Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-318-z Alpelisib

Stand: Oktober 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Alpelisib
zur Behandlung des HR-positiven/HER2-negativen, lokal fortgeschrittenen oder metastasierten Brustkrebs

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Grundsätzlich im Anwendungsgebiet in Betracht kommende nicht-medikamentöse Behandlungen: • Operative Resektion • Strahlentherapie • Ovariektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen.	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Abemaciclib (in Kombination mit Fulvestrant): Beschlüsse vom 2. Mai 2019 und 3. September 2020 • Abemaciclib (in Kombination mit einem Aromatasehemmer): Beschluss vom 2. Mai 2019 • Palbociclib: Beschlüsse vom 18. Mai 2017 und 22. März 2019 • Ribociclib (in Kombination mit Fulvestrant): Beschlüsse vom 4. Juli 2019 und 20. August 2020 • Ribociclib (in Kombination mit einem Aromatasehemmer): Beschlüsse vom 4. Juli 2019 und 20. August 2020
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Alpelisib L01XX65 Piqray®	Zugelassenes Anwendungsgebiet: „Piqray wird in Kombination mit Fulvestrant angewendet 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.“
Antiestrogene:	
Tamoxifen L02BA01 Nolvadex®	• Adjuvante Therapie nach Primärbehandlung des Mammakarzinoms. • Metastasierendes Mammakarzinom.
Toremifen L02BA02 Fareston®	First-line Behandlung des hormonabhängigen metastasierenden Mammakarzinoms bei postmenopausalen Patientinnen. Fareston kann bei Patientinnen mit Östrogenrezeptor-negativen Tumoren nicht empfohlen werden.
Fulvestrant L02BA03 Faslodex®	Faslodex® ist angezeigt als Monotherapie zur Behandlung von Östrogenrezeptor-positivem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom bei postmenopausalen Frauen: • die keine vorhergehende endokrine Therapie erhalten haben, oder • mit Rezidiv während oder nach adjuvanter Antiöstrogen-Therapie oder bei Progression der Erkrankung unter Antiöstrogen-Therapie. -in Kombination mit Palbociclib zur Behandlung des Hormonrezeptor-(HR)-positiven humanen Wachstumsfaktor-Rezeptor-2-(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinoms bei Frauen, die eine vorhergehende endokrine Therapie erhalten haben
Aromatase-Inhibitoren (nicht-steroidal):	

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Anastrozol L02BG03 Arimidex®	Arimidex® ist angezeigt für die: • Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen. • Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen. • Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen, die bereits 2 bis 3 Jahre adjuvant Tamoxifen erhalten haben.
Letrozol L02BG04 Femara®	• Adjuvante Therapie postmenopausaler Frauen mit hormonrezeptor-positivem primärem Mammakarzinom. • Erweiterte adjuvante Therapie des hormonabhängigen primären Mammakarzinoms bei postmenopausalen Frauen nach vor-heriger adjuvanter Standardtherapie mit Tamoxifen über 5 Jahre. • First-Line-Therapie des hormonabhängigen fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen. • Behandlung des Mammakarzinoms im fortgeschrittenen Stadium nach Rezidiv oder Progression der Erkrankung bei Frauen, die sich physiologisch oder nach einem künstlichen Eingriff in der Postmenopause befinden und die zuvor mit Antiöstrogenen behandelt wurden. • Neoadjuvante Behandlung postmenopausaler Frauen mit hormonrezeptor-positivem, HER-2-negativem Mammakarzinom, bei denen eine Chemotherapie nicht in Betracht kommt und ein sofortiger chirurgischer Eingriff nicht indiziert ist.
Aromatase-Inhibitoren (steroidal):	
Exemestan L02BG06 Aromasin®	• adjuvante Behandlung eines Östrogenrezeptor-positiven, invasiven, frühen Mammakarzinoms bei postmenopausalen Frauen nach 2 – 3 Jahren adjuvanter Initialtherapie mit Tamoxifen. • Behandlung des fortgeschrittenen Mammakarzinoms bei Frauen mit natürlicher oder induzierter Postmenopause nach Progression unter Antiöstrogenbehandlung. Bei Patientinnen mit negativem Östrogenrezeptor-Status ist die Wirksamkeit nicht belegt.
Gestagene:	
Megestrolacetat L02AB01 Megestat®	Megestat® ist angezeigt: • zur palliativen Behandlung fortgeschrittener Mammakarzinome (nicht operable metastasierende bzw. rekurrente Erkrankungen), bei Progression nach einer Therapie mit Aromatasehemmern
Medroxyproges-teronacetat L02AB02 MPA Hexal®	Zur palliativen Behandlung bei folgenden hormonabhängigen Tumoren: • metastasierendes Mammakarzinom • […].

II. Zugelassene Arzneimittel im Anwendungsgebiet

Gonadotropin-Releasing-Hormon-Analoga:	
Leuprorelin L02AE02 Enantone-Gyn®	Mammakarzinom prä- und perimenopausaler Frauen, sofern eine endokrine Behandlung angezeigt ist.
Goserelin L02AE03 Zoladex®	Behandlung von Patientinnen mit Mammakarzinom (prä- und perimenopausale Frauen), bei denen eine endokrine Behandlung angezeigt ist.
Proteinkinase-Inhibitoren:	
Everolimus L01XE10 Afinitor®	Hormonrezeptor-positives, fortgeschrittenes Mammakarzinom: Afinitor wird in Kombination mit Exemestan zur Therapie des Hormonrezeptor-positiven, HER2/neu-negativen, fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen ohne symptomatische viszerale Metastasierung angewendet, nachdem es zu einem Rezidiv oder einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.
Palbociclib L01XE33 IBRANCE®	IBRANCE ist angezeigt zur Behandlung von Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen lokal fortgeschrittenen oder metastasierten Brustkrebs: • in Kombination mit einem Aromatasehemmer • in Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinizing Hormone-Releasing Hormone) kombiniert werden.
Ribociclib L01XE42 Kisqali®	Kisqali wird zur Behandlung von Frauen mit einem Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrin-basierte Therapie oder bei Frauen mit vorangegangener endokriner Therapie angewendet. Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Abemaciclib L01XE50 Verzenios®	Verzenios ist angezeigt zur Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie. Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-318-z (Alpelisib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	13. Oktober 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABC	Advanced Breast Cancer
AE	Adverse Events
AI	Aromatase Inhibitor
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BC	Breast Cancer
CBR	Clinical Benefit Rate
CDK	Cyclin-Dependent Kinase
CR	Complete Response
ECRI	ECRI Guidelines Trust
ER	Estrogen Receptor
ET	Endokrine Therapie
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HER2-	Humaner epidermaler Wachstumsfaktor-Rezeptor-2(HER2)-negativ
HR	Hazard Ratio
HR+	Hormonrezeptor (HR)-positiv
ITC	Indirect Treatment Comparison
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LHRH	LHRH = Luteinising Hormone-Releasing Hormone
LoE	Level of Evidence
MBC	Metastatic Breast Cancer
mTOR	mechanistic Target of Rapamycin
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival

PgR	Progesterone Receptor
PFS	Progression Free Survival
PR	Partial Response
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TTF	Time to Treatment Failure
TTP	Time To Progression
WHO	World Health Organization

1 Indikation

Initiale endokrine Behandlung des Hormonrezeptor-(HR)-positiven, humanen Wachstumsfaktor-Rezeptor-2-(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinoms bei prä- und postmenopausalen Frauen und bei Männern.

Hinweis: Es wird davon ausgegangen, dass im vorliegenden AWG keine Indikation für eine Chemotherapie besteht (siehe Leitlinien). Daher werden SR und CR, in denen verschiedene Chemotherapie-Regimen (z.B. Monochemotherapie vs. Monochemotherapie; Monochemotherapie vs. Kombinationschemotherapie; Kombination aus Chemotherapie plus zielgerichtete Therapie vs. Chemotherapie) bei Patienten mit fortgeschrittenen Brustkrebs verglichen werden, nicht in der vorliegenden Evidenzsynopse abgebildet.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Mammakarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 15.06.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Erstrecherche wurde am am 09.11.2018 durchgeführt, die Folgerecherchen am 29.07.2019 und 10.02.2020. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherchen übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 3909 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 18 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2020 [4].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V vom 20. August 2020 - Ribociclib (Neubewertung nach Fristablauf: Mammakarzinom, HR+, HER2-, Kombination mit einem Aromatasehemmer)

Anwendungsgebiet

Kisqali wird zur Behandlung von Frauen mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrinbasierte Therapie oder bei Frauen mit vorangegangener endokriner Therapie angewendet.

Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.

Hinweis:

Die vorliegende Bewertung bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Ribociclib in Kombination mit einem Aromatasehemmer. Für die Bewertung des Zusatznutzens von Ribociclib mit Fulvestrant wird auf das separate Nutzenbewertungsverfahren für diese Kombinationstherapie verwiesen. Gegenstand des vorliegenden Nutzenbewertungsverfahrens ist die Patientengruppe „postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Mammakarzinoms, die noch keine initiale endokrine Therapie erhalten haben.

a1) postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie

Anastrozol oder Letrozol oder Fulvestrant oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ribociclib in Kombination mit Letrozol gegenüber Letrozol:

Anhaltspunkt für einen geringen Zusatznutzen

G-BA, 2020 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V vom 20. August 2020 - Ribociclib (Neubewertung nach Fristablauf: Mammakarzinom, HR+, HER2-, Kombination mit Fulvestrant)

Anwendungsgebiet

Kisqali wird zur Behandlung von Frauen mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrinbasierte Therapie oder bei Frauen mit vorangegangener endokriner Therapie angewendet.

Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.

Hinweis:

Der Beschluss vom 20. August 2020 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Ribociclib in Kombination mit Fulvestrant in den Teilpopulationen: a1) postmenopausale Patientinnen, die noch keine initiale endokrine Therapie erhalten haben und b1) Postmenopausale Patientinnen mit vorangegangener endokriner Therapie

a1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

Anastrozol oder Letrozol oder Fulvestrant, oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ribociclib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Hinweis auf einen geringen Zusatznutzen

b1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:

- Tamoxifen oder
- Anastrozol oder
- Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung

oder

• Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nichtsteroidalen Aromataseinhibitor gekommen ist.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ribociclib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Anhaltspunkt für einen geringen Zusatznutzen

G-BA, 2019 [7].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Mai 2019 und 05. Dezember 2019 - Abemaciclib (Mammakarzinom, HR+, HER2-, Kombination mit Fulvestrant)

Gütig bis: Patientengruppe a1), b1), b2) 15. März 2020

Anwendungsgebiet

Verzenios ist angezeigt zur Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie.

Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.

Hinweis:

Der vorliegende Beschluss bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant. Für die Bewertung des Zusatznutzens von Abemaciclib mit einem Aromatasehemmer wird auf das separate Nutzenbewertungsverfahren für diese Kombinationstherapie verwiesen.

a1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

Anastrozol oder Letrozol oder Fulvestrant oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

a2) Prä-/perimenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

Tamoxifen in Kombination mit einer Ausschaltung der Ovarialfunktion.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:

- Tamoxifen oder
- Anastrozol oder
- Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung oder
- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b2) Prä-/perimenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligen Zulassung.

Im vorliegenden Anwendungsgebiet sind Tamoxifen, Letrozol, Exemestan, Megestrolacetat und Medroxyprogesteronacetat zugelassen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

G-BA, 2019 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Mai 2019 - Abemaciclib (Mammakarzinom, HR+, HER2-, Kombination mit Aromatasehemmer)

Gültig bis: Patientengruppe a1) 31. Dezember 2022

Anwendungsgebiet

Verzenios ist angezeigt zur Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie.

Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.

Hinweis:

Der vorliegende Beschluss bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer. Für die Bewertung des Zusatznutzens von Abemaciclib mit Fulvestrant wird auf das separate Nutzenbewertungsverfahren für diese Kombinationstherapie verwiesen.

a1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

Anastrozol oder Letrozol oder Fulvestrant oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Anastrozol oder Letrozol gegenüber Anastrozol oder Letrozol:

Ein Zusatznutzen ist nicht belegt

a2) Prä-/perimenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

Tamoxifen in Kombination mit einer Ausschaltung der Ovarialfunktion.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:

- Tamoxifen oder
- Anastrozol oder
- Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung oder
- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b2) Prä-/perimenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligen Zulassung.

Im vorliegenden Anwendungsgebiet sind Tamoxifen, Letrozol, Exemestan, Megestrolacetat und Medroxyprogesteronacetat zugelassen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

G-BA, 2019 [8].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 18. Juli 2019 - Palbociclib) Neubewertung nach Fristablauf – Patientenpopulation b1 und b2)

gültig bis: Patientengruppe a1) bis 02.01.2021

Anwendungsgebiet

Ibrance ist angezeigt zur Behandlung von Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen lokal fortgeschrittenen oder metastasierten Brustkrebs:

- in Kombination mit einem Aromatasehemmer

- in Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten

Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH =Luteinizing Hormone-Releasing Hormone) kombiniert werden.

Hinweis:

Der Beschluss vom 22. März 2019 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Palbociclib in Kombination mit Fulvestrant in den Teilpopulationen: b1) Postmenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist und b2) Prä-/ perimenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist.

a1) Postmenopausale Patientinnen in Erstlinientherapie:

Zweckmäßige Vergleichstherapie:

Anastrozol oder Letrozol oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Letrozol:

Ein Zusatznutzen ist nicht belegt

a2) Prä-/perimenopausale Patientinnen in Erstlinientherapie:

Zweckmäßige Vergleichstherapie:

Tamoxifen in Kombination mit einer Ausschaltung der Ovarialfunktion.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b1) Postmenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist:

Zweckmäßige Vergleichstherapie:

Eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:

- Tamoxifen

oder

- Anastrozol

oder

- Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung,

oder

- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung,

oder

- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung,

oder

- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Palbociclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b2) Prä-/perimenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist:

Zweckmäßige Vergleichstherapie:

Eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligen Zulassung.

Im vorliegenden Anwendungsgebiet sind Tamoxifen, Letrozol, Exemestan, Megestrolacetat und Medroxyprogesteronacetat zugelassen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Palbociclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

3.2 Cochrane Reviews

Lee C et al., 2017 [9].

Fulvestrant for hormone-sensitive metastatic breast cancer.

Fragestellung

To assess the efficacy and safety of fulvestrant for hormone-sensitive locally advanced or metastatic breast cancer in postmenopausal women, as compared to other standard endocrine agents.

Methodik

Population:

Postmenopausal women who had hormone-sensitive breast cancer (ER-positive or PgR-positive, or both) and who were diagnosed with locally advanced breast cancer (TNM classifications: stages IIIA, IIIB, and IIIC) or metastatic breast cancer (TNM classification: stage IV).

Intervention:

Fulvestrant with or without other standard anticancer treatments (e.g. endocrine therapy or chemotherapy, or both).

Komparator:

- any standard endocrine agents (tamoxifen and aromatase inhibitors) not containing fulvestrant

- any other anticancer treatment (e.g. chemotherapy).

Endpunkte:

- PFS, TTP, TTF, OS; Quality of life, Tolerability
- Clinical benefit rate: defined as the proportion of women with an objective response or a best overall tumour assessment of stable disease

Recherche/Suchzeitraum:

- Recherche am 7.7.2015
- CENTRAL (via the Cochrane Library, Issue 6, 2015
- MEDLINE and EMBASE from 2008 to 7 July 2015
- WHO ICTRP for all prospectively registered and ongoing trials
- major conference proceedings (ASCO and San Antonio Breast Cancer Symposium) and practice guidelines from major oncology groups (ASCO, ESMO, NCCN and Cancer Care Ontario).
- Handsearch in reference lists from relevant studies

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool, Assessment of heterogeneity by using Chi^2 test and I^2 statistic
- Assessment of quality of evidence by GRADE approach ('Summary of findings' tables)

Ergebnisse

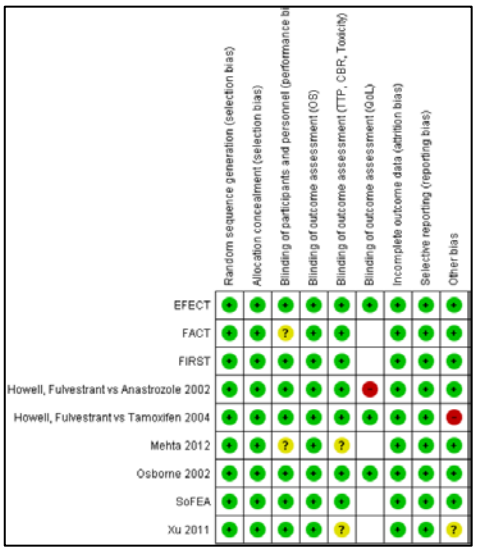
Anzahl eingeschlossener Studien: N=9 (n=4514)

Charakteristika der Population /der Studien:

- All participants postmenopausal women with hormone-sensitive breast cancer
- 4 studies with patients who had relapsed in the first instance and were naïve to treatment in the metastatic setting (FACT; FIRST; Howell, Fulvestrant vs Tamoxifen 2004; Mehta 2012) →first-line endocrine.
- Five studies enrolled women who had received prior endocrine treatment for metastatic disease (EFECT; Howell, Fulvestrant vs Anastrozole 2002; Osborne 2002; SoFEA; Xu 2011) → second-line endocrine or more.
- All 9 included studies compared fulvestrant as the intervention against an established standard breast cancer treatment, that is:
  - the aromatase inhibitors anastrozole (non-steroidal) and
  - exemestane (steroidal),
  - and the selective oestrogen receptor modulator tamoxifen.
- All studies except one tested fulvestrant at the 250 mg dose level (with 500mg loading dose); FIRST was the only study to dose fulvestrant at the now-approved current and standard dosing of 500mg intramuscular injections monthly

Qualität der Studien:

- Most studies were high quality studies; 1 study with high risk of bias due to lack of blinded outcome assessment, 1 further study with high risk of other bias



Studienergebnisse (Results for fulvestrant vs. comparators (other endocrine therapy)

OS:

- Overall: HR 0.97, 95% CI 0.87 to 1.09; (p=0.62; 2480 women; I^2=66%; high quality evidence) → no sign. difference
- Subgroup with approved dose (FIRST): HR 0.70, 95%CI 0.50 to 0.98 → superiority of fulvestrant (=firstline)

PFS:

- Overall: HR 0.95; 95%CI 0.89 to1.02 (4258 women; 9 studies; moderate-quality evidence)→ no significant differences
- Subgroup with approved dose (FIRST): HR of 0.66 (95% CI 0.47 to 0.93) 205 women
- second-line treatment: HR 0.96, 95% CI 0.88 to 1.04; 2255 women; 5 studies

Clinical benefit rate:

- Overall: RR 1.03 (95% CI 0.97 to 1.10); 4105 women; high-quality evidence
- Secondline: RR 1.03, 95% CI 0.92 to 1.15; 2105 women, 5 studies)

Quality of life:

- 4 studies reported quality of life (Functional Assessment of Cancer Therapy-Breast (FACT-B) or Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES) questionnaires) with follow-up ranging from 8.9 months to 38 months.
- None of the studies reported a difference in quality of life as per their analyses between participants receiving fulvestrant and other endocrine treatments but numerical data were not presented.

Toxicity: Assessment of 3 most common toxicities vasomotor, arthralgia + gynaecological toxicities (*nicht nach first- und secondline treatment differenziert*):

- Although there was some variation between the individual trials in the 3 examined toxicities, overall summary statistics were not significantly different between fulvestrant and the comparator drugs.

- vasomotor toxicity: RR 1.02 (95% CI 0.89, 1.18); 8 trials, 3544 women; I^2=55%, high-quality evidence,
- arthralgia: RR 0.96 (95%CI 0.86, 1.09); 7 trials, 3244 women; I^2=59%; high-quality evidence
- Gynaecological toxicity (urinary tract infection, vulvovaginal dryness, vaginal haemorrhage, vaginitis, and pelvic pain: RR 1.22 (95% CI 0.94, 1.57); 2848 women; I^2= 66%; high-quality evidence

Anmerkung/Fazit der Autoren

As evidenced from our pooled data from 4514 women, fulvestrant (mostly administered at the anachronistic dose of 250 mg) was as effective as other standard endocrine therapies with respect to efficacy (measured by PFS, CBR, overall survival), toxicity, and quality of life. It is important to highlight that even at this inferior dose, fulvestrant was as effective and well tolerated as other comparator endocrine therapies. In our one included study of fulvestrant at the 500 mg dose level, fulvestrant was superior to anastrozole (FIRST).

Kommentare zum Review

- HER2 Status der eingeschlossenen Studien unklar

Tosello et al., 2018 [18].

Breast surgery for metastatic breast cancer

Fragestellung

To assess the effect of breast surgery on women with metastatic breast cancer.

Methodik

Population:

- Women with metastatic breast cancer at initial diagnosis: TNM (tumour, lymph nodes, metastases) stage IV (Sobin 2002). This includes when breast cancer has spread beyond the breast, chest wall, and regional nodes. We applied no restrictions regarding age or histological type. If a study contained a subset of eligible participants, we would include them in the review as long as we could extract the relevant results.

Intervention:

- surgery plus systemic therapy

Komparator:

- systemic therapy alone

Endpunkte:

- primary outcomes were overall survival and quality of life.
- Secondary outcomes were progression-free survival (local and distant control), breast cancer-specific survival, and toxicity from local therapy.

Recherche/Suchzeitraum:

- Cochrane Breast Cancer Specialised Register, CENTRAL, MEDLINE (by PubMed) and Embase (by OvidSP) on 22 February 2016. We also searched ClinicalTrials.gov (22 February 2016) and the WHO International Clinical Trials Registry Platform (24 February 2016).

Qualitätsbewertung der Studien:

- Cochrane approach/GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

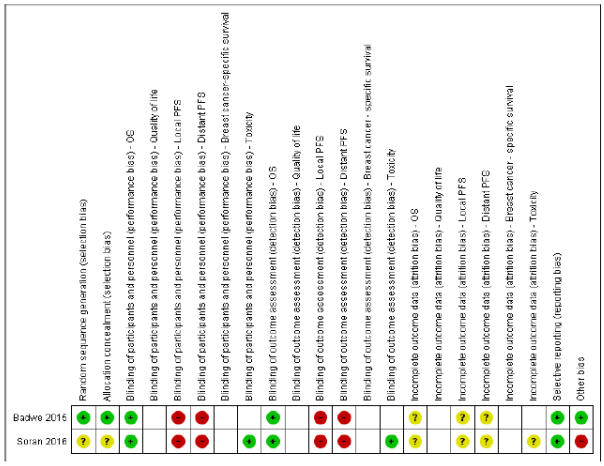
- We included two trials enrolling 624 women

Charakteristika der Population:

- There were 426 women with ER-positive tumours; 200 women with ER negative tumours; 192 women with HER2-positive tumours; 421 with HER2-negative tumours; and 226 women with bone-only metastases.

Qualität der Studien:

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



- Siehe weitere Details bei Ergebnisdarstellung

Studienergebnisse:

- It is uncertain whether breast surgery improves overall survival as the quality of the evidence has been assessed as very low (n.s.; 2 studies; 624 women). Breast surgery may improve local progression-free survival (HR 0.22, 95% CI 0.08 to 0.57; 2 studies; 607 women; low quality evidence), while it probably worsened distant progression-free survival (HR 1.42, 95% CI 1.08 to 1.86; 1 study; 350 women; moderate-quality evidence).
  - For both HER2-positive and -negative subgroups, the results were consistent with the main analysis.
  - For both ER-positive and -negative subgroups, the results were consistent with the main analysis.
- The two included studies did not measure breast cancer-specific survival.
- The two studies did not report quality of life.

- Toxicity from local therapy was reported by 30-day mortality and did not appear to differ between the two groups (RR 0.99, 95% CI 0.14 to 6.90; 1 study; 274 women; low-quality evidence).

Anmerkung/Fazit der Autoren

Based on existing evidence from two randomised clinical trials, it is not possible to make definitive conclusions on the benefits and risks of breast surgery associated with systemic treatment for women diagnosed with metastatic breast cancer. Until the ongoing clinical trials are finalised, the decision to perform breast surgery in these women should be individualised and shared between the physician and the patient considering the potential risks, benefits, and costs of each intervention.

Kommentare zum Review

- Heterogene Patientenpopulation hinsichtlich Rezeptorstatus:
  - Einschluss von ER+ und ER- Patientinnen
  - Einschluss von HER + und HER- Patientinnen
- 1 Studie mit Patientinnen mit Chemotherapie-Vorbehandlung

3.3 Systematische Reviews

Ding W et al., 2018 [3].

The CDK4/6 inhibitor in HR-positive advanced breast cancer: A systematic review and meta-analysis

Fragestellung

To explore whether CDK4/6 inhibitors had a significantly benefit to treating hormone receptor-positive (HR-positive)/human epidermal growth factor receptor 2 negative (HER2-negative) advanced breast cancer

Methodik

Population:

- patients with HR-positive/HER2-negative advanced breast cancer

Intervention:

- CDK4/6 inhibitors

Komparator:

- K.A. siehe ,,Charakteristika der Population“

Endpunkte:

- progression-free survival, response, and adverse events

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Library from January 1980 to December 2017

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs (2x Palbociclib, 2x Ribociclib, 2 Abemaciclib) records containing 3182 patients

Charakteristika der Population:

Table 1

Characteristics of included studies and outcome events.

Trials	Finn 2014[9]	Finn 2016[10]	Hortobagyi 2016 [11]	Cristofanilli 2016[13]	Sledge 2017[14]	Goetz 2017[15]
Information of the included trials						
Regions	50 sites in 12 countries	186 sites in 17 countries	223 sites in 29 countries	144 sites in 17 countries	142 sites in 19 countries	158 sites in 22 countries
Phases	I	II	II	II	III	II
Accrual dates	December 22, 2009, and May 12, 2012	February 2013 and July 2014	January 24, 2014, and March 24, 2015	October 7, 2013, and August 26, 2014	August 7, 2014, and December 29, 2015	November 18, 2014, and November 11, 2015
Inclusion criteria and study design						
Inclusion criteria	Postmenopausal; HR+, HER2− ABC; first-line	Postmenopausal; HR+, HER2− ABC; first-line	Postmenopausal; HR+, HER2− ABC; first-line	Any menopausal status; HR+, HER2− ABC; second-line	Any menopausal status, HR+, HER2− ABC; second-line	Postmenopausal; HR+, HER2− ABC; first-line
Study design	Palbociclib (125mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5mg daily)	Palbociclib (125mg daily for 21 d every 28 d) + letrozole (2.5mg daily) vs placebo + letrozole (2.5mg daily)	Ribociclib (600mg daily for 21 d every 28 d) + letrozole (2.5mg daily) vs placebo + letrozole (2.5 mg daily)	Palbociclib (125mg daily for 21 d every 28 d) + fulvestrant (500mg every 28 d) vs placebo + fulvestrant (500mg every 28 d)	Abemaciclib (150mg twice daily every 28 d) + fulvestrant (500 mg every 28 d) vs placebo + fulvestrant (500 mg every 28 d)	Abemaciclib (150 mg twice daily every 28 d) + anastrozole (1mg daily) or letrozole (2.5 mg daily) vs placebo + anastrozole (1 mg daily) or letrozole (2.5 mg daily)
Patient demographic characteristic						
Age, y	T: 63 (54–71) C: 64 (56–70	T: 62 (30–89) C: 61 (28–88)	T: 62 (23–91) C: 63 (29–88)	T: 57 (30–88) C: 56 (29–80)	T: 59 (32–91) C: 63 (29–88)	T: 63 (38–87) C: 63 (32–88)
No. of patients	T: 84 C: 81	T: 444 C: 222	T: 334 C: 334	T: 347 C: 174	T: 446 C: 223	T: 328 C: 165
Outcomes assessment						
Primary end point	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival
Secondary end point	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response rate, the clinical benefit response	Objective response rate, the clinical benefit response

ABC = advanced breast cancer, C = control group, HER2− = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive, T = treatment group (also known as CDK4/6 inhibitor group).

Qualität der Studien:

- For allocation concealment, the risk of bias was unclear in 3 RCTs with an allocation scheme which was not mentioned in the trials. For random sequence generation, the risk of bias was unclear in 2 RCT studies. For the performance bias and detection bias, the risk was high in one study and unclear in another one. Except these 3 outliers, no high or unclear risk of bias was observed in any other studies.

Studienergebnisse:

- The result showed the CDK4/6 inhibitor group had a longer progression-free survival (PFS) (hazard ratio=0.51; 95% confidence interval [CI], 0.46–0.57, P < .00001), a better objective response (risk rate=1.53; 95% CI, 1.35–1.74, P < .00001), as well as a better clinical benefit response (risk rate=1.29; 95% CI, 1.13–1.47, P=.0001).
- Besides, subgroup analyses of PFS according to stratification factors and other baseline characteristics confirmed a great performance of CDK4/6 inhibitors across the all subgroups.
- As for neutropenia, all grades of it were substantially more frequent in the CDK4/6 inhibitor group (65%), compared with the control group (5%). Interestingly, grade 3 or 4 neutropenia was found among 43% of patients in the CDK4/6 inhibitor group and among 1% of patients in the control group. Meanwhile, leucopenia with all grades also appeared much more common in the CDK4/6 inhibitor group than in the control group (35% and 3% respectively), especially grade 3 or 4 leucopenia. Furthermore, infection, fatigue, nausea, anemia,

thrombocytopenia, alopecia, nausea, rash, constipation, vomiting, and stomatitis were also more common in the CDK4/6 inhibitor group. Serious adverse events from any cause were occurred among 308 (19%) persons of 1974 patients in the CDK4/6 inhibitor group, and among 121 people (12%) of 1185 patients in the control group.

Subgroup sensitivity and analysis for progression-free survival

	HR (95% CI)	*P*	I^2, %
1. Subgroup analysis			
Age			
<65 y	0.50 (0.44–0.57)	<.00001	11
≥65 y	0.56 (0.47–0.67)	<.00001	0
Visceral metastasis			
Yes	0.57 (0.47–0.62)	<.00001	0
No	0.50 (0.42–0.59)	<.00001	23
Bone-only metastasis			
Yes	0.47 (0.34–0.65)	<.0001	17
No	0.56 (0.47–0.66)	<.00001	35
Race			
Asian	0.46 (0.36–0.59)	<.00001	0
Non-Asian	0.56 (0.49–0.64)	<.00001	24
Disease-free interval			
<12 mo	0.51 (0.38–0.68)	<.00001	20
≥12 mo	0.48 (0.37–0.61)	<.00001	0
Newly metastatic disease			
Yes	0.58 (0.43–0.79)	.0005	33
No	0.55 (0.45–0.67)	<.00001	0
Previous hormonal therapy			
Yes	0.48 (0.40–0.56)	<.00001	0
No	0.56 (0.48,0.66)	<.00001	0
Previous chemotherapy			
Yes	0.51 (0.43–0.61)	<.00001	0
No	0.51 (0.41–0.62)	<.00001	47
ECOG performance status			
0	0.55 (0.45–0.65)	<.00001	0
1 or 2	0.55 (0.46,0.67)	<.00001	0
Hormone-receptor status			
ER and PR-positive	0.55 (0.45–0.67)	<.0001	0%
Other	0.48 (0.36–0.64)	<.00001	0%
Palbociclib vs ribociclib vs abemaciclib			
Palbociclib	0.51 (0.43–0.60)	<.00001	37
Ribociclib	0.56 (0.43–0.72)	<.00001	—
Abemaciclib	0.49 (0.41,0.59)	<.00001	0
First-line vs second-line			
First-line	0.56 (0.48–0.65)	<.00001	0
Second-line	0.46 (0.39–0.55)	<.00001	—
2. Sensitivity analysis			
Excluding Finn 2014 trial	0.51 (0.46–0.58)	<.00001	3

Anmerkung/Fazit der Autoren

CDK4/6 inhibitors can significantly prolong the PFS and improve the objective response or clinical benefit response, which was confirmed in every subgroup of the meta-analysis we performed. Adverse events are reversible, and the rate of discontinuation due to adverse events is low. Further studies should focus on whether treating with CDK4/6 inhibitors can significantly prolong the overall survival of patients with advanced breast cancer.

Kommentare zum Review

- Eingeschlossene Studien umfassen first- oder secondline endocrine setting, Subgruppenanalyse nach Setting durchgeführt

Messina C et al., 2018 [12].

CDK4/6 inhibitors in advanced hormone receptor-positive/HER2-negative breast cancer: a systematic review and meta-analysis of randomized trials

Fragestellung

We performed a meta-analysis of randomized clinical trials (RCTs) to better define the benefit and the risk of CDK4/6 inhibitors plus ET for endocrine-sensitive or endocrine-resistant population in metastatic HR+/HER2− breast cancer.

