8	n	42	35	
			LS Mean	-5.802	-2.269	-3.533
			SEM	4.551	4.966	4.715
			95% CI	(-14.8, 3.2)	(-12.1, 7.6)	(-12.9, 5.8)
		Pr >  t			0.4553	
		Week 16	n	35	22	
			LS Mean	-3.514	-0.247	-3.268
			SEM	4.711	5.517	5.275
			95% CI	(-12.9, 5.8)	(-11.2, 10.7)	(-13.7, 7.2)
		Pr >  t			0.5366	
		Week 24	n	28	16	
			LS Mean	-7.993	-0.820	-7.173
			SEM	4.862	5.846	5.777
			95% CI	(-17.6, 1.6)	(-12.4, 10.7)	(-18.6, 4.2)
		Pr >  t			0.2160	
		Week 32	n	22	16	
			LS Mean	-4.192	-1.030	-3.163
			SEM	5.114	5.862	5.948
			95% CI	(-14.3, 5.9)	(-12.6, 10.6)	(-14.9, 8.6)
		Pr >  t			0.5955	
		Week 40	n	19	12	
			LS Mean	-1.039	-4.661	3.621
			SEM	5.249	6.201	6.401
			95% CI	(-11.4, 9.3)	(-16.9, 7.6)	(-9.0, 16.2)
		Pr >  t			0.5721	
		Week 48	n	16	10	
			LS Mean	-9.526	-1.384	-8.141
			SEM	5.420	6.468	6.796
95% CI	(-20.2, 1.2)		(-14.1, 11.4)	(-21.5, 5.2)		
Pr >  t			0.2320			
Week 56	n	14	7			
	LS Mean	-8.613	-0.443	-8.170		
	SEM	5.573	7.072	7.495		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-19.6, 2.4)	(-14.4,13.5)	(-22.9, 6.6)
		Pr >  t			0.2765
	Week 64	n	8	7	
		LS Mean	-0.728	-3.001	2.273
		SEM	6.355	7.072	8.105
		95% CI	(-13.2,11.8)	(-16.9,10.9)	(-13.7,18.2)
		Pr >  t			0.7793
	Week 72	n	12	6	
		LS Mean	-5.746	4.666	-10.41
		SEM	5.762	7.381	7.928
		95% CI	(-17.1, 5.6)	(-9.9,19.2)	(-26.0, 5.2)
		Pr >  t			0.1900
	Week 84	n	8	5	
		LS Mean	-11.43	-5.340	-6.085
		SEM	6.394	7.784	8.739
		95% CI	(-24.0, 1.2)	(-20.7,10.0)	(-23.3,11.1)
		Pr >  t			0.4867
	Week 96	n	5	5	
		LS Mean	-7.921	-2.006	-5.914
		SEM	7.357	7.784	9.465
		95% CI	(-22.4, 6.6)	(-17.3,13.3)	(-24.5,12.7)
		Pr >  t			0.5325
	Week 108	n	7	5	
		LS Mean	-6.011	1.326	-7.337
		SEM	6.642	7.784	8.922
		95% CI	(-19.1, 7.1)	(-14.0,16.6)	(-24.9,10.2)
		Pr >  t			0.4115
	Week 120	n	5	3	
		LS Mean	-11.14	6.694	-17.84
		SEM	7.366	9.190	10.66
		95% CI	(-25.6, 3.3)	(-11.4,24.8)	(-38.8, 3.1)
		Pr >  t			0.0951
	Week 132	n	2	2	
		LS Mean	-19.04	-10.93	-8.107
		SEM	10.33	10.61	13.93
		95% CI	(-39.4, 1.3)	(-31.8, 9.9)	(-35.5,19.3)
		Pr >  t			0.5610
	Week 144	n	2		
		LS Mean	-15.34	NE	NE
		SEM	10.33	NE	NE

