Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-245 Abemaciclib

Stand: Dezember 2019

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

Abemaciclib
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“. Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für: • das HER2/neu-positive Mammakarzinom
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): Beschluss vom 2. Mai 2019 • Abemaciclib (in Kombination mit einem Aromatasehemmer): Beschluss vom 2. Mai 2019 • Palbociclib: Beschluss vom 18. Mai 2017 und 22. März 2019 • Ribociclib (in Kombination mit Fulvestrant): Beschluss vom 4. Juli 2019 • Ribociclib (in Kombination mit einem Aromatasehemmer): Beschluss vom 16. März 2018 und 4. Juli 2019
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:	
Abemaciclib L01XE50 Verzenios®	Zugelassenes 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.“
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

II. Zugelassene Arzneimittel im Anwendungsgebiet

Aromatase-Inhibitoren (nicht-steroidal):	
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 behan-delt 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

II. Zugelassene Arzneimittel im Anwendungsgebiet

Medroxyproges-teronacetat L02AB02 MPA Hexal®	Zur palliativen Behandlung bei folgenden hormonabhängigen Tumoren: • metastasierendes Mammakarzinom • […].
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.
Monoklonale Antikörper:	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Paclitaxel zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet. Bevacizumab wird in Kombination mit Capecitabin zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet, bei denen eine Behandlung mit anderen Chemotherapie-Optionen, einschließlich Taxanen oder Anthracyclinen, als nicht geeignet angesehen wird. Patienten, die innerhalb der letzten 12 Monate Taxan- und Anthracyclin-haltige Therapieregime im Rahmen der adjuvanten Behandlung erhalten haben, sollten nicht mit Avastin in Kombination mit Capecitabin therapiert werden.
PARP-Inhibitoren:	
Olaparib L01XX46 Lynparza®	Lynparza wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom haben. Die Patienten sollten zuvor mit einem Anthrazyklin und einem Taxan im (neo)adjuvanten oder metastasierten Setting behandelt worden sein, es sei denn, die Patienten waren für diese Behandlungen nicht geeignet (siehe Abschnitt 5.1). Patienten mit Hormonrezeptor (HR)-positivem Mammakarzinom sollten außerdem eine Krankheitsprogression während oder nach einer vorherigen endokrinen Therapie aufweisen oder für eine endokrine Therapie nicht geeignet sein.
Talazoparib L01XX60 Talzenna ®	Talzenna wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom aufweisen. Die Patienten sollten zuvor mit einem Anthrazyklin und/ oder einem Taxan im (neo)adjuvanten, lokal fortgeschrittenen oder metastasierten Setting behandelt worden sein, es sei denn, sie waren für diese Behandlungen nicht geeignet (siehe Abschnitt 5.1). Patienten mit Hormonrezeptor (HR)-positivem Brustkrebs sollten außerdem bereits eine endokrin-basierte Therapie erhalten haben oder für diese als nicht geeignet eingestuft sein.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Zytostatika:	
Cyclophospha-mid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: […] • Adjuvante Therapie des Mammakarzinoms nach Resektion des Tumors beziehungsweise Mastektomie • Palliative Therapie des fortgeschrittenen Mammakarzinoms.
Capecitabin L01BC06 Capecitabin medac®	Capecitabin medac wird angewendet: • in Kombination mit Docetaxel zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom nach Versagen einer zytotoxischen Chemotherapie. Eine frühere Behandlung sollte ein Anthracyclin enthalten haben. • als Monotherapie zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom, bei denen eine Therapie mit Taxanen und Anthracyclinen versagt hat oder eine weitere Anthracyclinbehandlung nicht angezeigt ist.
Docetaxel L01CD02 Taxotere®	Taxotere ist in Kombination mit Doxorubicin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs ohne vorausgegangene Chemotherapie angezeigt. Die Taxotere-Monotherapie ist zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die vorausgegangene Chemotherapie sollte ein Anthracyclin oder Alkylanzien enthalten haben. Taxotere ist in Kombination mit Capecitabin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die frühere Behandlung sollte ein Anthracyclin enthalten haben. [Weitere Indikationen: Adjuvante Therapie; HER2-überexprimierendes Mammakarzinom].
Doxorubicin L01DB01 Adrimedac®	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: • Mammakarzinom. Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Liposomales Doxorubicin L01DB01 Caelyx®	Caelyx® ist indiziert: Als Monotherapie bei Patientinnen mit metastasierendem Mammakarzinom mit erhöhtem kardialen Risiko.
Epirubicin L01DB03 Riboepi®	• Mammakarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Eribulin L01XX41 Halaven®	Halaven ist indiziert für die Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Brustkrebs, bei denen nach mindestens einer Chemotherapie zur Behandlung einer fortgeschrittenen Brustkrebserkrankung eine weitere Progression eingetreten ist. Die Vortherapien sollen ein Anthrazyklin und ein Taxan entweder als adjuvante Therapie oder im Rahmen der metastasierten Situation enthalten haben, es sei denn, diese Behandlungen waren ungeeignet für den Patienten.
5-Fluorouracil L01BC02 Fluorouracil-GRY®	• fortgeschrittenes und/oder metastasiertes Mammakarzinom
Gemcitabin L01BC05 Gemzar®	Gemcitabin ist angezeigt in Kombination mit Paclitaxel für die Behandlung von Patientinnen mit nicht operablem, lokal rezidiviertem oder metastasiertem Brustkrebs, bei denen es nach einer adjuvanten/neoadjuvanten Chemotherapie zu einem Rezidiv kam. Die vorausgegangene Chemotherapie sollte ein Anthracyclin enthalten haben, sofern dieses nicht klinisch kontraindiziert war.
Ifosfamid L01AA06 Holoxan®	Zur Palliativtherapie bei fortgeschrittenen, therapierefraktären bzw. rezidivierenden Mammakarzinomen.
Methotrexat L01BA01 Methotrexat-GRY®	Mammakarzinome: In Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.
Mitomycin L01DC03 Urocin®	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] • Mammakarzinom
Mitoxantron L01DB07 Onkotrone®	• fortgeschrittenes und/oder metastasiertes Mammakarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet

Paclitaxel L01CD01 Bendatax®	BENDATAX ist zur First-line Chemotherapie bei Patientinnen mit lokal fortgeschrittenem oder metastasierendem Mammakarzinom angezeigt entweder in Kombination mit einem Anthrazyklin bei Patientinnen, bei denen eine Anthrazyklin-Therapie in Betracht kommt, oder in Kombination mit Trastuzumab, bei Patientinnen, die den humanen, epidermalen Wachstumsfactor-Rezeptor 2 (HER-2) – ermittelt durch immunhistochemische Methoden – mit Grad 3+ überexprimieren und für die eine Anthrazyklin-haltige Therapie nicht in Betracht kommt. Als Monotherapie ist BENDATAX für die Behandlung des metastasierenden Mammakarzinoms bei Patientinnen indiziert, bei denen eine Standardtherapie mit Anthrazyklinen erfolglos war oder nicht angezeigt ist.
Paclitaxel Nanopartikel L01CD01 Abraxane®	Abraxane-Monotherapie ist indiziert für die Behandlung des metastasierten Mammakarzinoms bei erwachsenen Patienten, bei denen die Erstlinientherapie der metastasierten Erkrankung fehlgeschlagen ist und für die eine standardmäßige Anthracyclin-enthaltende Therapie nicht angezeigt ist.
Vinblastin L01CA01 Vinblastinsulfat TEVA®	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: • rezidivierendes oder metastasierendes Mammakarzinom (wenn eine Behandlung mit Anthracyclinen nicht erfolgreich war)
Vincristin L01CA02 Vincristinsulfat Teva®	Vincristinsulfat-Teva® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: […] soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom.
Vinorelbin L01CA04 Navelbine®	Als Monotherapie bei Patientinnen mit metastasierendem Brustkrebs (Stadium 4), bei denen eine Behandlung mit einer anthrazyklin- und taxanhaltigen Chemotherapie versagt hat oder nicht angezeigt ist.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABC	Advanced Breast Cancer
AI	aromatase inhibitors
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BC	Breast Cancer
CDK	cyclin-dependent kinase
CR	complete response CR
DAHTA	DAHTA Datenbank
ER	Estrogene rezeptor
ET	Endokrine Therapie
G	Grade
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
ITC	Indirect treatment comparison
KI	Konfidenzintervall
LEE	Ribociclib
LHRH	Luteinizing 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
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 Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen WachstumsfaktorRezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs

- als initiale endokrine Therapie (AWG 1) oder
- nach vorangegangener endokriner Therapie (AWG 2)

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 Patientinnen mit fortgeschrittenen oder metastasierten Brustkrebs verglichen werden, nicht in der vorliegenden Evidenzsynpose 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 02.09.2019 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 2905 Quellen, 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 25 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [9].

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)

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

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 - Abemaciclib (in Kombination mit Fulvestrant) 2019, (09.10.2019):

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 [10].

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 - Abemaciclib (in Kombination mit einem Aromatasehemmer)

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 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 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, 2018 [8], iVm G-BA, 2019 [5].

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

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 – Ribociclib (neues Anwendungsgebiet: Mammakarzinom, in Kombination mit einem Aromatasehemmer) vom 04. Juli 2019

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 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.

Hinweis:

Der vorliegende Beschluss 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.

Für die Bewertung des Zusatznutzens für die Patientengruppe a1 wird auf das zurückliegende Nutzenbewertungsverfahren zu Ribociclib mit Beschluss vom 16. März 2018 verwiesen. Diese Patientengruppe ist nicht Gegenstand des vorliegenden Nutzenbewertungsverfahrens.

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

Fazit / Ausmaß des Zusatznutzens

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,
- ggf. Letrozol in Kombination mit einer Ausschaltung der Ovarialfunktion bei Frauen, die zuvor mit Antiöstrogenen behandelt wurden

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

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 Ribociclib 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 Ribociclib in Kombination mit einem Aromatasehemmer gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

G-BA, 2019 [6].

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 – Ribociclib (neues Anwendungsgebiet: Mammakarzinom, in Kombination mit Fulvestrant) vom 04. Juli 2019

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 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.

Hinweis:

Der vorliegende Beschluss bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Ribociclib in Kombination mit Fulvestrant. Für die Bewertung des Zusatznutzens von Ribociclib 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 Ribociclib 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,
- ggf. Letrozol in Kombination mit einer Ausschaltung der Ovarialfunktion bei Frauen, die zuvor mit Antiöstrogenen behandelt wurden

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

Ein Zusatznutzen ist nicht belegt.

IQWiG, 2016 [11].

