



of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicina Products with New Active Ingredients According to Section 35a SGB V Abemaciclib (Reassessment after the Deadline: Breast Cancer, HR+, HER2-, Combination with enetitase euticals **Fulvestrant**)

of 3 September 2020

At its session on 3 September 2020, the Federal Point Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (Pharmaceuticals Directive, AM-RL) in the version dated 18 December 2008/22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended on DD Month YYYY (Federal Gazette, BAnz AT DD MM YYYY BX), as follows:

I. With the repeal of the limitation for patient groups a1, b1 and b2, the findings set out in Annex XII for the active ingredient abemaciclib as amended by the resolution of 2 May 2019 shall remain part of the Pharmaceuticals Directive in accordance with the following amendments:

1. The information for abemaciclib on the date and entry into force of the resolutions is adopted as follows:

Resolution of: 2 May 2019 Entry into force on: 2 May 2019 Federal Gazette, BAnz AT 28 June 2019 B5

Resolution of: 5 December 2019 Entropinto force on: 5 December 2019 Federal Gazette, BAnz AT 24 December 2019 B5

Resolution of: 3 September 2020 Entry into force on: 3 September 2020 Federal Gazette, BAnz AT DD MM YYYY Bx

2. The following findings are added to the findings under "Approved therapeutic indication (according to the marketing authorisation of 27 September 2018)":

The following sentence is hereby supplemented to the information contained in the point above:

"The resolution of 3 September 2020 relates exclusively to the assessment of the additional benefit of abemaciclib in combination with fulvestrant in the following sub-populations: a1) postmenopausal women as initial endocrine-based therapy, b1) postmenopausal women who have received prior endocrine therapy and b2) pre- or perimenopausal women who have received prior endocrine therapy."

3. The findings under "1. Additional benefit of the medicinal product in relation to fulvestrant" for the patient populations "a1)", "b1)" and "b2)" are formulated as follows

a1) Postmenopausal women with hormone receptor (HR)-positive: HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrinebased therapy

Appropriate comparator therapy:

- anastrozole or
- letrozole or -
- fulvestrant or tamoxifen, if aromatase inhibitors are not appropriate

Extent and probability of the additional benefit of abemaciclib in combination with fulvestrant compared with fulvestrant:

An additional benefitis notoroven

b1) women with hormone receptor (HR)-positive, HER2-negative locally Postmenopausal advanced or metastatic breast cancer who have received prior endocrine therapy

Appropriate comparator therapy:

A further endocrine therapy depending on the previous therapy with:

tamoxifen or

Sanastrozole or

- fulvestrant; only for patients with relapse or progress after anti-oestrogen treatment
- letrozole; only for patients with relapse or progress after anti-oestrogen treatment or
- exemestane; only for patients with progress after anti-oestrogen treatment or
- everolimus in combination with exemestane; only for patients without symptomatic visceral metastasis after progression after a non-steroidal aromatase inhibitor

Extent and probability of the additional benefit of abemaciclib in combination with fulvestrant compared with fulvestrant:

Hint for a minor additional benefit

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<section-header><section-header><section-header><section-header><section-header><section-header><section-header><section-header> b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine

Endocrine therapy according to the doctor's instructions, taking into account the

Tamoxifen, letrozole, exemestane, megestrol acetate, and medroxyprogesterone

Extent and probability of the additional benefit of abemaciclib in combination

Study results according to endpoints:1

a1) <u>Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally</u> <u>advanced or metastatic breast cancer who have not yet received initial endocrinebased therapy:</u>

MONARCH2 study: Abemaciclib + fulvestrant vs placebo + fulvestrant

Study design: randomised, double-blind, two-armed

Relevant sub-population: Postmenopausal patients as initial endocrine-based therapy (52.5 % of the study population)

Endpoint		bemaciclib + fulvestrant		Abemaciclib	Intervention vs control
	Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	N	Median time to event in months [95% CI] ^b Patients with event n (%)	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^s
Overall survival			ò	ne gut	
	246	43.96 [37.78; 51.65] 123 (50.0)	128	37.25 [33.04; 48.89] 68 (53.1)	0.82 [0.61; 1.10] 0.186