Methodik

Population:

- Patientes with metastatic HR+/HER2− breast cancer

Intervention:

- CDK4/6 inhibitors plus endocrine therapy (ET)

Komparator:

- ET

Endpunkte:

- PFS, ORR, Safety

Recherche/Suchzeitraum:

- Pubmed, Embase, and the Cochrane Library with no data restriction was carried out up to 30 June 2018

Qualitätsbewertung der Studien:

- Risk of Incomplete outcome data addressed bias assessment: Adequate sequence generation, Allocation concealment, Masking, Free of selective reporting

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs with 4.578 patients

Charakteristika der Population:

- 5 RCTs first-line
- 2 RCTs seconed-line
- 1 RCT first and seconed-line
- Genaue Beschreibung der Studien siehe Anhang 1

Qualität der Studien:

Table 2 Risks of bias assessment of the randomized studies included in the present meta-analysis

Trial	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting
MONALEESA-2 [9]	A computer-generated randomization schedule was used	Parallel assignment	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONARCH-2 [11]	A computer-generated randomization schedule was used	Web-based randomization scheme	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONARCH-3 [12]	A computer-generated randomization schedule was used	Centralized interactive Web response system	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
PALOMA-1 [7]	A computer-generated randomization schedule was used	Centralized interactive Web-based randomization system	Open label design	All randomized patients included in analyses	All outcome of interest reported
PALOMA-2 [8]	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
PALOMA-3 [10]	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONALEESA-3	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONALEESA-7	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature

Studienergebnisse:

- PFS: A total of 2009 patients were enrolled in the CDKi plus ET arm and 1381 in the ET arm.
  - The addition of CDKi to ET was associated with a statistically significant PFS benefit (HR 0.55, 95% CI 0.50–0.62) for metastatic HR+/ HER2− breast cancer patients in endocrine-sensitive setting. Moreover, combination treatment improved PFS both in women with visceral metastasis at presentation (HR 0.55, 95% CI 0.47–0.65) and in those with non-visceral metastasis (HR 0.56, 95% CI 0.46–0.68).
  - Three phase III trials [10, 11] assessed the efficacy of CDKi plus ET versus ET alone and reported PFS HRs in endocrine-resistant setting: hence results were suitable for our meta-analysis (Fig. 2b). A total of 791 women were enrolled in the CDKi plus ET arm and 395 in the ET arm. All the women included in the two trials had been previously treated with ET. The addition of CDKi to ET was associated with a statistically significant PFS benefit (HR 0.51, 95% CI 0.43–0.61). The PFS advantage was significantly maintained both in patients with visceral metastasis (HR 0.47, 95% CI 0.38–0.58) and in those with non-visceral metastasis (HR 0.56, 95% CI 0.43–0.73).

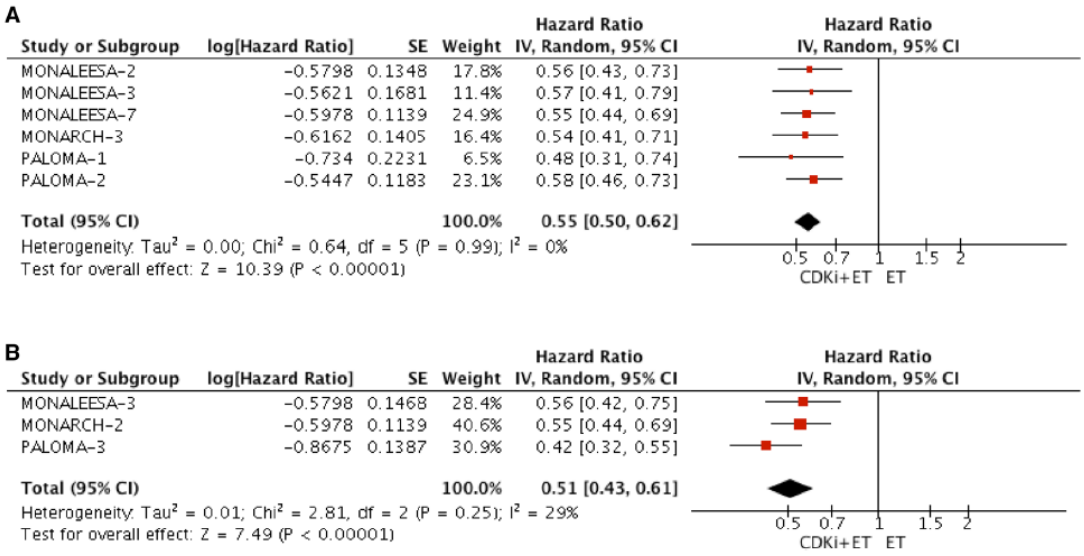


Fig. 2 Forest plot of hazard ratios (HRs) for progression-free survival (PFS) in eight randomized trials of CDK inhibitors plus endocrine therapy compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**) advanced HR+ HER2− breast cancer women. Pooling HRs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy

- Response: One phase II trial [7] and four phase III trials [8, 9, 12, 13] included in our systematic review reported on ORR events occurring in the CDKi plus ET arm and in the ET alone arm, respectively (Fig. 4). A total of 871 ORR events occurred among 1525 patients treated with CDKi plus ET, and 786 in the 1139 women receiving ET alone.
  - The combination of CDKi plus ET significantly improved the ORR compared to ET alone (ORs: 0.62, 95% CI 052–0.73) (Fig. 4a).
  - Two phase III trials reported the OR events occurring in the CDKi plus ET arm and in the ET alone arm, respectively, in endocrine-resistant setting: hence results were suitable for our meta-analysis (Fig. 4b). A total of 570 ORR events occurred among 793 patients treated with CDKi plus ET and 350 in the 397 women assigned to fulvestrant alone. The addition of CDKi–ET was associated with a statistically significant ORR benefit (ORs 0.33, 95% CI 0.24–0.47).

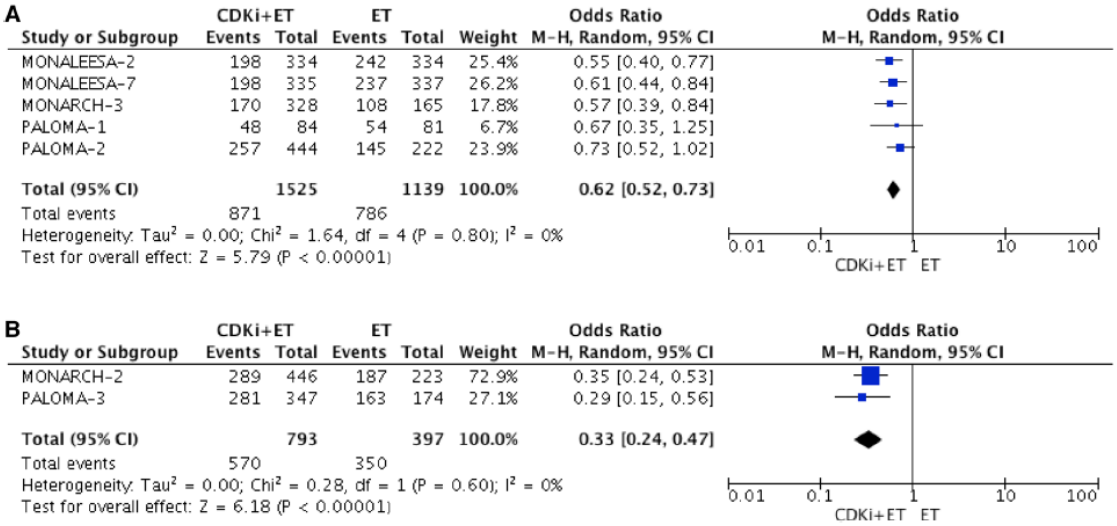


Fig. 4 Forest plot of Odds ratios (ORs) objective response rate (ORR) in seven randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive disease (**a**), endocrine-resistant disease (**b**) in advanced or metastatic HR+ HER2– breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* Odds ratios

- Toxicities: All the trials included in our systematic review reported G3–G4 AEs occurring in the CDKi plus ET arm and in the ET alone arm (Fig. 5a). A total of 1107 out of 1541 patients (71.8%) treated with CDKi plus ET developed G3–G4 AEs compared to 313 out of 1127 women (27.8%) assigned to treatment with ET alone in endocrine-sensitive setting. The pooled ORs was 7.51 (95% CI 5.52–10.21), indicating a much higher probability of developing ≥ G3–G4 AEs for patients treated with CDKi and ET (Fig. 5a); however, significant heterogeneity between the four studies emerged (I2 63%).
  - Two phase III trials [10, 11] included in our systematic review assessed the activity of CDKi plus ET vs ET alone in endocrine-resistant setting: hence again results were suitable for our meta-analysis. A total of 506 out of 791 patients (64%) treated with CDKi plus ET, and 82 out of 395 women (20.7%) assigned to ET alone developed G3–G4 AEs. The pooled ORs was 7.09 (95% CI 3.53–14.25), again indicating a much higher probability of developing G3–G4 AEs for patients treated with CDKi plus ET (Fig. 5b); however, significant heterogeneity between the two studies emerged (I2 83%).
  - Again, we pooled together the eight randomized trials to assess the global impact in terms of G3–G4 AEs of combining CDKi with ET compared to ET alone. A total of 2006 out of 2815 patients (71.2%) treated with CDKi plus ET and 411 out of 1763 women (23.3%)

assigned to ET alone developed G3–G4 AEs. The pooled ORs was 9.64 (95% CI 6.00–15.49), indicating a much higher probability of developing G3–G4 AEs for patients treated with CDKi and ET (Fig. 5c); significant heterogeneity between the eight studies emerged (I2 90%). However, the increased chance of developing G3–G4 toxicities for patients treated with CDKi plus ET may be influenced mostly by the odds to develop G3–G4 neutropenia (OR 10.88, 95% CI 6.53–18.14; Fig. 6).

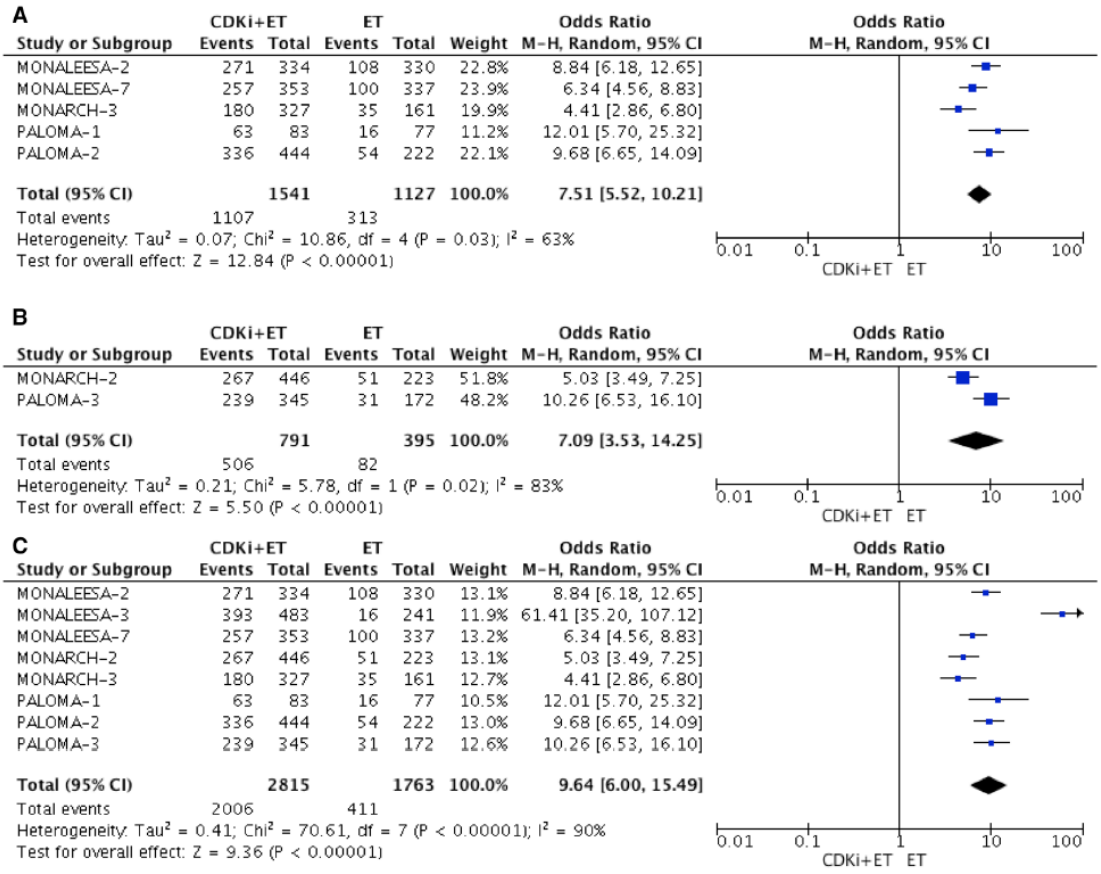


Fig. 5 Forest plot of odds ratios (ORs) for ≥G3–G4 AE in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population in advanced HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* odds ratios

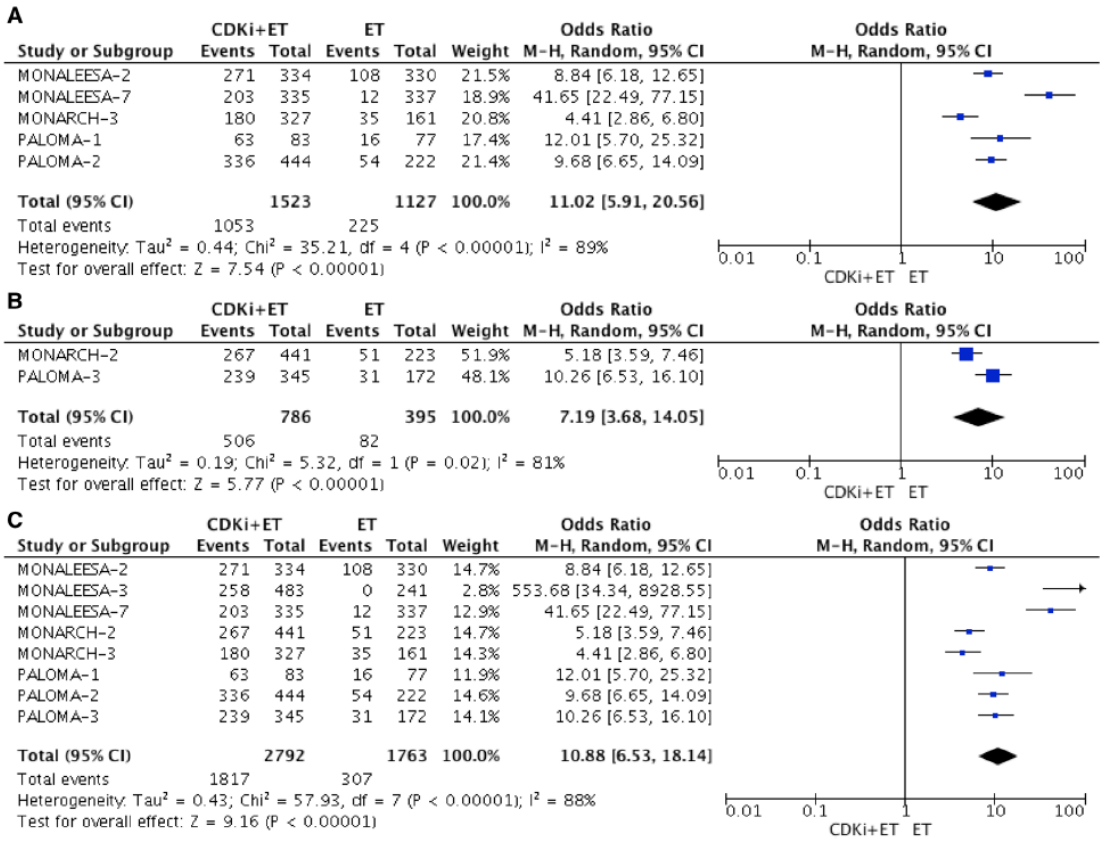


Fig. 6 Forest plot of odds ratios (ORs) for ≥G3–G4 neutropenia in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population (**c**) in advanced HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* odds ratios

Anmerkung/Fazit der Autoren

Emerging data provide a new standard treatment for advanced HR+/Her2− breast cancer, regardless of menopausal status, prior hormonal/chemotherapy treatments delivered, sites of metastasis. However, benefits should be balanced with longer treatment duration, toxicities, and costs. Mature OS data are awaited. Head-to-head trials are warranted to compare the efficacy of CDKi plus ET or chemotherapy especially for women with high tumour burden and visceral metastases in order to improve patient's selection and maximize the benefit from the combined approach.

Kommentare zum Review

- Eingeschlossene Studien umfassen firstline und/oder secondline endocrine therapy, Analysen getrennt nach setting
- Weitere Reviews zu dem Thema:
  - SR von Shohdy et al. 2017 [17]. thematisiert gastrointestinale Nebenwirkungen von CDK4/6 Inhibitoren (Fazit: CDK4/6 inhibitors not associated with higher-grade GI toxicities, but stat. sign. higher risk for all-grade GI toxicities)

Patterson-Lomba O et al., 2019 [14].

Systematic literature review of clinical trials of endocrine therapies for premenopausal women with metastatic HR+ HER2- breast cancer

Fragestellung

We conducted a systematic review and assessed the feasibility of an indirect treatment comparison (ITC) to characterize the comparative efficacy of endocrine-based therapies in this setting.

Methodik

Population:

- Premenopausal women with metastatic HR+ HER2- breast cancer

Intervention/Komparator:

The interventions will include at least one of the following therapies, either as monotherapy or as part of a combination therapy:

- Endocrine therapy: letrozole, anastrozole, exemestane, tamoxifen, fulvestrant
- Targeted therapy: palbociclib, ribociclib/LEE011, abemaciclib
- Chemotherapy: capecitabine, doxorubicin, paclitaxel, docetaxel, cyclophosphamide, eribulin

Endpunkte:

At least one of the following outcomes is reported:

- Efficacy outcomes: Overall survival (OS), Progression-free survival (PFS), Time to progression (TTP) , Overall response rate (ORR)
- Safety outcomes: Adverse events (AEs), Serious AEs (SAEs), Discontinuation due to AE, All-cause discontinuation
- HRQOL outcomes: European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23), Functional assessment of cancer therapy for breast cancer (FACT-B), EQ-5D, Other QoL measures

Recherche/Suchzeitraum:

- MEDLINE (2007-December 26, 2017), MEDLINE (R) In-Process (2007-December 26, 2017), EMBASE (2007 week 1-2017 week 52), Cochrane Database of Systematic Reviews (CDSR) (2007-December 19 2017), Cochrane Central Register of Controlled Trials (CENTRAL) (2007-November 2017), and Database of Abstracts of Reviews of Effects (DARE) (2007-2017). The search also included several conference proceedings.

Qualitätsbewertung der Studien:

- adapted from the “Systematic reviews: CRD's guidance for undertaking reviews in health care”

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs

Charakteristika der Population:

- The sample size per treatment arm of premenopausal women in the identified trials was relatively small (range, 36-72), except for the MONALEESA-7 trial (335-337)
- MONALEESA-7 trial is the only trial in the first-line treatment setting for metastatic disease, whereas the patient population in the other trials had progressed after prior ET either in the metastatic setting, and in the case of MONARCH 2, patients either progressed ≤12 months after adjuvant ET or while receiving ET for mBC.

TABLE 2 Baseline characteristics

	PALOMA-3*		MONARCH-2		KCSG BR10-04*			MONALEESA-7*	
Characteristics[a]	Palbociclib + fulvestrant + goserelin	Placebo + fulvestrant + goserelin	Abemaciclib + fulvestrant + GnRHa	Placebo + fulvestrant + GnRHa	Fulvestrant + goserelin	Anastrozole + goserelin	Goserelin alone	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin
Trial phase	III		III		II			III	
Sample size, N	72	36	72	42	44	47	47	335	337
Age (y)									
Median (Range)	NR[b]	NR[b]	46 (32-57)	47 (32-66)	42.9 (28.0-53.0)	44.1 (23.0-53.0)	42.3 (32.0-55.0)	43 (25-58)	45 (29-58)
Race/Ethnicity, N (%)									
White	37 (51.4)	21 (58.3)	14 (19.4)[c]	16 (38.1)[c]	NR	NR	NR	187 (55.8)	201 (59.6)
Asian	31 (43.1)	13 (36.1)	51 (70.8)[c]	24 (57.1)[c]	NR	NR	NR	99 (29.6)	99 (29.4)
Black	NR[b]	NR[b]	NR[c]	NR[c]	NR	NR	NR	10 (3.0)	9 (2.7)
Native American	NR	NR	NR[c]	NR[c]	NR	NR	NR	3 (0.9)	3 (0.9)
Other	4 (5.6)[d]	2 (5.6)[d]	7 (9.7)[d]	2 (4.7)[d]	NR	NR	NR	16 (4.8)[d]	7 (2.1)[d]
Unknown	NR	NR	NR[c]	NR[c]	NR	NR	NR	20 (6.0)	18 (5.3)
Performance status, N (%)									
ECOG 0	NR	NR	NR	NR	27 (61.4)	26 (55.3)	31 (66.0)	245 (73.1)	255 (75.7)
ECOG 1	NR	NR	NR	NR	16 (36.4)	19 (40.4)	16 (34.0)	87 (26.0)	78 (23.1)
ECOG 2	NR	NR	0 (0.0)	0 (0.0)	1 (2.6)	2 (4.3)	0 (0.0)	0 (0.0)	1 (0.3)
ECOG >2	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	NR	NR	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	3 (0.9)
Prior therapy, N (%)									
Endocrine therapy	72 (100.0)	36 (100.0)	72 (100)	42 (100)	NR	NR	NR	127 (37.9)[e]	141 (41.8)[e]
Chemotherapy	23 (31.9)[f]	12 (33.3)[f]	NR	NR	10 (22.7)	10 (21.3)	12 (25.5)	185 (55.2)[g]	185 (54.8)[g]
Cancer stage, N (%)			NR	NR					
Locally advanced	NR	NR	0 (0.0)[c]	0 (0.0)[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Metastatic	NR	NR	72 (100.0)[c]	42 (100.0)[c]	44 (100.0)	47 (100.0)	47 (100.0)	334 (99.7)	336 (99.7)

Abbreviation(s): ECOG, Eastern Cooperative Oncology Group; GnRHa, gonadotropin-releasing hormone agonist (eg, goserelin); NR, not reported; NSAI, nonsteroidal aromatase inhibitor.
[a]Baseline characteristics are for the entire trial population. Trials with * have 100% pre- or peri-menopausal population or report baseline characteristics for the pre- or peri-menopausal population.
[b]Age was reported as number and percentage for the following age groups: ≤40, 40-50, and >50 y old.
[c]The data has been extracted from the 2018 ASCO Annual Meeting Presentation.
[d]Other includes Black, Native American and etc when these categories have not been reported separately.
[e]Prior (neo) adjuvant endocrine therapy.
[f]Previous chemotherapy in metastatic setting. Subjects are counted for each treatment of metastatic disease (± neoadjuvant) received.
[g]Calculated as the sum of chemotherapy for (neo) adjuvant only and advanced disease.

Qualität der Studien:

- The included trials were all well-conducted and the risk of bias was low to moderate, with concealment of allocation (with the exception of KCSG BR10-04).

Studienergebnisse:

- PFS HR for the premenopausal population was reported in PALOMA-3 (palbociclib vs placebo arm: 0.50 [0.29-0.87]), MONARCH-2 (abemaciclib vs placebo arm: 0.45, [0.26-0.75]), KCSG BR 10-04 (fulvestrant + goserelin vs goserelin: 0.61 [0.37-1.00]; anastrozole + goserelin vs goserelin: 0.98 [0.62-1.55]) and MONALEESA-7 (ribociclib vs placebo arm: 0.55 [0.44-0.69]).
- PALOMA-3, MONARCH-2 and MONALEESA-7 reported median PFS, while KCSG BR 10-04 reported TTP. The median time to progression or death is longer in MONALEESA-7 compared to the other three trials, partly due to the former trial being in the first-line setting. Overall response rate (ORR) was larger in MONARCH-2 compared to MONALEESA-7 and PALOMA-3. Only MONALEESA-7 reported quality of life outcomes in the premenopausal

population. Although there were differences between the PALOMA-3 and MONARCH-2 trials (eg, reference arms were slightly different [in MONARCH it was not specified that goserelin was the only GnRHa used], and patients had different prior treatment history [more patients in MONARCH-2 progressed within 12 months of adjuvant ET]), a naïve comparison of the PFS HR between these two trials indicates that abemaciclib + fulvestrant + GnRHa (HR = 0.45) is associated with a lower hazard of progression or death than palbociclib + fulvestrant + goserelin (HR = 0.50). However, due to the small sample size limitation, the confidence around these estimates are large and overlapping.

- No NMA conducted: disconnected network of the four identified trials corresponding to the PFS HR outcome (the only outcome reported for all trials): In order to form a fully connected network, strong clinical assumptions are needed, such as “pooling” endocrine-based therapies (ie, assume that the clinical efficacies of the comparator arms in PALOMA-3 [fulvestrant + goserelin], MONARCH-2 [fulvestrant + GnRHa] and MONALEESA-7 [NSAI/tamoxifen + goserelin] are all similar in terms of PFS). Moreover, MONALEESA 7 is in the first-line (ET-naïve) setting, while all other studies are in the ET-failure setting. Hence, to be able to compare the ribociclib arm with the rest of the therapies, it would have to be assumed that the PFS HRs are similar in the first-line and second line settings.

Anmerkung/Fazit der Autoren

To conclude, this systematic literature evaluation provides a comprehensive review of the available clinical trial evidence on the efficacy and safety of ET as treatments for premenopausal women with HR+/HER2− mBC. The search demonstrated the paucity of RCTs focusing on premenopausal HR+ HER2− mBC, with only four trials having reported relevant data in this setting. MONALEESA-7 is currently the only phase 3 trial focused on premenopausal HR+ HER2− mBC in the first-line setting. Efficacy results from the selected trials indicated that combining a CDK4/6 inhibitor with an endocrine monotherapy and a GnRHa led to improvements in PFS and ORR in premenopausal women with HR+/HER2− mBC in the first-line and ET-failure settings.

Kommentare zum Review

Review umfasst Studien mit ET-naiven Patientinnen als auch Studien mit ET-vorbehandelten Patientinnen (MONALEESA 7 is in the first-line (ET-naïve) setting, while all other studies are in the ET-failure setting)

Bottcher TM et al., 2019 [1].

Treatment of advanced HR+/HER2- breast cancer with new targeted agents in combination with endocrine therapy: a review of efficacy and tolerability based on available randomized trials on everolimus, ribociclib, palbociclib and abemaciclib

Fragestellung

To evaluate available randomized trials on the mammalian target of rapamycin (mTOR) inhibitor, everolimus, and the cyclin-dependent kinase (CDK) 4/6 inhibitors, ribociclib, palbociclib and abemaciclib in combination with endocrine therapy (ETs) in HR+/HER2- MBC regarding efficacy, tolerability and safety.

Methodik

Population:

- HR+/HER2- MBC

Intervention:/Komparator:

- everolimus, abemaciclib, ribociclib or palbociclib in combination with ET vs. ET

Endpunkte:

- OS, PFS, ORR, AE

Recherche/Suchzeitraum:

- A Pubmed search on the 2 November 2017

Qualitätsbewertung der Studien:

- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs
  - 4 Studies Patients received treatments as first-line metastatic treatment
  - 2 Studies previously treated for metastatic disease
  - 2 Studies: Mixed population

Charakteristika der Population:

Table 1. Study information and patient populations.

Studies	Bachelot et al. [25]	BOLERO-2 [26]	MONALEESA-2 [27]	PALOMA-1 [28]	PALOMA-2 [29]	PALOMA-3 [30]	MONARCH 2 [31]	MONARCH 3 [32]
Phase	II	III	III	II	III	III	III	III
Agent	EVE	EVE	RIB	PAL	PAL	PAL	ABE	ABE
ET combination	Tamoxifen	Exemestane	Letrozole	Letrozole	Letrozole	Fulvestrant	Fulvestrant	Letrozole 79.1% or anastrozole
No. of patients	111	724	668	165	666	521	669	493
Median age (yrs)	65	62	63	64	62	57	60	63
ECOG PS (%)								
0	50	60	61	55	52	62	60	60
1	41	36	39	45	47	38	39	40
2	6	3	0	0	1	0	0	0
Menopausal status (%)[a]								
Pre- or peri-menopausal	~	~	~	~	~	21	17	~
Postmenopausal	All	All	All	All	All	79	82.4	All
Prior ET (%)	All	All					All	
None	~	~	–	–	–	~	1	53
As neo-/adjuvant	41[b]	–	52	33	56	22	59	47
As metastatic	67[b]	–	~	~	~	78	38	~
First-line met. Treatment	~	21%	x	x	x	~	~	x
Prior met. Treatment	x	79%	~	~	~	x	38.20%	~
De novo metastatic disease	~	~	34	49	36	~	~	40
Site of metastases:								
Bone only (%)	27	–	22	18	22	–	27	22
Visceral (%)	53	56	59	49	49	60	56	53

When the sum does not equal 100%, it is due to missing patient information.
[a]pre- or peri-menopausal women received a gonadotropin-releasing hormone agonist.
[b]in Bachelot et al. previous ET only refers to aromatase inhibitor treatment.
~ refers to not relevant.
– refers to no data.
EVE: everolimus; RIB: ribociclib; PAL: palbociclib; ABE: abemaciclib; ET: endocrine therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; met: metastatic; mo: months; NR: Not Relevant.

Qualität der Studien:

	Risk of selection bias§: Randomization of patients	Risk of performance bias: Blinding	Loss to follow-up / risk of attrition bias: intervention group vs ET only group	ITT principle or PP analysis of results	Risk of detection bias: investigators of outcomes from tumor assessment (PFS etc.)	Other	Conclusion
Bachelot et al. [25]	Randomized, stratified Imbalance in PS 0; 59% vs 40%, favoring the everolimus group	Open label	0 (reported) lost to follow-up / 5.6% vs 3.5%	ITT and PP	Local (not blinded)		Serious limitations
BOLERO-2 [26]	Adequate, stratified	Double-blind	* No loss to follow-up was reported / Attrition: 8.5% vs. 2.5%	ITT	Both local and central results available		No serious limitations
MONALEESA-2 [27]	Adequate, stratified	Double-blind	* No loss to follow-up was reported / Attrition: 4.5% vs. 5.4%	ITT	Local results on PFS, only a HR was listed from the independent review committee	Stopped early	Serious limitations
PALOMA-1 [28]	Randomized, stratified. Imbalance of visceral metastases; 44% vs. 53% favoring the palbociclib group	Open label	No loss to follow-up was reported / Attrition: 7.1% vs 13.6%	ITT	Local only (not blinded)		Serious limitations
PALOMA-2 [29]	Randomized, stratified. Imbalance in PS 0; 57.9% vs 45.9% favoring the palbociclib group	Double-blind	*1 of 666 lost to follow-up / Attrition: 4.5% vs. 6.3%	ITT	Both local and blinded, independent central review results available		No serious limitations
PALOMA-3 [30]	Adequate, stratified	Double-blind	No loss to follow-up was reported / Attrition: 2.3% vs. 4.6%	ITT	Masked, independent central review		No serious limitations
MONARCH 2 [31]	Randomized, stratified.	Double-blind	Loss to follow-up: 6 of 446 vs 4 of 223 / Attrition: 2.5% vs. 1.8%	ITT	Both local and blinded, independent central review results available		No serious limitations
MONARCH 3 [32]	Randomized, stratified. Imbalance in treatment-free interval ≥ 36 months; 62.7% vs 50% favoring the abemaciclib group	Double-blind	Loss to follow-up: 3 of 328 vs. 1 of 165 / Attrition: 1.5% vs. 2.4%	ITT	Both local and blinded, independent central review results available		No serious limitations

The attrition was calculated as the sum of those who never received the study treatments, protocol deviators, loss to follow up, the withdrawn consent at any time and other, divided by the ITT group.
§: selection bias also includes allocation concealment, but the information was unclear from all eight studies. According to GRADE 4, blinded trials are very likely to be concealed, and thus only the two open-label trials have a risk of bias.
*indicates that data was found in the supplementary data of the articles.
Abbreviations: ITT=Intention to treat, PP=per protocol, PS=performance status, HR=hazard ratio, PFS=progression free survival, ET=endocrine therapy

Studienergebnisse:

- The efficacy results reported in the eight RCTs are listed in Table 2. In terms of first-line trials, the two palbociclib trials reported a median PFS of 20.2 months in the combination group versus 10.2 months in the ET only group (the corresponding hazard ratio (HR) for disease progression or death was 0.49; 95% CI 0.32–0.75; one-sided p<.0001), and 30.5 versus 19.3 months (HR 0.65; 95% CI 0.51–0.84; p=.001). It suggests an increase of the PFS of 10–11 months when adding palbociclib to ET. The PFSs were not reached in the first-line abemaciclib trial (HR 0.51 (0.36–0.72; p=.0001) [32], nor in the ribociclib group in MONALEESA-2, where the HR determined by blinded reviewers was 0.59 (95% CI 0.43–0.72; p=.002) [27], both suggesting a significant benefit from adding a CDK4/6 inhibitor.