Aromatasehemmer beim Mammakarzinom der Frau; Abschlussbericht; Auftrag A10-03

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 [12]. (AWG 1 /AWG 2)

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

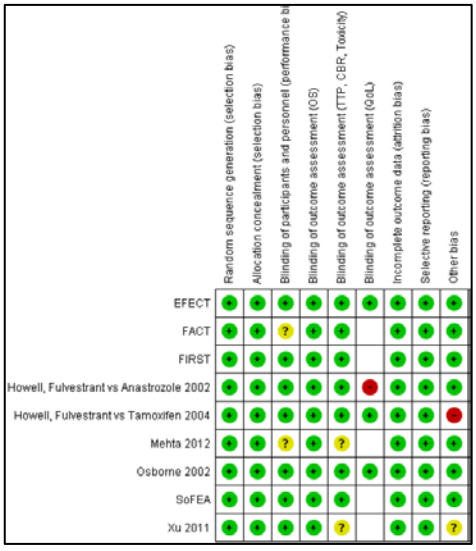
Anzahl eingeschlossener Studien: N=9 (n=4514)

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
- first-line treatment: HR 0.93, 95%CI 0.84 to 1.03; 1996 women; 4 studies
- 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
- Firstline: RR 1.00, 95% CI 0.94 to 1.07; 1999 women; 4 studies)
- 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 G et al., 2018 [22].

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:

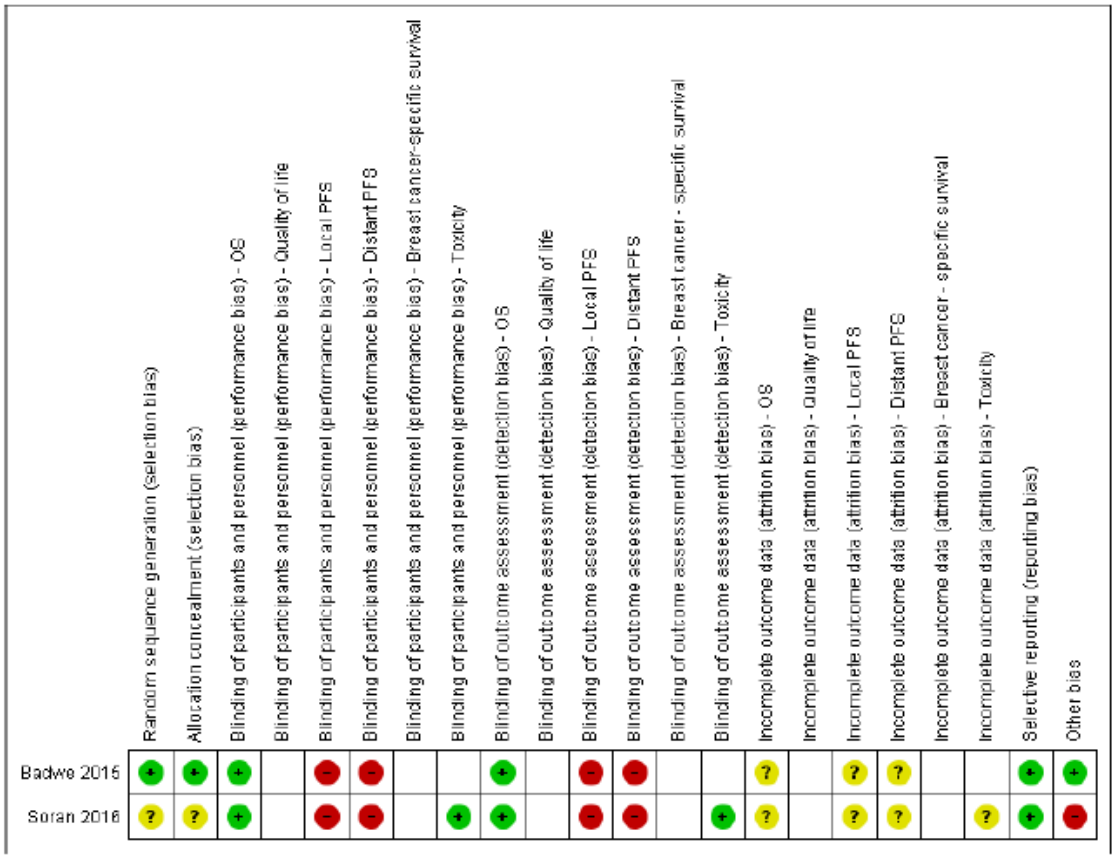
- We included two trials enrolling 624 women

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.
- Badwe 2015 included women with metastatic breast cancer with objective response to first-line chemotherapy (> or = 50% clinical response).
- Soran 2016 enrolled treatment-naïve women with resectable primary tumour and randomly assigned women to upfront surgery followed by systemic therapy or systemic therapy alone

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

Ramos-Esquivel A et al., 2018 [19]. (AWG 1)

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: Risk of bias was categorized as ‘low risk’, ‘high risk’, or as ‘unclear risk

No funding source had any role in study design, data analysis, or writing of this manuscript.

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

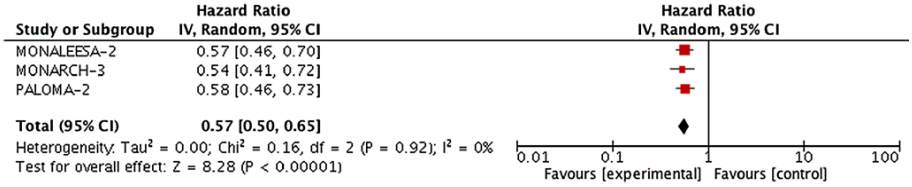
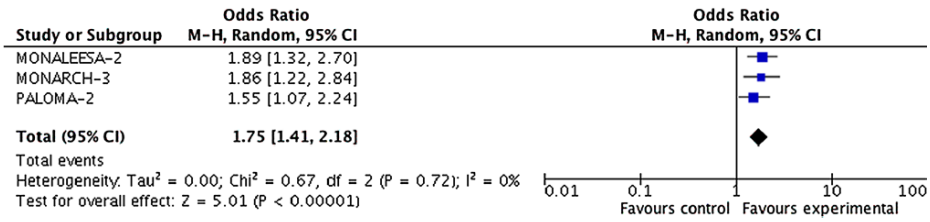