N	lorbidity		my Kor			
	Endpoint	Abemaciclib + fulvestrant			Fulvestrant	Intervention vs control
		Ν	Median time to event in months [95% CI] ^b	Ν	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d
			Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a
	Progression-free	surviva	ll (PFS)º			
000	Time to first sub-	246	16.44 [14.17; 19.73] 163 (66.3)	128	11.08 [7.43; 15.91] 109 (85.2)	0.596 [0.467; 0.761] < 0.0001 AD: +5.4 months
~~~	Time to first sub	sequent	chemotherapy ^e			
X		246	25.81 [19.63; 32.19] 148 (60.2)	128	22.13 [16.60; 26.37] 92 (71.9)	0.730 [0.562; 0.947] < 0.0175 AD: +3.68 months
	Endpoint		bemaciclib + fulvestrant		Fulvestrant	Intervention vs control

¹ Data from the dossier assessment of the IQWiG (A20-32) unless otherwise indicated.

		N	Median time to event in months [95% CI] ^b Patients with event n (%)	N	Median time to event in months [95% CI] ^b Patients with event n (%)	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a
			until permanent de	teriora	ation [*]	
	Symptom scales					(0.)
	Fatigue	245	41.33 [32.48; 52.08] 90 (36.7)	128	22.59 [11.51; 39.19] 53 (41.4)	[0(3)1; 1,03] 0.068
	Nausea/vomitin g	245	n.a. [47.67; n.c.] 50 (20.4)	128	30.71 [22.68; 46.09] 35 (27.3)	0.54 (0.35; 0.84] 0.006
	Pain	245	51.85 [42.90; n.c.] 64 (26.1)	128	33,34 [17,79, n.c.]) 39(29,7)	0.69 [0.46; 1.04] 0.075
	Dyspnoea	245	47.21 [42.84; 51.35] 65 (26.5)	128	(40.37; n.c.] (40.37; n.c.] (23 (18.0)	1.16 [0.72; 1.88] 0.540
	Insomnia	245	51.85 [46,88; n.c.] 47 (19.2)	128	n.a. [30.08; n.c.] 25 (19.5)	0.71 [0.43; 1.16] 0.169
	Loss of appetite	245	n a. [47,05, n.C.] 95 (22,4)	128	48.46 [27.68; n.c.] 26 (20.3)	0.93 [0.58; 1.49] 0.768
	Constipation	245	n.a. (47.67; n.c.] 33 (13.5)	128	49.74 [35.97; n.c.] 24 (18.8)	0.53 [0.31; 0.90] 0.017
	Diarrhoea	245	49.91 [44.48; n.c.] 65 (26.5)	128	n.a. [48.46; n.c.] 15 (11.7)	2.13 [1.21; 3.75] 0.007
	Symptom scales	of the E	ORTC QLQ-BR23			
65	Side effects of systemic treatment	245	42.77 [39.42; n.c.] 76 (31.0)	128	38.96 [23.01; n.c.] 30 (23.4)	1.17 [0.76; 1.79] 0.488
Ple	Breast symptoms	245	n.a. [53.03; n.c.] 28 (11.4)	128	n.a. [32.22; n.c.] 20 (15.6)	0.50 [0.28; 0.90] 0.020
	Arm symptoms	245	51.52 [41.03; n.c.] 65 (26.5)	128	25.12 [13.18; 40.37] 51 (39.8)	0.48 [0.33; 0.70] < 0.001 AD: +26.4 months
	Endpoint		bemaciclib + fulvestrant		Fulvestrant	Intervention vs control

	N	Median time to event in months [95% CI] ^b Patients with event n (%)	Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a		
Burden of hair loss			No	usable data ^h			
Health status ^e					Weill		
EQ-5D VAS (time	e until de	eterioration by ≥ 7 p	ooints	)k	ceoet		
	245	48.36 [45.70; n.a.] 66 (26.9)	128	24.23 [16.67; 48.89] 48 (37.5)	0.58 [0.40; 0.85] 0.004 AD = 24.1 months		
EQ-5D VAS (time	e until de	eterioration by ≥ 10	point	s) ^k	0		
	245	48.36 [45.70; n.a.] 63 (25.7)	128	26.76 [19.76; 0.a.] 46 (35.9)	0.58 [0.40; 0.85] 0.005 AD = 21.6 months		
EQ-5D VAS (mea	EQ-5D VAS (mean change over the course of the study)						
	Analyses of differences in mean values are not available.						
V 2100 Phice							

н	Health-related quality of life     Health-related quality of life       Endpoint     Abemaciclib + fulvestrant     Fulvestrant     Intervention vs control									
	Endpoint	A	bemaciclib + fulvestrant		Fulvestrant	Intervention vs control				
		Ν	Median time to event in months [95% CI] ^b	Ν	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d				
			Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a				
	Health-related qu	ality of	life – time until per	manei	nt deterioration ^g					
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	General health st	tatus an	d functional scales	of the	EORTC QLQ-C30					
P10	Clobal health status	245	45.99 [40,31; n.c.] 71 (29.0)	128	32.48 [22,68; n.c.] 36 (28.1)	0.84 [0.56; 1.26] 0.390				
	Endpoint		bemaciclib + fulvestrant		Fulvestrant	Intervention vs control				
		Ν	Median time to event in months [95% CI] ^b	N	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a				

Endpoint	Abema	ciclib + fulvestrant		Fulvestrant	Intervention vs
Future perspective de effects Endpoint	<u>,</u>				
Future perspective	245	n.a. [51.85; n.c.] 38 (15.5)	128	54.81 [40.60; 54.81] 17 (13.3)	1.0 [0.56; 1.78] 0.987
Sexual enjoyment	nor	Jifieon or	No	usable data ^h	
Sexual functioning	245	33 (13(5))	128	n.a. 15 (11.7)	1.07 [0.58; 1.98] 0.827
Body image	245	n.a. [43.50; n.c.] 58 (23.7)	128	44.78 [37.58; n.c.] 28 (21.9)	0.87 [0.55; 1.37] 0.542
Functional scale	s of the	EORTC QLQ-BR23	, pe		
Social functioning	245	51.85 [44.48; n.c.] 63 (25.7)	128	33 24 [20 32; 40 60] 42 (32.8)	0.58 [0.39; 0.87] 0.007 AD: +18.6 month
Cognitive functioning	245	50.43 [43.30; n.c.] 65 (26.5)	128	44.78 [25.05; 54.81 37 (28.9)	0.76 [0.50; 1.14] 0.177
Emotional functioning	245	55.13 [51.85; 55.59] 48 (19.6)	128	51.91 [51,91; n.c.] 23 (18.0)	0.88 0.53;(1.45] 0.605
Role functioning	245	47.67 [38.93; 55.59] 71 (29.0)	128	40.37 [22.16; 49.74] 42 (32.8)	0.72 [0.49; 1.07] 0.100
Physical functioning	245	47.67 [39.81; n.c.] 66 (26.9)	128	44.78 [26.76; n.c.] 34 (26.6)	0.85 [0.56; 1.29] 0.452
		Patients with event n (%)		Patients with event n (%)	

Res	Endpoint	Aben	emaciclib + fulvestrant		Fulvestrant	Intervention vs control
Ple		Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a
	Adverse events i	n total	(presented additiona	ully)		
		245	0.13 [0.10; 0.13] 242 (98.8)	128	0.58 [049; 0.95] 117 (91.4)	-

	245	n.a. [36.82; n.c.] 72 (29.4)	128	51.98 [42.51; n.c.] 18 (14.1)	1.96 [1.17; 3.30 0.009