Table 2. Efficacy outcomes of included clinical trials.

Studies	Bachelot et al. [25]		BOLERO-2 [26, 33]		MONALEESA-2 [27][a]		PALOMA-1 [28][a]		PALOMA-2 [29][a]		PALOMA-3 [30]		MONARCH2 [31]		MONARCH 3 [32][a]	
Study groups	EVE + ET	ET only	EVE + ET	P + ET	RIB + ET	P + ET	PAL + ET	ET only	PAL + ET	P + ET	PAL + ET	P + ET	ABE + ET	P + ET	ABE + ET	P + ET
Med. PFS (mo) (95% CI)	–	–	10.6[b] (9.5–NR)	4.1[b] (2.8–5.8)	NR (19.3–NR)	14.7 (13–16.5)	20.2 (13.8–27.5)	10.2 (5.7–12.6)	30.5[b] (24.7–NR)	19.3[b] (16.4–30.6)	9.5 (9.2–11)	4.6 (3.5–5.6)	22.4[b]	10.2[b]	NR[b]	19.2[b]
Med. TTP (mo) (95% CI)	8.6 (6 –14)	4.5 (3.6–8.7)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
HR (95% CI; *p*-value)	0.54 (0.36–81; $p = .0021$)		0.36[b] (0.27–0.47; $p < .001$)		0.59[b] (0.43–0.72; $p = .002$)		0.49 (0.32–0.75; one–sided $p < .0001$)		0.65[b] (0.51–0.84; $p = .001$)		0.46 (0.36–0.59; $p < .0001$)		0.46[b] (0.36–0.58; $p < .001$)		0.51[b] (0.36–0.72; $p = .000102$)	
Med. OS (mo)	NR	32.9	31.0	26.6	NR	NR	37.5	33	NR	NR	NR	NR	NR	NR	NR	NR
HR (95% CI)	0.45 (0.24–0.81)		0.89 (0.73–1.10)		–		0.81 (0.49–1.35)		–		–		–		–	
Best overall response:																
ORR. ITT (%)	8.7	9.2	7 (4.9–9.7)	0.4 (0.0–2.3)	40.7 (35.4–46.0)	27.5 (22.8–32.3)	43 (32–54)	33 (23–45)	42.1 (37.5–46.9)	34.7 (28.4–41.3)	19 (15.0–23.6)	9 (4.9–13.8)	35.2 (30.8–39.6)	16.1 (11.3–21.0)	48.2 (42.8–53.6)	34.5 (27.3–41.8)
OR, *p*–value	–		–, $p < .001$		–, $p < .001$		–, $p = .13$		1.4, $p = .06$		2.47, $p = .0019$		2.82, $p < .001$		1.8, $p = .002$	
SD. ITT (%)	–	–	74.6	64.4	28.4	33.2	38	25	–	–	61	54	37.0	39.9	29.9	37.0
ORR. MD (%)	14	13	–	–	52.7	37.1	55	39	55.3	44.4	25	11	48.1	21.3	59.2	43.8
SD. MD (%)	–	–	–	–	37.1	45.3	31	33	–	–	53	47	25.2	30.5	20.2	25.4
CBR ITT (%)	61	42	–	–	79.6	72.8	81	58	84.9	70.3	67	40	72.2	56.1	78.0	71.5
(95% CI)	(47–74)	(29–56)			(75–84)	(68–76)	(71–89)	(47–69)	(81–88)	(64–76)	(61–72)	(32–47)	(68–76.4)	(49.5–62.6)	(73.6–82.5)	(64.6–78.4)
p–value	–		–		.02		.0009		<.001		.0001		<.001		.101	

[a]Indicates the trials analyzing first-line treatment.
[b]Numbers were the ones assessed by blinded reviewers, when more was available. See Table A in supplementary material for more details on blinding.
EVE: everolimus; RIB: ribociclib; PAL: palbociclib; ABE: abemaciclib; P: placebo; med: median; PFS: progression free survival; TTP: time to progression; ET: endocrine therapy; MO: months; HR: Hazard ratio; OS: overall survival (defined as time from randomization to death); ORR: objective response rate (including complete and partial response); SD: stable disease (Note the definitions vary across studies); MD: for patients with measurable disease (as defined in the RECIST criteria; except for in BOLERO-2 and MONALEESA-2); CBR: clinical benefit rate for the ITT population defined as the sum of ORR and SD; NR: not reached.

Adverse Events

- Everolismus: Bachelot et al. [25] and BOLERO-2 [26] the most common grade 3 and 4 adverse events (AEs) in the everolimus groups included stomatitis (8% and 11%), anemia (6% and 2%), pneumonitis (3% and 2%) and hyperglycemia (4%). These adverse events (AEs) only occurred in 0–1% of the ET only group. In BOLERO-2, serious AEs occurred in 23% of patients in the everolimus group and in only 12% in the ET only group [26]. In total, 19% discontinued everolimus treatment because of AEs (versus 4% in the placebo arm) in the BOLERO-2 study [26], and 11% (versus 4%) in the study by Bachelot et al. [25]. The death of 1.4% of patients was considered to be attributable to AEs caused by everolimus [26]. No deaths were reported by Bachelot et al. [25].
- CDK 4/6: The most common grade 3 and 4 AE of the CDK 4/6 inhibitors was neutropenia. The rates were highest in the ribociclib-; 59.3% [27] and palbociclib trials; 54%, 66.4% and 65% [28–30], compared to 26.5% and 21.1% in the abemaciclib trials [31,32]. The corresponding rates in all placebo groups were 1–2%. Other common grade 3 and 4 AEs were leukopenia (19%, 24.8% and 28%) and anemia (6%, 5.4% and 3%) in the palbociclib groups [28–30]; diarrhea (13.4% and 9.5%), leukopenia (8.8% and 7.6%), anemia (7.2% and 5.8%) and elevated alanine aminotransferase (ALT) level (4.1% and 6.1%) in the abemaciclib groups [31,32]; and for the ribociclib group: leukopenia (21%), lymphopenia (6.9%) and increased ALT- (9.3%) and aspartate aminotransferase (AST) level (5.7%) [27]. Serious AEs occurred in 21.3% (vs 11.8% in the placebo arm) in the ribociclib trial [27]; in 19.6% and 13% (versus 12.6% and 17%) in the palbociclib trials [29,30]; and in 22.4% and 27.5% (vs 10.8% and 14.9%) in the two abemaciclib trials [31,32]. Discontinuation of treatment due to AEs occurred in 7.5% (versus 2.1% in the placebo arm) of patients in the ribociclib study [27]; in 13%, 9.7% and 4% (versus 2%, 5.9% and 2%, respectively) in the palbociclib studies [28–30]; and in 15.2% and 19.6% (vs 3.1% and 2.5%) in the abemaciclib trials [31,32]. AEs led to the death of 2.4% and 2.0% of patients in the abemaciclib arms (vs 1.2% and 0.9% in the placebo arms) in MONARCH 2 and -3, respectively [31,32]. No deaths were directly linked to the toxic effect of palbociclib in any of the three trials [28–30]. In the ribociclib group, 2.7% experienced QTcF prolongation, leading to one death (among 334 patients) [27].

Anmerkung/Fazit der Autoren

The four new targeted agents are all associated with an

improvement of the PFS and have an acceptable tolerability. Thus, they should be offered to women with advanced HR+/ HER2- breast cancer both as first-line therapy as well as among

patients previously treated for metastatic disease. However, further data regarding the impact on overall survival are required to evaluate the full benefit. As the effect is comparable, price and differences in AEs could become substantial arguments for the individual choice of therapy.

Kommentare zum Review

Einschluss von hinsichtlich des Therapielinien-Settings heterogenen Studien.

Ramos-Esquivel A et al., 2018 [15].

Cyclin-dependent kinase 4/6 inhibitors as first-line treatment for post-menopausal metastatic hormone receptor-positive breast cancer patients: a systematic review and meta-analysis of phase III randomized clinical trials

Fragestellung

To compare the efficacy and safety of the CDK 4/6 inhibitors used in combination with an AI as first-line treatment for metastatic HR-positive, HER2-negative breast cancer patients

Methodik

Population:

- metastatic HR-positive, HER2-negative breast cancer

Intervention:

- CDK 4/6 inhibitors plus AI as first-line treatment

Komparator:

- AI as first-line treatment

Endpunkte:

- PFS, ORR, clinical benefit (CR, PR)
- Safety

Recherche/Suchzeitraum:

- In MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials) from October 2007 to October 2017
- Proceedings of the American Society of Clinical Oncology (ASCO) Annual Meeting, San Antonio Breast Cancer Annual Symposium, and the European Society of Medical Oncology Annual Meeting were also queried from 2012 to 2017 for relevant abstracts

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=3

Charakteristika der Studien:

Table 1 General characteristics of patients and trials

Trial	MONARCH-3 trial		PALOMA-2 trial		MONALEESA-2 trial	
Drug	Abemaciclib $N = 328$	Control $N = 165$	Palbociclib $N = 444$	Control $N = 222$	Ribociclib $N = 334$	Control $N = 334$
Dose	150 mg BID on continuous schedule	Anastrozole 1 mg/day or letrozole 2.5 mg/d (continuous schedule)	125 mg/day (3 weeks of treatment followed by one week off)	Letrozole 2.5 mg/day (continuous schedule)	600 mg/day (3 weeks of treatment followed by one week off)	Letrozole 2.5 mg/day (continuous schedule)
Median age (years) (range)	63 (38–87)	63 (32–88)	62 (30–89)	61 (28–88)	62 (23–91)	63 (29–88)
Previous treatment, no. (%)						
Neoadjuvant or adjuvant chemotherapy	125 (38.1)	66 (40)	213 (48)	109 (49.1)	146 (43.7)	145 (43.4)
Neoadjuvant or adjuvant endocrine therapy	150 (45.7)	80 (48.5)	229 (56.1)	126 (56.8)	175 (52.4)	171 (51.2)
No. of metastatic sites, no. (%)	Not reported	Not reported				
0			0	0	2 (0.6)	1 (0.3)
1			138 (31.1)	66 (29.7)	100 (21.9)	117 (35)
2			117 (26.4)	52 (23.4)	118 (35.3)	103 (30.8)
≥ 3			189 (42.5)	104 (46.9)	114 (34.1)	113 (33.8)

Qualität der Studien:

- All included trials were double blind with low risk of selection, performance, attrition, detection, and reporting bias.

Studienergebnisse:

PFS: superiority of CDK 4/6 inhibitors

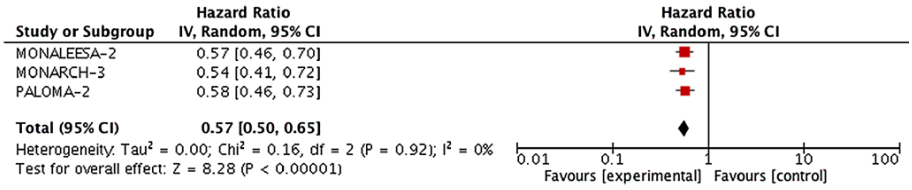
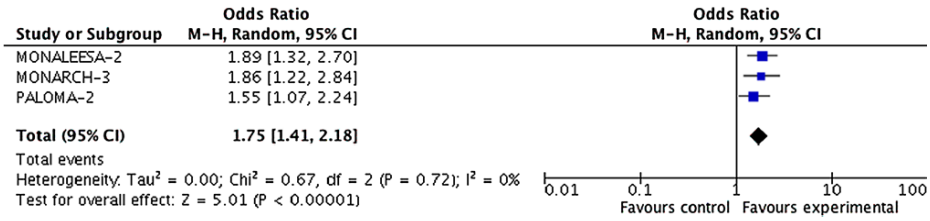


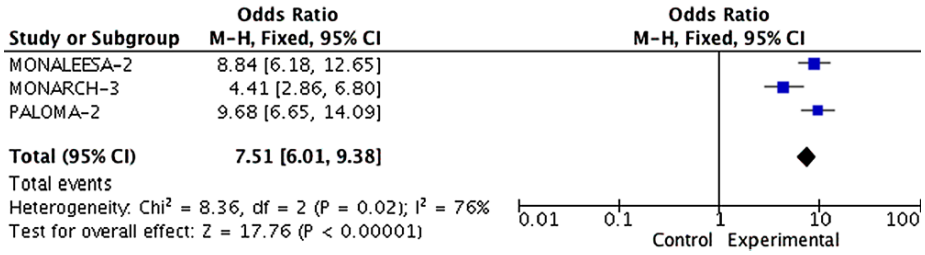
Fig. 2 Forest plot for progression-free survival

ORR: superiority of CDK 4/6 inhibitors



ig. 3 Forest plot for objective response

Adverse events: inferiority of CDK 4/6 inhibitors



ı. 5 Forest plot for treatment-related side effects

Anmerkung/Fazit der Autoren

The addition of CDK 4/6 inhibitors (abemaciclib, palbociclib, or ribociclib) to an AI (anastrozole or letrozole) significantly improved PFS, ORR and CBR when compared with a nonsteroidal AI used alone, with an acceptable safety profile, similarly in three major randomized phase III clinical trials. Therefore, CDK 4/6 inhibitors represent an important therapeutic advance that changes the paradigm of first-line treatment for metastatic HR-positive and HER2- negative breast cancer.

Li J et al., 2020 [11].

Cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer: a meta-analysis of randomized clinical trials

Fragestellung

To further evaluate the efficacy and safety of CDK4/6 inhibitors for HR+ /HER2− ABC, and explore the prefer population through subgroup analysis.

Methodik

Population:

- Women of any menopausal status who were 18 years old or older with HR+/HER2− ABC

Intervention/ Komparator:

- CDK4/6 inhibitors plus standard ET in comparison to ET alone

Endpunkte:

- Primary outcome: progression-free survival (PFS)
- Secondary outcomes: clinical benefit rate (CBR, defined as a confirmed complete response, a partial response, or stable disease for 24 weeks), objective response rate (ORR, defined as a confirmed complete response or partial response), overall survival (OS, defined as the time from the date randomized to death during the study), and toxicity that recorded the occurrence of all grades of AEs and grade 3 or 4 AEs including three hematologic toxicities (neutropenia, leucopenia, and anemia) and four non-hematologic toxicities (diarrhea, fatigue, nausea, and arthralgia)

Recherche/Suchzeitraum:

- We searched the following databases from Jan 2008 up to April 2019: PUBMED, MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials.

Qualitätsbewertung der Studien:

- Cochrane‘s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=14 (8 different RCTs (n=4580): 3 RCTs palbociclib (n=1352 patients), 3 RCTs ribociclib (n=2066 patients) and 2 RCTs abemaciclib (n=1162 patients)

Charakteristika der Population:

- Two trials enrolled patients receiving treatment in the first-line setting for advanced breast cancer, two trials was in the second-line setting and four trials both in the first-line and the second-line setting
- Five trials used AI as a combination treatment of CDK4/6 inhibitors, three trials used Fulvestrant as endocrine therapy
- Five studies enrolled only postmenopausal women, one study enrolled premenopausal and perimenopausal women, and two studies enrolled women with any menopausal status
- Two trials allowed previous chemotherapy for advanced breast cancer

Qualität der Studien:

Table 1 Risk of bias summary (review authors' judgement about each risk of bias item for each included study)

	Random sequence generation(selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (PFS)	Blinding of outcome assessment (CBR/ORR/toxicity)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
PALOMA-1 [23]	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	Low risk
PALOMA-2 [24]	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
PALOMA-3 [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONALESSA-2 [26]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
MONALESSA-3 [27]	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
MONALESSA-7 [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONARCH-2 [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONARCH-3 [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Studienergebnisse:

Progression-free Survival (PFS)

- The HRs significantly favored the CDK4/6 inhibitors containing groups over the endocrine therapy alone groups in first-line setting (HR 0.56, 95% CI 0.49–0.63, p < 0.00001, Fig. 3).

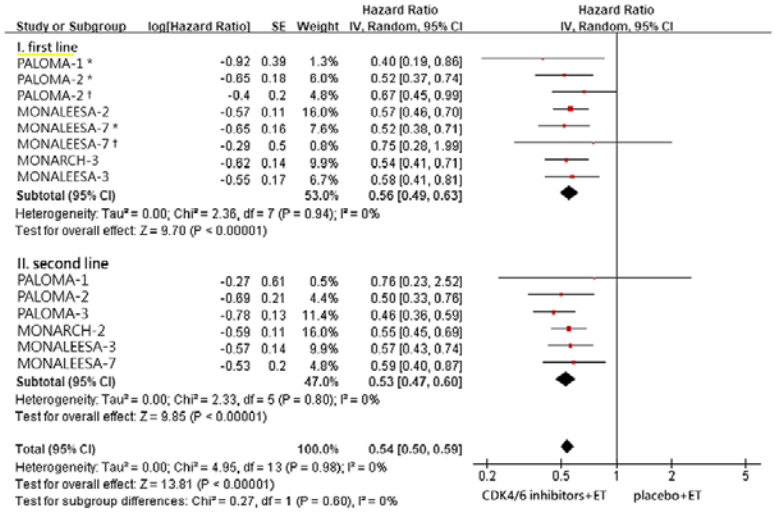


Fig. 3 PFS first line vs second line (*Patients with disease-free interval (the time from the end of adjuvant or neoadjuvant treatment to disease recurrence) > 12 months. †Patients with de novo metastatic breast cancer)

Overall survival (OS)

- Overall survival data were reported in three enrolled studies: Patients in the CDK4/6 inhibitors containing group were observed to have a significantly longer overall survival than those in the ET alone group with an HR = 0.79, 95% CI 0.67–0.93, and p = 0.004 (keine Angabe ob first oder secondline).

Objective response rate (ORR) and Clinical benefit rate (CBR)

- In the first-line setting we found that the RR of ORR using CDK4/6 inhibitors was better than in the ET alone group, where RR = 1.44, 95% CI 1.23–1.69, and p < 0.00001.
- We also observed the improvements of CBR in both the first-line setting (RR = 1.09)

Toxicity

- All-grade neutropenia is the most commonly observed AEs in CDK4/6 intervention
- arms (RR 14.24, 95% CI 10.91–18.59)
- Similarly, all-grade leucopenia and anemia were recorded more in CDK4/6 inhibitor containing regiments
- For all-grade non-hematologic toxicity, the RR were 1.71 (95% CI 1.23–2.37) for diarrhea,
- 1.24 (95% CI 1.08–1.41) for fatigue, 1.63 (95% CI 1.44–1.84) for nausea, and 0.98 (95% CI 0.87–1.09) for arthralgia
- The grades 3 and 4 (G3-4) neutropenia were increased in intervention arms than control arms, the RR was 31.95 (95% CI 17.75–57.50) with substantial heterogeneity among different interventions (I^2 = 58.8%)
- In the subgroup analysis of different interventions, the incidence of G3-4 diarrhea was significantly higher in patients receiving abemaciclib (RR 12.62, 95% CI 3.48–45.82).

Anmerkung/Fazit der Autoren

The CDK4/6 inhibitors (including palbociclib, abemaciclib, and ribociclib) plus standard endocrine agents prolong PFS and OS and show benefit in ORR and CBR in HR+ /HER2− ABC irrespective of the prior therapy for advanced disease, menopausal status, the existence of visceral metastases, and different races. Though followed by the increasing occurrence of neutropenia, leucopenia, and diarrhea, most of the adverse events are reversible, manageable and acceptable. Given their superior efficacy and tolerable toxicity, the CDK4/6 inhibitors could be recommended as a preferred option for the majority of patients with HR+ /HER2− ABC.

Deng Y et al., 2018 [2].

CDK4/6 inhibitors in combination with hormonal therapy for HR+/HER2- advanced breast cancer: A systematic review and meta-analysis of randomized controlled trials

Fragestellung

We conducted this meta-analysis based on available RCTs to evaluate the efficacy and safety of CDK4/6 inhibitors in combination with hormonal therapy for the treatment of HR+/HER2-advanced breast cancer, comparing with hormonal therapy alone.

Methodik

Population:

- HR+/HER2-advanced breast cancer

Intervention/Komparator:

- CDK4/6 inhibitors plus hormonal therapy versus hormonal therapy alone or with placebo

Endpunkte:

- progression free survival (PFS), the number of patients who experienced a partial response or complete response, all grade adverse events (AEs) and grade 3/4 AEs.

Recherche/Suchzeitraum:

- Electronic searches were conducted among varied databases including Cochrane Library (2018), PubMed, EMBASE (from 1946) (OvidSP) and Web of Science (from 1900) up till March 24th, 2018.

Qualitätsbewertung der Studien:

- Cochrane’s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs (n=3,854 patients)
- Among four of the included studies, CDK4/6 inhibitors were combined with letrozole or anastrozole in the experimental arms as first-line therapy for postmenopausal advanced disease

- Two studies used CDK4/6 inhibitors with fulvestrant as subsequent line therapy for patients that went progression from prior endocrine therapy without restriction on menopausal status.
- While the MONALEESA-7 study was conducted to assess the efficacy and safety of ribociclib in combination with hormonal therapy and ovarian function suppression therapy in pre- or perimenopausal patients

Charakteristika der Population:

Table 1: Characteristics of included studies.

Study (ClinicalTrials.gov Identifier)	Year	Phase	Participants	No. of patients	Median age (year)	Interventions	Treatment strategy	Median follow-up (months)	Outcomes	
									mPFS (months)	ORR
PALOMA-1 (NCT00721409)	2015	II	Postmenopausal women with ER+/HER-ABC	165	63(64)	Palbociclib +letrozole vs letrozole	First line therapy	29.6	20.2 vs 10.2	42.9% vs 33.3%
PALOMA-2 (NCT01740427)	2016	III	Postmenopausal women with ER+/HER-ABC	666	62(61)	Palbociclib +letrozole vs letrozole	First line therapy	23	24.8 vs 14.5	42.1% vs 34.7%
PALOMA-3 (NCT01942135)	2016	III	Women with HR+/HER-ABC	521	57(56)	Palbociclib + fulvestrant vs placebo + fulvestrant	Subsequent line therapy	8.9	9.5 vs 4.6	19% vs 9%
MONARCH-2 (NCT02107703)	2017	III	Women with HR+/HER-ABC	669	59(62)	Abemaciclib + fulvestrant vs placebo + fulvestrant	Subsequent line therapy	19.5	16.4 vs 9.3	35.2% vs 16.1%
MONARCH-3 (NCT02246621)	2017	III	Postmenopausal women with HR+/HER-ABC	493	63(63)	Abemaciclib + NSAI vs placebo + NSAI	First line therapy	17.8	NR vs 14.7	48.2% vs 34.5%
MONALEESA-2 (NCT01958021)	2016	III	Postmenopausal women with HR+/HER-ABC	668	62(63)	Ribociclib + letrozole vs placebo + letrozole	First line therapy	15.3	NR vs 14.7	40.7% vs 27.5%
MONALEESA-7 (NCT02278120)	2017	III	Pre- or peri-menopausal women with HR+/HER2- ABC	672	-	Ribociclib + ET(tamoxifen/NSAI + goserelin) vs placebo + ET	First line ET	19.2	23.8 vs 13.0	51.0% vs 36.0%*

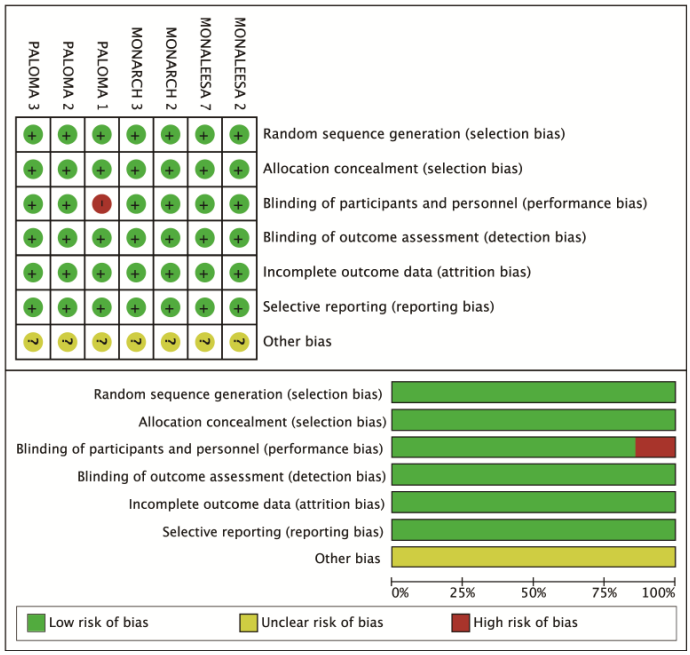
* ORR in patients with measurable disease.

ER+: Estrogen receptor positive; HR+: Hormonal receptor positive; HER2-: Human epidermal growth factor receptor 2 negative; ABC: Advanced breast cancer; mPFS: Median progression free survival; ORR: Objective response rate; NSAI: Nonsteroidal aromatase inhibitor (letrozole or anastrozole in MONARCH-3 and MONALEESA-7). ET: Endocrine therapy; NR: Not reached.

Palbociclib: 125mg per day orally for 3 weeks with 1 week off. Abemaciclib: 150mg twice daily orally and continuously. Ribociclib: 600mg per day orally for 3 weeks with 1 week off. Letrozole:1mg per day orally and continuously. Anastrozole: 2.5mg per day orally and continuously. Fulvestrant: 500mg intramuscularly on day 1 and 15 of the first cycle, then on day 1 of every 4 weeks. Tamoxifen: 20mg per day orally and continuously. Goserelin: 3.6mg subcutaneous injection every 28 days. All the drugs were administrated every 4 weeks a cycle.

Qualität der Studien:

Figure 6: Risk of bias for selected publications



Studienergebnisse:

- The HR for PFS for first line therapy was 0.56 (95% CI: 0.48-0.64; P<0.001, I^2=0)
- The pooled relative risk (RR) for objective response rate (ORR) for first line therapy was 1.35 (95% CI: 1.19-1.52; P<0.001, I^2=0)
- A higher rate of AEs in all grades as well as high grades (grade 3/4) were observed in the experimental arms where additional CDK4/6 inhibitors were added to regular hormonal therapy. And the pooled RR for all grade AEs was 1.07 (95% CI: 1.03-1.11; P=0.0002), the heterogeneity was significant (I^2=78%; P=0.0004) thus random effects model was adopted.
- For grade 3/4 AEs, the pooled RR was 2.81 (95% CI: 2.54-3.11; P<0.001) with slight heterogeneity (I2=17.7%; P=0.299). Hematological and gastrointestinal adverse events were the most common side effects of CDK4/6 inhibitors.

Anmerkung/Fazit der Autoren

Our meta-analysis demonstrated that additional use of CDK4/6 inhibitors can significantly prolong the PFS of patients with HR+/HER2- advanced breast cancer and improve the ORR with the basis of conventional hormonal therapy. Simultaneously, the combined regimen had higher rate of well-tolerated adverse events.

3.4 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften), 2017 [10].

Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 4.3

Fragestellung

Die Ziele der S3-LL für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms wurden aus der Ursprungsversion und der ersten beiden Aktualisierungen beibehalten und für die dritte Neuauflage ergänzt bzw. konkretisiert:

Methodik

Grundlage der Leitlinie

- 3. Aktualisierung der Leitlinie von 2017
- Repräsentatives Gremium: Interdisziplinäre LL-Entwicklergruppe, Beteiligung von Patientenvertreterinnen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt. Es wurde ein durch die AWMF moderierter, mehrteiliger Nominaler Gruppenprozess durchgeführt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

- Regelmäßige Überprüfung der Aktualität gesichert: Die S3-Leitlinie ist bis zur nächsten Aktualisierung gültig, die Gültigkeitsdauer wird auf 5 Jahre geschätzt.

Systematische Recherche, Auswahl und Bewertung von bestehenden Leitlinien:

- Recherche nach LL, die nach Nov. 2013 veröffentlicht wurden, in Datenbanken von G-I-N, NGC, NICE, Library NHS, SIGN u.a. im Juni 2015 und Oktober 2015 (inkl. Abgleich mit LL-Bericht des IQWiG),
- AGREE-II-Bewertung der identifiziertten LL; Einschlusskriterium: Erfüllen von ≥ 50% der Domäne 3 (Rigour of Development) des AGREE II (Bewertung durch 2 Begutachter)

Systematische Recherche, Auswahl und Bewertung der Primärliteratur und SR:

- Formulierung von PICO-Fragen
- Recherche in Medline, CDSR, CENTRAL, DARE; Zeitraum: 06. April – 2. November 2016
- Methodische Bewertung der Literatur: SIGN-Checklisten für SR, RCT, Observational Studies (jeweils Version 2004) sowie Studies of Diagnostic Accuracy (Version 2006)

LoE

- Evidenzgraduierung nach Klassifikation des Oxford Centre for Evidence-based Medicine (Version 2009)

Formulierung der Empfehlungen und formale Konsensusfindung

- Entwurferstellung und Diskussion der Empfehlungen durch Arbeitsgruppen (nach Regeln des nominalen Gruppenprozesses)
- Konsentierung der Empfehlungen und der dazu gehörigen Empfehlungsgrade durch Leitliniengruppe im moderierten, formalen Konsensusverfahren (Nominaler Gruppenprozess).

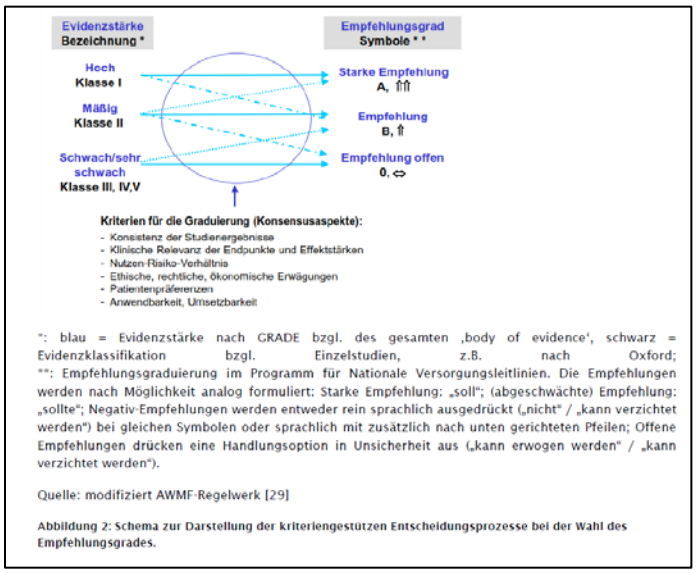
  GoR:

Tabelle 9: verwendete Empfehlungsgrade

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

- Empfehlungen, welche nicht durch Leitlinienadaptation oder durch Primärrecherche generiert wurden, sind als Expertenkonsens (EK) ausgewiesen. Der Empfehlungsgrad ergibt sich lediglich anhand der Ausdrucksweise (soll/sollte/kann) und wird nicht explizit mit A/B/0 gekennzeichnet.

Festlegung des Empfehlungsgrades



*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford; **: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden").

Quelle: modifiziert AWMF-Regelwerk [29]

Abbildung 2: Schema zur Darstellung der kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades.