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-35.7, 5.0)	NE	NE
		Pr >  t			NE
	Week 156	n	2		
		LS Mean	-2.314	NE	NE
		SEM	10.35	NE	NE
		95% CI	(-22.7,18.0)	NE	NE
		Pr >  t			NE
	Week 168	n	1		
		LS Mean	-6.010	NE	NE
		SEM	13.95	NE	NE
		95% CI	(-33.5,21.4)	NE	NE
		Pr >  t			NE
Positive	Week 8	n	98	104	
		LS Mean	-5.347	3.246	-8.592
		SEM	3.196	3.170	2.616
		95% CI	(-11.6, 0.9)	(-3.0, 9.5)	(-13.7,-3.4)
		Pr >  t			0.0011
	Week 16	n	87	84	
		LS Mean	-3.537	0.520	-4.057
		SEM	3.260	3.263	2.783
		95% CI	(-10.0, 2.9)	(-5.9, 6.9)	(-9.5, 1.4)
		Pr >  t			0.1456
	Week 24	n	76	65	
		LS Mean	-5.553	1.768	-7.321
		SEM	3.331	3.398	2.987
		95% CI	(-12.1, 1.0)	(-4.9, 8.5)	(-13.2,-1.5)
		Pr >  t			0.0145
	Week 32	n	62	57	
		LS Mean	-3.388	-1.595	-1.793
		SEM	3.434	3.477	3.163
		95% CI	(-10.1, 3.4)	(-8.4, 5.2)	(-8.0, 4.4)
		Pr >  t			0.5711
	Week 40	n	54	50	
		LS Mean	-2.940	-0.684	-2.255
		SEM	3.503	3.559	3.314
		95% CI	(-9.8, 4.0)	(-7.7, 6.3)	(-8.8, 4.3)
		Pr >  t			0.4965
	Week 48	n	52	41	
		LS Mean	-2.136	-1.121	-1.015
		SEM	3.522	3.678	3.462

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-9.1, 4.8)	(-8.4, 6.1)	(-7.8, 5.8)
	Pr >  t			0.7694
Week 56	n	44	38	
	LS Mean	-2.618	-0.178	-2.440
	SEM	3.613	3.730	3.611
	95% CI	(-9.7, 4.5)	(-7.5, 7.2)	(-9.5, 4.6)
	Pr >  t			0.4994
Week 64	n	39	35	
	LS Mean	-5.224	-0.171	-5.053
	SEM	3.688	3.787	3.745
	95% CI	(-12.5, 2.0)	(-7.6, 7.3)	(-12.4, 2.3)
	Pr >  t			0.1776
Week 72	n	36	29	
	LS Mean	-4.488	0.641	-5.129
	SEM	3.741	3.928	3.941
	95% CI	(-11.8, 2.9)	(-7.1, 8.4)	(-12.9, 2.6)
	Pr >  t			0.1934
Week 84	n	32	28	
	LS Mean	-7.120	-1.096	-6.023
	SEM	3.832	3.958	4.049
	95% CI	(-14.6, 0.4)	(-8.9, 6.7)	(-14.0, 1.9)
	Pr >  t			0.1372
Week 96	n	30	19	
	LS Mean	-3.753	-5.798	2.046
	SEM	3.874	4.334	4.462
	95% CI	(-11.4, 3.9)	(-14.3, 2.7)	(-6.7, 10.8)
	Pr >  t			0.6467
Week 108	n	18	16	
	LS Mean	-3.716	-2.285	-1.431
	SEM	4.373	4.541	5.078
	95% CI	(-12.3, 4.9)	(-11.2, 6.6)	(-11.4, 8.5)
	Pr >  t			0.7781
Week 120	n	23	13	
	LS Mean	-3.654	-1.161	-2.494
	SEM	4.108	4.821	5.123
	95% CI	(-11.7, 4.4)	(-10.6, 8.3)	(-12.5, 7.6)
	Pr >  t			0.6265
Week 132	n	18	6	
	LS Mean	-8.832	-3.189	-5.642
	SEM	4.374	6.287	6.686