Severe adverse e	vents	(CTCAE grade ≥ 3)			
	245	3.72 [2.73; 5.56] 166 (67.8)	128	42.51 [20.84; n.c.] 38 (29.7)	3.39 [2.37; 4.8 < 0.001 AD: - 38.8 m
Therapy disconti	nuatio	n due to adverse eve	ents ⁱ		1000 nor
	245	n.a. 52 (21.2)	128	n.a. 7 (5.5)	3.50 (1.59; 7.72 < 0.001
Specific adverse	events	5		esile	
Neutropoenia (PT, CTCAE grade ≥ 3) ^j	245	no data available 62 (25.3)	128	no date available 2 (1.6)	no data avail
Diarrhoea (PT, CTCAE grade ≥ 3) ^j	245	no data available 35 (14.3)	128	no data available 1 (0.8)	no data availa
 baseline without s a result. A permanent deter baseline without s a result. For the EORTC C loss and whether data is not usable Discontinuation of Since the PC has populations exper A decrease of the deterioration Fime to deterioration the last 24 hours" 	subsequ rioration ubsequ by O-BR they ex as the at leas not sub iencing score h on defin) from b	n was defined as a dec on was defined as a dec open improvement to a 23 scales evaluating the perienced sexual pleas percentage of patients tone of the two medical mitted any time-to-even the specific listed side by 7 points or 10 points and as an increase of 2	score b score a score a ne exten sure du include ations nt analy effects compa	of at least 10 points con below this level. Deaths of at least 10 points con bove this level. Deaths int to which patients wer ring the period of treatmed in the evaluation was yses, by way of exceptions in the study groups are ared with baseline was of a (on the symptom scale edication use by more the	were not counte npared to the were not counte e burdened by h nent, the presen s very low. on, the patient e presented. considered a
	:				

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/	Summary
	Risk of bias	
Mortality	\leftrightarrow	No differences relevant for the benefit assessment
Morbidity	1	Benefits in health status and symptomatolog
Health-related quality of life	\leftrightarrow	No differences relevant for the benefit assessment
Side effects	ţţ	Detriments in the endpoints serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3), and therapy discontinuation due to AEs as well as in detail for specific AEs

Explanations:

↑: statistically significant and relevant positive effect with low/unclear reliability of data

↓: statistically significant and relevant negative effect with low/unclear reliability of data

- $\uparrow\uparrow:$ statistically significant and relevant positive effect with high reliability of data
- $\downarrow\downarrow$: statistically significant and relevant negative effect with high reliability of data

↔: no statistically significant or relevant difference

- Ø: There are no usable data for the benefit assessment.
- n.a.: not assessable
- b1) <u>Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally</u> <u>advanced or metastatic breast cancer who have received prior endocrine therapy</u>

MONARCH2 study. Abemaciclib + fulvestrant vs placebo + fulvestrant

Study design randomised, double-blind, two-armed

Relevant sub-population: Postmenopausal patients who have received prior endocrine therapy (29.5 % of the study population)

N	lortality 🔨					
S	Endpoint		Abemaciclib + fulvestrant		Fulvestrant	Intervention vs control
P P P		Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a
	Overall survival					
		144	48.82 [35.18; n.c.] 66 (45.8)	66	34.78 [28.83; 41.29] 44 (66.7)	0.67 [0.46; 0.98] 0.037 AD = 14 months

Endpoint	Ribo	ciclib + fulvestrant		Fulvestrant	Intervention vs control
	N	Median time to event in months [95% CI] ^b	Ν	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d
		Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a
Progression-fre	e surviv	/al (PFS) ^e			80 t
	144	16.14 [12.0; 19.69] 103 (71.5)	66	6.84 [4.14; 9.47] 59 (89.4)	0.476 [0.344; 0.659] 0.0001 AD: + 9.3 month
Time to first sul	osequei	nt chemotherapy ^e		551.0	
	144	21.07 [17.72; 25.71] 89 (61.8)	66	10,52 [7,63; 19:17] 58 (87.9)	0.497 [0.356; 0.694] < 0.0001 AD: + 10.6 months
Endpoint		Abemaciclib + fulvestrant	Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI] ^b Patients with event	Ν	Median time to event in months [95% CI] ^b Patients with event	Hazard Ratio [95% CI] ^c p value ^d Absolute
		n (%)		n (%)	difference (AD) ^a
Symptomatolog	ıy – tim	e until permanent de	teriora	ation ^{f,g}	
Symptom scale	s of the	EORTC QLQ-C30			
Fatigue	J ¹⁴³	22.8 [14.60; 29.95] 71 (49.7)	66	7.59 [4.67; 28.47] 37 (56.1)	0.68 [0.45; 1.01] 0.054
Nausea/comitin	143	44.94 [41.46; n.c.] 32 (22.4)	66	28.47 [9.63; n.c.] 21 (31.8)	0.49 [0.28; 0.86] 0.011 AD = 16.5 month
Pain	143	44.19 [29.95; n.c.] 41 (28.7)	66	22.95 [12.69; 37.48] 26 (39.4)	0.49 [0.29; 0.80] 0.004 AD = 21.2 month
Dyspnoea	143	44.94 [33.37; 49.02] 44 (30.8)	66	n.a. [23.97; n.c.] 16 (24.2)	0.93 [0.52; 1.67] 0.809
Insomnia	143	41.95 [34.32; n.c.]	66	34.95 [15.72; n.c.]	0.58 [0.33; 1.03]

Last revised: 31.08.2020 Courtesy translation – only the German version is legally binding.