Tabelle 10: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 – 75% der Stimmberechtigten
Dissens	≤50% der Stimmberechtigten

Sonstige methodische Hinweise

Stand der LL: 01.12.2017, gültig bis 30.11.2022

Empfehlungen

4.72 Endokrine Therapie

4.108.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Patientinnen mit östrogen- und/oder progesteronrezeptor-positiven (°) invasiven Tumoren sollen eine endokrine Therapie erhalten. ° (>/=10% progesteronrezeptor-positive Tumorzellkerne)
Level of Evidence **1a**	Quellen: [29, 726-729]
	Starker Konsens

4.109.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Eine endokrine Therapie soll erst nach Abschluss der Chemotherapie begonnen werden, kann aber parallel zur Strahlentherapie erfolgen.
Level of Evidence **1a**	Quellen: [29, 580, 726-729]
	Starker Konsens

4.110.	Evidenzbasierte Empfehlung
Empfehlungsgrad A/B	Nach 5 Jahren Tamoxifen soll für jede Patientin mit einem ER+-Mammakarzinom die Indikation zu einer erweiterten endokrinen Therapie geprüft werden. Die Indikationsstellung sollte in der Abwägung des Rückfallrisikos und den therapieassoziierten Nebenwirkungen (Toxizität, verminderte Adhärenz) erfolgen (Empfehlungsgrad B). Bei der Wahl der endokrinen Therapie soll der aktuelle Menopausenstatus der Patientin berücksichtigt werden.
Level of Evidence 1a	Leitlinienadaptation: [737]
	Starker Konsens

Therapie bei prämenopausalen Patientinnen:

4.111.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Bei prämenopausalen Patientinnen soll eine Tamoxifentherapie für mindestens 5 Jahre durchgeführt werden. Die antiöstrogene Therapie mit Tamoxifen 20 mg pro Tag soll in Abhängigkeit des Rezidivrisikos über eine Zeitdauer von 5 – 10 Jahren bzw. bis zum Rezidiv erfolgen. Die Indikation der erweiterten Therapie ist vom Rezidivrisiko und Wunsch der Patientin abhängig.
Level of Evidence 1a	Quellen: [726, 727, 738, 739, 741]
	Starker Konsens

4.112.	Konsensbasierte Empfehlung
EK	Für Patientinnen mit einem ER+-Mammakarzinom und erhöhtem Risiko, die nach abgeschlossener Chemotherapie noch prämenopausal sind, kann unter Ausschaltung der Ovarfunktion ein Aromatasehemmer eingesetzt werden.
	Konsens

4.113.	Evidenzbasierte Empfehlung
Empfehlungsgrad 0	Die alleinige Ovarialsuppression kann entweder durch Gabe eines GnRHa oder durch eine bilaterale Ovarektomie für prämenopausale Frauen mit einem ER+-Mammakarzinom erwogen werden, die kein Tamoxifen erhalten können oder wollen.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

4.114.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Die Ovarialsuppression (GnRHa oder bilaterale Ovarektomie) zusätzlich zu Tamoxifen oder einem Aromatasehemmer soll nur bei hohem Rezidivrisiko und prämenopausaler Situation nach adjuvanter Chemotherapie erwogen werden. Bei Einsatz eines Aromatasehemmers soll eine Ovarialsuppression obligat erfolgen.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

Therapie bei postmenopausalen Patientinnen:

4.115.	Evidenzbasierte Empfehlung
Empfehlungsgrad B	Die adjuvante endokrine Therapie für postmenopausale Patientinnen mit einem ER+ Mammakarzinom sollte einen Aromatasehemmer enthalten.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

Lokal fortgeschrittenes Mammakarzinom

4.90.	Evidenzbasiertes Statement
Level of Evidence 1a	Die postoperative Radiotherapie der Brustwand nach Mastektomie senkt das Risiko eines lokoregionären Rezidivs und verbessert das Gesamtüberleben bei lokal fortgeschrittenen und nodal-positiven Mammakarzinomen.
	Quelle: [650]
	Starker Konsens

Quelle:
650. McGale, P., et al., Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet, 2014. 383(9935): p. 2127-35

Radiotherapie bei lokal weit fortgeschrittenem Tumor und bei primärer Inoperabilität

4.104.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Bei Patientinnen mit primär inoperablen bzw. inflammatorischen Karzinomen soll eine primäre Systemtherapie, gefolgt von Operation und postoperativer Strahlentherapie, oder bei weiter bestehender Inoperabilität alleiniger oder präoperativer Strahlentherapie durchgeführt werden.
Level of Evidence 1b	Quellen: [700, 701]
	Starker Konsens

Quellen:
700. Bartelink, H., et al., Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer Randomized Phase III Trial. J Clin Oncol, 1997. 15(1): p. 207-15.
701. Scotti, V., et al., Management of inflammatory breast cancer: focus on radiotherapy with an evidence-based approach. Cancer Treat Rev, 2013. 39(2): p. 119-24.

Primäre Hormontherapie bei postmenopausalen Patientinnen

4.127.	Konsensbasierte Empfehlung
EK	Bei postmenopausalen Patientinnen mit endokrin sensitivem Mammakarzinom kann, wenn eine Operation oder Chemotherapie nicht möglich oder nicht gewünscht sind, eine primäre endokrine Therapie durchgeführt werden.
	Starker Konsens

4.128.	Konsensbasierte Empfehlung
EK	Die neoadjuvante endokrine Therapie ist keine Standardtherapie, in speziellen Situationen (inoperabel, multimorbide Patientin) kann eine neoadjuvante endokrine Therapie erwogen werden.
	Starker Konsens

5. Das rezidivierte oder metastasierte Mammakarzinom

5.4 Fernmetastasen

5.4.1. Systemische Therapie des metastasierten Mammakarzinoms

Systemische endokrine Therapie

5.26.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Die endokrine Therapie +/- zielgerichteter Therapie ist die Therapie der Wahl bei positivem Hormonrezeptorstatus und negativem HER2-Status. Die endokrine Therapie ist nicht indiziert bei Patientinnen, bei denen die Notwendigkeit des Erreichens einer schnellen Remission zur Abwendung von ausgeprägten Symptomen des betroffenen Organs besteht.
Level of Evidence 1b	Quellen: [29, 985-990]
	Starker Konsens

Quellen:
29. NICE. The National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [addendum 2014]; Available from: https://www.nice.org.uk/guidance/cg81/evidence/addendum-242246990
986. Fossati, R., et al., Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol, 1998. 16(10): p. 3439-60.
987. Stockler, M., et al., The management of advanced breast cancer: systemic reviews of randomised controlled trials regarding the use of cytotoxic chemotherapy and endocrine therapy. Woolloomooloo, NHMRC National Breast Cancer Centre, 1997.
988. Stockler, M., et al., Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. Cancer Treat Rev, 2000. 26(3): p. 151-68.
989. Rugo, H.S., et al., Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol, 2016. 34(25): p. 3069-103.
990. Cancer Australia. Recommendations for the management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation. 2014 Available from: http://guidelines.canceraustralia.gov.au/guidelines/guideline_17.pdf.
991. Partridge, A.H., et al., Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol, 2014. 32(29): p. 3307-29

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5.27.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Eine kombinierte chemo-endokrine Therapie wird nicht empfohlen. Sie kann zwar die Remissionsraten erhöhen, führt aber auch zu gesteigerter Toxizität ohne Verlängerung des progressionsfreien Intervalls oder des Gesamtüberlebens.
Level of Evidence 1a	Conchrane: [1003] Quelle: [1004]
	Starker Konsens

Quellen:
1004. Carrick, S., et al., Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev, 2005(2): p. Cd003372.
1005. Sledge, G.W., Jr., et al., Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An Eastern Cooperative Oncology Group study. J Clin Oncol, 2000. 18(2): p. 262-6.

Ovarialsupression und Tamoxifen bei prämenopausalen Patientinnen

5.28.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Bei prämenopausalen Patientinnen ist die Ausschaltung der Ovarialfunktion (GnRH-Analoga, Ovarektomie) in Kombination mit Tamoxifen die Therapie der ersten Wahl, wenn die Therapie mit Tamoxifen nicht vor weniger als 12 Monaten beendet wurde. Alternativ kann unter Ausschaltung der Ovarfunktion wie bei postmenopausalen Patientinnen vorgegangen werden und die endokrine Therapie mit CDK4/6-Inhibitoren kombiniert werden.
Level of Evidence 1b	Quellen: [29, 988, 1005, 1006]
	Starker Konsens

Weitere Therapien bei prämenopausalen Patientinnen

5.29.	Evidenz- /konsensbasierte Empfehlung
Empfehlungsgrad 0	In der Folge kann in der Prämenopause eine Ovarialsuppression in Kombination z.B. mit einem Aromatasehemmer oder Fulvestrant ggf. in Kombination mit Palbociclib zum Einsatz kommen. Die Therapie kann somit unter Beibehaltung der ovariellen Suppression in Analogie zu der Behandlung postmenopausaler Patientinnen durchgeführt werden.
2c/EK	Quellen: [29, 1007, 1008]
	Starker Konsens

Quellen:
29. NICE. The National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [addendum 2014]; Available from: https://www.nice.org.uk/guidance/cg81/evidence/addendum-242246990
989. Rugo, H.S., et al., Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol, 2016. 34(25): p. 3069-103.
1006. Klijn, J.G., et al., Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol, 2001. 19(2): p. 343-53.
1007. (NBOCC)., N.B.a.O.C.C., Recommendations for use of Chemotherapy for the treatment of advanced breast cancer. 2010, Surry Hills
1008. Taylor, C.W., et al., Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol, 1998. 16(3): p. 994-9.

Endokrine Therapie bei postmenopausalen Patientinnen

5.30.	Evidenzbasierte Empfehlung
Empfehlungsgrad B	Als erster endokriner Behandlungsschritt bei Metastasierung sollte bei postmenopausalen Patientinnen ein Aromatasehemmer eingesetzt werden, wenn adjuvant ausschließlich Tamoxifen oder keine adjuvante Therapie erfolgt ist. Eine klare Empfehlung, ob primär ein steroidaler oder nicht-steroidaler Aromatasehemmer eingesetzt werden sollte, kann nicht ausgesprochen werden. Letrozol kann mit einem CDK4/6-Inhibitor kombiniert werden.
Level of Evidence 1a	Conchrane: [993] Quellen: [29, 985, 988, 1014-1017]
	Starker Konsens

Quellen:
29. NICE. The National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [addendum 2014]; Available from: https://www.nice.org.uk/guidance/cg81/evidence/addendum-242246990
986. Fossati, R., et al., Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol, 1998. 16(10): p. 3439-60.
989. Rugo, H.S., et al., Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol, 2016. 34(25): p. 3069-103.
994. Gibson, L., et al., Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev, 2009(4): p. Cd003370
1015. Ellis, M., D. Hayes, and M. Lippman, Treatment of metastatic breast cancer. Cancer, 2000. 2000: p. 749-797.
1016. Hayes, D.F., I.C. Henderson, and C.L. Shapiro, Treatment of metastatic breast cancer: present and future prospects. Semin Oncol, 1995. 22(2 Suppl 5): p. 5-19; discussion 19-21.
1017. Mouridsen, H., et al., Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol, 2001. 19(10): p. 2596-606.
1018. Mouridsen, H., et al., First-line therapy with letrozole (femara®) for advanced breast cancer prolongs time to worsening of Karnofsky Performance Status compared with tamoxifen. Breast Cancer Research and Treatment, 2001. 69(3): p. 291

5.31.	Konsensbasierte Empfehlung
EK	Eine Behandlung mit Fulvestrant sollte insbesondere nach Vorbehandlung mit einem Aromatasehemmer erfolgen, kann aber auch als erste Therapielinie eingesetzt werden, insbesondere bei noch nicht endokrin vorbehandelten Patientinnen.
	Starker Konsens

Kombinationstherapien bei postmenopausalen Patientinnen

5.32.	Konsensbasierte Empfehlung
EK	Eine bestimmte Therapiesequenz kann nicht empfohlen werden. Eine Kombinationsbehandlung von Letrozol oder Fulvestrant mit einem CDK4/6-Inhibitor stellt eine Therapiealternative zur Monotherapie dar. Nach antihormoneller Vortherapie mit einem nicht-steroidalen Aromatasehemmer kann eine Folgetherapie mit Exemestan und dem mTOR-Inhibitor Everolimus durchgeführt werden. Kombinationstherapien konnten in Studien eine Verlängerung des progressionsfreien Überlebens, bislang aber nicht des Gesamtüberlebens zeigen.
	Starker Konsens

5.33.	Konsensbasierte Empfehlung
EK	Weitere Schritte in der endokrinen Behandlungssequenz bei postmenopausalen Patientinnen stellen je nach Vorbehandlung der Einsatz von Antiöstrogenen, Östrogenrezeptor-Antagonisten, der Wechsel des Aromatasehemmers von einem steroidalen auf einen nicht-steroidalen Aromatasehemmer oder vice versa oder der Einsatz von hoch dosierten Gestagenen dar. Nach Progress unter einem nicht-steroidalen Aromatasehemmer kann die Kombination von Letrozol oder Fulvestrant mit Palbociclib oder die von Exemestan und Everolimus eingesetzt werden.
	Starker Konsens

9. Mammakarzinom des Mannes

9.7.	Konsensbasierte Empfehlung
EK	Die adjuvante Chemotherapie sowie die Antikörpertherapie (Anti-HER2) soll nach den gleichen Regeln wie bei der Frau indiziert und durchgeführt werden.
	Konsens

9.8.	Konsensbasierte Empfehlung
EK	Patienten mit einem Hormonrezeptor-positiven Mammakarzinom sollen eine adjuvante endokrine Therapie mit Tamoxifen in der Regel über 5 Jahre erhalten. Für eine Behandlung über 5 Jahre hinaus liegen keine Daten vor. Analog zum weiblichen Mammakarzinom kann diese in Einzelfällen erwogen werden.
	Starker Konsens

9.9.	Konsensbasierte Empfehlung
EK	a.) Die Therapie bei metastasierter Erkrankung sollte nach den gleichen Regeln wie bei der Frau erfolgen. b.) Es ist unklar, ob Aromatasehemmer ohne Suppression der testikulären Funktion beim Mann ausreichend wirksam sind. Daher sollten Aromatasehemmer in Kombination mit einer Suppression der testikulären Funktion gegeben werden.
	Starker Konsens

NICE, 2009 [13].

Advanced breast cancer (update) Diagnosis and treatment; Issued: February 2009, last modified: August 2017. NICE (CG81)

Leitlinienorganisation/Fragestellung

What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer?

Methodik

Grundlage der Leitlinie

- systematische Evidenzaufbereitung (Formulierung von PICO-Fragen; Systematische Literaturrecherche in mehreren Datenbanken; Datenextraktion, Qualitätsbewertung der gefundenen Literatur auf Basis der SIGN Kriterien für systematische Reviews/Meta-analysen und RCTs)
- Formulierung der Empfehlung basierend auf klinischer und ökonomischer Evidenz in Konsensusprozessen; bei schwacher Evidenz basierend auf informellen Konsens

Recherche/Suchzeitraum:

- Literaturrecherche der LL-Version 2009: bis 30.06.2008. Future guideline updates will consider evidence published after this cut-off date.

LoE

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

Table A Levels of evidence for intervention studies. Data source: 'NICE guidelines manual' (NICE 2007).

GoR

- Anwendung von GRADE - GoR finden sich in den Formulierungen wieder: "To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations."

Sonstige methodische Hinweise

- Regelmäßige Überprüfung der Aktualität der Empfehlungen: letzter Surveillance Report vom Januar 2018: Es wurden in Bezug auf die Therapieempfehlungen keine neue Evidenz identifiziert, die zu einer Änderung dieser Empfehlungen führen würde

Aktualisierungen:

- Update 2014: review of the evidence on exercise for people with or at risk of lymphoedema and addition of 2 recommendations to section 1.5

- Update 2017: Review of the evidence and update of recommendations in section 1.1 on assessing oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status on disease recurrence.

Empfehlungen

Systemic disease-modifying therapy

Recommendations

1.3.1 Offer endocrine therapy as first-line treatment for the majority of patients with ER positive advanced breast cancer. [2009]

1.3.2 Offer chemotherapy as first-line treatment for patients with ER-positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity. [2009]

1.3.3 For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first line treatment, offer endocrine therapy following the completion of chemotherapy. [2009]

Qualifying statement: These recommendations are based on one systematic review and GDG consensus

Clinical Evidence: Only one paper was appraised for this topic. A high quality systematic review (Wilcken et al. 2006) examined ten RCTs of chemotherapy vs endocrine therapy, the most recent of which was published in 1995 (even though Cochrane databases were searched as recently as October 2006).

Neither chemotherapy nor endocrine therapy demonstrated an advantage in overall survival and tumour response was variable between studies. No data were presented for quality of life (QOL) or adverse events but, in narrative form, the reviewers stated that in the majority of studies chemotherapy had resulted in higher levels of toxicity (predominantly nausea, vomiting and alopecia) but that it was not clear in which direction QOL had been affected as the results were conflicting.

Endocrine Therapy

Recommendation

1.3.4 Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
- postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. [2009]

Qualifying statement: These recommendations are based on high quality evidence of clinical and cost effectiveness. There is no evidence directly comparing these agents so it is not possible to recommend any particular aromatase inhibitor. All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival).

1.3.5 Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. [2009]

1.3.6 Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression. [2009]

Qualifying statement: These recommendations are based on 1 moderate quality RCT report showing a survival benefit for combination therapy over single agents in pre-menopausal patients. There is also evidence of clinical effectiveness from one high-quality systematic review of randomised trials in pre-menopausal women. There was GDG consensus that perimenopausal women should be treated in the same manner. The GDG has made no recommendation on the optimal endocrine management of patients with ER-positive disease who relapse whilst on adjuvant tamoxifen as there is no data in this area. Current UK practice varies, with the use of either ovarian suppression or ovarian suppression in combination with aromatase inhibitors being used.

Clinical Evidence: The evidence base for this topic comprises one guideline (Eisen et al. 2004), five systematic reviews (Mauri et al. 2006; Gibson et al. 2007; Ferretti et al. 2006; Klijn et al. 2001 and Crump et al. 1997), five RCTs (Chia et al. 2008; Mouridsen et al. 2007; Taylor et al. 1998; Klijn et al. 2000 and Goss et al. 2007) a pooled analysis of RCT data (Howell et al. 2005) and a small, low quality comparative study (Catania et al. 2007a). The number of study participants exceeded 30,500 women, the majority of whom were post-menopausal with metastatic breast cancer. Most of the papers were of moderate to high quality, although the guideline did review non-published abstracts.

[1)] Mauri D, et al. (2006) Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 98(18): 1285–1291.

[2)] Chia S, et al. (2008) Double-blind, Randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptorpositive, advanced breast cancer: Results from EFECT. J Clin Oncol 26: 1664–1670.

[3)] Mouridsen HT (2007) Letrozole in advanced breast cancer: the PO25 trial. Breast Cancer Res Treat 105(1): 19–29.

[4)] Catania C, et al. (2007a) Fulvestrant in heavily pre-treated patients with advanced breast cancer: results from a single compassionate use programme centre. Breast Cancer Res Treat 106: 97–103.

Pre-menopausal women with metastatic breast cancer experienced no significant difference in tumour response or survival between ovarian ablation and tamoxifen as first-line therapy. Atamestane and toremifine as first-line combination therapy resulted in similar tumour response and survival compared with letrozole alone.

Fulvestrant and exemestane showed equal clinical benefit for women that had previously received non-steroidal AIs for the treatment of advanced breast cancer. Limited evidence also suggested that fulvestrant conferred short term benefit to heavily pre-treated women with metastatic disease by postponing the requirement for chemotherapy. An equivalence analysis of pooled data (Howell et al. 2005) from two trials showed that fulvestrant and anastrozole were not significantly different from one another in their effects on overall survival. Study participants given fulvestrant reported fewer incidences of joint pain.

[5)] Howell A, et al. (2005) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. Cancer 104: 236–239 –nicht systematisch erstellt, Dosierung von 250mg/Monat Fulvestrant nicht zulassungskonform, identisch mit Robertson, et al. 2003 (siehe oben)

Good evidence showed that there was significant clinical benefit, increased progression-free survival and ~13% reduction in the risk of death with third generation AIs compared with standard endocrine therapy (the analyses included all treatment lines). No individual AI was better than another in this regard. Very limited evidence suggested that there was no significant difference between the AIs and standard therapy in patient reported quality of life. However, more gastro-intestinal symptoms and hot flushes were associated with AI therapy compared to standard endocrine therapy but there were fewer reports of blood clots and vaginal bleeding.

A moderate quality systematic review (Klijn et al. 2001) and meta-analysis of data from four RCTs (one unpublished) concluded that combination therapy with LHRH agonists, buserelin or goserelin, combined with tamoxifen produced significant improvements in tumour response, reduction in the risk of death (~22%) and disease progression (~30%) than LHRH agonist monotherapy. Lack of methodological detail suggests caution in the interpretation of these results.

One RCT (Klijn et al. 2000) compared buserelin alone versus tamoxifen alone versus the two agents combined. Tumour response was not significantly different between combined and monotherapies unless data from patients with stable disease for > 6 months was included. The re-analysis showed a superior response for the combined therapy compared with tamoxifen but not LHRH. Combined therapy significantly improved actuarial survival at 5 and 7 years, together with overall urvival and progression-free survival compared with monotherapy with either buserelin or tamoxifen.

A second RCT (Taylor et al. 1998) compared goserelin with surgical ovarian ablation (ovariectomy). The authors found that the outcomes for tumour response, overall survival and failure free survival were not significantly different between treatments and concluded that either treatment could reasonably be offered to patients and their physicians. The study was terminated prematurely due to poor accrual, believed to be because of the unwillingness of patients to be randomised to the surgical arm.

1.3.7 Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer. [2009]

Rugo HS et al., 2016 [16].

Endocrine therapy for women with hormone receptor (HR) –positive metastatic breast cancer (MBC).

Leitlinienorganisation/Fragestellung

- American Society of Clinical Oncology (ASCO) Clinical Practice Guideline
- Guideline Questions:

1. Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for hormone receptor (HR) –positive metastatic breast cancer (MBC)?
    1.1 For postmenopausal women: What are the optimal sequence and duration?
    1.2 Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?
    1.3 For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?
    1.4 Are there demonstrated differences between pre- and postmenopausal patients?
2. Is there an optimal second- or later-line endocrine therapy for HR-positive MBC?
    2.1 Should other treatment or disease-free interval play a role in treatment selection?
    2.2 Which hormone therapy should be offered?
    2.3 What are the optimal timing, dose, and schedule of treatment?
3. How or should endocrine therapies be used in combination or sequence with:
    3.1 Mammalian target of rapamycin inhibitors (everolimus)?
    3.2 Cyclin-dependent kinase 4/6 inhibitors (palbociclib)?
4. Does estrogen or progesterone expression (high v low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women?
5. How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting?
6. In which patients or settings is hormone therapy recommended over chemotherapy?
    6.1 Is there a role for combined cytotoxic and endocrine therapies?
    6.2 What is the optimal duration of treatment with hormonal therapy?
7. Is there a role for additional biomarkers in the selection of treatment for patients with HR-positive disease?
    7.1 What is the role of genomic profiling or intrinsic subtypes in this population?
8. How does human epidermal growth factor receptor 2 (HER2) positivity affect treatment of patients with HR-positive MBC?
9. What are the future directions for treatment in this patient population?

Methodik

<u>Grundlage der Leitlinie</u>

- multidisciplinary Expert Panel (medical oncology, radiation oncology, psycho-oncology, patient advocacy, and guideline methodology).
- All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests... In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy.
- ASCO guidelines are based on systematic reviews of evidence from 2008 through 2015:
    - A protocol for each guideline defines the parameters for a targeted literature search, including relevant study designs, literature sources, types of reports, and prespecified study selection criteria for literature identified

- Formal assessment of Study Quality (siehe Anhang Detaillierte Informationen + Bewertungsergebnisse)

Recherche/Suchzeitraum:

- Literature search: in Medline to 4/2014; Cochrane Library databases to Issue 3 of March 2013; Antonio Breast Cancer Symposium (2011 to 2014) and ASCO abstracts (2012 to 2014); targeted literature search update: in June 2015

LoE/ GoR

- Definitions for Types + Strengths of recommendation, Strengths of evidence: → Anhang 2
- Recommendations reflect high, moderate or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases.

Sonstige methodische Hinweise

- Revision Dates: The co-chairs determine the need for guideline updates or revisions on the basis of periodic review and consideration of the literature. If new and compelling data are identified, the Expert Panel or an update committee is reconvened to discuss revisions to the document
- Evidenzgrundlage im Anhang abgebildet

Empfehlungen

ASCO Key Guideline Recommendations for HR-positive MBC

Hormone therapy should be offered to patients whose tumors express any level of estrogen and/or progesterone receptors. (*Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Treatment recommendations should be offered on the basis of type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence. A specific hormonal agent may be used again if recurrence occurs >12 months from last treatment. (*Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Endocrine therapy should be recommended as initial treatment for patients with HR-positive MBC, except for patients with immediately life-threatening disease or for those experiencing rapid visceral recurrence during adjuvant endocrine therapy. (*Type: Evidence-based; benefits outweigh harms, Evidence quality: Intermediate; Strength of Recommendation: Strong*)

Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. *(Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)*

The use of combined endocrine therapy and chemotherapy is not recommended. *(Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)*

First-line therapy for HR-positive metastatic breast cancer

Postmenopausal women with HR-positive MBC should be offered aromatase inhibitors (AIs) as first-line endocrine therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Combination hormone therapy with fulvestrant, with a loading dose followed by 500 mg every 28 days, plus a nonsteroidal AI may be offered to patients with MBC without prior exposure to adjuvant endocrine therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate*).

Premenopausal women with HR-positive MBC should be offered ovarian suppression or ablation in combination with hormone therapy because contemporary hormonal agents have only been studied among postmenopausal women. (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*)

Treatment should take into account the biology of the tumor and the menopausal status of the patient with careful attention paid to ovarian production of estrogen. (*Type: Evidence and Consensus-based; benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Moderate*)

Targeted Therapy

A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-naıve HR-positive MBC, because PFS but not OS was improved compared with the nonsteroidal AI letrozole alone. Palbociclib may also be offered in combination with fulvestrant in patients exposed to prior hormone therapy and up to one line of chemotherapy, on the basis of data from the phase III PALOMA-3 trial. PFS was improved compared with fulvestrant alone; OS data are immature (*Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: intermediate*).

Postmenopausal women

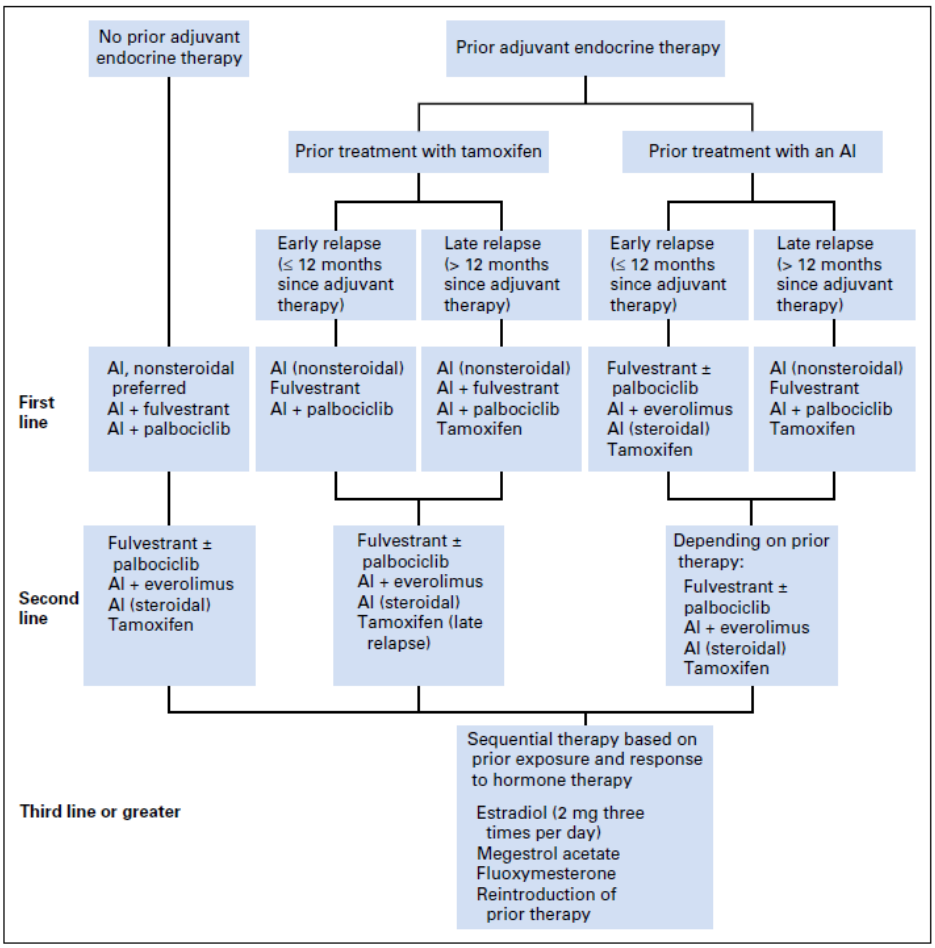

Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then once per month as an intramuscular injection. Withdrawal of tamoxifen or progestinswas reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates anastrozole or letrozole. AI, aromatase inhibitor

Premenopausal women

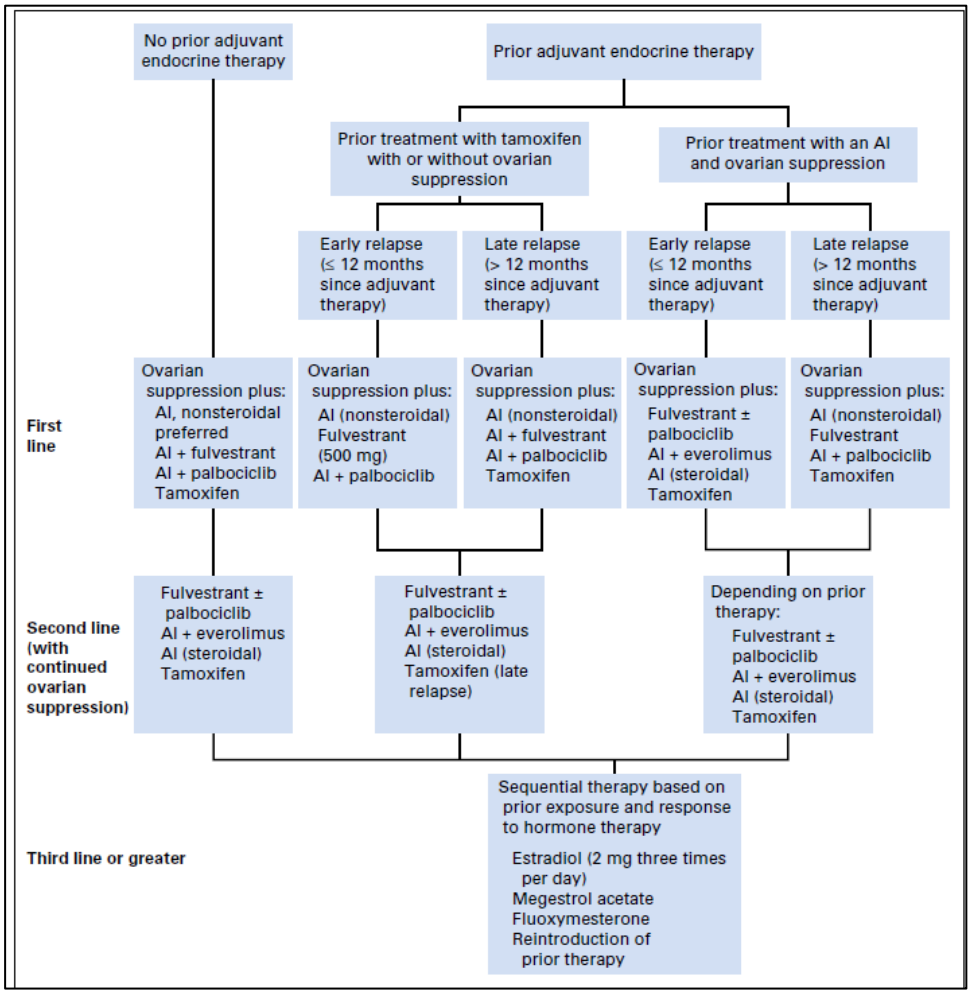

Fig 2. Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then monthly as an intramuscular injection. Withdrawal of tamoxifen or progestins was reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates anastrozole or letrozole.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, Feb 2020) am 04.02.2020

#	Suchfrage
1	[mh "Breast Neoplasms"]
2	(breast OR mamma*):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Feb 2015 to present

Systematic Reviews in Medline (PubMed) am 04.02.2020

#	Suchfrage
1	breast neoplasms/therapy[majr]
2	(breast[ti]) OR mamma*[ti]
3	(((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]) OR malignan*[ti]
4	(treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
5	#2 AND #3 AND #4
6	#1 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR

	Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	((#7) AND ("2015/02/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 04.02.2020

#	**Suchfrage**
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	(((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]) OR malignan*[ti]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2015/02/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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Anhang

Messina C et al., 2018 [12].