Fig. 2 Forest plot for progression-free survival

ORR: superiority of CDK 4/6 inhibitors



ig. 3 Forest plot for objective response

Adverse events: inferiority of CDK 4/6 inhibitors

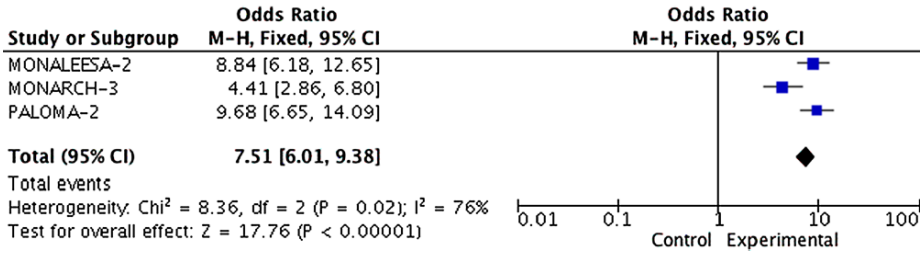


Fig. 5 Forest plot for treatment-related side effects

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.

Kommentare zum Review

- Untersuchung der Wirksamkeit basiert nur auf PFS, ORR, CR und PR

Ayyagari R et al., 2018 [1]. (AWG 1)

Progression-free Survival With First-line Endocrine-based Therapies Among Postmenopausal Women With HR+/HER2- Metastatic Breast Cancer: A Network Meta-analysis.

Fragestellung

- To quantitatively synthesize the available evidence on PFS associated with endocrine therapies first-line treatments for HR+/HER2– mBC among postmenopausal women,
- To evaluate the efficacy of these agents in pre-identified patient populations in an effort to identify subsets of patients most likely to benefit from novel targeted therapies (TT) as well as to explore comparative efficacy in more homogeneous settings

Methodik

Population:

Postmenopausal women with HR+/HER2– mBC in first-line therapy setting

Intervention:/Komparator:

endocrine therapy (ie, letrozole, anastrozole, exemestane, tamoxifen, fulvestrant) or targeted therapies (ie, palbociclib, everolimus, ribociclib, abemaciclib), either as monotherapy or as part of a combination therapy

Endpunkte: PFS

Recherche/Suchzeitraum:

- search on June 7, 2016 in Medline, EMBASE, Cochrane databases (Cochrane Central Register of Con- trolled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects), and conference proceedings from 2013 to 2016

Qualitätsbewertung der Studien: Cochrane Risk of Bias tool

Statistische Analysen: Network Meta-analysis

- core analysis: To enable the formation of evidence networks, and based on clinical input, the AIs anastrozole, letrozole, and exemestane were pooled together into a single arm in the core analysis.
- Subgroup analyses:
  - Subgroup of late progressors: patients with a disease-free interval ≥12 months from completion of (neo)adjuvant therapy with letrozole or anastrozole at time of randomization
  - subgroup of "de novo" patients : patients whose initial BC diagnosis is mBC)
- Bayesian approach using a normal likelihood model with linear link; Non informative previous distributions were used as parameters in the NMA to avoid artificially biasing results and ensuring maximal objectivity ofther esults
- Heterogeneity in the evidence network was assessed by comparing the deviance information criterion for the fixed and random effects models.
- I^2 and Cochran's Q statistics used to assess the heterogeneity

Ergebnisse

Anzahl eingeschlossener Studien: N=5

Charakteristika der Studien

Table II. Baseline demographic characteristics and disease status. The values are given as no. (%) unless otherwise indicated.