Loss of appetite 143 39.65 [28.47; n.c.] 66 (31.95; n.c.] 34.95 (9.27; n.c.] 0.60 (0.35; 1.01] 0.051 Constipation 143 n.a. [38.96; n.c.] 66 (15.68; n.c.] n.a. (15.68; n.c.] 0.54 (0.29; 1.03] 0.057 Diarrhoea 143 45.40 (38.96; 54.41] 66 (12.30; n.c.] n.a. (12.305; n.c.] 0.66 (0.29; 1.03] 0.057 Symptom scales of the EORTC QLQ-BR23 52 (36.4) 66 (13.87; n.c.] 12 (18.2) 66 (12.847 (13.87; n.c.] 107 (13.87; n.c.] Side effects of systemic treatment 143 40.70 (25.32; 49.02) 66 (12.44) 28.47 (13.87; n.c.] 60 (10.51) Breast symptoms 143 n.a. (13.9.1) 66 (12.29; 0.60 (0.51) 0.71 (0.25; 2.06] (0.531) 0.71 (0.25; 2.06] (0.531) Endpoint Abemaciclib + fulvestrant Fulvestrant Intervention vs control N Median time to event in months [95% CI] ^b N Median time to event in months [95% CI] ^b 9 (20.48; 1.53] (0.62, 20) Arm symptoms 143 36.56 (12.69; 51.45] 0.74 (16.57; n.c.] 0.48 (16.67; n.c.] 0.48 (16.42.2) Suffering due to hair loss 143 27.65 (16.63; 38.73] (16.24; 34) 66 (12.69; 34.95] (2.55; 1.45] (2.63; 1.45] (0.55; 1.45] (0.55; 1.45								
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$		Loss of appetite	143	[28.47; n.c.]	66	[9.27; n.c.]	[0.35; 1.01]	
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$		Constipation	143	[38.96; n.c.]	66	[15.68; n.c.]	[0.29; 1.03]	
Side effects of systemic treatment 143 40.70 66 28.47 607 systemic treatment 143 n.a. 13(9.1) 16(24.2) 0.61; 1.89] 0.820 Breast symptoms 143 n.a. 13(9.1) 66 n.a. 0.71 0.820 Endpoint Abemaciclib + fulvestrant Intervention vs control 0.531 0.531 0.531 Endpoint N Median time to event in months [95% CI] ^b N Median time to event in months [95% CI] ^b Hazard Ratio [95% CI] ^b p valued Absolute difference (AD) ^a Arm symptoms 143 36.83 66 37.48 0.85 [0.48; 1.53] 0.592 Suffering due to hair loss N Valued Absolute Absolute difference (AD) ^a 0.592 0.592 0.592 Health status EQ-5D VAS (time until deterioration by ≥ 7 points) ^k EQ-5D VAS (time until deterioration by ≥ 10 points) ^k 0.88 0.632 0.88 0.531 EQ-5D VAS (time until deterioration by ≥ 10 points) ^k 143 30.44 66 19.36 0.88 0.532 EQ-5D VAS (time until deterioration by ≥ 10 points) ^k 143 30.44 <td< td=""><td></td><td>Diarrhoea</td><td>143</td><td>[38.96; 54.41]</td><td>66</td><td>[23.05; n.c.]</td><td></td></td<>		Diarrhoea	143	[38.96; 54.41]	66	[23.05; n.c.]		
systemic treatment[25.32; 49.02] 52 (36.4)[13.87; n.c.] 16 (24.2)(0.61; 1.89] 0.820Breast symptoms143n.a. 13 (9.1)66n.a. (23.976n.c)0.71 [0.25; 2.06] 0.531EndpointAbemaciclib + fulvestrantFulvestrantIntervention vs controlNMedian time to event in months [95% CI] ^b N Patients with event n (%)Hazard Ratio [95% CI] ^b p valued Absolute difference (AD) ^a Arm symptoms14336.83 (28.63) (30.1)6637.48 (16.57; n.c.) 16 (24.2)0.85 (14.57; n.c.) (0.48; 1.53) (0.48; 1.53) (0.592)Suffering due to hair loss14327.65 (16.6); 38.73] 62 (43.4)No usable data ^h (11.66); 34.95] (23.04.8)0.89 (0.55; 1.45] (0.532)EQ-5D VAS (time until deterioration by ≥ 10 points) ^k EQ-5D VAS (time until deterioration by ≥ 10 points) ^k EQ-5D VAS (time until deterioration by ≥ 10 points) ^k EQ-5D VAS (time until deterioration by ≥ 10 points) ^k		Symptom scales	of the	EORTC QLQ-BR23			conet	
$ \begin{array}{ c c c c c c } \mbox{symptoms} & 13 (9.1) & 13 (9.1) & 13 (9.1) & 123 9 \mbox{f.o.}{C} & 0 & 0 & 0 & 0 \\ \hline \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \$		systemic	143	[25.32; 49.02]	66	28.47 [13.87; n.c.] 16 (24.2)	4.07 40.61; 1.89] 0.820	
Image: second			143		66	[23.970 n.c.)	[0.25; 2.06]	
event in months [95% CI] ^b Patients with event $n (\%)$ event in months [95% CI] ^b Patients with event $n (\%)$ [95% CI] ^c p valued Absolute difference (AD) ^a Arm symptoms14336.89 [28,93, 50.63] (30.1)6637.48 [16.57; n.c.] 16 (24.2)0.85 [0.48; 1.53] 0.592Suffering due to hair lossNo usable data ^h Health statusItal (16.60; 38.73] 62 (43.4)27 points) ^k EQ-5D VAS (time until deterioration by \ge 7 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k EQ-5D VAS (time until deterioration by \ge 10 points) ^k		Endpoint			Fulvestrant			
Arm symptoms 143 36.89 66 37.48 0.85 Image: Arm symptoms 143 Image: Spice S			Ν	event in months [95% CI] ^b Patients with event	N	event in months [95% CI]⁵ Patients with event	[95% CI]⁰ p value ^d Absolute	
hair loss Health status EQ-5D VAS (time until deterioration by \geq 7 points) ^k EQ-5D VAS (time until deterioration by \geq 7 points) ^k Itic 143 27.65 66 16.6 0.89 Itic 143 27.65 66 19.36 0.632 Itic 143 30.44 66 19.36 0.88 0.596 Itic 143 30.44 66 19.36 0.586 0.596 0.596 Itic 143 30.44 66 19.36 0.596 0.596 Itic 143 30.44 66 19.36 0.596 0.596 Itic <		Arm symptoms	143	36.85	66	37.48 [16.57; n.c.]	[0.48; 1.53]	
EQ-5D VAS (time until deterioration by \geq 7 points) ^k Image: Problem 143 27.65 [16.60; 38.73] 62 (43.4) 66 16.6 [12.69; 34.95] 23 (34.8) 0.89 [0.55; 1.45] 0.632 EQ-5D VAS (time until deterioration by \geq 10 points) ^k 66 19.36 [12.69; 34.95] 23 (34.8) 0.88 [0.54; 1.43] 0.596 EQ-5D VAS (time until deterioration by \geq 10 points) ^k 66 19.36 [12.69; 34.95] 23 (34.8) 0.88 [0.54; 1.43] 0.596 EQ-5D VAS (mean change over the course of the study) 67 143 0.596		-		70,	No usable data ^h			
$F_{\text{c}}^{\text{c}} = \begin{bmatrix} 143 & 27.65 \\ [16.60; 38.73] \\ 62 & (43.4) \end{bmatrix} \begin{bmatrix} 66 & 16.6 \\ [12.69; 34.95] \\ 23 & (34.8) \end{bmatrix} \begin{bmatrix} 0.55; 1.45] \\ 0.632 \end{bmatrix} \\ \begin{bmatrix} 645D \text{ VAS (time until deterioration by } \ge 10 \text{ points})^k \end{bmatrix} \\ \begin{bmatrix} 143 & 30.44 \\ [16.60; 38.73] \\ 61 & (42.7) \end{bmatrix} \begin{bmatrix} 66 & 19.36 \\ [12.69; 34.95] \\ 23 & (34.8) \end{bmatrix} \\ \begin{bmatrix} 0.54; 1.43] \\ 0.596 \end{bmatrix} \\ \begin{bmatrix} 0.54; 1.43] \\ 0.596 \end{bmatrix} \\ \begin{bmatrix} 0.54; 1.43] \\ 0.596 \end{bmatrix} \\ \end{bmatrix}$		Health status	it's					