Tabelle 1: Characteristics of RCTs included in the meta-analysis

Table 1 Main characteristics of the randomized studies included in the present meta-analysis

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS	PFS bone+	PFS viscera+	ORR	Toxicity G3/G4 (≥ 2%)
Paloma 1 [7]	Open label, randomized, phase II, palbociclib + letrozole versus letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.49 (95% CI 0.32–0.75)	HR 0.29 (95% CI 0.09–0.94)	HR 0.55 (95% CI 0.32–0.94)	43% (95% CI 32–54) in the palbociclib + letrozole arm vs 33% (95% CI 23–45) $P = 0{\cdot}13$ in the letrozole arm	54% neutropenia, 19% leukopenia, 6% anaemia, 5% fatigue, 4% diarrhoea, 2% nausea, 2% thrombocytopenia, 2% nausea, 2% dyspnoea, 2% back pain
Paloma 2 [8]	Double blind, randomized (2:1), phase III, palbociclib + letrozole versus placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.58 (95% CI 0.46–0.72)	HR 0.36 (95% CI 0.22–0.59)	HR 0.63 (95% CI 0.47–0.85)	42.1% (95% CI 37.5–46.9) in the palbociclib + letrozole arm versus 34.7% (95% CI 28.4–41.3) in the placebo + letrozole arm	66% neutropenia, 25% leukopenia, 5% anaemia, 2% febrile neutropenia, 2% fatigue, 2% asthenia, 2% thrombocytopenia
Monaleesa 2 [9]	Double blind, randomized (1:1), phase III trial, ribociclib + letrozole vs placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.56 (95% CI 0.43–0.72)	HR 0.69 (CI 95% 0.38–1.25)	NA	40.7% in the ribociclib + letrozole arm vs 27.5% in the placebo + letrozole arm	59% neutropenia, 21% leukopenia, 9% increased alanine aminotransferase (ALT), 6% increased aspartate aminotransferase (AST), 4% infections, 4% vomiting, 2% fatigue, 2% nausea
Monarch 3 [12]	Double blind, randomized (2:1), phase III, abemaciclib + AI (letrozole or anastrozole) versus abemaciclib + AI	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.54 (95% CI 0.41–0.72)	HR 0.58 (CI 95% 0.27–1.25)	HR 0.61 (95% CI 0.42–0.87)	48.2% in the abemaciclib + AI arm vs 24.5% in the placebo + AI arm	20% neutropenia, 9.5% diarrhoea, 8% leukopenia, 6% anaemia, 6% increased ALT, 5% infections, 2% fatigue, 2% increased blood creatinine

Table 1 (continued)

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS	PFS bone+	PFS viscera+	ORR	Toxicity G3/G4 (≥ 2%)
Paloma 3 [10]	Double blind, randomized (2:1), phase III, palbo + ful vs palbo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.42 (95% CI 0.32–0.56)	HR 0.36 (95% CI 0.22–0.60)	HR 0.45 (95% CI 0.32–0.63)	10.4% (95% CI 7.4–14.1) in the palbociclib + fulvestrant arm vs 6.3% (95% CI 3.2–11.0) in the placebo + fulvestrant arm (P = 0.16)	62% neutropenia, 25% leukopenia, 3% anaemia, 2% fatigue, 2% thrombocytopenia
Monarch 2 [11]	Double blind, randomized (2:1), phase III, abemaciclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.55 (95% CI 0.45–0.68)	HR 0.54 (95% CI 0.35–0.83)	HR 0.48 (95% CI 0.37–0.63)	35.2% (95% CI 30.8% − 39.6%) in the abemaciclib + fulvestrant arm vs 16.1% (95% CI 11.3% − 21.0%) in the placebo + fulvestrant arm (P = 0.001)	26.5% neutropenia, 13% diarrhoea, 9% leukopenia, 7% anaemia, 4% increased ALT, 3% fatigue, 3% nausea, 3% thrombocytopenia, 3% dyspnoea, 2.5% abdominal pain, 2% increased AST
Monaleesa 3 [14]	Double blind, randomized (2:1), phase III, ribociclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts, newly diagnosed or relapse > 12 months from (neo)-adjuvant ET, or progressed after one line of ET	1°and 2°line	PFS	HR 0.59 (95% CI 0.48–0.73)	HR 0.37 (95% CI 0.23–0.61)	HR 0.64 (95% CI 0.48–0.86)	32.4% (95% CI 28.3–36.6%) in the ribociclib + fulvestrant versus 21.5% (95% CI 16.3–26.7%) in placebo + fulvestrant (P = < 0.001)	46.6% neutropenia,13.5% leukopenia, 6.6% increased ALT, 45.3% nausea, 31.5% fatigue
Monaleesa 7 [13]	Double blind, randomized (1:1), phase III, ribociclib + tamoxifen or AI versus placebo + tamoxifen or AI	HR+ HER2−, premenopausal or perimenopausal pts, progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	1° line	PFS	HR 0.55 (95% CI 0.44–0.69)	HR 0.70 (95% CI 0.41–1.19)	HR 0.50 (95% CI 0.38–0.68)	35.1% (95% CI 30.1–40.6) in the ribociclib + tamoxifen or AI versus 24.6% (95% CI 20.2–29.6%)	61% neutropenia, 14% leukopenia, 5% increased ALT, 31% nausea, 22% fatigue

ET endocrine therapy, *HR+* hormone receptor positive, *ORR* overall response rates, *PFS* progression-free survival, *pts* patients

Rugo HS et al., 2016 [16].

ASCO-Guidelines: Definitions for Types + Strengths of recommendation, Strengths of evidence

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Definitions for Types of recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

Definitions for Strengths of evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits *v* harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Definitions for Strengths of recommendation

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

ASCO-Guidelines: Endocrine therapy for women with hormone receptor–positive metastatic breast cancer.

Ergebnisse der syst. Literaturauswertung: Systematic reviews:

Table 1. Main Findings From Systematic Review (all included meta-analyses)

Study	Evidence Base	Main Findings
Endocrine *v* chemotherapy		
Wilcken[8]	Six trials including 692 patients with MBC (for OS comparison)	No significant difference in OS was detected (hazard ratio, 0.94; 95% CI, 0.79 to 1.12; $P = .5$), with nonsignificant heterogeneity detected
	Compared single-agent endocrine treatment with single-agent chemotherapy	Significant benefit in response rates (eight trials involving 817 women) for chemotherapy over endocrine therapy was detected (RR, 1.25; 95% CI, 1.01 to 1.54; $P = .04$)
		Authors conclude that standard first-line treatment for patients with MBC should be endocrine therapy rather than chemotherapy, except in presence of rapidly progressing disease
Single-agent *v* single-agent hormone therapies		
Chi[30]	23 trials including 7,242 patients (patients with advanced breast cancer were subset of total population)	Toremifene was associated with more vaginal bleeding (OR, 0.45; 95% CI, 0.26 to 0.80; $P < .05$) and greater decrease in serum triglyceride levels (SMD, −1.15; 95% CI, −1.90 to −0.39; $P < .05$) than tamoxifen
	Compared toremifene and tamoxifen	Evidence suggests toremifene could be an alternative to tamoxifen for patients with advanced breast cancer
Cope[31]	11 RCTs including 5,808 postmenopausal women with advanced breast cancer after endocrine therapy failure	Fulvestrant 500 mg was superior to fulvestrant 250 mg, megestrolacetate, and anastrozole for PFS ($P < .05$)
	Compared fulvestrant 500 mg, fulvestrant 250 mg, fulvestrant 250 mg loading dose, anastrozole 1 mg, megestrol acetate, letrozole 2.5 mg, letrozole 0.5 mg, and exemestane	
Xu[32]	Six RCTs including 2,560 postmenopausal patients with HR-positive advanced breast cancer	AIs were superior to tamoxifen alone for response (ORR; OR, 1.56; 95% CI, 1.17 to 2.07; $P < .05$) and CBR (OR, 1.70; 95% CI, 1.24 to 2.33; $P < .05$)
	Compared AIs *v* tamoxifen	
Single-agent *v* combination endocrine therapies		
Tan[33]	Two RCTs including patients with HR-positive advanced breast cancer (total patients, NR)	None of the comparisons for PFS, OS, or response showed statistically significant difference
	Compared fulvestrant + AI *v* AI alone (both studied anastrozole in combination with fulvestrant)	
Valachis[34]	Four RCTs including 2,125 patients with HR-positive advanced breast cancer	No difference detected between fulvestrant + AIs and tamoxifen for OS, TTP, CBR, or ORR
	Compared fulvestrant + AIs *v* tamoxifen	Hormonal agents other than fulvestrant were associated with great likelihood of joint disorders ($P < .05$)
Endocrine therapy ± mTOR inhibitors		
Bachelot[35]	Six RCTs (total patients, NR)	Everolimus + exemestane was superior to fulvestrant 250 mg and fulvestrant 500 mg for PFS and TTP (hazard ratio, 0.47; 95% CI, 0.38 to 0.58; $P < .05$ and hazard ratio, 0.59; 95% CI, 0.45 to 0.77; $P < .05$, respectively)
	All patients had HR-positive, HER2-negative advanced breast cancer	Analysis suggests that everolimus + exemestane is superior to fulvestrant 250 mg and 500 mg for PFS and TTP in patients with HR-positive, HER2-negative breast cancer with disease progression after endocrine therapy; however, there are no RCTs currently available providing direct comparison
	Included studies identified by systematic literature review (sources: Cochrane Library, National Horizon Scanning Centre, and NICE Web sites)	
	Comparisons were: everolimus + exemestane or everolimus + tamoxifen *v* fulvestrant	

Abbreviations: AI, aromatase inhibitor; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NICE, National Institute for Health and Care Excellence; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, response rate; TTP, time to progression.

1. **Bottcher TM, Cold S, Jensen AB.** Treatment of advanced HR+/HER2- breast cancer with new targeted agents in combination with endocrine therapy: a review of efficacy and tolerability based on available randomized trials on everolimus, ribociclib, palbociclib and abemaciclib. Acta Oncol 2019;58(2):147-153.

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7. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Mai 2019 und 05. Dezember 2019 - Abemaciclib (Mammakarzinom, HR+, HER2-, Kombination mit Fulvestrant) [online]. Berlin (GER): G-BA; 2019. [Zugriff: 18.08.2020]. URL: https://www.g-ba.de/downloads/91-1385-409/2019-12-05_Geltende-Fassung_Abemaciclib_D-401.pdf.

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Mammakarzinoms, Langversion 4.3 [online]. AWMF-Registernummer 032-045OL. 08.2019. Berlin (GER): Deutsche Krebsgesellschaft; 2017. [Zugriff: 18.08.2020]. URL: https://www.awmf.org/uploads/tx_szleitlinien/032-045OLl_S3_Mammakarzinom_2019-08.pdf.

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Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2020-B-318-z (Alpelisib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	23. Oktober 2020

Gemeinsamer Bundesausschuss

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Abkürzungsverzeichnis

ABC	Advanced Breast Cancer
AI	aromatase inhibitors
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDK	cyclin-dependent kinase
CR	complete response CR
DAHTA	DAHTA Datenbank
ER	Estrogene rezeptor
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HER2	Human epidermal growth factor receptor 2
HR	Hormonrezeptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LEE	Ribociclib
LHRH	Luteinizing Hormone-Releasing Hormone
LoE	Level of Evidence
mTOR	mechanistic Target of Rapamycin
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PAL	Palbociclib
PgR	progesterone receptor
PFS	Progression free survival
PR	Partial response

RR	Relatives Risiko
SERD	Selective estrogen receptor degrader
SERM	Selective estrogen receptor modulators
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TTF	Time to treatment failure
TTP	Time to progression
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

1 Indikation

zur Behandlung von postmenopausalen Frauen und Männern mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, fortgeschrittenen Mammakarzinom mit Progression unter oder nach einer endokrin-basierten Therapie.

Hinweis: Es wird davon ausgegangen, dass im vorliegenden AWG keine Indikation für eine Chemotherapie besteht (siehe Leitlinien). Daher werden SR und CR, in denen verschiedene Chemotherapie-Regimen (z.B. Monochemotherapie vs. Monochemotherapie; Monochemotherapie vs. Kombinationschemotherapie; Kombination aus Chemotherapie plus zielgerichtete Therapie vs. Chemotherapie) bei Patienten mit fortgeschrittenen Brustkrebs verglichen werden, nicht in der vorliegenden Evidenzsynpose abgebildet.

2 Systematische Recherche

Es wurden einen zwei systematische Literaturrecherchen nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur den Indikationen Mammakarzinom bei Frauen und bei Männern durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherchen am 25.01.2019 (für Männer) bzw. .30.11.2018 (für Frauen) abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 414 Quellen (für Männer) und 3857 Quellen (für Frauen), die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

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3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2018 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. März 2018 befristet bis 01. März 2019 – Ribociclib.

Anwendungsgebiet

Kisqali® (Ribociclib) wird in Kombination mit einem Aromatasehemmer zur Behandlung von postmenopausalen Frauen mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom als initiale endokrin-basierte Therapie angewendet.

Zweckmäßige Vergleichstherapie

Anastrozol oder Letrozol oder Fulvestrant oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Letrozol: Ein Zusatznutzen ist nicht belegt.

G-BA, 2018 [7].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. September 2018 – Palbociclib.

Anwendungsgebiet

Ibrance ist angezeigt zur Behandlung von Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen lokal fortgeschrittenen oder metastasierten Brustkrebs:

- in Kombination mit einem Aromatasehemmer
- in Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten

Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH =Luteinizing Hormone-Releasing Hormone) kombiniert werden.

Vergleichstherapie

a1) Postmenopausale Patientinnen in Erstlinientherapie:

Zweckmäßige Vergleichstherapie:

- Anastrozol oder Letrozol oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

b1) Postmenopausale Patientinnen mit Progression nach einer vorangegangenen endokrinen Therapie:

Zweckmäßige Vergleichstherapie:

- Tamoxifen

oder

- Anastrozol

oder

- Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung,

oder

- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung,

oder

- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung,

oder

- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a1) Postmenopausale Patientinnen in Erstlinientherapie:

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Letrozol: Ein Zusatznutzen ist nicht belegt

b1) Postmenopausale Patientinnen mit Progression nach einer vorangegangenen endokrinen Therapie:

- Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie: Ein Zusatznutzen ist nicht belegt

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IQWiG, 2016 [8].

Aromatasehemmer beim Mammakarzinom der Frau. Abschlussbericht; Auftrag A10-03. IQWiG-Berichte 437.

Fazit

Zweitlinientherapie nach Vorbehandlung mit Antiöstrogenen

Für die Zweitlinientherapie des fortgeschrittenen Mammakarzinoms nach Vorbehandlung mit Antiöstrogenen sind alle 3 Wirkstoffe Anastrozol, Exemestan und Letrozol zugelassen.

Für keinen der 3 Wirkstoffe liegen relevante Studien zum Nutzen einer solchen Therapie vor. Es gibt daher keinen Anhaltspunkt für einen Nutzen einer Zweitlinientherapie des fortgeschrittenen Mammakarzinoms mit Aromatasehemmern.

Da der Nutzen einer Zweitlinientherapie nicht nachgewiesen ist, sind die Ergebnisse direkt vergleichender Studien zwischen den Aromatasehemmern nur von untergeordneter Relevanz. Aus den vorliegenden Daten zeigt sich allerdings auch kein Anhaltspunkt für einen Zusatznutzen oder höheren Schaden eines Aromatasehemmers den anderen gegenüber.

Drittlinientherapie

Für die Drittlinientherapie wurde keine relevante Studie identifiziert. Es gibt daher keinen Anhaltspunkt für einen Nutzen einer Drittlinientherapie des fortgeschrittenen Mammakarzinoms mit einem Aromatasehemmer.

3.2 Cochrane Reviews

Lee C et al., 2017 [9].

Fulvestrant for hormone-sensitive metastatic breast cancer.

Fragestellung

To assess the efficacy and safety of fulvestrant for hormone-sensitive locally advanced or metastatic breast cancer in postmenopausal women, as compared to other standard endocrine agents.

Methodik

Population:

Postmenopausal women who had hormone-sensitive breast cancer (ER-positive or PgR-positive, or both) and who were diagnosed with locally advanced breast cancer (TNM classifications: stages IIIA, IIIB, and IIIC) or metastatic breast cancer (TNM classification: stage IV).

Intervention:

Fulvestrant with or without other standard anticancer treatments (e.g. endocrine therapy or chemotherapy, or both).

Komparator:

- any standard endocrine agents (tamoxifen and aromatase inhibitors) not containing fulvestrant
- any other anticancer treatment (e.g. chemotherapy).

Endpunkte:

- PFS, TTP, TTF, OS; Quality of life, Tolerability
- Clinical benefit rate: defined as the proportion of women with an objective response or a best overall tumour assessment of stable disease

Recherche/Suchzeitraum:

- Recherche am 7.7.2015
- CENTRAL (via the Cochrane Library, Issue 6, 2015
- MEDLINE and EMBASE from 2008 to 7 July 2015
- WHO ICTRP for all prospectively registered and ongoing trials
- major conference proceedings (ASCO and San Antonio Breast Cancer Symposium) and practice guidelines from major oncology groups (ASCO, ESMO, NCCN and Cancer Care Ontario).
- Handsearch in reference lists from relevant studies

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool, Assessment of heterogeneity by using Chi^2 test and I^2 statistic
- Assessment of quality of evidence by GRADE approach (’Summary of findings’ tables)

Ergebnisse

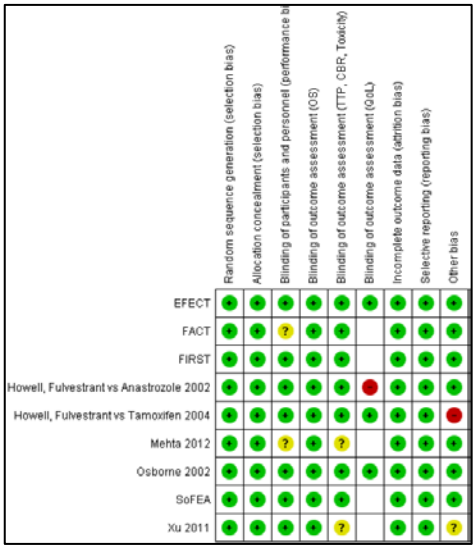
Anzahl eingeschlossener Studien: N=9 (n=4514)

Charakteristika der Population /der Studien:

- All participants postmenopausal women with hormone-sensitive breast cancer
- 4 studies with patients who had relapsed in the first instance and were naïve to treatment in the metastatic setting (FACT; FIRST; Howell, Fulvestrant vs Tamoxifen 2004; Mehta 2012) →first-line endocrine.
- Five studies enrolled women who had received prior endocrine treatment for metastatic disease (EFECT; Howell, Fulvestrant vs Anastrozole 2002; Osborne 2002; SoFEA; Xu 2011) → second-line endocrine or more.
- All 9 included studies compared fulvestrant as the intervention against an established standard breast cancer treatment, that is:
  - the aromatase inhibitors anastrozole (non-steroidal) and
  - exemestane (steroidal),
  - and the selective oestrogen receptor modulator tamoxifen.
- All studies except one tested fulvestrant at the 250 mg dose level (with 500mg loading dose); FIRST was the only study to dose fulvestrant at the now-approved current and standard dosing of 500mg intramuscular injections monthly

Qualität der Studien:

- Most studies were high quality studies; 1 study with high risk of bias due to lack of blinded outcome assessment, 1 further study with high risk of other bias



Studienergebnisse (Results for fulvestrant vs. comparators (other endocrine therapy)

OS:

- Overall: HR 0.97, 95% CI 0.87 to 1.09; (p=0.62; 2480 women; I^2=66%; high quality evidence) → no sign. difference
- Subgroup with approved dose (FIRST): HR 0.70, 95%CI 0.50 to 0.98 → superiority of fulvestrant (=firstline)

PFS:

- Overall: HR 0.95; 95%CI 0.89 to1.02 (4258 women; 9 studies; moderate-quality evidence)→ no significant differences
- Subgroup with approved dose (FIRST): HR of 0.66 (95% CI 0.47 to 0.93) 205 women
- second-line treatment: HR 0.96, 95% CI 0.88 to 1.04; 2255 women; 5 studies

Clinical benefit rate:

- Overall: RR 1.03 (95% CI 0.97 to 1.10); 4105 women; high-quality evidence
- Secondline: RR 1.03, 95% CI 0.92 to 1.15; 2105 women, 5 studies)

Quality of life:

- 4 studies reported quality of life (Functional Assessment of Cancer Therapy-Breast (FACT-B) or Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES) questionnaires) with follow-up ranging from 8.9 months to 38 months.
- None of the studies reported a difference in quality of life as per their analyses between participants receiving fulvestrant and other endocrine treatments but numerical data were not presented.

Toxicity: Assessment of 3 most common toxicities vasomotor, arthralgia + gynaecological toxicities (*nicht nach first- und secondline treatment differenziert*):

- Although there was some variation between the individual trials in the 3 examined toxicities, overall summary statistics were not significantly different between fulvestrant and the comparator drugs.
  - vasomotor toxicity: RR 1.02 (95% CI 0.89, 1.18); 8 trials, 3544 women; I^2=55%, high-quality evidence,
  - arthralgia: RR 0.96 (95%CI 0.86, 1.09); 7 trials, 3244 women; I^2=59%; high-quality evidence
  - Gynaecological toxicity (urinary tract infection, vulvovaginal dryness, vaginal haemorrhage, vaginitis, and pelvic pain: RR 1.22 (95% CI 0.94, 1.57); 2848 women; I^2= 66%; high-quality evidence

Anmerkung/Fazit der Autoren

As evidenced from our pooled data from 4514 women, fulvestrant (mostly administered at the anachronistic dose of 250 mg) was as effective as other standard endocrine therapies with respect to efficacy (measured by PFS, CBR, overall survival), toxicity, and quality of life. It is important to highlight that even at this inferior dose, fulvestrant was as effective and well tolerated as other comparator endocrine therapies. In our one included study of fulvestrant at the 500 mg dose level, fulvestrant was superior to anastrozole (FIRST).

Kommentare zum Review

- HER2 Status der eingeschlossenen Studien unklar

Tosello et al., 2018 [15].

Breast surgery for metastatic breast cancer

Gemeinsamer Bundesausschuss

Fragestellung

To assess the effect of breast surgery on women with metastatic breast cancer.

Methodik

Population:

- Women with metastatic breast cancer at initial diagnosis: TNM (tumour, lymph nodes, metastases) stage IV (Sobin 2002). This includes when breast cancer has spread beyond the breast, chest wall, and regional nodes. We applied no restrictions regarding age or histological type. If a study contained a subset of eligible participants, we would include them in the review as long as we could extract the relevant results.

Intervention:

- surgery plus systemic therapy

Komparator:

- systemic therapy alone

Endpunkte:

- primary outcomes were overall survival and quality of life.
- Secondary outcomes were progression-free survival (local and distant control), breast cancer-specific survival, and toxicity from local therapy.

Recherche/Suchzeitraum:

- Cochrane Breast Cancer Specialised Register, CENTRAL, MEDLINE (by PubMed) and Embase (by OvidSP) on 22 February 2016. We also searched ClinicalTrials.gov (22 February 2016) and the WHO International Clinical Trials Registry Platform (24 February 2016).

Qualitätsbewertung der Studien:

- Cochrane approach/GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

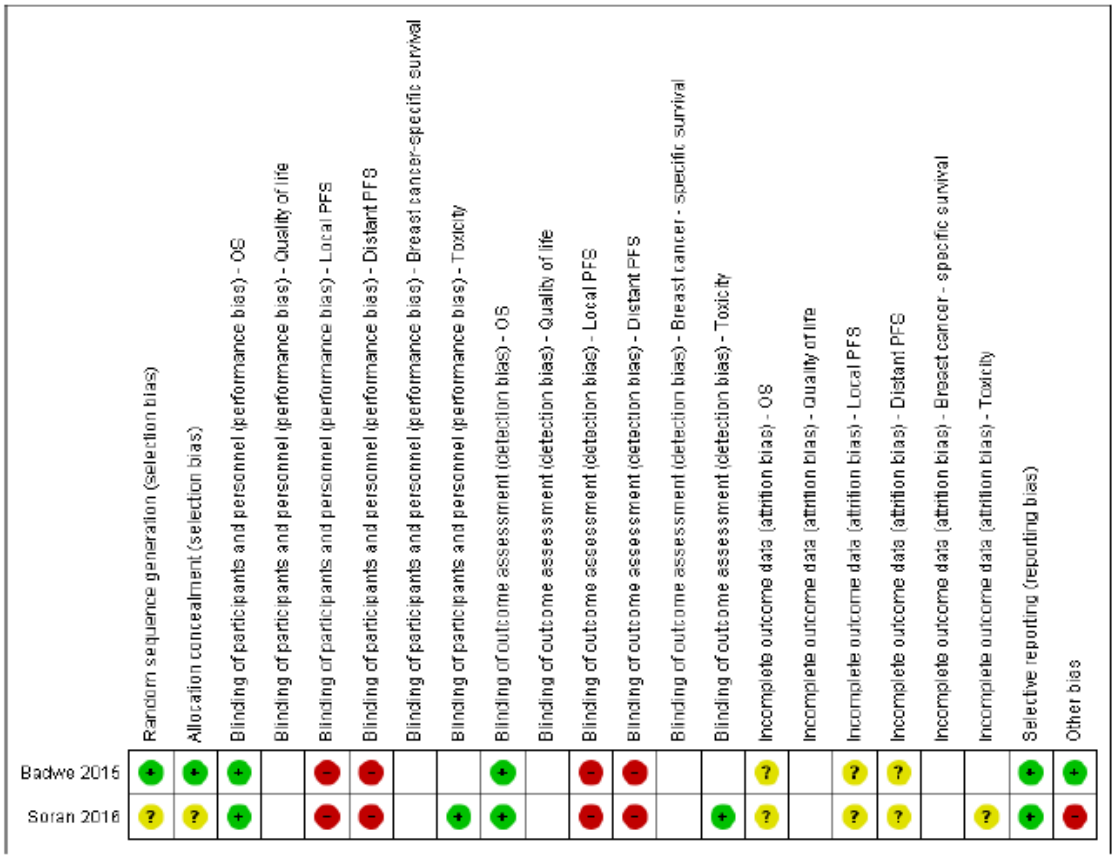
- We included two trials enrolling 624 women

Charakteristika der Population:

- There were 426 women with ER-positive tumours; 200 women with ER negative tumours; 192 women with HER2-positive tumours; 421 with HER2-negative tumours; and 226 women with bone-only metastases.

Qualität der Studien:

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



- Siehe weitere Details bei Ergebnisdarstellung

Studienergebnisse:

- It is uncertain whether breast surgery improves overall survival as the quality of the evidence has been assessed as very low (n.s.; 2 studies; 624 women). Breast surgery may improve local progression-free survival (HR 0.22, 95% CI 0.08 to 0.57; 2 studies; 607 women; low quality evidence), while it probably worsened distant progression-free survival (HR 1.42, 95% CI 1.08 to 1.86; 1 study; 350 women; moderate-quality evidence).
  - For both HER2-positive and -negative subgroups, the results were consistent with the main analysis.
  - For both ER-positive and -negative subgroups, the results were consistent with the main analysis.
- The two included studies did not measure breast cancer-specific survival.
- The two studies did not report quality of life.
- Toxicity from local therapy was reported by 30-day mortality and did not appear to differ between the two groups (RR 0.99, 95% CI 0.14 to 6.90; 1 study; 274 women; low-quality evidence).

Anmerkung/Fazit der Autoren

Based on existing evidence from two randomised clinical trials, it is not possible to make definitive conclusions on the benefits and risks of breast surgery associated with systemic treatment for women diagnosed with metastatic breast cancer. Until the ongoing clinical trials are finalised, the decision to perform breast surgery in these women should be individualised and shared between the physician and the patient considering the potential risks, benefits, and costs of each intervention.

3.3 Systematische Reviews

Beith J et al., 2016 [2].

Hormone receptor positive, HER2 negative metastatic breast cancer: A systematic review of the current treatment landscape.

Fragestellung

To assess the effectiveness and safety of novel combinations with standard endocrine therapy options in women with hormone receptor positive, HER2 negative metastatic breast cancer

Methodik

Population: women with hormone receptor positive, HER2 negative metastatic breast cancer

Intervention/ Komperator (exclusion of adjuvant therapy):

- aromatase inhibitors (AIs), letrozole, anastrozole and exemestane;
- selective estrogen receptor modulators (SERMs) tamoxifen, raloxifene, toremifene
- selective estrogen receptor degrader (SERD) fulvestrant;
- mTOR (mechanistic Target of Rapamycin)- inhibitors everolimus, temsirolimus and ridaforolimus;
- VEGF inhibitors bevacizumab, cediranib and enzastaurin;
- Pi3K inhibitors buparlisib and pictilisib;
- cyclin-dependent kinase (CDK) 4/6 inhibitor palbociclib;
- IGFR inhibitors ganitumab, figitumumab, dalotuzumab and AS1402;
- androgen antagonist abiraterone acetate;
- EGFR tyrosine kinase inhibitors (TKIs) gefitinib and lapatinib (also an HER2 TKI);
- GnRH agonist goserelin;
- HDAC inhibitor entinostat;
- and the SRC TKI dasatinib.

Endpunkt:

- PFS; OS, clinical benefit rate, AEs on grade 3 or 4 events

Recherche/Suchzeitraum:

- December 2015 in Cochrane Central Register of Controlled Trials, Cochrane Database of Reviews of Effect, Cochrane Database of Systematic Reviews, EMBASE, MEDLINE and Daily MEDLINE plus handsearch in ASCO, ESMO, EBCC, SABCS libraries

Qualitätsbewertung der Studien:

- using the MERGE criteria for evaluating the quality of studies and assessing the effect of interventions

Ergebnisse

Anzahl eingeschlossener Studien: 32 Studien (n=10.405 Patienten)

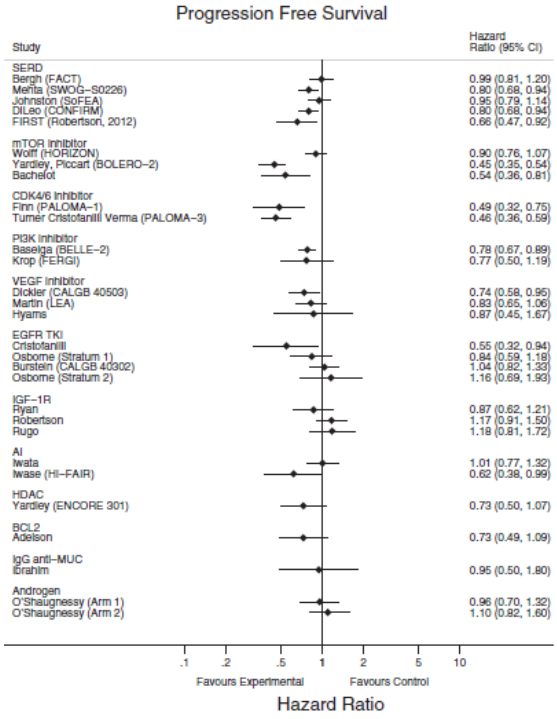
Charakteristika der Population:

- 555 (5%) had HER2 positive metastatic breast cancer.
- Interventions: addition of a trial agent to standard treatment (n=24), optimization strategies (n=8)
- 12 Studien= Firstline; 5 Studien= First- oder Secondline; 9 Studien= Secondline und später; 6 Studien ohne nähere Informationen
- The majority (n = 21) of the studies were in endocrine resistant settings, with a further 10 studies with a mixed population of women with endocrine resistant or sensitive tumors

Qualität der Studien:

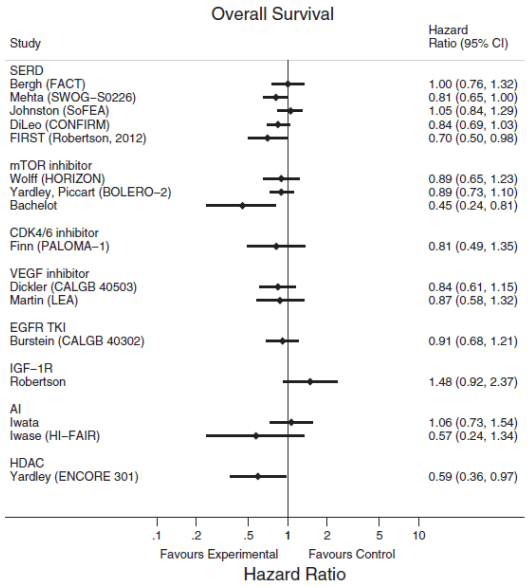
- MERGE assessment: 15 studies had a low risk of bias, 13 had low to moderate risk of bias and 7 had moderate to high risk of bias

Studienergebnisse (**Anhang 1**: Charakteristik und Studienergebnisse auf Einzelstudienbasis)



- greatest difference in PFS between arms was seen with the addition of a CDK4/6 inhibitor to either an AI or a SERD (HR between 0.36 and 0.75).
- Addition of treatment with an mTOR inhibitor (HR between 0.35 and 1.07), Pi3K inhibitor (HR between 0.50 and 1.19), SERD (HR between 0.47 and 1.20) and VEGF inhibitors (HR between 0.45 and 1.67) showed significant benefit in PFS in some studies.
- With the exception of one study, no significant PFS improvement was seen with EGFR TKIs and all IGFR inhibitor studies failed to show a benefit.
- Phase 2 data from a study with an HDAC inhibitor and another with a BCL2 inhibitor showed a trend toward benefit (HR 0.73 [95% CI 0.50, 1.07]; HR 0.73 [95% CI 0.49, 1.09], respectively), but this needs to be confirmed in larger ongoing phase III studies.

Overall survival



- None of the studies included in this review were powered for OS; results were reported for 16 of the 32 studies.
- No significant improvements in OS were reported with SERDs (HR between 0.24 and 1.34) and VEGF inhibitors (HR between 0.58 and 1.32)
- Of the 3 mTOR inhibitor studies with OS results, 1 showed a significant OS advantage (HR 0.45; 95% CI 0.24–0.81) for the combination of an mTOR inhibitor with tamoxifen.
- The results of the phase 2 HDAC study look promising, but need to be confirmed in larger studies.