	Mehta et al, 2012[13,*]		PALOMA-1[15]		PALOMA-2[16]		MONALEESA-2[17]		FALCON[12]	
Trial	Anastrozole + Fulvestrant	Anastrozole	Letrozole + Palbociclib	Letrozole	Letrozole + Palbociclib	Letrozole	Letrozole + LEE	Letrozole	Fulvestrant	Anastrozole
Age, median (range), y	NR	NR	63 (54-71)	64 (56-70)	62 (30-89)	61 (28-88)	63 (29-88)	62 (23-91)	64 (38-87)	62 (36-90)
Ethnicity										
White	NR	NR	NR	NR	344 (77.5)	172 (77.5)	269 (80.5)	280 (83.8)	175 (76.1)	174 (75.0)
Asian	NR	NR	NR	NR	65 (14.6)	30 (13.5)	28 (8.4)	23 (6.9)	NR	NR
Black	NR	NR	NR	NR	8 (1.8)	3 (1.4)	10 (3.0)	7 (2.1)	NR	NR
Native American	NR	NR	NR	NR	0	0	1 (0.3)	0	NR	NR
Pacific Islander	NR	NR	NR	NR	0	0	1 (0.3)	0	NR	NR
Other	NR	NR	NR	NR	27 (6.1)	17 (7.7)	12 (3.6)	8 (2.4)	NR	NR
Unavailable	NR	NR	NR	NR	0	0	13 (3.9)	16 (4.8)	NR	NR
Hormone receptor status										
ER+, PR+	NR	NR	NR	NR	NR	NR	269 (80.5)	277 (82.9)	175 (76.1)	179 (77.2)
ER+, PR-	NR	NR	NR	NR	NR	NR	NR	NR	44 (19.1)	43 (18.5)
ER+, PR unknown	NR	NR	NR	NR	NR	NR	NR	NR	10 (4.3)	7 (3.0)
ER- or unknown, PR+	NR	NR	NR	NR	NR	NR	NR	NR	1 (0.4)	3 (1.3)
ER unknown, PR unknown	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Performance status										
ECOG 0	NR	NR	46 (55.0)	45 (56.0)	257 (57.9)	102 (45.9)	205 (61.4)	202 (60.5)	NR	NR
ECOG 1	NR	NR	38 (45.0)	36 (44.0)	178 (40.1)	117 (52.7)	129 (38.6)	132 (39.5)	NR	NR
ECOG 2	NR	NR	0	0	9 (2.0)	3 (1.4)	0	0	NR	NR
ECOG >2	NR	NR	0	0	0	0	0	0	NR	NR
Unavailable	NR	NR	0	0	0	0	0	0	NR	NR
Disease stage										
Locally advanced[†]	NR	NR	2 (2.0)	1 (1.0)	72 (16.2)	39 (17.6)	1 (0.3)	3 (0.9)	28 (12.2)	32 (13.8)
Metastatic[‡]	NR	NR	82 (98.0)	80 (99.0)	138 (31.1)	72 (32.4)	333 (99.7)	331 (99.1)	202 (87.8)	200 (86.2)
Metastatic site of cancer										
Bone	NR	NR	NR	NR	NR	NR	246 (73.7)	244 (73.1)	NR	NR
Bone only	NR	NR	17 (20.0)	12 (15.0)	103 (23.2)	48 (21.6)	69 (20.7)	78 (23.4)	NR	NR
Visceral	NR	NR	37 (44.0)	43 (53.0)	214 (48.2)	110 (49.5)	197 (59.0)	196 (58.7)	135 (58.7)	119 (51.3)
Measurable disease	NR	NR	65 (77.4)	66 (81.5)	338 (76.1)	171 (77.0)	256 (76.6)	245 (73.4)	193 (83.9)	196 (84.5)
Disease-free interval										
De novo	NR	NR	44 (52.0)	37 (46.0)	167 (37.6)	81 (36.5)	114 (34.1)	113 (33.8)	NR	NR
≤ 2 mo	NR	NR	59 (70.0)	51 (63.0)	99 (22.3)	48 (21.6)	4 (1.2)	10 (3.0)	NR	NR
>12 mo	NR	NR	25 (30.0)	30 (37.0)	178 (40.1)	93 (41.9)	216 (64.7)	210 (62.9)	NR	NR
Unknown	NR	NR	NR	NR	NR	NR	0	1 (0.3)	NR	NR

ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; LEE = ribociclib; PR = progesterone receptor; NR = not reported.
[*]The overall population in the 2012 study by Mehta et al is hormone receptor-positive, which is broader than hormone receptor-positive/human epidermal growth factor receptor 2-negative. The human epidermal growth factor receptor 2-negative subgroup results were used.
[†]Stage III cancer was considered to be locally advanced disease.
[‡]Stage IV cancer was considered metastatic.

Although there was between-trial variability in the baseline characteristics of the selected trials, the distributions of these characteristics are largely similar clinically. Thus, the transitivity (similarity) assumption is not violated in the analyses presented in this study.

Qualität der Studien

risk of bias was characterized as low to moderate, with some trials not reporting some information such as concealment of allocation and blinding of care providers and participants. No adjustments were made to the analysis.

Supplementary Table 4. Risk of bias assessment table.

Trial no. (acronym)	Mehta 2012	PALOMA-1	PALOMA-2	MONALEESA-2	FALCON
Was randomisation carried out appropriately?	Yes	Yes	Yes	Yes	Not clear
Was the concealment of treatment allocation adequate?	Not clear	N/A	Not clear	Yes	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Not clear	N/A	Not clear	Yes	Not clear
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	No	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes	Yes	Not clear

Ergebnisse

PFS - Direkte Vergleiche:

Table III. Summary of trial-level treatment effects.

	Mehta et al, 2012[13,*]		PALOMA-1[15]		PALOMA-2[16]		MONALEESA-2[17]		FALCON[12]	
Trial	Anastrozole + Fulvestrant	Anastrozole	Letrozole + Palbociclib	Letrozole	Letrozole + Palbociclib	Letrozole	Letrozole + LEE	Letrozole	Fulvestrant	Anastrozole
Sample size, N										
Randomized	NR	NR	84	81	444	222	334	334	230	232
ITT (HER2-)	266	270	84	81	444	222	334	334	230	232
Hazard ratio	0.81	_	0.49	_	0.58	_	0.57	_	0.8	_
SE	0.07	_	0.09	_	0.06	_	0.07	_	0.08	_

FALCON = Fulvestrant and Anastrozole Compared in Hormonal Therapy-Naïve Advanced Breast Cancer; HER2- = human epidermal growth factor receptor 2-negative; ITT = intention-to-treat; LEE = ribociclib; MONALEESA-2 = Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety; PALOMA = Palbociclib: Ongoing Trials in the Management of Breast Cancer; NR = not reported.
*The overall population in the 2012 study by Mehta et al is hormone receptor-positive, which is broader than hormone receptor-positive/HER2-. Therefore, the HER2- subgroup results were used.