Image: constraint of the study) $\begin{bmatrix} 16.60; 38.73 \\ 62 (43.4) \end{bmatrix}$ $\begin{bmatrix} 12.69; 34.95 \\ 23 (34.8) \end{bmatrix}$ $\begin{bmatrix} 0.55; 1.45 \\ 0.632 \end{bmatrix}$ EQ-5D VAS (time until deterioration by ≥ 10 points) ^k $\begin{bmatrix} 14.69; 34.95 \\ 23 (34.8) \end{bmatrix}$ $\begin{bmatrix} 0.55; 1.45 \\ 0.632 \end{bmatrix}$ EQ-5D VAS (time until deterioration by ≥ 10 points) ^k $\begin{bmatrix} 14.60; 38.73 \\ 16.60; 38.73 \\ 61 (42.7) \end{bmatrix}$ $\begin{bmatrix} 66 \\ 19.36 \\ [12.69; 34.95] \\ 23 (34.8) \end{bmatrix}$ $\begin{bmatrix} 0.54; 1.43 \\ 0.596 \end{bmatrix}$ EQ-5D VAS (mean change over the course of the study) $\begin{bmatrix} 12.69; 34.95 \\ 23 (34.8) \end{bmatrix}$ $\begin{bmatrix} 0.54; 1.43 \\ 0.596 \end{bmatrix}$		EQ-5D VAS (time	until d	eterioration by ≥ 7 p	oints) ^k		
EQ-5D VAS (mean change over the course of the study) [12.69, 34.95] [0.54; 1.43]		hution the	143	27.65 [16.60; 38.73] 62 (43.4)		16.6 [12.69; 34.95] 23 (34.8)	[0.55; 1.45]	
EQ-5D VAS (mean change over the course of the study) [12.69, 34.95] [0.54; 1.43]	200	EQ-5D VAS (time	until d	eterioration by ≥ 10	point	s) ^k		
	P10	0	143	[10.00, 38.73]	66	[12.69, 34.95]	[0.54; 1.43]	
Analyses of differences in mean values are not available.		EQ-5D VAS (mea	n chan	ge over the course o	of the	study)		
			Analys	es of differences in m	nean v	alues are not available		

Health-related quality of life

Endpoint		bemaciclib + fulvestrant		Fulvestrant	Intervention vs control
	Ν	Median time to event in months [95% CI] ^b Patients with	Z	Median time to event in months [95% CI] ^b Patients with event	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a
		event n (%)		n (%)	
-	-	life – time until per d functional scales			evet
Global health status	143	30.81 [19.27; 38.96] 57 (39.9)	66	14.56 [5.98; 28.47] 28 (42.4)	0.63 0.40; 1.00] 0.049 AD: 16.3 months
Endpoint		bemaciclib + fulvestrant		Fulvestrant	Intervention vs control
	N	Median time to event in months [95% CI] ^b	N	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d Absolute
		Patients with event n (%)		Patients with event n (%)	difference (AD) ^a
Physical functioning	143	44,91 [27:68; n.č.] 37 (25:9)	66	28.47 [9.27; n.c.] 22 (33.3)	0.54 [0.31; 0.92] 0.021 AD = 16.4 month
Role functioning	1430 1430	35.97 (27.29; 44.94] 56 (39.2)	66	19.89 [7.99; 33.11] 26 (39.4)	0.72 [0.45; 1.16] 0.180
Emotional functioning	JI 143	44.22 [29.95; n.c.] 37 (25.9)	66	23.05 [13.18; 37.48] 22 (33.3)	0.47 [0.27; 0.81] 0.005 AD = 21.2 month
Cognitive functioning	143	33.93 [19.76; 41.46] 52 (36.3)	66	16.57 [9.63; 28.47] 25 (37.9)	0.66 [0.40; 1.06] 0.085
Social functioning	143	31.23 [22.75; 46.55] 53 (37.1)	66	23.05 [12.69; n.c.] 23 (34.8)	0.79 [0.48; 1.29] 0.338
Functional scale	s of the	EORTC QLQ-BR23			ſ
Body image	143	n.a. [24.89; n.c.] 40 (28.0)	66	34.55 [17.06; n.c.] 13 (19.7)	1.10 [0.59; 2.07] 0.763
Sexual functioning	143	n.a. 17 (11.9)	66	42.41 [42.41; n.c.] 8 (12.1)	0.62 [0.26; 1.46] 0.270

Sexual enjoyment	No usable data ^h					
Future perspective	143	41.72 [32.38; n.a.] 37 (25.9)	66	n.a. [37.48; n.c.] 7 (10.6)	1.53 [0.67; 3.46] 0.309	

Endpoint	Aben	naciclib + fulvestrant		Fulvestrant	Intervention vs control
	N	Median time to event in months [95% CI] ^b	Ν	Median time to event in months [95% CI] ^b	[95% CI] ^c p value ^d
		Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a
Adverse even	ts in total	(presented additiona	lly)	SS S	
	143	0.10 [0.07; 0.13] 140 (97.9)	66	.0.54 [0.26; 0.95] (59 (89.4)	-
Serious adver	se events	s (SAEs)	50	NO.	I
	143	47.11 [34.03; n.c.) 40 (28.0)	66	29.92 [15.06; n.c.] 14 (21.2)	0.96 [0.52; 1.78] 0.896
Severe advers	se events	(CTCAE grade ≥ 3)			
	143	4,64 [1-9]; 9.01] 99 (69.2)	66	27.98 [9.93; n.c.] 21 (31.8)	2.61 [1.63; 4.19] < 0.001 AD: - 23.3 month
Therapy disco	ontinuatio	n due to adverse eve	nts ⁱ	•	
has	2 J143	n.a. [38.07; n.c.] 34 (23.8)	66	n.a. 2 (3.0)	6.49 [1.55; 27.12] 0.003
Specific adve	rse event	S		_	
Neutropoenia (PT, CTCAE grade ≥ 3) ^j	143	no data available 42 (29.4)	66	no data available 1 (1.5)	no data availabl
Diarrhoea (PT, CTCAE grade 3) ^j		no data available 25 (17.5)	66	no data available 0 (0)	no data availabl
calculation ^b Median time to ^c Effect and CI: ^d p value: unstra ^e Information fro ^f A permanent d	o event an Cox propo atified log- om the dos eterioratio	given only in the case of d associated 95% CI we ortional hazard model, un rank test sier of the pharmaceution n was defined as an incluent improvement to a s	ere est nstratif cal cor rease	imated using the Kaplar fied Cox proportional ha npany of at least 10 points cor	n-Meier method zard model npared to the

- ^g A permanent deterioration was defined as a decrease of at least 10 points compared to the baseline without subsequent improvement to a score above this level. Deaths were not counted as a result.
- ^h For the EORTC QLQ-BR23 scales evaluating the extent to which patients experienced hair loss and whether they experienced sexual pleasure during the period of treatment, the presented data is not usable as the percentage of patients included in the evaluation was very low.
- Discontinuation of at least one of the two medications
- ^jThe results are not utilisable for the assessment of additional benefit, as the PC has not submitted time-to-event analyses. The rates are, however, presented as a supplement.
- * A decrease of the score by 7 points or 10 points compared with baseline was considered at deterioration

Abbreviations used:

AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23; EQ-5D: European Quality of Life Questionnaire-5 Dimensions; HR = hazard ratio; CI = confidence interval; mBPI_SF: modified Brief Pain Index – Short Form; N = number of patients evaluated; n = number of patients with (at least one) event; n.c. = not calculable; n.a. = not achieved; PT = preferred term; RCT = randomised controlled trial; SAE = serious adverse event; AE = adverse event; VAS = visual analogue scale; vs = versus

Summary of results for relevant clinical endpoints

1					
Direction of effect/	Summary				
Risk of bias					
A NO	Advantage in overall survival				
Sted TOT	Benefits in symptomatology (nausea/vomiting and pain)				
dl'i gi0`↑	Benefits as measured by global health, physical and emotional functioning scales				
11	Detriments in the endpoints, severe AEs (CTCAE grade ≥ 3) and therapy discontinuation due to AEs as well as in detail for specific AEs				
Explanations:					
	Risk of bias				

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy

MONARCH2 study: Abemaciclib + fulvestrant vs placebo + fulvestrant

Study design: randomised, double-blind, two-armed

Relevant sub-population: Pre- or perimenopausal patients who have received prior endocrine-based therapy (6.5 % of the study population) (°.11.

4.

N	lortality					×11 + 11.
	Endpoint		Abemaciclib + fulvestrant		Fulvestrant	Intervention vs control
		N Median time to event in months [95% CI] ^b		N	Median time to event in months [95% CI] ^b	Hazard Ratio [95% Cl] ^c p value ^d
			Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a
	Overall survival				at as als	
		26 n.a. [38.96; n.c.] 8 (30.8)		20	45.83 27,16; n.c.] 9 (45.0)	0.55 [0.21; 1.45] 0.217
N	lorbidity		nothe	han		
	Endpoint	Ribo	ciclib + fulvestrant	Fulvestrant		Intervention vs control
		N	Median time to event in months [95% CI] ^b	N	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d
			Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a
	Progression-free	surviv	/al (PFS) ^e			
S	Progression-free	26 28.21 [14.83; 50.60] 17 (65.4)		20	9.67 [4.31; 15.62] 16 (80)	0.372 [0.181; 0.766] 0.0055 AD: + 18.5 months
0	Fime to first sub	sequei	nt chemotherapy ^e			
2/0		26	50.24 [18.28; n.a.] 11 (42.3)	20	17.46 [9.93; 31.13] 17 (85.0)	0.271 [0.122; 0.601] 0.0006 AD: + 32.8 months
	Symptomatology	/ – time	e until permanent de	teriora	ation ^{f,g}	
	Symptom scales	of the	EORTC QLQ-C30			
	Fatigue	26	n.a. [18.94; n.c.]	20	17.16 [7.43; n.c.]	0.45 [0.17; 1.24]

Courtesy translation – only the German version is legally binding.

		9 (34.6)		8 (40.0)	0.115
Nausea/vomitin g	26	53.23 [19.92; 53.23] 8 (30.8)	20	n.a. [10.59; n.c.] 2 (10.0)	1.63 [0.33; 8.19] 0.546
Endpoint	Ribo	ciclib + fulvestrant		Fulvestrant	Intervention vs control
	N	Median time to event in months [95% CI] ^b Patients with event	N	Median time to event in months [95% CI] ^b Patients with event	Hazard Ratio [95% CI] ^c p value ^d Absolute
		n (%)		n (%)	difference (AD)
Pain	26	47.70 [38.96; n.c.] 9 (34.6)	20	35.93 [10.59; n-o.] 5 (25 0)	0.71 [0.22; 2.32] 0.565
Dyspnoea	26	n.a. [19.92; n.c.] 8 (30.8)	20	h.a. [9.27; n.c.] 4 (20.0)	0.93 [0.27; 3.19] 0.899
Insomnia	26	51.35 [47.70; n.c.] 7 (26.9)	20	19.69 [3.75; n.c.] 8 (40.0)	0.34 [0.11; 1.05] 0.050
Loss of appetite	26	51.75 [38.96; 53.23] 8 (30,8)	20	32.12 [11.51; n.c.] 5 (25.0)	0.46 [0.14; 1.58] 0.210
Constipation	26	0 n.a.0 3 (11.5)	20	39.85 [9.21; 39.85] 5 (25.0)	0.21 [0.05; 0.93] 0.026
Diarrhoea	26	39.12 [5.56; 47.70] 14 (53.8)	20	n.a. [11.51; n.c.] 2 (10.0)	3.36 [0.73; 15.49] 0.100
Symptomscales	of the	EORTC QLQ-BR23			
Side effects of systemic treatment	26	n.a. [42.21; n.c.] 6 (23.1)	20	30.51 [9.34; n.c.] 7 (35.0)	0.31 [0.09; 1.03] 0.045
Breast symptoms	26	n.a. [47.24; n.c.] 4 (15.1)	20	n.a. [10.59; n.c.] 2 (10.0)	0.77 [0.12; 4.86] 0.779
Arm symptoms	26	52.08 [31.04; 52.08] 7 (26.9)	20	n.a. [9.53; n.c.] 5 (25.0)	0.42 [0.11; 1.56] 0.185
Suffering due to hair loss			No	usable data ^h	
Health status					
EQ-5D VAS (time	e until c	leterioration by ≥ 7 p	oints) ^k	
	26	44.25	20	n.a.	0.94

		[30.51; n.a.] 9 (34.6)		[10.59; n.a.] 4 (20.0)	[0.28; 3.23] 0.923
Endpoint	Riboc	iclib + fulvestrant	Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI] ^b	Ν	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d
		Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a
EQ-5D VAS (time	until de	eterioration by ≥ 10	point	s) ^k	or pri
	26	44.25 [30.51; n.a.] 9 (34.6)	20	n.a. [10.59; n.a. 4 (20.0)	0.94 [0.28; 3.23] 0.923
EQ-5D VAS (mea	n chang	ge over the course of	of the	study)	
	Analyse	es of differences in m	nean v	alues are not available	
ealth-related qua	lity of li	ife 📈	t ber	alues are not available	
Endpoint	Abemaciclib + fulvestrant		Fulvestrant		Intervention vs control
	N	Median time to event in months [95% CI] ^b	N	Median time to event in months [95% CI]⁵	Hazard Ratio [95% Cl] ^c p value ^d
	N	event in months	Ν	event in months	Hazard Ratio [95% CI]°
Health-related qu		event in months [95% CI] ^b <i>Patients with</i>		event in months [95% CI] ^b Patients with event n (%)	Hazard Ratio [95% CI] ^c p value ^d Absolute
	iality čí	event in months [95% CI] ^b Patients with event n (%)	manei	event in months [95% CI] ^b <i>Patients with event</i> <i>n (%)</i> nt deterioration ^g	Hazard Ratio [95% CI] ^c p value ^d Absolute
	iality čí	event in months [95% CI] ^b <i>Patients with</i> <i>event n (%)</i> Jife – time until per	manei	event in months [95% CI] ^b <i>Patients with event</i> <i>n (%)</i> nt deterioration ^g	Hazard Ratio [95% CI] ^c p value ^d Absolute