Subgroup	Time Window		Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		95% CI	(-17.4,-0.2)	(-15.5, 9.1)	(-18.8, 7.5)
		Pr >  t			0.3989
	Week 144	n	13	5	
		LS Mean	-7.307	0.408	-7.715
		SEM	4.780	6.754	7.394
		95% CI	(-16.7, 2.1)	(-12.8,13.7)	(-22.2, 6.8)
		Pr >  t			0.2969
	Week 156	n	8	3	
		LS Mean	-7.870	-5.119	-2.751
		SEM	5.627	8.344	9.344
		95% CI	(-18.9, 3.2)	(-21.5,11.3)	(-21.1,15.6)
		Pr >  t			0.7685
	Week 168	n	3	2	
		LS Mean	-7.572	0.989	-8.561
		SEM	8.312	9.983	12.44
		95% CI	(-23.9, 8.7)	(-18.6,20.6)	(-33.0,15.9)
		Pr >  t			0.4915
	Week 180	n	1	1	
		LS Mean	7.821	2.475	5.346
		SEM	13.76	13.76	19.09
		95% CI	(-19.2,34.8)	(-24.5,29.5)	(-32.1,42.8)
		Pr >  t			0.7795
	Week 192	n	1	1	
		LS Mean	-8.839	2.475	-11.31
		SEM	13.76	13.76	19.09
		95% CI	(-35.8,18.2)	(-24.5,29.5)	(-48.8,26.2)
		Pr >  t			0.5536

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis  
-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

<b>Subgroup</b>		<b>Time Window</b>		<b>Alpelisib 300mg qd + Fulv N=169</b>	<b>Placebo qd + Fulv N=172</b>	<b>Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv</b>
ER and PR Status (L)	Both positive	Week 8	n	96	104	
			LS Mean	-5.178	3.279	-8.457
			SEM	3.219	3.184	2.639
			95% CI	(-11.5, 1.2)	(-3.0, 9.5)	(-13.6,-3.3)
			Pr >  t			0.0015
		Week 16	n	85	84	
			LS Mean	-3.715	0.556	-4.271
			SEM	3.285	3.277	2.808
			95% CI	(-10.2, 2.8)	(-5.9, 7.0)	(-9.8, 1.2)
			Pr >  t			0.1290
		Week 24	n	75	65	
			LS Mean	-5.654	1.796	-7.450
			SEM	3.354	3.412	3.008
			95% CI	(-12.3, 0.9)	(-4.9, 8.5)	(-13.4,-1.5)
			Pr >  t			0.0136
		Week 32	n	61	57	
			LS Mean	-3.469	-1.567	-1.902
			SEM	3.460	3.491	3.188
			95% CI	(-10.3, 3.3)	(-8.4, 5.3)	(-8.2, 4.4)
			Pr >  t			0.5509
		Week 40	n	53	50	
			LS Mean	-2.896	-0.656	-2.240
			SEM	3.531	3.573	3.342
			95% CI	(-9.8, 4.0)	(-7.7, 6.4)	(-8.8, 4.3)
			Pr >  t			0.5028
		Week 48	n	51	41	
			LS Mean	-2.404	-1.094	-1.310
			SEM	3.551	3.692	3.489
95% CI	(-9.4, 4.6)		(-8.4, 6.2)	(-8.2, 5.5)		
Pr >  t				0.7074		
Week 56	n	43	38			
	LS Mean	-2.931	-0.150	-2.780		
	SEM	3.645	3.744	3.642		