Netzwerkgeometrie:

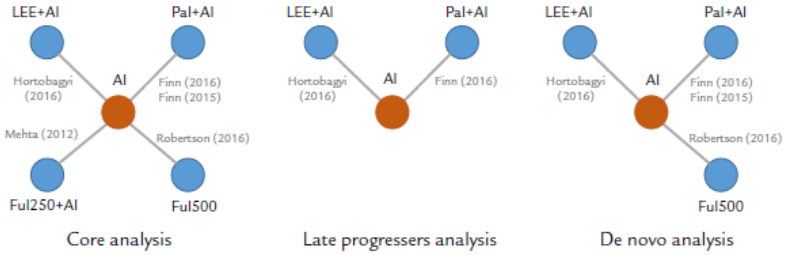


Figure 2. Evidence network according to type of analysis. AI = aromatase inhibitor; Ful250 = fulvestrant 250 mg; Ful500 = fulvestrant 500 mg; LEE = ribociclib; Pal = palbociclib. The references in the figure are: Hortobagyi (2016)[17], Finn (2015)[15], Finn (2016)[16], Mehta (2012)[13], Robertson (2016)[12].

- Consistency between direct and indirect comparisons could not be assessed due to the lack of loops in the evidence network

Treatment Comparisons for Core Analysis:

Stat. sign. longer PFS for combination treatment than endocrine treatment alone (Table iV)

Table IV. Pairwise treatment comparison, core analysis. Results are given as median and 95% credible intervals of hazard ratio (column versus row).

Variable	AI	Ful250 + AI	Ful500	LEE + AI	Pal + AI
AI	1	0.81 (0.67, 0.98)	0.80 (0.63, 1.00)	0.57 (0.46, 0.71)	0.56 (0.46, 0.68)
Ful250+AI	1.23 (1.02, 1.49)	1	0.98 (0.73, 1.32)	0.70 (0.53, 0.94)	0.69 (0.53, 0.91)
Ful500	1.25 (1.00, 1.58)	1.02 (0.76, 1.37)	1	0.71 (0.52, 0.98)	0.70 (0.52, 0.95)
LEE + AI	1.76 (1.42, 2.18)	1.43 (1.07, 1.90)	1.40 (1.02, 1.91)	1	0.98 (0.74, 1.32)
Pal + AI	1.79 (1.46, 2.18)	1.45 (1.10, 1.90)	1.43 (1.05, 1.92)	1.02 (0.76, 1.36)	1

AI = aromatase inhibitor; Ful250 = fulvestrant 250 mg; Ful500 = fulvestrant 500 mg; LEE = ribociclib; Pal = palbociclib.

Ranking probabilities: LEE + AI had a 46%probability of being the most efficacious treatment, whereas Pal + AI had a 54%probability (figure 3)

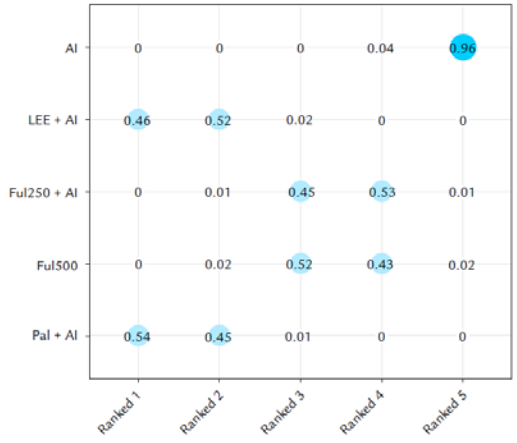


Figure 3. Ranking probabilities according to treatment, core analysis. AI = aromatase inhibitor; Ful250 = fulvestrant 250 mg; Ful500 = fulvestrant 500 mg; LEE = ribociclib; Pal = palbociclib.

Subgroup analyses:

- Treatment Comparisons for Late Progressors Analysis: LEE + AI and Pal+ AI also had significantly longer PFS than AI (95% CrI upper bound ≤1)
- Treatment Comparisons for De Novo Analysis: LEE + AI and Pal + AI had significantly better efficacy than other treatments in terms of PFS.

Anmerkung/Fazit der Autoren

These analyses indicate that women in this population receiving Pal + AI, LEE +AI, FUL + AI, or FUL as first-line treatment had longer PFS than those who received AIs alone. Pal + AI and LEE + AI had the highest probability of being the most effective at delaying progression among all treatments compared in all the patient populations studied herein.

Kommentare zum Review

- NMA-Annahme der Transitivität grob diskutiert, allerdings keine Informationen zur Verteilung der Effektmodifikatoren über die Vergleiche hinweg berichtet
- Annahme der Konsistenz zwischen direkter und indirekter Evidenz aufgrund der Netzwerkstruktur nicht überprüfbar (kein closed loop)
- Nur PFS als Endpunkt untersucht
- Funding for this research was provided by Novartis Pharmaceuticals Corporation

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Zhang J et al. 2017 [25]. (AWG 1)
Efficacy and safety of endocrine monotherapy as first-line treatment for hormone-sensitive advanced breast cancer: A network meta-analysis

Fragestellung

We performed a network meta-analysis for a comprehensive analysis of 6 first-line endocrine monotherapies (letrozole, anastrozole, exemestane, tamoxifen, fulvestrant 250 and 500mg) for HR+ HER2- in postmenopausal patients with advanced breast cancer (ABC)

Methodik

Population:

HR+ (ER+ and/or PgR+) postmenopausal women with metastatic or LABC who

- had no endocrine or cytotoxic chemotherapy for advanced disease, or
- had received no adjuvant endocrine therapy within 12 months before entry into the trials.