Clinical benefit rate

- relative risk of clinical benefit was not improved in any studies regardless of the class of experimental agent

Safety

- Of the 32 studies included in the review, 28 reported toxicity data.
- Where more than 1 study reported discontinuation rates, they were generally highest with VEGF inhibitors (between 20.5% and 39%), with the LEA study reporting an unexpectedly high rate of toxicity-related deaths (4.2%; n = 8) with the combination of a VEGF inhibitor with endocrine therapy compared to no deaths with endocrine therapy alone, prompting the authors to suggest a possible toxicity interaction between these agents EGFR TKIs (12–20%), mTOR inhibitors (7.5–29%) and SERDs (2–27%) also reported higher discontinuation rates than those seen with AIs (0–6%) and IGF-1R inhibitors (1–12.8%).
- Stomatitis and hyperglycemia were commonly reported with mTOR inhibitors; pain and fatigue with SERDs; hypertension, diarrhea, proteinuria and dyspnea with VEGF inhibitors; stomatitis and neutropenia with IGFR inhibitors; neutropenia, leukopenia and anemia with CDK4/6 inhibitors; and hyperglycemia, rash and abnormal blood chemistry levels with Pi3K inhibitors.
- In addition, a study of an IGFR inhibitor in combination with an mTOR inhibitor and an AI was stopped early due to high rates of stomatitis with an overall rate of 68% (22/33 patients) and

grade 3 stomatitis in 11 (35%) patients. Dose reduction of the mTOR inhibitor improved rates of grade 3 stomatitis but rates remained high for grade 1 and 2 stomatitis.

Anmerkung/Fazit der Autoren

Limitations: The studies included in this review were too heterogeneous to allow for meta-analysis. While we excluded studies of patients with HER2 positive metastatic breast cancer from this review, a small number of patients (5%) were included in the studies we reviewed. We attempted to separate studies according to whether the patient populations were endocrine resistant or sensitive; however, it was unclear in most publications whether all or some patients had received prior endocrine therapy.

Conclusion: PFS benefit has been shown with the addition of a SERD or novel agents targeting CDK4/6,mTOR and Pi3K pathways. If early results can be confirmed by phase 3 studies, the benefits of new combination therapy may lead to significant changes to the way we treat these patients. Phase 3 studies with CDK4/6 inhibitors, Pi3K inhibitors and HDAC inhibitors are currently ongoing.

Kommentare zum Review

- Heterogenes Patientenkollektiv, insbesondere hinsichtlich Therapielinie, keine separate Auswertung nach Therapielinie.
- Nicht alle im Review adressierten Wirkstoffe haben eine Zulassung im AWG
- Funding and Conflict of Interests reported
- Risk of bias –Bewertung nur als Zusammenfassung dargestellt, Verknüpfung der Ergebnisse der Einzelstudien mit dem individuellen Verzerrungsrisiko nicht mgl.

Lin WZ et al., 2017 [11].

Fulvestrant plus targeted agents versus fulvestrant alone for treatment of hormone-receptor positive advanced breast cancer progressed on previous endocrine therapy: a meta-analysis of randomized controlled trials.

Fragestellung

To evaluate the efficacy and toxicity of adding targeted agents to fulvestrant (combination therapy) compared with fulvestrant alone in metastatic breast cancer patients progressed on previous endocrine treatment.

Methodik

Population: metastatic breast cancer patients progressed on previous endocrine treatment

Intervention: targeted therapy plus fulvestrant

Komparator: fulvestrant plus placebo

Endpunkt:

- partial response (PR), complete response (CR), and stable disease (SD), PFS,
- toxicity

Recherche/Suchzeitraum:

- Medline, Embase, Cochrane Central Register of Controlled Trials: between 2000- June 2016

Qualitätsbewertung der Studien: Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien: N=8

Charakteristika der Studien/Population:

Table 2 Characteristics of studies in the meta-analysis

Author year	Targeted agent	Pathway inhibited	HER2 expression	Postmenopausal status (%)	Prior endocrine therapy
Hyams DM21 2013	Cediranib	VEGF	−/+	100	Tam/AIs
Robertson JFR22 2013	Ganitumab	IGF	−/+ (7%)	100	Tam/AIs
Burstein HJ23 2014	Lapatinib	EGFR	−/+ (16%)	100	AIs
Clemons MJ24 2014	Vandetanib	VEGF	−/+ (5%)	100	Tam/AIs
Zaman K25 2015	Selumetinib	MAPK	–	100	AIs
Baselga J20 2015	Buparlisib	PI3K-mTOR	–	100	AIs
Cristofanilli M26 2016	Palbociclib	CDK4/CDK6	–	80	Tam/AIs
Krop IE27 2016	Pictilisib	PI3K-mTOR	–	100	AIs

Nur Palbociclib im AWG zugelassen → 1 Studie: Cristofanilli (PALOMA-3)

Qualität der Studien: The quality was high in all studies (Jadad score >=3).

Studienergebnisse:

Results of PALOMA-3 (Palbociclib + Fulvestrant vs Fulvestrant)

- PFS HR 0.46 [95%CI 0.36; 0.59]
- ORR: RR 2.21 [95% CI 1.30; 3.75]
- Disease control rate: RR 1.68 [95% CI 1,38; 2.05]
- Grade 3 or higher toxicity: RR 3.84 [95% CI 2.77; 5.33]

Fazit der Autoren

Adding targeted agents with fulvestrant showed ORR and PFS benefit in patients with advanced breast cancer compared with fulvestrant alone.

Kommentare zum Review

- Nur 1 der untersuchten Medikamente im AWG zugelassen und relevant
- Patientenrelevanz der Wirksamkeits-EP unklar

Wang J et al., 2018 [16].

Efficacy and safety of fulvestrant in postmenopausal patients with hormone receptor-positive advanced breast cancer: a systematic literature review and meta-analysis.

Fragestellung

to compare the efficacy and safety of fulvestrant with aromatase inhibitors in postmenopausal women with hormone receptor-positive (estrogen and/or progesterone receptor positive) advanced breast cancer.

Methodik

Population:

- Postmenopausal hormone receptor-positive advanced breast cancer patients

Intervention:

- fulvestrant

Komparator:

- aromatase inhibitors (anastrozole, exemestane, letrozole)

Endpunkte:

- Time to progression/progression-free survival was the primary outcome, while overall survival and safety were the secondary outcomes
- Time to progression/progression-free survival was evaluated in subgroups determined on age, hormone receptor status, visceral metastasis, and measurable disease

Recherche/Suchzeitraum:

- through August 31, 2017

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Total of seven randomized controlled trials, with 3168 patients

Qualität der Studien:

Table 2 Risk bias assessment

Study	Random sequence allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified
Howell [24]	Yes	No	No	Unclear	Yes	Unclear	No
Osborne [25]	Yes	No	Yes	Yes	Yes	Unclear	Yes
Xu [26]	Yes	No	Yes	Yes	Yes	No	No
Johnston [27]	Yes	Yes	Yes	Yes	Yes	No	No
Chia [28]	Yes	No	Yes	Yes	Unclear	No	No
Robertson [29]	Yes	No	No	No	Unclear	No	No
Robertson [30]	Yes	Yes	Yes	Yes	Yes	No	Yes

Studienergebnisse:

- In the overall population, fulvestrant and aromatase inhibitors had similar time to progression/progression-free survival; however, time to progression/progression-free survival for fulvestrant 500 mg was significantly longer compared with aromatase inhibitors (hazard ratio 0.75; 95% confidence interval 0.62–0.91, P = 0.003).
- Subgroup analysis revealed significant prolongation of time to progression/progression-free survival with fulvestrant compared with aromatase inhibitors in the patients of estrogen and progesterone receptor-positive (hazard ratio 0.86; 95% confidence interval, 0.75–0.98, P = 0.022) and patients aged ≥ 65 years (hazard ratio 0.81; 95% confidence interval 0.68–0.96, P = 0.014).
- Overall survival was similar in both groups
- Safety:

Table 3 Safety events

AE	Number of reported studies	Total number of patients (*N*)	Patients with AE		RR (95% CI)	*Z* value	*P* value
			Fulvestrant arm (n1)	AI arm (n2)			
Hot flushes[a]	5 [26–30]	2056	156	164	0.98 (0.81, 1.19)	0.16	0.874
Diarrhea[a]	3 [27, 28, 30]	1628	79	70	1.18 (0.88, 1.59)	1.11	0.267
Nausea[a]	5 [24–26, 28, 30]	2231	96	92	1.03 (0.79, 1.36)	0.24	0.813
Anemia[a]	3 [27, 28, 30]	1628	23	33	0.70 (0.42, 1.19)	1.32	0.188
Myalgia[a]	3 [27, 28, 30]	1628	35	27	1.30 (0.80, 2.13)	1.05	0.294
Arthralgia[b]	4 [26–28, 30]	1852	154	159	1.09 (0.68, 1.73)	0.36	0.716
Fatigue[b]	3 [27, 28, 30]	1628	56	61	0.94 (0.49, 1.79)	0.17	0.868
Dyspnea[b]	2 [27, 30]	927	44	39	1.07 (0.51, 2.22)	0.18	0.860

AE adverse events, *RR* risk ratio, *CI* confidence interval, *AI* aromatase inhibitor

[a]Fixed effects model

[b]Random effects model

$P < 0.05$ is considered statistically significant

Anmerkung/Fazit der Autoren

In postmenopausal women with hormone receptor-positive advanced breast cancer, fulvestrant 500 mg demonstrated better efficacy than aromatase inhibitor, which was not seen with fulvestrant 250 mg. When compared with aromatase inhibitors, fulvestrant prolonged time to progression/progression-free survival in the subgroups including estrogen and progesterone-positive patients and those aged ≥ 65 years.

Ding W et al., 2018 [5].

The CDK4/6 inhibitor in HR-positive advanced breast cancer: A systematic review and meta-analysis

Fragestellung

to explore whether CDK4/6 inhibitors had a significantly benefit to treating hormone receptor-positive (HR-positive)/human epidermal growth factor receptor 2 negative (HER2-negative) advanced breast cancer

Methodik

Population:

- atients with HR-positive/HER2-negative advanced breast cancer

Intervention:

- CDK4/6 inhibitors

Komparator:

- K.A. siehe ,,Charakteristika der Population“

Endpunkte:

- progression-free survival, response, and adverse events

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Library from January 1980 to December 2017

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCT records containing 3182 patients

Charakteristika der Population:

Table 1

Characteristics of included studies and outcome events.

Trials	Finn 2014[9]	Finn 2016[10]	Hortobagyi 2016 [11]	Cristofanilli 2016[13]	Sledge 2017[14]	Goetz 2017[15]
Information of the included trials						
Regions	50 sites in 12 countries	186 sites in 17 countries	223 sites in 29 countries	144 sites in 17 countries	142 sites in 19 countries	158 sites in 22 countries
Phases	I	II	II	II	III	II
Accrual dates	December 22, 2009, and May 12, 2012	February 2013 and July 2014	January 24, 2014, and March 24, 2015	October 7, 2013, and August 26, 2014	August 7, 2014, and December 29, 2015	November 18, 2014, and November 11, 2015
Inclusion criteria and study design						
Inclusion criteria	Postmenopausal; HR+, HER2− ABC; first-line	Postmenopausal; HR+, HER2− ABC; first-line	Postmenopausal; HR+, HER2− ABC; first-line	Any menopausal status; HR+, HER2− ABC; second-line	Any menopausal status, HR+, HER2− ABC; second-line	Postmenopausal; HR+, HER2− ABC; first-line
Study design	Palbociclib (125 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Palbociclib (125 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Ribociclib (600 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Palbociclib (125 mg daily for 21 d every 28 d) + fulvestrant (500 mg every 28 d) vs placebo + fulvestrant (500 mg every 28 d)	Abemaciclib (150 mg twice daily every 28 d) + fulvestrant (500 mg every 28 d) vs placebo + fulvestrant (500 mg every 28 d)	Abemaciclib (150 mg twice daily every 28 d) + anastrozole (1 mg daily) or letrozole (2.5 mg daily) vs placebo + anastrozole (1 mg daily) or letrozole (2.5 mg daily)
Patient demographic characteristic						
Age, y	T: 63 (54–71) C: 64 (56–70	T: 62 (30–89) C: 61 (28–88)	T: 62 (23–91) C: 63 (29–88)	T: 57 (30–88) C: 56 (29–80)	T: 59 (32–91) C: 63 (29–88)	T: 63 (38–87) C: 63 (32–88)
No. of patients	T: 84 C: 81	T: 444 C: 222	T: 334 C: 334	T: 347 C: 174	T: 446 C: 223	T: 328 C: 165
Outcomes assessment						
Primary end point	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival
Secondary end point	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response rate, the clinical benefit response	Objective response rate, the clinical benefit response

ABC = advanced breast cancer, C = control group, HER2− = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive, T = treatment group (also known as CDK4/6 inhibitor group).

Qualität der Studien:

- For allocation concealment, the risk of bias was unclear in 3 RCTs with an allocation scheme which was not mentioned in the trials. For random sequence generation, the risk of bias was unclear in 2 RCT studies. For the performance bias and detection bias, the risk was high in one study and unclear in another one. Except these 3 outliers, no high or unclear risk of bias was observed in any other studies.

Studienergebnisse:

- The result showed the CDK4/6 inhibitor group had a longer progression-free survival (PFS) (hazard ratio=0.51; 95% confidence interval [CI], 0.46–0.57, P < .00001), a better objective response (risk rate=1.53; 95% CI, 1.35–1.74, P < .00001), as well as a better clinical benefit response (risk rate=1.29; 95% CI, 1.13–1.47, P=.0001).
- Besides, subgroup analyses of PFS according to stratification factors and other baseline characteristics confirmed a great performance of CDK4/6 inhibitors across the all subgroups.
- As for neutropenia, all grades of it were substantially more frequent in the CDK4/6 inhibitor group (65%), compared with the control group (5%). Interestingly, grade 3 or 4 neutropenia was found among 43% of patients in the CDK4/6 inhibitor group and among 1% of patients in the control group. Meanwhile, leucopenia with all grades also appeared much more common in the CDK4/6 inhibitor group than in the control group (35% and 3% respectively), especially grade 3 or 4 leucopenia. Furthermore, infection, fatigue, nausea, anemia, thrombocytopenia, alopecia, nausea, rash, constipation, vomiting, and stomatitis were also more common in the CDK4/6 inhibitor group. Serious adverse events from any cause were occurred among 308 (19%) persons of 1974 patients in the CDK4/6 inhibitor group, and among 121 people (12%)of 1185 patients in the control group.

Anmerkung/Fazit der Autoren

CDK4/6 inhibitors can significantly prolong the PFS and improve the objective response or clinical benefit response, which was confirmed in every subgroup of the meta-analysis we performed. Adverse events are reversible, and the rate of discontinuation due to adverse events is low. Further studies should focus on whether treating with CDK4/6 inhibitors can significantly prolong the overall survival of patients with advanced breast cancer.

Chanchan G et al., 2018 [4].

The efficacy and safety of targeted therapy plus fulvestrant in postmenopausal women with hormone-receptor positive advanced breast cancer: A meta-analysis of randomized-control trials.

Fragestellung

To evaluate the efficacy and safety of targeted therapy plus fulvestrant for postmenopausal patients with hormone receptor-positive advanced breast cancer.

Methodik

Population:

- postmenopausal women with hormone receptor-positive (estrogen-receptor positive and/or progesterone-receptor positive) advanced breast cancer

Intervention:

- targeted therapy plus fulvestrant (the intervention group)

Komparator:

- fulvestrant alone

Endpunkte:

- progression-free survival, overall survival, objective response rate, clinical benefit rate and toxicities

Recherche/Suchzeitraum:

- Pubmed, Embase and Web of Science databases were systematically searched on February 26, 2018

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

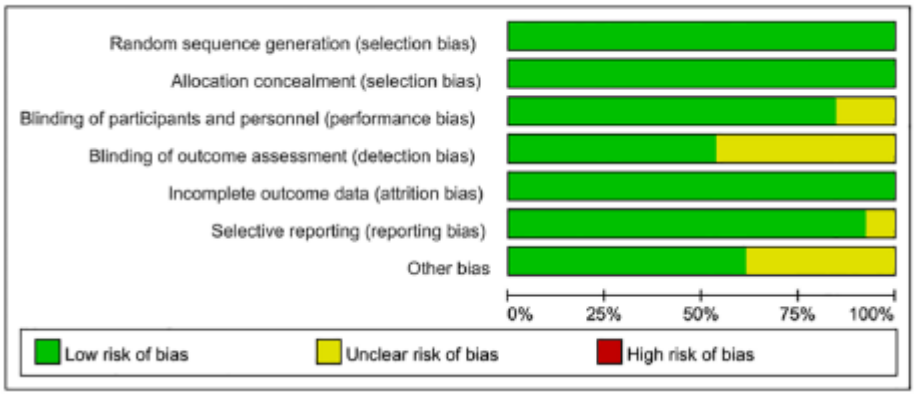
- Thirteen articles including twelve randomized-control trials

Charakteristika der Population:

-

Qualität der Studien:

- There was no evidence regarding the existence of publication bias and high-risk bias of quality in the selected studies.



Studienergebnisse:

- In previously endocrine therapy-treated postmenopausal patients with hormone-receptor positive advanced breast cancer, the PFS (HR = 0.77, 95%CI: 0.66± 0.91) and ORR (RR = 1.78, 95%CI: 1.35±2.34) of combination therapy group were significantly higher than that from fulvestrant monotherapy group.
  - Besides, a statistically significant difference in PFS was found across the two arms in postmenopausal women with PIK3CA-mutant ctDNA tumor (HR = 0.52, 95% CI: 0.39±0.69).
- Moreover, the risk of adverse events (RR = 1.09, 95%CI: 1.05±1.13), CTCAE3 (RR = 1.97, 95%CI: 1.49±2.60) and discontinuation due to adverse events (RR = 4.91, 95%CI: 3.37±7.15) were also significantly different between two treatment groups.

Anmerkung/Fazit der Autoren

In conclusion, compared with fulvestrant monotherapy, targeted therapy plus fulvestrant slightly improved PFS and ORR of postmenposaul women with HR+ advanced breast cancer; besides, combination therapy also increased toxicity. To date, the majority of RCTs have not identified cancer biomarkers, which might decrease the efficacy of target drugs. Therefore, more

measures should be taken to promote the progress of precision medicine for advanced breast cancer

Kommentare zum Review

- Sensitivity analysis showed PLOMA-3 trial was an important factor of heterogeneity.

Ayyagari R et al., 2018 [1].

Progression-free survival with endocrine-based therapies following progression on non-steroidal aromatase inhibitor among postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative metastatic breast cancer: a network meta-analysis.

Fragestellung

To quantify the comparative efficacy of currently available endocrine-based therapies (ETs) for postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative (HRþ/HER2) metastatic breast cancer (mBC) after non-steroidal aromatase inhibitor (NSAI) progression.

Methodik

Population:

- Women with HRþ/HER2- mBC who had previously failed on an NSAI (either during adjuvant or metastatic setting)

Intervention/Komparator:

- At least one of the following therapies, either as monotherapy or as part of a combination therapy
  - Endocrine Monotherapy
  - o Letrozole
  - o Anastrozole
  - o Exemestane
  - o Tamoxifen
  - o Fulvestrant
  - Targeted Therapy
  - o Palbociclib
  - o Everolimus
  - o Ribociclib
  - o Abemaciclib

Endpunkt:

- PFS

Recherche/Suchzeitraum:

- in June 2016

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs
- The selected four RCTs included the following six regimens: fulvestrant 250mgþanastrozole (Ful+AI), fulvestrant 250mg (Ful), fulvestrant 500mg (Ful), exemestane (AI), palbociclib+fulvestrant 500mg (PalþFul), everolimus+fulvestrant 500mg (Eve+Ful), and everolimus+exemestane (Eve+AI). In each arm, the sample sizes ranged from 66 to 485.

Qualität der Studien:

- The included trials were all well conducted and the risk of bias was assessed as low to moderate, with some studies not reporting concealment of allocation and blinding of care providers and participants.

Studienergebnisse:

- A total of 4 trials and 6 regimens (palbociclib+fulvestrant, everolimus+fulvestrant, everolimus+AI, fulvestrant+AI, fulvestrant and AI) were eligible for inclusion.

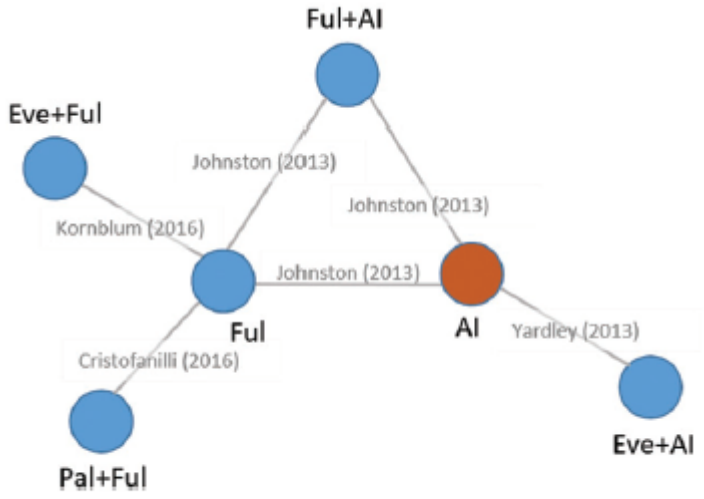


Figure 2. Evidence network. Abbreviations. AI, aromatase inhibitor; Ful, fulvestrant; Pal, palbociclib; Eve, everolimus. References: Johnston[27]; Cristofanilli[28]; Kornblum[29]; Yardley[14].

- Palbociclib+fulvestrant and everolimus+AI had 50% and 55% reduced hazard of progression or death vs. AI (95% CrI upper bound ≤1), respectively.

Table 3. Pairwise treatment comparison: median and 95% CrI of hazard ratio (column vs. row).

	AI	Pal + Ful	Eve + AI	Eve + Ful	Ful	Ful + AI
AI	1	0.49 (0.34, 0.69)	0.45 (0.38, 0.54)	0.64 (0.40, 1.03)	1.06 (0.83, 1.35)	1.01 (0.79, 1.28)
Pal + Ful	2.05 (1.45, 2.90)	1	0.92 (0.63, 1.36)	1.31 (0.80, 2.11)	2.17 (1.70, 2.78)	2.07 (1.46, 2.91)
Eve + AI	2.22 (1.86, 2.65)	1.08 (0.73, 1.59)	1	1.42 (0.85, 2.35)	2.36 (1.75, 3.17)	2.24 (1.65, 3.03)
Eve + Ful	1.57 (0.97, 2.52)	0.76 (0.47, 1.25)	0.71 (0.42, 1.18)	1	1.66 (1.10, 2.52)	1.58 (0.97, 2.56)
Ful	0.94 (0.74, 1.20)	0.46 (0.36, 0.59)	0.42 (0.32, 0.57)	0.6 (0.40, 0.91)	1	0.95 (0.75, 1.21)
Ful + AI	0.99 (0.78, 1.27)	0.48 (0.34, 0.68)	0.45 (0.33, 0.61)	0.63 (0.39, 1.03)	1.05 (0.82, 1.34)	1

Abbreviations. AI, aromatase inhibitor; Ful, fulvestrant; Pal, palbociclib; Eve, everolimus.

- Palbociclib+fulvestrant, everolimus+AI and everolimus+fulvestrant had 54%, 58% and 40% reduced hazard vs. fulvestrant (95% CrI upper bound ≤1), while palbociclib+fulvestrant and everolimus+AI had 52% and 55% reduced hazard vs. fulvestrant+AI (95% CrI upper bound ≤1), respectively.

Anmerkung/Fazit der Autoren

This SLR and NMA summarized and compared the efficacy of available ETs, in monotherapy or in combination with TTs, among postmenopausal women with HRþ/HER2- mBC who previously failed an NSAI. The results consistently indicated that, in this setting, patients who received palbociclib+fulvestrant, everolimus+AI, or everolimus+fulvestrant had longer PFS compared to those who received fulvestrant or AI alone.

Wibowo E et al., 2016 [17].

Tamoxifen in men: a review of adverse events.

Fragestellung

to summarize and evaluate the AE profile of tamoxifen in different male populations, specifically men with prostate cancer, breast cancer, infertility, and idiopathic gynecomastia. We discuss how the tamoxifen AE profile appears to differ in men from what has been reported in female breast cancer patients.

Methodik

Population:

- Prior to analysis, the studies were divided into the following patient populations: (i) prostate cancer receiving antiandrogens, (ii) prostate cancer not receiving antiandrogens, (iii) breast cancer, (iv) infertility, and (v) idiopathic gynecomastia.
- Studies were evaluated using a two-step process (Figure S1).
  - In the first step, we reviewed the abstracts from the original search results, and we excluded studies if they presented data on: (i) women; (ii) unrelated medical conditions; (iii) other SERMs (e.g., toremifene, raloxifene). In the second step, we evaluated each paper and excluded the study if: (i) it did not present safety and toxicity outcomes; (ii) tamoxifen was administered in combination with chemotherapy.

- Study designs, which were not RCTs, such as case reports, observational and retrospective studies describing tamoxifen use in men, were included as an additional analysis in this review.

Endpunkte:

- toxicities

Recherche/Suchzeitraum:

- PubMed: until March 17, 2014.

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- No RCTs in prostate cancer patients without antiandrogens nor male breast cancer patients receiving tamoxifen were identified.
- 39 non-RCTs on tamoxifen-treated men: one in prostate cancer patients with antiandrogen, 11 in prostate cancer patients without antiandrogen, 11 in breast cancer patients, six in men with infertility, and 10 in men with idiopathic gynecomastia.
  - Eleven non-RCT studies with a total sample size of 454 patients were identified. The patients' age ranged from 30 to 93 years old (unspecified in five of 11 studies). Tamoxifen treatment was a daily dose of 20 or 40 mg tamoxifen (unspecified dose in five studies), and in some patients, tamoxifen was combined with anastrozole, letrozole, radiotherapy, or aminoglutethimide. Treatment duration varied greatly (1 month to 10 years; unspecified in five studies).

Studienergebnisse:

- Male breast cancer patients:
  - Seven of these studies reported psychiatric disorder AEs with up to 113 reported cases Among the most commonly listed psychiatric AEs were decreased libido (44 cases), anxiety (23 cases), and sleep disorder (22 cases). For five men, reduced libido was the sole reason for discontinuing tamoxifen, whereas for another two men, either depression or emotional lability was the stated reasons for stopping tamoxifen.
  - Additionally, five men withdrew from tamoxifen treatment because of psychiatric AEs combined with other AEs. A few AEs (notably erectile dysfunction and weight gain) were described by many male breast cancer patients, but in most cases, they did not prompt patients to stop tamoxifen treatment without the presence of other AEs. In contrast, AEs under the cardiac and vascular disorder categories were more likely to cause withdrawal from treatment.
  - A total of 18 men discontinued tamoxifen because of cardiovascular events (Table 3) and the reasons include cerebrovascular and coronary event, hot flashes, pulmonary embolism, thromboembolic event, and thrombosis.
  - Other AEs also have led to tamoxifen discontinuation. For example, five breast cancer patients withdrew from tamoxifen after reporting hair loss or rash, and another five discontinued tamoxifen because of AEs in the musculoskeletal and connective tissue categories (bone pain, myalgia, leg aches, and cramps). (…)

Anmerkung/Fazit der Autoren

Gastrointestinal and cardiovascular disorders have been associated with tamoxifen treatment in men, however, treatment appears to be well-tolerated. From a total of 1645 subjects, less than 5% discontinued tamoxifen treatment. Although few male patients discontinued tamoxifen treatment, men offered tamoxifen to block antiandrogen-induced gynecomastia should be advised about the more common side effects in men, such as cardiovascular and gastrointestinal events. Some of the tamoxifen side effects, e.g. cardiovascular events, are consistent with tamoxifen blocking the normal roles of E2 in males. Future research should explore the mechanisms by which tamoxifen affects the various organ systems in men. Such studies would help clarify how different adverse events occur in men of different ages receiving tamoxifen treatment for various medical conditions.

Kommentare zum Review

- Die Quelle erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund fehlender höherwertiger Evidenz, wird der Review jedoch ergänzend dargestellt.

3.4 Leitlinien

AWMF, 2017 [10].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.1, 2017 AWMF Registernummer: 032-045OL

Fragestellung

Die Ziele der S3-LL für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms wurden aus der Ursprungsversion und der ersten beiden Aktualisierungen beibehalten und für die dritte Neuauflage ergänzt bzw. konkretisiert:

Methodik

Grundlage der Leitlinie

- Aktualisierung der LL-Version von 2012; Inhalt: 29 Themen zur Früherkennung, Diagnostik, Therapie und Nachsorge von Patientinnen mit Mammakarzinom.
- Interdisziplinäre LL-Entwicklergruppe, Beteiligung von Patientenvertreterinnen; Interessenkonflikterklärungen vorliegend und bewertet
- Bearbeitung der Themen: Leitlinienadaptation für ca. 80% der Statements/ Empfehlungen, De-novo-Recherche nach systematischen Reviews oder Primärliteratur für 20% der Statements/Empfehlungen

Systematische Recherche, Auswahl und Bewertung von bestehenden Leitlinien:

- Recherche nach LL, die nach Nov. 2013 veröffentlicht wurden, in Datenbanken von G-I-N, NGC, NICE, Library NHS, SIGN u.a. im Juni 2015 und Oktober 2015 (inkl. Abgleich mit LL-Bericht des IQWiG),
- AGREE-II-Bewertung der identifiziertten LL; Einschlusskriterium: Erfüllen von ≥ 50% der Domäne 3 (Rigour of Development) des AGREE II (Bewertung durch 2 Begutachter)

Systematische Recherche, Auswahl und Bewertung der Primärliteratur und SR:

- Formulierung von PICO-Fragen
- Recherche in Medline, CDSR, CENTRAL, DARE; Zeitraum: 06. April – 2. November 2016
- Methodische Bewertung der Literatur: SIGN-Checklisten für SR, RCT, Observational Studies (jeweils Version 2004) sowie Studies of Diagnostic Accuracy (Version 2006)

LoE

- Evidenzgraduierung nach Klassifikation des Oxford Centre for Evidence-based Medicine (Version 2009)

Formulierung der Empfehlungen und formale Konsensusfindung

- Entwurferstellung und Diskussion der Empfehlungen durch Arbeitsgruppen (nach Regeln des nominalen Gruppenprozesses)
- Konsentierung der Empfehlungen und der dazu gehörigen Empfehlungsgrade durch Leitliniengruppe im moderierten, formalen Konsensusverfahren (Nominaler Gruppenprozess).

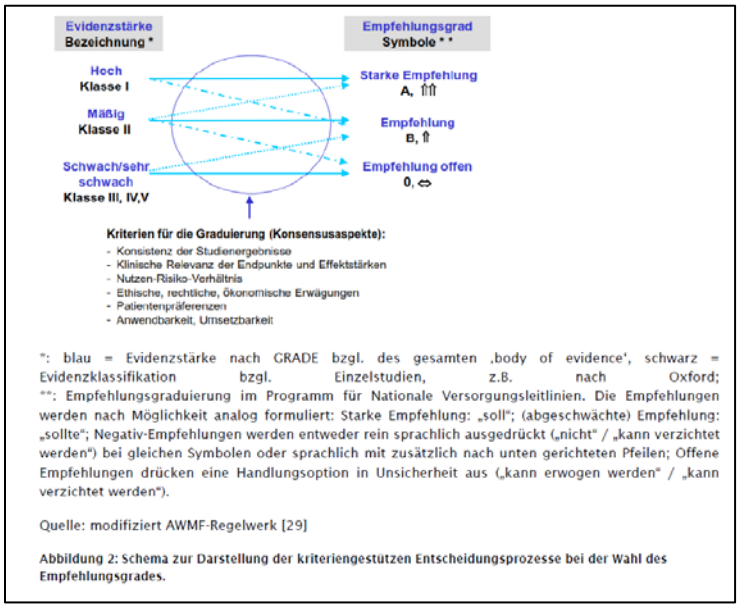
  GoR:

Tabelle 9: verwendete Empfehlungsgrade

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

- Empfehlungen, welche nicht durch Leitlinienadaptation oder durch Primärrecherche generiert wurden, sind als Expertenkonsens (EK) ausgewiesen. Der Empfehlungsgrad ergibt sich lediglich anhand der Ausdrucksweise (soll/sollte/kann) und wird nicht explizit mit A/B/0 gekennzeichnet.

Festlegung des Empfehlungsgrades



*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford; **: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden").

Quelle: modifiziert AWMF-Regelwerk [29]

Abbildung 2: Schema zur Darstellung der kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades.