General health st Global health status	ality of	event in months [95% CI] ^b <i>Patients with</i> <i>event n (%)</i> Jife – time until per of functional scales n.a. [35.54; n.c.]	manei of the	event in months $[95\% CI]^b$ Patients with event n (%) at deterioration ^g EORTC QLQ-C30 22.65 [9.21; n.c.]	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a 0.33 [0.09; 1.22]
General health st Global health status	ality of atus an 26	event in months [95% CI] ^b Patients with event n (%) Jife – time until per d functional scales n.a. [35.54; n.c.] 5 (19.2) n.a.	manei of the 20	event in months $[95\% CI]^b$ Patients with event n (%) at deterioration ^g EORTC QLQ-C30 22.65 [9.21; n.c.] 6 (30.0) 33.17 [10.59; n.c.]	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a 0.33 [0.09; 1.22] 0.083 0.37 [0.10; 1.45]
General health st Global health status Physical functioning	ality of atus an 26 26	event in months [95% CI] ^b <i>Patients with</i> <i>event n (%)</i> Jife – time until per d functional scales n.a. [35.54; n.c.] 5 (19.2) n.a. 4 (15.4) 47.70 [37.58; n.c.]	maner of the 20 20	event in months [95% CI] ^b Patients with event n (%) the deterioration ^g EORTC QLQ-C30 22.65 [9.21; n.c.] 6 (30.0) 33.17 [10.59; n.c.] 5 (25.0) 38.70 [10.59; 42.87]	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a 0.33 [0.09; 1.22] 0.083 0.37 [0.10; 1.45] 0.140 0.37 [0.12; 1.12]

Endpoint	Riboo	ciclib + fulvestrant		Fulvestrant	Intervention vs control		
	N	Median time to event in months [95% CI] ^b	N	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d		
		Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a		
Social functioning	26	n.a. [51.42; n.c.] 5 (19.2)	20	24.89 [9.34; n.c.] 5 (25.0)	0.34 [0.09; 1.29] 0.098		
Functional sca	les of the	EORTC QLQ-BR23		*	Or Prin		
Body image	26	n.a. [23.54; n.c.] 6 (23.1)	20	n.a. 3 (15.0)	0.98 [0.24; 4.04] 0.979		
Sexual functioning	26	n.a. [11.93; n.c.] 7 (26.9)	20	45,63 [12,89; 45,63] 4 (20.0)	0.93 [0.27; 3.23] 0.907		
Sexual enjoyment			Not	usable data ^h			
Future perspective	26	n.a. 3 (11.5)	20,	36.89 [13.15; n.c.] 3 (6.7)	0.32 [0.05; 2.06] 0.208		
Future perspective 26 n.a. 20 36.89 0.32 3 (11.5) 3 (11.5) [13.15; n.c.] [0.05; 2.06] 0.208 ide effects ifie ifie ifie ifie ifie							
ide effects							

Side effects

	Endpoint	Aben	bemaciclib + fulvestrant		Fulvestrant	Intervention vs control
		N	Median time to event in months [95% CI] ^b	N	Median time to event in months [95% CI] ^b	Hazard Ratio [95% CI] ^c p value ^d
			Patients with event n (%)		Patients with event n (%)	Absolute difference (AD) ^a
	Adverse events i	n total	(presented additiona	ally)		
Ple	26 26 26		0.13 [0.07; 0.23] 25 (96.2)	20	0.44 [0.16; 1.58] 19 (95.0)	-
	Serious adverse	events	s (SAEs)			
		26	n.a. [37.45; n.c.] 7 (26.9)	20	n.a. 1 (5.0)	4.33 [0.52; 36.10] 0.140
	Endpoint	Ribo	Ribociclib + fulvestrant		Fulvestrant	Intervention vs control

	Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	Ν	Median time to event in months [95% CI] ^b Patients with event n (%)	Hazard Ratio [95% CI] ^c p value ^d Absolute difference (AD) ^a	
Severe adverse e	vents	(CTCAE grade ≥ 3)				
	26	3.02 [0.95; 6.77] 19 (73.1)	20	27.35 [9.24; n.c.] 4 (20.0)	5.75 [1.94; 17.06] < 0.001 AD: 24.3 months	
Therapy discontir	nuatio	n due to adverse eve	nts ⁱ		or prin	
	26	n.a. [48.72; n.c.] 3 (11.5)	20	n.a. 0 (0)	0.213	
Specific adverse	events	3		Ses Dille		
Neutropoenia (PT, CTCAE grade ≥ 3) ^j	26	no data available 14 (53.8)	20	no data available 0(0)	no data available	
Diarrhoea (PT, CTCAE grade ≥ 3) ^j	26	no data available 2 (7.7)	20 ⁰ 0	no data available 0 (0)	no data available	
 ^a Absolute difference (AD) given only in the case of a statistically significant difference; own calculation ^b Median time to event and associated 55% Chivere estimated using the Kaplan-Meier method ^c Effect and CI: Cox proportional bazard model, unstratified Cox proportional hazard model ^d p value: unstratified log-rank test ^e Information from the dossier of the pharmaceutical company ^t A permanent deterioration was defined as an increase of at least 10 points compared to the baseline without subsequent improvement to a score below this level. Deaths were not counted as a result. ^a A permanent deterioration was defined as a decrease of at least 10 points compared to the baseline without subsequent improvement to a score above this level. Deaths were not counted as a result. ^b For the EORTC QLQ-BR23 scales evaluating the extent to which patients experienced hair loss and whether they experienced sexual pleasure during the period of treatment, the presented data is no Usable as the percentage of patients included in the evaluation was very low. ⁱ Disontinuation of at least one of the two medications ⁱ The results cannot be used in the assessment of additional benefit, as the PC has not submitted time to event analyses. The rates are, however, presented as a supplement. ^k A decrease of the score by 7 points or 10 points compared with baseline was considered a deterioration ^k HR cannot be reasonably estimated (no event in control arm) Abbreviations used: AD = absolute difference; CTCAE = Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Grancer 3; EQ-5D: European Quality of Life Questionnaire-S Dimensions; HR = hazard ratio; CI = confidence interval; mBPI_SF: modified Brief Pain Index – Short Form; N = number of patients evaluated; n = number of patients with (at lea						