Intervention: anastrozole, letrozole, exemestane, tamoxifen, fulvestrant 250 and 500mg, for first-line monotherapy

Komparator: k. A.

Endpunkte: ORR, TTP, PFS, AE

Recherche/Suchzeitraum:

- MEDLINE via PubMed through May 2015
- reference lists of retrieved articles and websites of ASCO, San Antonio Breast Cancer Symposium, and ClinicalTrials.gov were checked for further studies.

Qualitätsbewertung der Studien: Cochrane Collaboration Risk of Bias tool

Statistische Methoden:

1. pair-wise meta-analysis to synthesize studies comparing the same pair of treatments.
2. Bayesian network meta-analysis to synthesize direct and indirect treatment comparisons to assess the treatment effect between all interventions and rank the treatments graphically
   - Analysis based on noninformative priors for effect sizes and precision involved Markov chain Monte Carlo method with 10,000 initial iterations to burn in and the next 55,000 iterations for estimations.
   - fixed effects model
   - Checking the assumption of consistency by the Bucher method to determine whether it was similar enough to combine the direct and indirect evidence
   - sensitivity analysis repeating the main computations with a random-effects model.
   - Deviance information criteria (DIC) was used to compare the fit of the fixed-effects and random-effects models

Ergebnisse

Anzahl eingeschlossener Studien: N=8

Charakteristika der Studien

Characteristics of included studies.

Study	Comparison	Design	No. of patients randomized	Median age, years (range)	WHO performance status, (%) (0/1/2)	HR+ unknown (%)	HER2− (%)	Bone metastases (%)	Visceral disease (%)
Bonneterre et al, 2000[28]	Anastrozole (1 mg/d) vs. Tamoxifen (20 mg/d)	Randomized, double-blind, multicenter study	668	67 (34–92)	100 (0–2)	55	NR	47	34
Nabholtz et al, 2000[29]	Anastrozole (1 mg/d) vs. Tamoxifen (20 mg/d)	Randomized, double-blind, multicenter study	353	67 (30–92)	100 (0–2)	11	NR	59	48
Howell et al, 2004[42]	Fulvestrant (250 mg/mo) vs. Tamoxifen (20 mg/d)	Randomized, double-blind, double-dummy, parallel-group study	587	67 (43–93)	100 (0–2)	19	NR	30	NR
Mouridsen et al, 2001[33]	Letrozole (2.5 mg/d) vs. Tamoxifen (20 mg/d)	Phase III, randomized, double-blind, double-dummy, parallel-group study	907	65 (31–96)	57 (90–100)/35 (70–80)/8 (50–60) (Karnofsky)	34	NR	30	44
Paridaens et al, 2008[49]	Exemestane (25 mg/d) vs. Tamoxifen (20 mg/d)	Phase II/III, randomized, multicenter, open-label study	371	63 (37–87)	44/44/12	7	NR	35	47
Robertson et al, 2012[51]	Fulvestrant (HD) (500 mg/mo plus 500 mg on day14 of month 1) vs. Anastrozole (1 mg/d)	Phase II, randomized, multicenter, open-label study	205	66 (40–89)	100 (0–2)	0	48	8	56
Llombart-Cussac et al, 2012[50]	Exemestane (25 mg/d) vs. Anastrozole (1 mg/d)	Phase II, randomized, open-label, cross-over study	103	72 (45–94)	44/26/19	2	NR	NR	52
Iwata et al, 2013[52]	Exemestane (25 mg/d) vs Anastrozole (1 mg/d)	Phase III, randomized, double-blind study	298	64 (44–95)	82/18	NR	NR	27	49

HD = high dose, HER− = human epidermal growth factor receptor-2-negative, HR+ = hormone receptor-positive, NR = not reported, WHO = World Health Organization.

Qualität der Studien:

- methodological quality of 5 double-blind studies was high and that of 3 other open-label studies was moderate.
- All studies were considered to have no selective reporting bias or other bias, but most did not report the techniques for concealment.

Ergebnisse:

Direct pairwise metaanalyses

Meta-analysis of direct comparisons for efficacy of objective response rate (ORR) and time to progression or progression-free survival (TTP/PFS)

Comparisons	ORR				TTP/PFS			
	OR	95% CI	I^2	P	HR	95% CI	I^2	P
Tamoxifen vs Anastrozole	0.92	0.70,1.22	0.0	0.438	1.19	0.82,1.71	82.9	0.016
Exemestane vs Anastrozole	1.04	0.68,1.58	36.2	0.210	1.04	0.83,1.31	0.0	0.657
Fulvestrant 250 mg vs Tamoxifen	0.90	0.64,1.27	-	-	1.18	0.98,1.44	-	-
Letrozole vs Tamoxifen	**1.71**	**1.26,2.31**	-	-	**0.70**	**0.60,0.82**	-	-
Exemestane vs Tamoxifen	**1.85**	**1.21,2.82**	-	-	0.87	0.70,1.08	-	-
Fulvestrant 500 mg vs Anastrozole	0.97	0.54,1.75	-	-	**0.66**	**0.47,0.92**	-	-