Tabelle 10: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 – 75% der Stimmberechtigten
Dissens	≤50% der Stimmberechtigten

Sonstige methodische Hinweise

Stand der LL: 01.12.2017, gültig bis 30.11.2022

Empfehlungen

Endokrine Therapie

4.50.	Evidenzbasierte Empfehlungen
	Indikationen für eine endokrine Therapie
Empfehlungsgrad **A**	a.) Patientinnen mit östrogen- und/oder progesteronrezeptor-positiven (°) invasiven Tumoren sollen eine endokrine Therapie erhalten. ° (>/=10% progesteronrezeptor-positive Tumorzellkerne)
Level of Evidence **1a**	Quellen: [29, 726-729]
	Starker Konsens
Empfehlungsgrad **A**	b.) Diese soll erst nach Abschluss der Chemotherapie begonnen werden, kann aber parallel zur Strahlentherapie erfolgen.
Level of Evidence **1a**	Quellen: [580, 726-728] [29, 729]
	Starker Konsens

4.51.	Evidenzbasierte Empfehlung
	Endokrine Therapie
Empfehlungsgrad **A/B**	Nach 5 Jahren Tamoxifen soll für jede Patientin mit einem ER+-Mammakarzinom die Indikation zu einer erweiterten endokrinen Therapie geprüft werden. Die Indikationsstellung sollte in der Abwägung des Rückfallrisikos und den therapieassoziierten Nebenwirkungen (Toxizität, verminderte Adhärenz) erfolgen. Bei der Wahl der endokrinen Therapie soll der aktuelle Menopausenstatus der Patientin berücksichtigt werden.
Level of Evidence **LL-Adapt.**	Leitlinienadaptation: [737]
	Starker Konsens

4.54.	Evidenzbasierte Empfehlung
	Therapie bei postmenopausalen Patientinnen
Empfehlungsgrad **B**	Die adjuvante endokrine Therapie für postmenopausale Patientinnen mit einem ER+ Mammakarzinom sollte einen Aromatasehemmer enthalten.
Level of Evidence **1b**	Leitlinienadaptation: [730]
	Starker Konsens

4.40.	Evidenzbasierte Empfehlung
	Postmastektomie-Radiotherapie (PMRT)
Empfehlungsgrad **A**	Die postoperative Radiotherapie der Brustwand nach Mastektomie senkt das Risiko eines lokoregionären Rezidivs und verbessert das Gesamtüberleben bei lokal fortgeschrittenen und nodal positiven Mammakarzinomen.
Level of Evidence **1a**	Quelle: [650]
	Starker Konsens

Quelle:
650. McGale, P., et al., Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet, 2014. 383(9935): p. 2127-35

4.48.	Evidenzbasierte Empfehlung
	Radiotherapie bei lokal weit fortgeschrittenem Tumor und bei primärer Inoperabilität
Empfehlungsgrad **A**	Bei Patientinnen mit primär inoperablen bzw. inflammatorischen Karzinomen soll eine primäre Systemtherapie, gefolgt von Operation und postoperativer Strahlentherapie oder bei weiter bestehender Inoperabilität alleiniger oder präoperativer Strahlentherapie durchgeführt werden.
Level of Evidence **1b**	Quellen: [700, 701]
	Starker Konsens

Quellen:
700. Bartelink, H., et al., Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer Randomized Phase III Trial. J Clin Oncol, 1997. 15(1): p. 207-15.
701. Scotti, V., et al., Management of inflammatory breast cancer: focus on radiotherapy with an evidence-based approach. Cancer Treat Rev, 2013. 39(2): p. 119-24.

4.58.	Konsensbasierte Empfehlung/Statement
	Neoadjuvante systemische Therapie
EK	a.) Eine neoadjuvante (primäre, präoperative) systemische Therapie wird als Standardbehandlung bei Patientinnen mit lokal fortgeschrittenen, primär inoperablen oder inflammatorischen Mammakarzinomen im Rahmen eines multimodalen Therapiekonzeptes angesehen.
	Starker Konsens
EK	b.) Wenn die gleiche postoperative, adjuvante Chemotherapie indiziert ist, sollte eine neoadjuvante systemische Therapie bevorzugt werden.
	Starker Konsens

4.59.	Evidenz- /konsensbasierte Statements
	Neoadjuvante oder adjuvante Chemotherapie
Level of Evidence 1a	a.) Ist eine Chemotherapie indiziert, kann diese vor der Operation (neoadjuvant) oder danach (adjuvant) durchgeführt werden. Beide Verfahren sind hinsichtlich des Gesamtüberlebens gleichwertig. Die neoadjuvante Therapie kann zu einer höheren Rate an brusterhaltenden Therapien führen.
	Quellen: [558, 560, 793]
	Starker Konsens
Level of Evidence 1a	b.) Der Effekt (pathohistologische Remission) ist bei hormonrezeptornegativen Karzinomen am Größten.
	Quellen: [558, 560, 794, 795]
	Starker Konsens
EK	c.) Eine Resektion in den neuen Tumorgrenzen ist möglich, wenn eine R0-Resektion erreicht werden kann.
	Starker Konsens

Quellen:
558. von Minckwitz, G., et al., Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat, 2011. 125(1): p. 145-56.
560. Cortazar, P., et al., Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet, 2014. 384(9938): p. 164-72.
793. Kaufmann, M., et al., Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol, 2006. 24(12): p. 1940-9.
794. Bear, H.D., et al., Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol, 2006. 24(13): p. 2019-27.
795. von Minckwitz, G., et al., In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. Ann Oncol, 2005. 16(1): p. 56-63.

4.60.	Konsensbasierte Empfehlungen
	Primäre Hormontherapie bei postmenopausalen Patientinnen
EK	a.) Bei postmenopausalen Patientinnen mit endokrin sensitivem Mammakarzinom kann, wenn eine Operation oder Chemotherapie nicht möglich oder nicht gewünscht sind, eine primäre endokrine Therapie durchgeführt werden.
	Starker Konsens
EK	b.) Die neoadjuvante endokrine Therapie ist keine Standardtherapie, in speziellen Situationen (inoperabel, multimorbide Patientin) kann eine neoadjuvante endokrine Therapie erwogen werden.
	Starker Konsens

5. Das rezidivierte oder metastasierte Mammakarzinom

5.4 Fernmetastasen

5.4.1. Systemische Therapie des metastasierten Mammakarzinoms

5.13.	Evidenzbasierte Empfehlung
	Systemische endokrine Therapie
Empfehlungsgrad A	Die endokrine Therapie +/- zielgerichteter Therapie ist die Therapie der Wahl bei positivem Hormonrezeptorstatus und negativem HER2-Status. Die endokrine Therapie ist nicht indiziert bei Patientinnen, bei denen die Notwendigkeit des Erreichens einer schnellen Remission zur Abwendung von ausgeprägten Symptomen des betroffenen Organs besteht.
Level of Evidence 1b	Quellen: [29, 986-991]
	Starker Konsens

Quellen:
29. NICE. The National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [addendum 2014]; Available from: https://www.nice.org.uk/guidance/cg81/evidence/addendum-242246990
986. Fossati, R., et al., Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol, 1998. 16(10): p. 3439-60.
987. Stockler, M., et al., The management of advanced breast cancer: systemic reviews of randomised controlled trials regarding the use of cytotoxic chemotherapy and endocrine therapy. Woolloomooloo, NHMRC National Breast Cancer Centre, 1997.
988. Stockler, M., et al., Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. Cancer Treat Rev, 2000. 26(3): p. 151-68.
989. Rugo, H.S., et al., Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol, 2016. 34(25): p. 3069-103.
990. Cancer Australia. Recommendations for the management of early breast cancer in women with an identified BRCA1 or BRCA2 gene mutation or at high risk of a gene mutation. 2014 Available from: http://guidelines.canceraustralia.gov.au/guidelines/guideline_17.pdf.
991. Partridge, A.H., et al., Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol, 2014. 32(29): p. 3307-29.

5.14.	Evidenzbasierte Empfehlung
	Kombinierte chemo-endokrine Therapie
Empfehlungsgrad A	Eine kombinierte chemo-endokrine Therapie wird nicht empfohlen. Sie kann zwar die Remissionsraten erhöhen, führt aber auch zu gesteigerter Toxizität ohne Verlängerung des progressionsfreien Intervalls oder des Gesamtüberlebens.
Level of Evidence 1a	Conchrane: [1004] Quelle: [1005]
	Starker Konsens

Quellen:
1004. Carrick, S., et al., Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev, 2005(2): p. Cd003372.
1005. Sledge, G.W., Jr., et al., Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An Eastern Cooperative Oncology Group study. J Clin Oncol, 2000. 18(2): p. 262-6.

5.17.	Evidenzbasierte Empfehlung
	Endokrine Therapie bei postmenopausalen Patientinnen
Empfehlungsgrad **A**	Als erster endokriner Behandlungsschritt bei Metastasierung sollte bei postmenopausalen Patientinnen ein Aromatasehemmer eingesetzt werden, wenn adjuvant ausschließlich Tamoxifen oder keine adjuvante Therapie erfolgt ist. Eine klare Empfehlung, ob primär ein steroidaler oder nicht-steroidaler Aromatasehemmer eingesetzt werden sollte, kann nicht ausgesprochen werden. Letrozol kann mit einem CDK4/6-Inhibitor kombiniert werden.
Level of Evidence **1a**	Conchrane: [994] Quellen: [29, 986, 989, 1015-1018]
	Starker Konsens

Quellen:
29. NICE. The National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [addendum 2014]; Available from: https://www.nice.org.uk/guidance/cg81/evidence/addendum-242246990
986. Fossati, R., et al., Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol, 1998. 16(10): p. 3439-60.
989. Rugo, H.S., et al., Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol, 2016. 34(25): p. 3069-103.
994. Gibson, L., et al., Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev, 2009(4): p. Cd003370
1015. Ellis, M., D. Hayes, and M. Lippman, Treatment of metastatic breast cancer. Cancer, 2000. 2000: p. 749-797.
1016. Hayes, D.F., I.C. Henderson, and C.L. Shapiro, Treatment of metastatic breast cancer: present and future prospects. Semin Oncol, 1995. 22(2 Suppl 5): p. 5-19; discussion 19-21.
1017. Mouridsen, H., et al., Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol, 2001. 19(10): p. 2596-606.
1018. Mouridsen, H., et al., First-line therapy with letrozole (femara®) for advanced breast cancer prolongs time to worsening of Karnofsky Performance Status compared with tamoxifen. Breast Cancer Research and Treatment, 2001. 69(3): p. 291

5.18.	Konsensbasierte Empfehlung
	Fulvestrant bei postmenopausalen Patientinnen
EK	Eine Behandlung mit Fulvestrant sollte insbesondere nach Vorbehandlung mit einem Aromatasehemmer erfolgen, kann aber auch als erste Therapielinie eingesetzt werden, insbesondere bei noch nicht endokrin vorbehandelten Patientinnen.
	Starker Konsens

5.19.	Konsensbasierte Empfehlung
	Kombinationstherapien bei postmenopausalen Patientinnen
EK	Eine bestimmte Therapiesequenz kann nicht empfohlen werden. Eine Kombinationsbehandlung von Letrozol oder Fulvestrant mit einem CDK4/6-Inhibitor stellt eine Therapiealternative zur Monotherapie dar. Nach antihormoneller Vortherapie mit einem nicht-steroidalen Aromatasehmmer kann eine Folgetherapie mit Exemestan und dem mTOR-Inhibitor Everolimus durchgeführt werden. Kombinationstherapien konnten in Studien eine Verlängerung des Progressionsfreien Überlebens, bislang aber nicht des Gesamtüberlebens zeigen.
	Starker Konsens

5.20.	Konsensbasierte Empfehlung
	Behandlungskaskade bei postmenopausalen Patientinnen
EK	Weitere Schritte in der endokrinen Behandlungssequenz bei postmenopausalen Patientinnen stellen je nach Vorbehandlung der Einsatz von Antiöstrogenen, Östrogenrezeptor-Antagonisten, der Wechsel des Aromataseinhibitors von einem steroidalen auf einen nicht-steroidalen Aromataseinhibitor oder vice versa oder der Einsatz von hoch dosierten Gestagenen dar. Nach Progress unter einem nicht-steroidalen Aromatasehemmer kann die Kombination von Letrozol oder Fulvestrant mit Palbociclib oder die von Exemestan und Everolimus eingesetzt werden.
	Starker Konsens

Männer mit Brustkrebs

6.39.	Konsensbasierte Empfehlung
	Männer mit Brustkrebs
EK	Männer mit Brustkrebs sollen wie Frauen eine jährliche bildgebende Diagnostik erhalten, insbesondere da ein höheres Risiko für ein kontralaterales Karzinom besteht.
	Konsens

Erläuterungen: Männer mit Brustkrebs haben ein höheres Risiko als Frauen mit Brustkrebs für ein kontralaterales Mammakarzinom. Eine Studie mit Daten aus dem Surveillance, Epidemiology, and End Results database mit Follow-up von n=1.788 Patienten zeigte ein 30-fach erhöhtes Risiko für ein kontralaterales Mammakarzinom (SIR [standardized incidence ratio] 29.64, 95% CI: 15–52) verglichen mit der allgemeinen männlichen Bevölkerung, während bei Frauen mit Brustkrebs nur ein 2-4-fach erhöhtes Risiko besteht.

Mammakarzinom des Mannes

Die Diagnostik und Therapie des Mammakarzinoms des Mannes sollte interdisziplinär erfolgen und erfordert aufgrund der tumorbiologischen Eigenschaften und Ähnlichkeit zu dem Mammakarzinom der Frau gynäkoonkologische Fachexpertise. Eine interdisziplinäre Zusammenarbeit von Brustzentren, niedergelassenen Gynäkologen, Urologen und Andrologen wird insbesondere angeraten bei der Behandlung der sexuellen Stö-rungen durch die Tamoxifentherapie, bei Männern mit BRCA-Mutationen mit einem damit einhergehenden erhöhten Risiko für Prostatakrebs und bei Männern mit Brustkrebs, bei denen eine Behandlung des benignen Prostatasyndroms erfolgen soll.

9.1.	Konsensbasierte Empfehlungen
EK	a.) Eine frühzeitige ärztliche Konsultation soll durch Information von Männern über die Erkrankung, insbesondere über Symptome und Veränderungen der Brust und durch die Aufforderung zur Selbstbeobachtung, gefördert werden. b.) Die Basisdiagnostik soll bei Verdacht auf maligne Befunde durch Anamnese, klinische Untersuchung, Mammographie sowie Ultraschalldiagnostik der Brust und der Lymphabflussregionen erfolgen. Zum diagnostischen Einsatz der KM-MRT liegen keine Daten vor. c.) Die weiterführende Diagnostik und das Staging/ Ausbreitungsdiagnostik soll bei Brust- und Axillabefunden entsprechend der Empfehlung für Frauen erfolgen, wobei zum diagnostischen Einsatz von KM-MRT keine Daten vorliegen.
	Starker Konsens

9.2.	Konsensbasierte Empfehlungen
EK	a.) Die Operation hat die vollständige Tumorentfernung zum Ziel und sollte als Mastektomie durchgeführt werden. Bei günstigem Größenverhältnis zwischen Tumor und Brust sollte die Brusterhaltung erwogen werden. b.) Bei klinisch unauffälliger Axilla (cN0) soll eine Sentinel-Lymphknotenentfernung nach den gleichen Regeln wie bei der Frau vorgenommen werden.
	Starker Konsens

9.3.	Konsensbasierte Empfehlung
EK	Bei größeren Tumoren (≥ 2cm), bei axillärem Lymphkotenbefall und bei negativem Hormonrezeptor soll eine adjuvante Radiotherapie der Brustwand und ggf. der Lymphabflusswege (Indikation wie bei der Frau) unabhängig vom Operationsverfahren erfolgen.
	Starker Konsens

9.4.	Konsensbasierte Empfehlung
EK	Die adjuvante Chemotherapie sowie die Antikörpertherapie (Anti-HER2) soll nach den gleichen Regeln wie bei der Frau indiziert und durchgeführt werden.
	Konsens

9.5.	Konsensbasierte Empfehlung
EK	Patienten mit einem Hormonrezeptor-positiven Mammakarzinom sollen eine adjuvante endokrine Therapie mit Tamoxifen in der Regel über 5 Jahre erhalten. Für eine Behandlung über 5 Jahre hinaus liegen keine Daten vor. Analog zum weiblichen Mammakarzinom kann diese in Einzelfällen erwogen werden.
	Starker Konsens

9.6.	Konsensbasierte Empfehlung
EK	a.) Die Therapie bei metastasierter Erkrankung sollte nach den gleichen Regeln wie bei der Frau erfolgen. b.) Es ist unklar, ob Aromatasehemmer ohne Suppression der testikulären Funktion beim Mann ausreichend wirksam sind. Daher sollten Aromatasehemmer in Kombination mit einer Suppression der testikulären Funktion gegeben werden.
	Starker Konsens

9.7.	Konsensbasierte Empfehlung
EK	Die Teilnahme an Studien/Registern sollte Männern mit Brustkrebs angeboten und ermöglicht werden.
	Konsens

9.8.	Konsensbasierte Empfehlung
EK	Eine genetische Beratung soll allen Männern mit Brustkrebs empfohlen werden.
	Konsens

9.9.	Konsensbasierte Empfehlung
EK	Die Ausgestaltung der Nachsorge einschließlich der bildgebenden Diagnostik soll in Analogie zum Vorgehen der Frauen erfolgen.
	Starker Konsens

9.10.	Konsensbasierte Empfehlung
EK	Qualifizierte und sachdienliche genderspezifische Informationen (Print und Internet) sollten dem Patienten von dem behandelnden Fachpersonal zur Verfügung gestellt werden und der Zugang zum speziellen Angebot der Selbsthilfegruppen ermöglicht werden.
	Starker Konsens

(…)

Es gibt ausgesprochen wenig Evidenz aus randomisierten Studien zu spezifischer Diagnostik, biologischen Parametern und Therapie des männlichen Mammakarzinoms. Die Daten beruhen derzeit überwiegend auf epidemiologischen Daten, retrospektiven Fallberichten, retrospektiven kleinen Kohorten und inhomogenen Studienkollektiven. Es gibt keine Behandlungsstandards, die sich auf größere randomisierte Studien beziehen könnten.

Derzeit richten sich die Empfehlungen zur Behandlung von Männern mit Brustkrebs überwiegend nach den Empfehlungen zur Diagnostik, Behandlung und Nachsorge der Erkrankung bei postmenopausalen Frauen. Wohl wissend, dass die Erkrankung bei Männern andere biologische Potenziale aufweist, die in der Versorgung von Patienten zu berücksichtigen sind. International besteht Konsens, die Wissensbasis zu Brustkrebs bei Männern durch Teilnahme an Registerstudien anzuheben.

Bei männlichen Brustkrebspatienten findet sich eine ähnliche Brustkrebssterblichkeit wie bei älteren postmenopausalen Frauen. Eine genetische Disposition liegt bei Männern häufiger vor, insbesondere Mutation BRCA1 und BRCA2. Darüber hinaus haben Männer mit Brustkrebs eine bis zu 20 % erhöhte Risikokonstellation für Zweitmalignome.

Bei über 90% der Patienten wird ein ER-positives invasivduktales Karzinom diagnostiziert. Die HER2-Überexpression wird in der Literatur inkonsistent mit 12-37% angegeben. Eine aktuelle Studie fand 97% ER-positive und nur 10% HER2-positive Tumoren in einer unizentrischen Kohorte von 61 invasiven Mammakarzinomen bei Männern. In 39–95% der Fälle wurde eine Androgenrezeptor-Expression nachgewiesen. Im Gegensatz zu den histopathologischen Ähnlichkeiten zum Brustkrebs bei Frauen weisen molekularbiologische Untersuchungen wesentliche Unterschiede auf.

Die meisten Männer wurden bisher durch Mastektomie und axilläre Lymphonodekto-mie (ALND) und ggf. mit Brustwandbestrahlung behandelt. Aktuelle Daten suggerieren insbesondere weniger radikale chirurgische Maßnahmen mit dem Ziel, die therapiebedingte Morbidität zu senken.

Männer mit Brustkrebs mit Lymphknotenbefall profitieren von einer adjuvanten Chemotherapie mit Verbesserung der Prognose (krankheitsfreies Überleben, Gesamtüber-leben). Bei der Entscheidung zur adjuvanten Therapie sind Komorbiditäten und Tolerabilität sowie Präferenzen des Patienten zu berücksichtigen. Verwendet werden die bei Frauen üblichen Substanzen und Schemata einschließlich der Anti-HER2-Therapie, wenn indiziert. Tamoxifen ist derzeit

Standardtherapie bei Hormonrezeptor-positivem Brustkrebs. Die Nebenwirkungen wie sexuelle Dysfunktionen führen zu einer hohen Therapieabbruchrate. Der Einsatz von Aromatasehemmern in der adjuvanten Therapie wird nicht empfohlen; Aromatasehemmer waren in einer retrospektiven Analyse deutscher Krebsregister mit einer signifikant erhöhten Mortalität verbunden.

Es gibt keine Evidenz aus klinischen Studien zur Behandlung des HER2-positiven Mammakarzinoms bei Männern; allerdings besteht Konsens, in Anlehnung an die Erfolge beim HER2-positiven Mammakarzinom der Frau auch Männer mit HER2-positivem Mammakarzinom adjuvant mit Trastuzumab zu behandeln.

In der Metastasierung können Aromatasehemmer second-line eingesetzt werden, am ehesten in Verbindung medikamentöser Suppression der Gonadenfunktion.

Bei fortgeschrittener metastasierter Erkrankung weisen Studien Behandlungsoptionen sowohl für Fulvestrant, Aromatasehemmern und Eribulin aus.

Die Rehabilitation und Nachsorge einschließlich der bildgebenden Diagnostik erfolgt in Anlehnung an die empfohlene Nachsorge für Frauen. Die Nachsorge für Männer fokussiert auf die zu beachtenden spezifischen Risiken, Komorbiditäten, Kurz- und Langzeitnebenwirkungen und schließt psychosoziale sowie psychoonkologische Aspekte ein.

Rugo HS et al. 2016 [13].

Endocrine therapy for women with hormone receptor (HR) –positive metastatic breast cancer (MBC).

Leitlinienorganisation/Fragestellung

- American Society of Clinical Oncology (ASCO) Clinical Practice Guideline
- Guideline Questions:

1. Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for hormone receptor (HR) –positive metastatic breast cancer (MBC)?
    1.1 For postmenopausal women: What are the optimal sequence and duration?
    1.2 Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?
    1.3 For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?
1.4 Are there demonstrated differences between pre- and postmenopausal patients?
2. Is there an optimal second- or later-line endocrine therapy for HR-positive MBC?
    2.1 Should other treatment or disease-free interval play a role in treatment selection?
    2.2 Which hormone therapy should be offered?
    2.3 What are the optimal timing, dose, and schedule of treatment?
3. How or should endocrine therapies be used in combination or sequence with:
    3.1 Mammalian target of rapamycin inhibitors (everolimus)?
    3.2 Cyclin-dependent kinase 4/6 inhibitors (palbociclib)?
4. Does estrogen or progesterone expression (high v low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women?
5. How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting?
6. In which patients or settings is hormone therapy recommended over chemotherapy?
    6.1 Is there a role for combined cytotoxic and endocrine therapies?
    6.2 What is the optimal duration of treatment with hormonal therapy?
7. Is there a role for additional biomarkers in the selection of treatment for patients with HR-positive disease?

7.1 What is the role of genomic profiling or intrinsic subtypes in this population?

8. How does human epidermal growth factor receptor 2 (HER2) positivity affect treatment of patients with HR-positive MBC?

9. What are the future directions for treatment in this patient population?

Methodik

Grundlage der Leitlinie

- multidisciplinary Expert Panel (medical oncology, radiation oncology, psycho-oncology, patient advocacy, and guideline methodology).
- All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests... In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy.
- ASCO guidelines are based on systematic reviews of evidence from 2008 through 2015:
  - A protocol for each guideline defines the parameters for a targeted literature search, including relevant study designs, literature sources, types of reports, and prespecified study selection criteria for literature identified
  - Formal assessment of Study Quality (Detaillierte Informationen + Bewertungsergebnisse zu finden im METHODOLOGY SUPPLEMENT)

Recherche/Suchzeitraum:

- Literature search: in Medline to 4/2014; Cochrane Library databases to Issue 3 of March 2013; Antonio Breast Cancer Symposium (2011 to 2014) and ASCO abstracts (2012 to 2014); targeted literature search update: in June 2015

LoE/ GoR

- Definitions for Types + Strengths of recommendation, Strengths of evidence: → Anhang 2
- Recommendations reflect high, moderate or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases.

Sonstige methodische Hinweise

- Revision Dates: The co-chairs determine the need for guideline updates or revisions on the basis of periodic review and consideration of the literature. If new and compelling data are identified, the Expert Panel or an update committee is reconvened to discuss revisions to the document
- Evidenzgrundlage im Anhang 3 abgebildet

Empfehlungen

ASCO Key Guideline Recommendations for HR-positive MBC

Hormone therapy should be offered to patients whose tumors express any level of estrogen and/or progesterone receptors. (*Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Treatment recommendations should be offered on the basis of type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence. A specific hormonal agent

may be used again if recurrence occurs >12 months from last treatment. (*Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Endocrine therapy should be recommended as initial treatment for patients with HR-positive MBC, except for patients with immediately life-threatening disease or for those experiencing rapid visceral recurrence during adjuvant endocrine therapy. (*Type: Evidence-based; benefits outweigh harms, Evidence quality: Intermediate; Strength of Recommendation: Strong*)

Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. *(Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)*

The use of combined endocrine therapy and chemotherapy is not recommended. *(Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)*

Second-line therapy for HR-positive MBC

The choice of second-line hormone therapy should take into account prior treatment exposure and response to previous endocrine therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Sequential hormone therapy should be offered to patients with endocrine-responsive disease. except in the case of rapid progression with organ dysfunction; no specific order of agents is recommended. (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

When fulvestrant is administered, it should be administered using the 500-mg dose and with a loading schedule (treatment start, day 15, day 28, then once per month). (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Targeted Therapy

A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-naıve HR-positive MBC, because PFS but not OS was improved compared with the nonsteroidal AI letrozole alone. Palbociclib may also be offered in combination with fulvestrant in patients exposed to prior hormone therapy and up to one line of chemotherapy, on the basis of data from the phase III PALOMA-3 trial. PFS was improved compared with fulvestrant alone; OS data are immature (*Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: intermediate*).

Exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC who experience progression during prior treatment with nonsteroidal AIs, with or without one line of prior chemotherapy, either before or after treatment with fulvestrant, because PFS but not OS was improved compared with exemestane alone. This combination should not be offered as first-line therapy for patients who experience relapse 12 months from prior nonsteroidal AI therapy or for those who are naıve to hormone therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Postmenopausal women

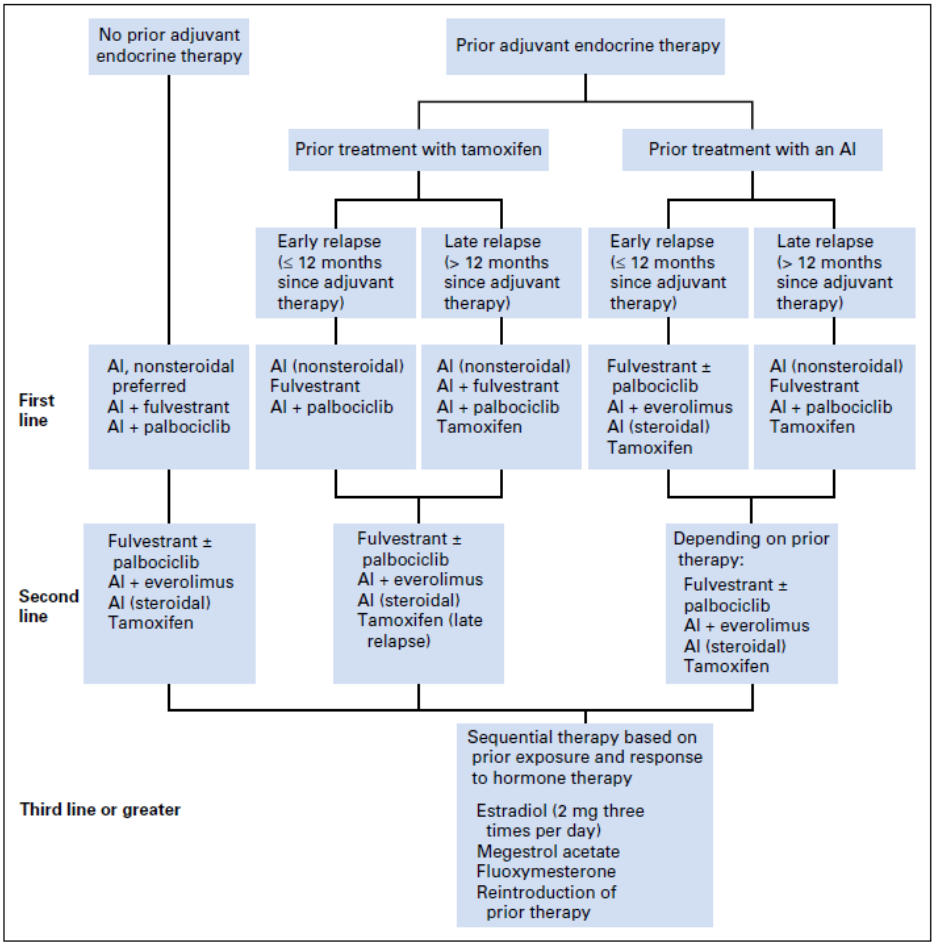


Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then once per month as an intramuscular injection. Withdrawal of tamoxifen or progestinswas reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates anastrozole or letrozole. AI, aromatase inhibitor

NICE, 2009 [12].

Advanced breast cancer (update) Diagnosis and treatment; Issued: February 2009, last modified: August 2017. NICE (CG81)

Leitlinienorganisation/Fragestellung

What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer?

Methodik

Grundlage der Leitlinie

- systematische Evidenzaufbereitung (Formulierung von PICO-Fragen; Systematische Literaturrecherche in mehreren Datenbanken; Datenextraktion, Qualitätsbewertung der gefundenen Literatur auf Basis der SIGN Kriterien für systematische Reviews/Meta-analysen und RCTs)
- Formulierung der Empfehlung basierend auf klinischer und ökonomischer Evidenz in Konsensusprozessen; bei schwacher Evidenz basierend auf informellen Konsens

Recherche/Suchzeitraum:

- Literaturrecherche der LL-Version 2009: bis 30.06.2008. Future guideline updates will consider evidence published after this cut-off date.

LoE

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

Table A Levels of evidence for intervention studies. Data source: 'NICE guidelines manual' (NICE 2007).

GoR

- Anwendung von GRADE - GoR finden sich in den Formulierungen wieder: "To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations."

Sonstige methodische Hinweise

- Regelmäßige Überprüfung der Aktualität der Empfehlungen: letzter Surveillance Report vom Januar 2018: Es wurden in Bezug auf die Therapieempfehlungen keine neue Evidenz identifiziert, die zu einer Änderung dieser Empfehlungen führen würde

Aktualisierungen:

- Update 2014: review of the evidence on exercise for people with or at risk of lymphoedema and addition of 2 recommendations to section 1.5

- Update 2017: Review of the evidence and update of recommendations in section 1.1 on assessing oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status on disease recurrence.

Empfehlungen

Endocrine Therapy

Recommendation

1.3.4 Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
- postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. [2009]

Qualifying statement: These recommendations are based on high quality evidence of clinical and cost effectiveness. There is no evidence directly comparing these agents so it is not possible to recommend any particular aromatase inhibitor. All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival).

Men:

- Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer. [2009]

Qualifying statement: This recommendation is based on evidence from two small retrospective case series and GDG consensus that this was an appropriate and effective treatment.

Cardoso F et al., 2018 [3].

European School of Oncology (ESO), European Society for Medical Oncology (ESMO)

4th ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4)

Leitlinienorganisation/Fragestellung

Its primary aim is the development of international consensus guidelines for the management of ABC patients.

Methodik

Grundlage der Leitlinie

The 4th International Consensus Conference for ABC (ABC 4) took place in Lisbon, Portugal on 2–4 November 2017, bringing together 1300 participants from 88 countries, including health professionals, patient advocates and journalists. Its primary aim is the development of international consensus guidelines for the management of ABC patientsBefore the ABC 4 Conference, a set of preliminary recommendation statements on the management of ABC were prepared, based on available published data and following the ESMO guidelines methodology. These recommendations were circulated to all 42 panel members by email for comments and corrections on content and wording. A final set of recommendations was presented, discussed and voted upon during the consensus session of ABC 4. All panel members were instructed to vote on all questions, with members with a potential conflict of interest or who did not feel comfortable answering the question (e.g. due to lack of expertise in a particular field) instructed to vote ‘abstain’.

A new possible answer was included in the Precision Medicine statements: ‘Insufficient data’, which should be selected if the panel member believes the existent data were not enough to

vote ‘yes’ or ‘no’, highlighting an area where research is needed. Additional changes in the wording of statements were made during the session.