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 64	95% CI	(-10.1, 4.2)	(-7.5, 7.2)	(-9.9, 4.4)
	Pr >  t			0.4454
	n	39	35	
	LS Mean	-5.324	-0.143	-5.180
	SEM	3.707	3.801	3.762
Week 72	95% CI	(-12.6, 2.0)	(-7.6, 7.3)	(-12.6, 2.2)
	Pr >  t			0.1689
	n	35	29	
	LS Mean	-4.615	0.669	-5.285
	SEM	3.780	3.943	3.977
Week 84	95% CI	(-12.0, 2.8)	(-7.1, 8.4)	(-13.1, 2.5)
	Pr >  t			0.1842
	n	31	28	
	LS Mean	-7.340	-1.069	-6.271
	SEM	3.875	3.972	4.090
Week 96	95% CI	(-15.0, 0.3)	(-8.9, 6.7)	(-14.3, 1.8)
	Pr >  t			0.1255
	n	29	19	
	LS Mean	-3.863	-5.770	1.907
	SEM	3.920	4.349	4.503
Week 108	95% CI	(-11.6, 3.8)	(-14.3, 2.8)	(-6.9, 10.7)
	Pr >  t			0.6720
	n	18	16	
	LS Mean	-3.819	-2.260	-1.559
	SEM	4.393	4.556	5.096
Week 120	95% CI	(-12.4, 4.8)	(-11.2, 6.7)	(-11.6, 8.4)
	Pr >  t			0.7597
	n	23	13	
	LS Mean	-3.755	-1.134	-2.622
	SEM	4.127	4.837	5.141
Week 132	95% CI	(-11.9, 4.4)	(-10.6, 8.4)	(-12.7, 7.5)
	Pr >  t			0.6102
	n	18	6	
	LS Mean	-8.937	-3.164	-5.772
	SEM	4.393	6.305	6.707
Week 144	95% CI	(-17.6, -0.3)	(-15.5, 9.2)	(-18.9, 7.4)
	Pr >  t			0.3896
	n	13	5	
	LS Mean	-7.411	0.432	-7.843
	SEM	4.799	6.773	7.415

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Positive Negative	Week 156	95% CI	(-16.8, 2.0)	(-12.9,13.7)	(-22.4, 6.7)
		Pr >  t			0.2904
		n	8	3	
		LS Mean	-7.974	-5.096	-2.878
		SEM	5.647	8.366	9.370
	Week 168	95% CI	(-19.1, 3.1)	(-21.5,11.3)	(-21.3,15.5)
		Pr >  t			0.7588
		n	3	2	
		LS Mean	-7.676	1.012	-8.688
		SEM	8.336	10.01	12.47
	Week 180	95% CI	(-24.0, 8.7)	(-18.6,20.6)	(-33.2,15.8)
		Pr >  t			0.4862
		n	1	1	
		LS Mean	7.724	2.490	5.234
		SEM	13.79	13.79	19.14
	Week 192	95% CI	(-19.3,34.8)	(-24.6,29.6)	(-32.3,42.8)
		Pr >  t			0.7846
		n	1	1	
		LS Mean	-8.936	2.490	-11.43
		SEM	13.79	13.79	19.14
	Week 8	95% CI	(-36.0,18.1)	(-24.6,29.6)	(-49.0,26.1)
		Pr >  t			0.5506
		n	42	35	
		LS Mean	-5.802	-2.269	-3.533
SEM		4.551	4.966	4.715	
Week 16	95% CI	(-14.8, 3.2)	(-12.1, 7.6)	(-12.9, 5.8)	
	Pr >  t			0.4553	
	n	35	22		
	LS Mean	-3.514	-0.247	-3.268	
	SEM	4.711	5.517	5.275	
Week 24	95% CI	(-12.9, 5.8)	(-11.2,10.7)	(-13.7, 7.2)	
	Pr >  t			0.5366	
	n	28	16		
	LS Mean	-7.993	-0.820	-7.173	
	SEM	4.862	5.846	5.777	
Week 32	95% CI	(-17.6, 1.6)	(-12.4,10.7)	(-18.6, 4.2)	
	Pr >  t			0.2160	
	n	22	16		
	LS Mean	-4.192	-1.030	-3.163	
	SEM	5.114	5.862	5.948	



Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
		95% CI	(-14.3, 5.9)	(-12.6,10.6)	(-14.9, 8.6)
		Pr >  t			0.5955
	Week 40	n	19	12	
		LS Mean	-1.039	-4.661	3.621
		SEM	5.249	6.201	6.401
		95% CI	(-11.4, 9.3)	(-16.9, 7.6)	(-9.0,16.2)
		Pr >  t			0.5721
	Week 48	n	16	10	
		LS Mean	-9.526	-1.384	-8.141
		SEM	5.420	6.468	6.796
		95% CI	(-20.2, 1.2)	(-14.1,11.4)	(-21.5, 5.2)
		Pr >  t			0.2320
	Week 56	n	14	7	
		LS Mean	-8.613	-0.443	-8.170
		SEM	5.573	7.072	7.495
		95% CI	(-19.6, 2.4)	(-14.4,13.5)	(-22.9, 6.6)
		Pr >  t			0.2765
	Week 64	n	8	7	
		LS Mean	-0.728	-3.001	2.273
		SEM	6.355	7.072	8.105
		95% CI	(-13.2,11.8)	(-16.9,10.9)	(-13.7,18.2)
		Pr >  t			0.7793
	Week 72	n	12	6	
		LS Mean	-5.746	4.666	-10.41
		SEM	5.762	7.381	7.928
		95% CI	(-17.1, 5.6)	(-9.9,19.2)	(-26.0, 5.2)
		Pr >  t			0.1900
	Week 84	n	8	5	
		LS Mean	-11.43	-5.340	-6.085
		SEM	6.394	7.784	8.739
		95% CI	(-24.0, 1.2)	(-20.7,10.0)	(-23.3,11.1)
		Pr >  t			0.4867
	Week 96	n	5	5	
		LS Mean	-7.921	-2.006	-5.914
		SEM	7.357	7.784	9.465
		95% CI	(-22.4, 6.6)	(-17.3,13.3)	(-24.5,12.7)
		Pr >  t			0.5325
	Week 108	n	7	5	
		LS Mean	-6.011	1.326	-7.337
		SEM	6.642	7.784	8.922

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	95% CI	(-19.1, 7.1)	(-14.0,16.6)	(-24.9,10.2)
	Pr >  t			0.4115
Week 120	n	5	3	
	LS Mean	-11.14	6.694	-17.84
	SEM	7.366	9.190	10.66
	95% CI	(-25.6, 3.3)	(-11.4,24.8)	(-38.8, 3.1)
	Pr >  t			0.0951
Week 132	n	2	2	
	LS Mean	-19.04	-10.93	-8.107
	SEM	10.33	10.61	13.93
	95% CI	(-39.4, 1.3)	(-31.8, 9.9)	(-35.5,19.3)
	Pr >  t			0.5610
Week 144	n	2		
	LS Mean	-15.34	NE	NE
	SEM	10.33	NE	NE
	95% CI	(-35.7, 5.0)	NE	NE
	Pr >  t			NE
Week 156	n	2		
	LS Mean	-2.314	NE	NE
	SEM	10.35	NE	NE
	95% CI	(-22.7,18.0)	NE	NE
	Pr >  t			NE
Week 168	n	1		
	LS Mean	-6.010	NE	NE
	SEM	13.95	NE	NE
	95% CI	(-33.5,21.4)	NE	NE
	Pr >  t			NE

-Only subjects with baseline scores and at least one non-missing post-baseline assessments will be included in analysis

-The following factors and covariates are included in the mixed effects model: treatment, time of visit (in weeks counting from the time of randomization to the time of a particular post baseline measurement), treatment by visit interaction, and baseline score.

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Final

**Table 11.2-18i**  
**Linear mixed effects model analysis on change from baseline in EORTC QLQ-C30 Social Functioning scale score**  
**in subgroups i**  
**(Full Analysis Set, PIK3CA mutant cohort)**

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference	
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv	
Visceral Disease (L)	No	Week 8	n	69	60	
			LS Mean	-0.546	5.337	-5.883
			SEM	6.923	7.155	3.070
			95% CI	(-14.3,13.2)	(-8.9,19.5)	(-11.9, 0.2)
				Pr >  t		0.0564
		Week 16	n	59	49	
			LS Mean	-2.020	4.038	-6.058
			SEM	6.949	7.212	3.276
			95% CI	(-15.8,11.8)	(-10.3,18.4)	(-12.5, 0.4)
			Pr >  t			0.0655
		Week 24	n	54	41	
			LS Mean	-1.879	6.880	-8.759
			SEM	6.963	7.266	3.436
			95% CI	(-15.7,11.9)	(-7.5,21.3)	(-15.5,-2.0)
			Pr >  t			0.0112
		Week 32	n	48	37	
			LS Mean	-1.153	2.198	-3.351
			SEM	6.986	7.296	3.557
			95% CI	(-15.0,12.7)	(-12.3,16.7)	(-10.3, 3.6)
			Pr >  t			0.3468
		Week 40	n	43	33	
			LS Mean	0.798	1.648	-0.850
			SEM	7.009	7.333	3.688
			95% CI	(-13.1,14.7)	(-12.9,16.2)	(-8.1, 6.4)
			Pr >  t			0.8177
		Week 48	n	41	28	
			LS Mean	-1.712	3.838	-5.549
			SEM	7.020	7.390	3.828
			95% CI	(-15.6,12.2)	(-10.8,18.5)	(-13.1, 2.0)
			Pr >  t			0.1478
		Week 56	n	35	22	
			LS Mean	-1.765	2.906	-4.671
			SEM	7.061	7.494	4.106
			95% CI	(-15.8,12.2)	(-11.9,17.8)	(-12.7, 3.4)
			Pr >  t			0.2558
		Week 64	n	26	23	
			LS Mean	-1.876	5.802	-7.677
			SEM	7.156	7.474	4.251
			95% CI	(-16.1,12.3)	(-9.0,20.6)	(-16.0, 0.7)