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/	Summary
	Risk of bias	
Mortality	\leftrightarrow	No differences relevant for the benefit assessment
Morbidity	\leftrightarrow	No differences relevant for the benefit assessment
Health-related quality of life	\leftrightarrow	No differences relevant for the benefit assessment
Side effects	$\downarrow\downarrow$	Detriments in the endpoint severe AEs (CCAE grade ≥ 3) as well as in detail for specific AEs

Explanations:

↑: statistically significant and relevant positive effect with low/unclear reliability of data

↓: statistically significant and relevant negative effect with low/unclear reliability of data

↑↑: statistically significant and relevant positive effect with high reliability of data

 $\downarrow\downarrow$: statistically significant and relevant negative effect with high reliability of data

 $\leftrightarrow: \text{no statistically significant or relevant difference}$

 \varnothing : There are no usable data for the benefit assessment.

n.a.: not assessable

4. The findings under "2. Number of patients or demarcation of patient groups eligible for treatment" for patient population "at)", "b1)" and "b2)" are formulated as follows:

- a1) <u>Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally</u> advanced or metastatic breast cancer who have not yet received initial endocrinebased therapy:
 - approx 7,400-34,790 patients
- b1) <u>Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally</u> <u>advanced or metastatic breast cancer who have received prior endocrine therapy</u>

• Sapprox. 5,470–24,900 patients

Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy:

• approx. 906–4,118 patients"

5. The findings under "3. Requirements for a quality-assured application" are formulated as follows:

"The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Verzenios® (active ingredient: abemaciclib) at the following publicly accessible link (last access: 2 June 2020):

https://www.ema.europa.eu/documents/product-information/verzenios-epar-productinformation_en.pdf

Treatment with abemaciclib should only be initiated and monitored by specialists in internal medicine, haematology, and oncology, specialists in gynaecology and obstetrics, and specialists participating in the Oncology Agreement who are experienced in the treatment of patients with locally advanced or metastatic breast cancer.

6. Under "4. Treatment costs", the findings on the annual treatment costs for patient populations "a1)", "b1)" and "b2)" are formulated as follows:

"The annual treatment costs shown refer to the first year of treatment.

a1) <u>Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally</u> advanced or metastatic breast cancer who have not yet received initial endocrine-based therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Abemaciclib difficion	€28,996.56
plus fulvestrant	
Fulvestrant	€8,338.76
Total:	€ 37,335.32
Appropriate comparator therapy:	
Anastrozole	€183.96
Letrozole	€164.58
Fulvestrant	€8,338.76
Tamoxifen	€69.28

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2020

Costs for additionally required SHI services: not applicable

b1) Postmenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy:

Designation of the therapy	Annual treatment costs/patient
Medicinal product to be assessed:	
Abemaciclib	€28,996.56
plus fulvestrant	Nu l
Fulvestrant	€ 8,338.76
Total:	£ 37,335.32
Appropriate comparator therapy:	
Tamoxifen	€69.28
Anastrozole	€ 69.28 € 183.96 € 8,338.76 € 164.58
Fulvestrant	€8,338.76
Letrozole	€ 164.58
Exemestane	€412.78
Everolimus + exemestane	
Everolimus + exemestane Everolimus Exemestane Total:	€17,144.37
Exemestane	€412.78
Total:	€17,557.15
Exemestane Total: Costs after deduction of statutory rebates (LA Costs for additionally required SHI service	UER-TAXE®) as last revised: 15 August 2020

b2) Pre- or perimenopausal women with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer previously treated with endocrine therapy

Designation of the therapy	Annual treatment costs/patient	
Medicinal product to be assessed:		
Abemaciclib	€28,996.56	
plus fulvestrant	ure 11	
Fulvestrant	€8,338.76	
Total:	€8,338.76 €37,335.32 €1,793.02-2,176.42	
LHRH analogue	€1,793.02-2,176.42	
Appropriate comparator therapy:		
Tamoxifen	€69.28	
Letrozole	€164.58 0 jil	
Exemestane	€ 69.28 € 164.58 € 412.78	
Megestrol	€5,510.38	
Medroxyprogesterone	€1,188.77–2,377.54	
LHRH analogue	€1,793.02–2,176.42	
Megestrol € 5,5 (0.38) Medroxyprogesterone € 1,188.77–2,377.54 LHRH analogue € 1,793.02–2,176.42 Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2020 Costs for additionally required SHI services: not applicable"		
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Costs for additionally required SHI services: not applicable"		
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II. Entry into force

1. The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 3 September 2020.

2. The period of validity of this resolution shall be limited in accordance with the following provisions:

The findings for patient groups

a1) postmenopausal women with hormone receptor (HR)-positive, HER2-negative. locally advanced or metastatic breast cancer who have not yet received initial endocrine-based therapy, and

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de. Berlin, 3 September 2020 b1) postmenopausal women with hormone receptor (HR)-positive, (HER2-negative

Resolution has been modified by a second a secon The Chair

Prof. Hecken