LoE/GoR

Levels of evidence

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions

Grades of recommendation

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Empfehlungen

Section IV: ER-positive/HER2-negative (luminal) ABC

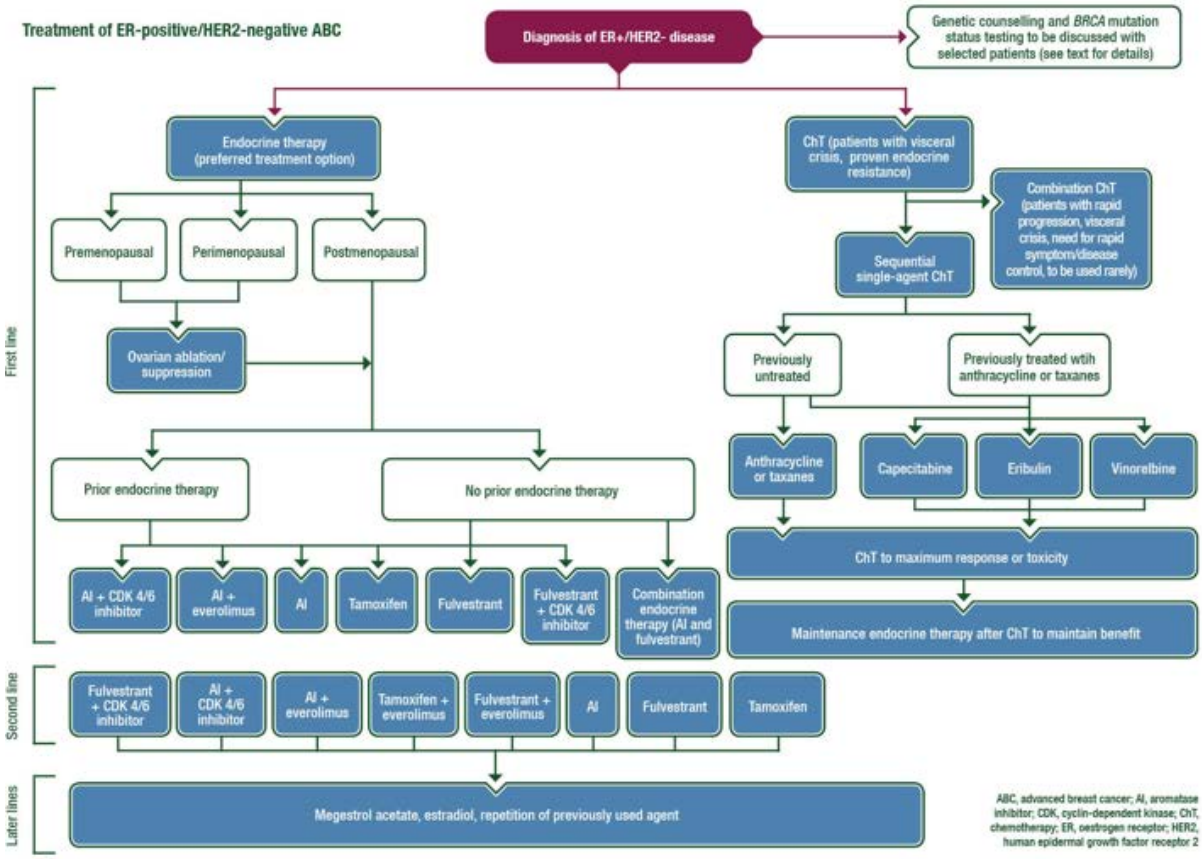
Guideline statement	LoE/GoR	Consensus
ET is the preferred option for HR-positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance.	I/A	93%
Many trials in ER-positive ABC have not included **PRE-MENOPAUSAL** women. Despite this, we recommend that young women with ER-positive ABC should have adequate OFS/OFA and then be treated in the same way as post-menopausal women, with endocrine agents and with or without targeted therapies.	Expert opinion/ A	95%
Future trials exploring new endocrine-based strategies should be designed to allow for enrolment of both pre- and post-menopausal women, and men.	Expert opinion/ A	92%

Guideline statement	LoE/GoR	Consensus
The addition of a CDK 4/6 inhibitor to an AI, in patients naïve or pre-exposed to ET, provided a significant improvement in median PFS (~10 months), with an acceptable toxicity profile, and is, therefore, one of the preferred treatment options for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women. Patients relapsing <12 months from the end of adjuvant AI	I/A	90%

were not included in the published studies and may not be suitable for this combination. OS results are still awaited. QoL was comparable to that with ET alone. **ESMO-MCBS v1.1 score: 3**		
The addition of a CDK 4/6 inhibitor to fulvestrant, in patients previously exposed to ET, provided significant improvement in median PFS (6–7 months) as well as improvement in QoL, and is one of the preferred treatment options, if a CDK 4/6 inhibitor was not previously used, for pre- and peri-menopausal women with OFS/OFA and post-menopausal women and men. OS results are awaited. **ESMO-MCBS v1.1 score: 4**	I/A	90%

Guideline statement	LoE/GoR	Consensus
The addition of everolimus to an AI is a valid option for some patients [for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women] previously exposed to ET, since it significantly prolongs PFS, albeit without evidence of OS benefit. The decision to treat must take into account the toxicities associated with this combination, lack of statistical significant OS benefit, cost and availability. **ESMO-MCBS v1.1 score: 2**	I/B	88%
Tamoxifen or fulvestrant can also be combined with everolimus.	II/B	80%
Adequate prevention, close monitoring and proactive treatment of adverse events is needed, particularly in older patients treated with everolimus due to the increased incidence of toxic deaths reported in the BOLERO-2 trial.	I/B	97%
The optimal sequence of endocrine-based therapy is uncertain. It depends on which agents were previously used [in the (neo)adjuvant or advanced settings], the burden of the disease, patients' preference, costs and availability. Available options [for pre- and peri-menopausal women with OFS/OFA, men (preferably with LHRH agonist) and post-menopausal women] include AI, tamoxifen, fulvestrant, AI/fulvestrant + CDK 4/6 inhibitor, AI/tamoxifen/fulvestrant + everolimus. In later lines, also megestrol acetate and oestradiol, as well as repetition of previously used agents, may be used.	I/A	95%

Guideline statement	LoE/GoR	Consensus
It is currently unknown how the different combinations of endocrine + targeted agents compare with each other, and with single-agent ChT. Trials are ongoing.		
Everolimus and CDK 4/6 inhibitors should not be used after PD on that specific agent (i.e. beyond progression).	n/a/E	74%
At present, no validated predictive biomarkers other than HR status exist to identify patients who will/will not benefit from the addition of a targeted agent (i.e. CDK 4/6 inhibitor, mTOR inhibitor) to ET and none of the studied biomarkers is ready for use in clinical practice. Research efforts must continue.	I/E	95%
Concomitant ChT and ET has not shown a survival benefit and should not be carried out outside a clinical trial.	II/D	100%
Endocrine treatment after ChT (maintenance ET) to maintain benefit is a reasonable option, though it has not been assessed in randomised trials.	III/B	88%


Treatment of ER-positive/HER2-negative ABC
Diagnosis of ER+/HER2- disease
Genetic counselling and BRCA mutation status testing to be discussed with selected patients (see text for details)
Endocrine therapy (preferred treatment option)
ChT (patients with visceral crisis, proven endocrine resistance)
Premenopausal
Perimenopausal
Postmenopausal
Combination ChT (patients with rapid progression, visceral crisis, need for rapid symptom/disease control, to be used rarely)
Sequential single-agent ChT
Ovarian ablation/ suppression
Previously untreated
Previously treated wtih anthracycline or taxanes
Prior endocrine therapy
No prior endocrine therapy
Anthracycline or taxanes
Capecitabine
Eribulin
Vinorelbine
AI + CDK 4/6 inhibitor
AI + everolimus
AI
Tamoxifen
Fulvestrant
Fulvestrant + CDK 4/6 inhibitor
Combination endocrine therapy (AI and fulvestrant)
ChT to maximum response or toxicity
Maintenance endocrine therapy after ChT to maintain benefit
Fulvestrant + CDK 4/6 inhibitor
AI + CDK 4/6 inhibitor
AI + everolimus
Tamoxifen + everolimus
Fulvestrant + everolimus
AI
Fulvestrant
Tamoxifen
Megestrol acetate, estradiol, repetition of previously used agent
First line
Second line
Later lines
ABC, advanced breast cancer; AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ChT, chemotherapy; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2

Section X: Specific populations

Guideline statement	LoE/GoR	Consensus
Advanced male breast cancer		
For ER-positive male ABC, which represents the majority of the cases, ET is the preferred option, unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response.	III/A	100%
For ER-positive male ABC tamoxifen is the preferred option.	IV/B	83%
For male patients with ABC who need to receive an AI, a concomitant LHRH agonist or orchidectomy is the preferred option. AI monotherapy may also be considered, with close monitoring of response.	IV/B	86%
Clinical trials are needed in this patient population.		
No new statements for this section were developed at ABC 4.		

ABC, advanced breast cancer; AI, aromatase inhibitor; Consensus, percentage of panel members in agreement with the statement; ER, oestrogen receptor; ET, endocrine therapy; GoR, grade of recommendation; LHRH, luteinising hormone-releasing hormone; LoE, available level of evidence.

SIGN, 2013 [14].

Scottish Intercollegiate Guidelines Network (SIGN)

Treatment of primary breast cancer. A national clinical guideline.

Leitlinienorganisation/Fragestellung

This guideline provides recommendations based on current evidence for best practice in the treatment of patients with operable early breast cancer.

Methodik

Grundlage der Leitlinie

Methodenreport beschreibt systematische Evidenzaufbereitung ohne formalisierte Konsensusprozesse - eigene Checklisten - teilweise Anwendung von GRADE - eigenes Graduierungssystem (siehe Tabellenblatt "SIGN LoE GoR") - repräsentative Gremien - CoI-Erklärungen auf Anfrage einsehbar - öffentliche Konsultation und Expertenreview

Sonstige methodische Hinweise

- Keine relevanten Empfehlungen abzuleiten für Frauen mit Brustkrebs.
- Gültigkeit: 3-7 Jahre Status bei SIGN

Empfehlungen

Breast cancer in men:

No trials on the treatment of men with breast cancer were identified for any of the key questions addressed in this guideline.

The consensus of the guideline development group is that men with breast cancer should be treated following the same recommendations as for women, with the exception of receiving tamoxifen as first line endocrine treatment

4 Detaillierte Darstellung der Recherchestrategie

Breast neoplasm male

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 24.01.2019

#	Suchfrage
1	[mh “Breast Neoplasms, Male“]
2	[mh "Breast Neoplasms"] AND ([mh Male] OR [mh Men])
3	#1 OR #2
4	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
5	((male OR man OR men) NEAR/5 (breast* OR mamma*)):ti,ab,kw
6	#3 OR (#4 AND #5)
7	#6 with Cochrane Library publication date from Jan 2014 to Jan 2019

SR, HTAs in Medline (PubMed) am 24.01.2019

#	Suchfrage
1	Breast Neoplasms, Male[mh]
2	Breast Neoplasms[mh] AND (men[mh] OR male[mh])
3	#1 OR #2
4	(men[tiab] OR male[tiab] OR man[tiab]) AND (breast*[tiab] OR mamma*[tiab])
5	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR neoplas*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) or malignan*[tiab]
6	#4 AND #5
	„male breast cancer“[tiab] (ist schon mit enthalten, deshalb nicht weiter verfolgt
7	#3 OR #6
8	(#7) AND ((Meta-Analysis[ptyp] OR ((systematic review [ti] OR meta-analysis [pt] OR meta-analysis [ti] OR systematic literature review [ti] OR this systematic review [tw] OR pooling project [tw] OR (systematic review [tiab] AND systematic review [pt]) OR meta synthesis [ti] OR meta-analy*[ti] OR integrative review [tw] OR integrative research review [tw] OR rapid review [tw] OR umbrella review [tw] OR consensus development conference [pt] OR practice guideline [pt] OR drug class reviews [ti] OR cochrane database syst rev [ta] OR acp journal club [ta] OR health technol assess [ta] OR evid rep technol assess summ [ta] OR jbi database system rev implement rep [ta]) OR (clinical guideline [tw] AND management [tw]) OR ((evidence based[ti] OR evidence-based medicine [mh] OR best practice* [ti] OR evidence synthesis [tiab]) AND (systematic review [pt] OR diseases category[mh] OR behavior and behavior mechanisms [mh] OR therapeutics [mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline [pt] OR pmcbook)) OR ((systematic [tw] OR systematically [tw] OR critical [tiab] OR (study selection [tw]) OR (predetermined [tw] OR inclusion [tw] AND criteri* [tw]) OR exclusion criteri* [tw] OR main outcome measures [tw] OR standard of care [tw] OR standards of care [tw]) AND (survey [tiab] OR surveys [tiab] OR overview* [tw] OR review [tiab] OR reviews [tiab] OR search* [tw] OR handsearch [tw] OR analysis [ti] OR critique [tiab] OR appraisal [tw] OR (reduction [tw]AND (risk [mh] OR risk [tw]) AND (death OR recurrence))) AND (literature [tiab] OR articles [tiab] OR publications [tiab] OR publication [tiab] OR bibliography [tiab] OR bibliographies [tiab] OR published [tiab] OR pooled data [tw] OR unpublished [tw] OR citation [tw] OR citations [tw] OR database [tiab] OR internet [tiab] OR textbooks [tiab] OR references [tw] OR scales [tw] OR papers [tw] OR datasets [tw] OR trials [tiab] OR meta-analy* [tw] OR (clinical [tiab] AND studies [tiab]) OR treatment outcome [mh] OR treatment outcome [tw] OR pmcbook)) NOT (letter [pt] OR newspaper article [pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR

	publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
9	((#8) AND ("2014/01/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 24.01.2019

#	Suchfrage
1	Breast Neoplasms, Male[mh]
2	Breast Neoplasms[mh] AND (men[mh] OR male[mh])
3	#1 OR #2
4	(men[tiab] OR male[tiab] OR man[tiab]) AND (breast*[tiab] OR mamma*[tiab])
5	(((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR neoplas*[tiab]) OR cancer*[tiab]) OR lesions*[tiab]) or malignan*[tiab]
6	#4 AND #5
7	#3 OR #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
9	(((#8) AND ("2014/01/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

Breast neoplasm female

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 30.11.2018

#	Suchfrage
1	[mh “Breast Neoplasms”]
2	(breast or mamma*):ti,ab,kw
3	(cancer* or tum*r* or carcinoma* or neoplas* or adenocarcinoma* or sarcoma* or lesions*):ti,ab,kw
4	(advanced or metastat* or metastas* or recurren* or relaps* or progression*):ti,ab,kw
5	#1 or (#2 and #3)
6	#4 and #5
7	#6 with Cochrane Library publication date from Nov 2013 to Nov 2018

SR, HTAs in Medline (PubMed) am 30.11.2018

#	Suchfrage
1	breast neoplasms/TH
2	((breast[ti]) OR mamma*[ti]) AND (neoplasm metastasis/TH OR neoplasm recurrence, local/TH)
3	(#1) OR #2
4	(breast[ti]) OR mamma*[ti]

5	(#4) AND (((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR malignan*[tiab])
6	(#5) AND (((((((advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab]) OR relaps*[tiab]) OR progression*[tiab]) OR progressive*[tiab]) OR disseminat*[tiab])
7	(#6) AND ((((((((((((treatment*[tiab]) OR therapy[tiab]) OR therapies[tiab]) OR therapeutic[tiab]) OR monotherap*[tiab]) OR polytherap*[tiab]) OR pharmacotherap*[tiab]) OR effect*[tiab]) OR efficacy[tiab]) OR treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]) OR chemotherap*[tiab])
8	#3 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
10	((#9) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 30.11.2018

#	Suchfrage
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	cancer*[ti] OR tumour*[ti] OR tumor[ti] OR tumors[ti] OR carcinom*[ti] OR neoplas*[ti] OR malignan*[ti]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
7	(((#6) AND ("2013/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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Anhang

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Studiencharakteristik

Table 1 Characteristics of included studies evaluating hormonal therapy in hormone receptor positive HER2 negative metastatic breast cancer

First author (study name)	Year*	Phase	Line	Class/Target of experimental agent	Experimental agents (*n*)	Control agents (*n*)	Endocrine status	Primary endpoint
Bergh (FACT)[5]	2012	3	First	SERD	Fulvestrant plus anastrozole (258)	Anastrozole alone (256)	Mixed	TTP
Mehta (SWOG-S0226)[6]	2012	3	First	SERD	Fulvestrant plus anastrozole (349)	Anastrozole alone (345)	Mixed	PFS
Johnston (SoFEA)[7]	2013	3	Second	SERD	Fulvestrant plus anastrozole (241) Fulvestrant alone (230)	Exemestane alone (61)	Resistant	PFS
DiLeo (CONFIRM)[8,9]	2010	3	Any	SERD	Fulvestrant 500 mg (362)	Fulvestrant 250 mg (374)	Resistant	PFS
Robertson 2012, Ellis 2015 (FIRST)[10,11]	2012	2	First	SERD	Fulvestrant (101)	Anastrozole alone (103)	Mixed	CBR
Wolff (HORIZON)[12]	2013	3	First	mTOR	Letrozole plus temsirolimus (550)	Letrozole alone (553)	Mixed	PFS
Yardley 2013[13], Piccart 2014[14] (BOLERO-2)	2014	3	Second	mTOR	Exemestane plus everolimus plus (485)	Exemestane plus placebo (239)	Resistant	PFS
Bachelot[15]	2012	2	First or Second	mTOR	Tamoxifen plus everolimus (54)	Tamoxifen alone (57)	Resistant	CBR
Finn (PALOMA-1)[16]	2015	2	First	CDK4/6	Letrozole plus palbociclib (84)	Letrozole alone (81)	Mixed	PFS
Turner 2015, Cristofanilli 2015, Verma, 2015, (PALOMA-3)[17–19]	2015	3	Second	CDK4/6	Fulvestrant plus palbociclib (347)	Fulvestrant plus placebo (174)	Resistant	PFS
Baselga (BELLE-2)[20]	2015	3	Second	Pi3K	Fulvestrant plus buparlisib plus (573)	Fulvestrant plus placebo (574)	Resistant	PFS
Krop (FERGI)[21]	2015	2	Any	Pi3K	Fulvestrant plus pictilisib (89)	Fulvestrant plus placebo (79)	Resistant	PFS
Dickler (CALGB 40503)[22]	2015	3	First	VEGF	Letrozole plus bevacizumab (172)	Letrozole alone (171)	Resistant	PFS
Martin (LEA)[23]	2015	3	First	VEGF	Letrozole or fulvestrant plus bevacizumab (184)	Letrozole or fulvestrant alone (190)	Mixed	PFS
De Jong[24]	2012	2	Second	VEGF	Fulvestrant plus enzastaurin (94)	Fulvestrant plus placebo (58)	Resistant	CBR
Hyams[25]	2013	2	Any	VEGF	Fulvestrant plus cediranib (31)	Fulvestrant plus placebo (31)	Sensitive	PFS
Carlson[26]	2012	2	First	EGFR TKI	Anastrozole plus gefitinib (72)	Fulvestrant plus gefitinib (69)	Mixed	CBR
Cristofanilli[27]	2010	2	First	EGFR TKI	Anastrozole plus gefitinib (43)	Anastrozole plus placebo (50)	Mixed	PFS

First author (study name)	Year*	Phase	Line	Class/Target of experimental agent	Experimental agents (*n*)	Control agents (*n*)	Endocrine status	Primary endpoint
Osborne[28]	2011	2	First (Stratum 1) Second (Stratum 2)	EGFR TKI	Tamoxifen plus gefitinib (Stratum 1: 105) (Stratum 2: 48)	Tamoxifen plus placebo (Stratum 1: 101) (Stratum 2: 36)	Resistant	PFS (stratum 1) CBR (stratum 2)
Burstein (CALGB 40302)[29]	2014	3	Second	EGFR TKi	Fulvestrant plus lapatinib (146)	Fulvestrant plus placebo (145)	Resistant	PFS
Ryan[30]	2011	2	First	IGF-1R	Exemestane plus figitumumab (103)	Exemestane alone (102)	NR	PFS
Robertson[31]	2013	2	First or Second	IGF-1R	Exemestane or fulvestrant plus ganitumab (106)	Exemestane or fulvestrant plus placebo (50)	Resistant	PFS
Rugo[32]	2015	2	Any	IGF-1R	Ridaforolimus, dalotuzumab plus exemestane (40)	Ridaforolimus plus exemestane (40)	Resistant	PFS
Paul[33]	2013	2	Second	Src TKI	Letrozole plus dasatinib (57)	Letrozole alone (63)	Resistant	CBR
Llombart[34]	2011	2	First	Src TKI	Exemestane plus dasatinib (79)	Exemestane plus placebo (78)	Resistant	PFS
Iwata[35]	2013	3	First	AI	Exemestane plus anastrozole (149)	Exemestane plus placebo (149)	Sensitive	TTP
Iwase(HI FAIR)[36]	2012	2	Second	AI	Toremifene (46)	Exemestane alone(45)	Resistant	CBR
Yardley (ENCORE 301)[13]	2013	2	Second	HDAC	Exemestane plus entinostat (64)	Exemestane plus placebo (66)	Mixed	PFS
Adelson[37]	2015	2	First or Second	BCL2	Fulvestrant plus bortezomib (57)	Fulvestrant alone (59)	Resistant	PFS
Ibrahim[38]	2011	2	First	IgG anti-MUC	Letrozole plus AS1402 (56)	Letrozole alone (54)	Mixed	ORR
O'Shaughnessy[39]	2015	2	Any	Androgen antagonist	Abiraterone alone (89) Abiraterone plus exemestane (102)	Exemestane alone (51)	Resistant	PFS
Kim (PRESTIGE)[40]	2014	3	NR	GnRH agonist	Goserelin 10.8 mg 12 weekly (109)	Goserelin 3.6 mg 4 weekly (113)	NR	PFS

*Year of publication or conference.

Studienergebnisse der Einzelstudien

First author (study name)	Line of therapy	Class/ Target of experimental agent	Experimental regimen	Control regimen	PFS/TTP* experimental arm months (*P* value)	PFS / TTP* control arm months	OS experimental arm months (*P* value)	OS control arm months	CBR experimental arm %	CBR control arm %
Bergh(FACT)[5]	First	SERD	Fulvestrant plus anastrozole	Anastrozole alone	10.8* (0.91)	10.2*	37.8 (1.0)	38.2	55	55
Mehta (SWOG-S0226)[6]	First	SERD	Anastrozole plus fulvestrant	Anastrozole alone	15 (0.007)	13.5	47.7 (0.05)	41.3	73	70
Johnston (SoFEA)[7]	Second	SERD	Fulvestrant plus anastrozole (arm 1) fulvestrant plus placebo (arm 2)	Exemestane alone (arm 3)	4.4 (0.98 *versus* arm 2)(arm 1) 4.8 (0.56) (arm 2)	3.4	20.2 (0.61 *versus* arm 2) (arm 1) 19.4 (0.68) (arm 2)	21.6	34 (arm 1) 32 (arm 2)	55 (arm 1) 54 (arm 2)
DiLeo (CONFIRM)[8]	Any	SERD	Fulvestrant 500 mg	Fulvestrant 250 mg	6.5 (0.006)	5.5	26.4 (0.02)	22.8	46	40
Robertson 2012 Ellis 2015 (FIRST)[10,11]	First	SERD	Fulvestrant	Anastrozole	23.4* (0.01)	13.1*	54.1 (0.04)	48.4	NR	NR
Wolff (HORIZON)[12]	Second	mTOR	Letrozole plus temsirolimus	Letrozole alone	8.9 (0.25)	9	NR	NR	44	46
Yardley, 2013[13] Piccart, 2014[14] (BOLERO-2)	Second	mTOR	Exemestane plus everolimus	Exemestane plus placebo	7.8 (<0.0001)	3.2	31 (0.14)	26.6	51.3	26
Bachelot[15]	First or Second	mTOR	Tamoxifen plus everolimus	Tamoxifen alone	8.6* (0.0021)	4.5*	not reached	32.9	61	42
Finn (PALOMA-1)[16]	First	CDK4/6	Letrozole plus palbociclib	Letrozole alone	20.2 (<0.001)	10.2	37.5 (0.42)	33.3	87	70
Turner 2015 Cristofanilli 2015 (PALOMA-3)[17,19]	Second	CDK4/6	Fulvestrant plus palbociclib	Fulvestrant plus placebo	9.5 (<0.001)	4.6	NR	NR	66.6	39.7
Baselga (BELLE-2)[20]	Second	Pi3K	Fulvestrant plus buparlisib	Fulvestrant plus placebo	6.9 (<0.0001)	5.0	NR	NR	NR	NR
Krop (FERGI)[21]	Any	Pi3K	Fulvestrant plus pictilisib	Fulvestrant plus placebo	6.2(NR)	3.8	NR	NR	NR	NR
Dickler (CALGB 40503)[22]	First	VEGF	Letrozole plus bevacizumab	Letrozole alone	20 (0.016)	16	47 (0.27)	41	NR	NR
Martin (LEA)[23]	First	VEGF	Letrozole OR fulvestrant plus bevacizumab	Letrozole OR fulvestrant alone	19.3 (0.13)	14.4	52.1(0.52)	51.8	79	65
De Jong[24]	Second	VEGF	Fulvestrant plus enzastaurin	Fulvestrant plus placebo	5.2 (0.59)	5.5	NR	NR	44	41
Hyams[25]	Any	VEGF	Fulvestrant plus cediranib	Fulvestrant plus placebo	7.4 (0.67)	3.7	NR	NR	42	42

First author (study name)	Line of therapy	Class/ Target of experimental agent	Experimental regimen	Control regimen	PFS/TTP* experimental arm months (*P* value)	PFS / TTP* control arm months	OS experimental arm months (*P* value)	OS control arm months	CBR experimental arm %	CBR control arm %
Carlson[26]	Any	EGFR TKI	Anastrozole plus gefitinib	Fulvestrant plus gefitinib	5.3 (NR)	5.2	30.3 (NR)	23.9	44	41
Cristofanilli[27]	First	EGFR TKI	Anastrozole plus gefitinib	Anastrozole plus placebo	14.7 (NR)	8.4	NR	NR	49	34
Osborne[28]	First (stratum 1) Second (stratum 2)	EGFR TKI	Tamoxifen plus gefitinib	Tamoxifen plus placebo	10.9 (0.314) (First Line) 5.7 (0.577) (Second Line)	8.8 (First Line) 7.0 (Second Line)	NR	NR	50 (Stratum 1) 29 (Stratum 2)	46 (Stratum 1) 31 (Stratum 2)
Burstein (CALGB 40302)[29]	Second	EGFR TKI	Fulvestrant plus lapatinib	Fulvestrant plus placebo	4.7 (0.37)	3.8	30 (0.25)	26.4	41	34
Ryan[30]	First	IGF-1R	Exemestane plus figitumumab	Exemestane alone	10.9 (0.39)	9.1	NR	NR	64	62
Robertson[31]	Second	IGF-1R	Exemestane or fulvestrant plus ganitumab	Exemestane or fulvestrant plus placebo	3.9 (0.44)	5.7	23.3 (0.025)	Not estimable	21	20
Rugo[32]	Any	IGF-1R	Ridaforolimus, dalotuzumab and exemestane	Ridaforolimus and exemestane	5.4 (0.57)	7.4	NR	NR	NR	NR
Paul[33]	Second	Src TKI	Letrozole plus dasatinib	Letrozole alone	22 (0.05)	11	NR	NR	64	61
Llombart[34]	Any	Src TKI	Exemestane plus dasatinib	Exemestane plus placebo	3.7 (NR)	4.2	NR	NR	NR	NR
Iwata[35]	First	AI	Exemestane plus anastrozole	Exemestane plus placebo	13.8* (NR)	11.1*	60.1 (NR)	NR	66	66
Yardley (ENCORE 301)[13]	Second	HDAC	Exemestane plus entinostat	Exemestane plus placebo	4.3 (0.055)**	2.3	28.1 (0.036)***	19.8	28	26
Adelson[37]	Second	BCL2	Fulvestrant plus bortezomib	Fulvestrant alone	2.7 (0.06)	2.7	NR	NR	NR	NR
Ibrahim[38]	First	IgG anti-MUC	Letrozole plus AS1402	Letrozole alone	NR	NR	NR	NR	70	76
O'Shaughnessy[39]	Any	Androgen antagonist	Abiraterone plus exemestane (arm 1) Abiraterone alone (arm 2)	Exemestane alone	4.5 (0.80) (arm 1) 3.7(0.44) (arm 2)	3.7	NR	NR	24 (arm 1) NR (arm 2)	12

Iwase 2012 (HI-FAIR) did not report any data for the above table;
*PFS not reported, figures shown for TTP; **one-sided; ***two-sided.

2. Rugo et al. 2016 [13].

ASCO-Guidelines: Endocrine therapy for women with hormone receptor–positive metastatic breast cancer.

Ergebnisse der syst. Literaturauswertung: Systematic reviews:

Table 1. Main Findings From Systematic Review (all included meta-analyses)

Study	Evidence Base	Main Findings
Endocrine *v* chemotherapy		
Wilcken[8]	Six trials including 692 patients with MBC (for OS comparison)	No significant difference in OS was detected (hazard ratio, 0.94; 95% CI, 0.79 to 1.12; $P = .5$), with nonsignificant heterogeneity detected
	Compared single-agent endocrine treatment with single-agent chemotherapy	Significant benefit in response rates (eight trials involving 817 women) for chemotherapy over endocrine therapy was detected (RR, 1.25; 95% CI, 1.01 to 1.54; $P = .04$)
		Authors conclude that standard first-line treatment for patients with MBC should be endocrine therapy rather than chemotherapy, except in presence of rapidly progressing disease
Single-agent *v* single-agent hormone therapies		
Chi[30]	23 trials including 7,242 patients (patients with advanced breast cancer were subset of total population)	Toremifene was associated with more vaginal bleeding (OR, 0.45; 95% CI, 0.26 to 0.80; $P < .05$) and greater decrease in serum triglyceride levels (SMD, −1.15; 95% CI, −1.90 to −0.39; $P < .05$) than tamoxifen
	Compared toremifene and tamoxifen	Evidence suggests toremifene could be an alternative to tamoxifen for patients with advanced breast cancer
Cope[31]	11 RCTs including 5,808 postmenopausal women with advanced breast cancer after endocrine therapy failure	Fulvestrant 500 mg was superior to fulvestrant 250 mg, megestrolacetate, and anastrozole for PFS ($P < .05$)
	Compared fulvestrant 500 mg, fulvestrant 250 mg loading dose, anastrozole 1 mg, megestrol acetate, letrozole 2.5 mg, letrozole 0.5 mg, and exemestane	
Xu[32]	Six RCTs including 2,560 postmenopausal patients with HR-positive advanced breast cancer	AIs were superior to tamoxifen alone for response (ORR; OR, 1.56; 95% CI, 1.17 to 2.07; $P < .05$) and CBR (OR, 1.70; 95% CI, 1.24 to 2.33; $P < .05$)
	Compared AIs *v* tamoxifen	
Single-agent *v* combination endocrine therapies		
Tan[33]	Two RCTs including patients with HR-positive advanced breast cancer (total patients, NR)	None of the comparisons for PFS, OS, or response showed statistically significant difference
	Compared fulvestrant + AI *v* AI alone (both studied anastrozole in combination with fulvestrant)	
Valachis[34]	Four RCTs including 2,125 patients with HR-positive advanced breast cancer	No difference detected between fulvestrant + AIs and tamoxifen for OS, TTP, CBR, or ORR
	Compared fulvestrant + AIs *v* tamoxifen	Hormonal agents other than fulvestrant were associated with great likelihood of joint disorders ($P < .05$)
Endocrine therapy ± mTOR inhibitors		
Bachelot[35]	Six RCTs (total patients, NR)	Everolimus + exemestane was superior to fulvestrant 250 mg and fulvestrant 500 mg for PFS and TTP (hazard ratio, 0.47; 95% CI, 0.38 to 0.58; $P < .05$ and hazard ratio, 0.59; 95% CI, 0.45 to 0.77; $P < .05$, respectively)
	All patients had HR-positive, HER2-negative advanced breast cancer	Analysis suggests that everolimus + exemestane is superior to fulvestrant 250 mg and 500 mg for PFS and TTP in patients with HR-positive, HER2-negative breast cancer with disease progression after endocrine therapy; however, there are no RCTs currently available providing direct comparison
	Included studies identified by systematic literature review (sources: Cochrane Library, National Horizon Scanning Centre, and NICE Web sites)	
	Comparisons were: everolimus + exemestane or everolimus + tamoxifen *v* fulvestrant	

Abbreviations: AI, aromatase inhibitor; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NICE, National Institute for Health and Care Excellence; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, response rate; TTP, time to progression.