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
		Pr >  t		0.0714
	Week 72	n	28	18
		LS Mean	-6.135	3.556
		SEM	7.130	7.597
		95% CI	(-20.3, 8.0)	(-11.5,18.6)
		Pr >  t		0.0286
	Week 84	n	22	18
		LS Mean	-9.034	3.714
		SEM	7.259	7.597
		95% CI	(-23.4, 5.4)	(-11.3,18.8)
		Pr >  t		0.0055
	Week 96	n	21	13
		LS Mean	-3.886	-2.904
		SEM	7.243	7.807
		95% CI	(-18.2,10.5)	(-18.3,12.5)
		Pr >  t		0.8428
	Week 108	n	17	12
		LS Mean	-1.520	-0.197
		SEM	7.395	7.869
		95% CI	(-16.2,13.1)	(-15.8,15.4)
		Pr >  t		0.7996
	Week 120	n	18	11
		LS Mean	-7.810	1.768
		SEM	7.317	7.941
		95% CI	(-22.3, 6.7)	(-13.9,17.5)
		Pr >  t		0.0699
	Week 132	n	13	5
		LS Mean	-8.860	-0.359
		SEM	7.572	8.897
		95% CI	(-23.8, 6.1)	(-17.9,17.2)
		Pr >  t		0.2158
	Week 144	n	12	3
		LS Mean	-4.781	4.337
		SEM	7.572	9.947
		95% CI	(-19.8,10.2)	(-15.2,23.9)
		Pr >  t		0.2687
	Week 156	n	7	2
		LS Mean	-2.508	-4.011
		SEM	8.187	11.11
		95% CI	(-18.7,13.6)	(-25.8,17.8)
		Pr >  t		0.8812
	Week 168	n	3	1
		LS Mean	-5.944	5.998
		SEM	9.741	14.03
		95% CI	(-25.1,13.2)	(-21.5,33.5)
		Pr >  t		0.4014

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Yes	Week 180	n	1	1	
		LS Mean	9.647	5.998	3.649
		SEM	13.89	14.03	17.33
		95% CI	(-17.6,36.9)	(-21.5,33.5)	(-30.4,37.7)
		Pr >  t			0.8333
	Week 192	n	1	1	
		LS Mean	-7.013	5.998	-13.01
		SEM	13.89	14.03	17.33
		95% CI	(-34.3,20.2)	(-21.5,33.5)	(-47.0,21.0)
		Pr >  t			0.4530
	Week 8	n	73	80	
		LS Mean	-9.285	-0.692	-8.592
		SEM	4.295	4.370	3.293
		95% CI	(-17.8,-0.8)	(-9.3, 7.9)	(-15.1,-2.1)
		Pr >  t			0.0095
	Week 16	n	65	58	
		LS Mean	-3.543	-2.465	-1.078
		SEM	4.417	4.575	3.570
		95% CI	(-12.2, 5.2)	(-11.5, 6.5)	(-8.1, 5.9)
		Pr >  t			0.7629
Week 24	n	51	40		
	LS Mean	-9.104	-3.620	-5.484	
	SEM	4.521	4.834	3.993	
	95% CI	(-18.0,-0.2)	(-13.1, 5.9)	(-13.3, 2.4)	
	Pr >  t			0.1704	
Week 32	n	38	36		
	LS Mean	-4.215	-4.198	-0.017	
	SEM	4.756	4.910	4.282	
	95% CI	(-13.6, 5.1)	(-13.9, 5.5)	(-8.4, 8.4)	
	Pr >  t			0.9968	
Week 40	n	32	29		
	LS Mean	-4.129	-3.616	-0.513	
	SEM	4.891	5.072	4.597	
	95% CI	(-13.8, 5.5)	(-13.6, 6.4)	(-9.5, 8.5)	
	Pr >  t			0.9111	
Week 48	n	28	23		
	LS Mean	-4.544	-5.656	1.112	
	SEM	4.992	5.276	4.920	
	95% CI	(-14.4, 5.3)	(-16.0, 4.7)	(-8.5,10.8)	
	Pr >  t			0.8213	
Week 56	n	24	23		
	LS Mean	-4.154	-2.845	-1.310	
	SEM	5.131	5.277	5.059	
	95% CI	(-14.2, 5.9)	(-13.2, 7.5)	(-11.2, 8.6)	
	Pr >  t			0.7958	
Week 64	n	21	19		

Subgroup	Time Window		Alpelisib 300mg	Placebo qd +	Treatment difference
			qd + Fulv N=169	Fulv N=172	Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
Week 72		LS Mean	-5.668	-7.039	1.372
		SEM	5.263	5.464	5.382
		95% CI	(-16.0, 4.7)	(-17.8, 3.7)	(-9.2,11.9)
		Pr >  t			0.7989
		n	20	17	
Week 84		LS Mean	0.063	-0.114	0.177
		SEM	5.317	5.584	5.556
		95% CI	(-10.4,10.5)	(-11.1,10.9)	(-10.7,11.1)
		Pr >  t			0.9746
		n	18	15	
Week 96		LS Mean	-4.508	-6.916	2.409
		SEM	5.418	5.740	5.811
		95% CI	(-15.2, 6.1)	(-18.2, 4.4)	(-9.0,13.8)
		Pr >  t			0.6786
		n	14	11	
Week 108		LS Mean	-2.534	-6.041	3.506
		SEM	5.735	6.186	6.521
		95% CI	(-13.8, 8.7)	(-18.2, 6.1)	(-9.3,16.3)
		Pr >  t			0.5909
		n	9	9	
Week 120		LS Mean	-5.965	-1.039	-4.926
		SEM	6.435	6.530	7.447
		95% CI	(-18.6, 6.7)	(-13.9,11.8)	(-19.5, 9.7)
		Pr >  t			0.5085
		n	10	5	
Week 132		LS Mean	3.477	2.316	1.161
		SEM	6.270	7.857	8.511
		95% CI	(-8.8,15.8)	(-13.1,17.7)	(-15.5,17.9)
		Pr >  t			0.8915
		n	7	3	
Week 144		LS Mean	-9.042	-9.927	0.886
		SEM	6.941	9.477	10.47
		95% CI	(-22.7, 4.6)	(-28.5, 8.7)	(-19.7,21.4)
		Pr >  t			0.9326
		n	3	2	
Week 156		LS Mean	-16.12	-3.323	-12.80
		SEM	9.408	11.19	13.62
		95% CI	(-34.6, 2.4)	(-25.3,18.7)	(-39.5,14.0)
		Pr >  t			0.3479
		n	3	1	
Week 168		LS Mean	-12.22	-3.597	-8.627
		SEM	9.420	15.22	17.08
		95% CI	(-30.7, 6.3)	(-33.5,26.3)	(-42.2,24.9)
		Pr >  t			0.6137
		n	1	1	
		LS Mean	-4.490	-3.597	-0.893

Subgroup	Time Window	Alpelisib 300mg qd + Fulv N=169	Placebo qd + Fulv N=172	Treatment difference Alpelisib 300mg qd + Fulv - Placebo qd + Fulv
	SEM	15.21	15.22	20.84
	95% CI	(-34.4,25.4)	(-33.5,26.3)	(-41.8,40.0)
	Pr >  t			0.9658

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