Meta-analysis of direct comparisons for safety

Comparisons	Hot flashes			Weight gain			Nausea			Bone pain		
	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P
Tamoxifen vs Anastrozole	1.25 (0.77,2.04)	64.2	0.095	1.40 (0.56,3.49)	0.2	0.317	0.89 (0.65,1.22)	0.0	0.802	0.97 (0.52,1.83)	-	-
Exemestane vs Anastrozole	1.64 (0.91,2.98)	-	-	2.29 (0.78,6.78)	-	-	-	-	-	0.49 (0.09,2.80)	-	-
Fulvestrant 250 vs Tamoxifen	**0.66 (0.44,0.98)**	-	-	1.54 (0.45,5.33)	-	-	0.55 (0.28,1.07)	-	-	-	-	-
Letrozole vs Tamoxifen	1.19 (0.84,1.69)	-	-	-	-	-	0.90 (0.63,1.30)	-	-	1.09 (0.78,1.52)	-	-
Exemestane vs Tamoxifen	0.88 (0.58,1.35)	-	-	1.58 (0.90-2.79)	-	-	0.84 (0.50,1.43)	-	-	0.92 (0.60,1.41)	-	-
Fulvestrant 500 vs Anastrozole	0.94 (0.42,2.11)	-	-	-	-	-	-	-	-	-	-	-

Direct MA results suggested that

- letrozole was more efficacious for both ORR and TTP/PFS than tamoxifen;
- exemestane was more efficacious for ORR than tamoxifen;
- fulvestrant 500mg was more efficacious for TTP/PFS than anastrozole.
- side-effects: fulvestrant 250mg produced fewer hot flash events than tamoxifen, with no difference between other adverse event types.

Network meta-analysis

Netzwerkgeometrie:

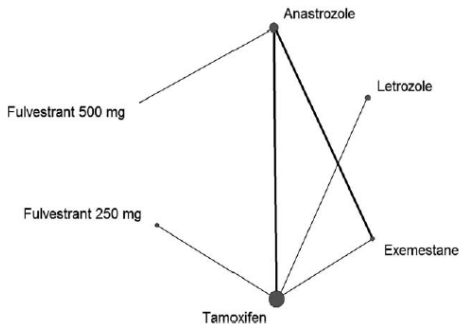

Figure 2. Network of eligible comparisons for the network meta-analysis for efficacy. The size of the nodes is proportional to the number of randomized participants (sample size), and the width of the lines is proportional to the number of trials comparing each pair of treatments.

Assessment of Consistency:

- 1 closed loop of comparisons connecting anastrozole, exemestane, and tamoxifen.
- Assessment of difference between direct + indirect estimates for this loop by inconsistency factors (IFs): IFs were compatible with zero (ORR, IF=0.61, 95% CI -0.17 to 1.39; TTP/PFS, IF=0.18, 95% CI -0.21 to 0.58), which indicated that the loops were consistent.

Results of NMA:

Network meta-analysis comparison of the efficacy of 6 first-line endocrine monotherapies for ORR and TTP/PFS.

Anastrozole	1.47 (0.99–2.16)	1.29 (0.93–1.77)	0.85 (0.66–1.09)	0.78 (0.50–1.18)	1.02 (0.55–1.79)	
1.21 (0.97–1.48)	Letrozole	0.91 (0.57–1.38)	0.59 (0.43–0.80)	0.54 (0.34–0.85)	0.72 (0.32–1.36)	
0.96 (0.80–1.15)	0.81 (0.62–1.01)	Exemestane	0.67 (0.48–0.91)	0.61 (0.37–0.97)	0.81 (0.39–1.54)	
0.84 (0.72–0.99)	0.70 (0.60–0.81)	0.88 (0.74–1.04)	Tamoxifen	0.91 (0.64–1.28)	1.22 (0.62–2.18)	ORR
0.72 (0.56–0.93)	0.60 (0.46–0.76)	0.75 (0.57–0.97)	0.86 (0.71–1.04)	Fulvestrant 250 mg	1.38 (0.64–2.72)	
1.54 (1.09–2.11)	1.29 (0.85–1.86)	1.61 (1.08–2.25)	1.84 (1.24–2.55)	2.17 (1.35–3.11)	Fulvestrant 500 mg	
			TTP/PFS			

ORR = objective response rate, PFS = progression-free survival, TTP = time to progression. Results are represented by the odds ratio and 95% confidence interval for ORR (upper right quadrant) and by the hazard ratio and 95% confidence interval for TTP/PFS (lower left quadrant). For ORR, odds ratio > 1 favour the column-defining treatment. For TTP/PFS, hazard ratio < 1 favour the column-defining treatment.

Ranking for efficacy with fixed-effects model:

Ranking for ORR

Treatment	Mean Rank	95% CI
Letrozole	1.49	1.00 - 3.00
Exemestane	1.99	1.00 - 4.00
Anastrozole	3.56	2.00 - 5.00
Fulvestrant 500 mg	3.77	1.00 - 6.00
Tamoxifen	4.85	3.00 - 6.00
Fulvestrant 250 mg	5.35	3.00 - 6.00

Probability of treatment rankings for TTP/PFS

Treatment	Ranking					
	1	2	3	4	5	6
Anastrozole	0.000	0.050	**0.625**	0.306	0.017	0.002
Letrozole	0.119	**0.822**	0.045	0.014	0.000	0.000
Exemestane	0.002	0.021	0.310	**0.608**	0.053	0.006
Tamoxifen	0.000	0.000	0.004	0.064	**0.884**	0.048
Fulvestrant 250 mg	0.000	0.000	0.003	0.007	0.046	**0.944**
Fulvestrant 500 mg	**0.879**	0.107	0.013	0.001	0.000	0.000

Sensitivity analysis of efficacy with random-effects model revealed no significant difference among the 6 endocrine therapies, but the rank orders are consistent with the fixed effects model.

Anmerkung/Fazit der Autoren

Our study found that fulvestrant 500mg and letrozole might be the preferred first-line endocrine monotherapy choices for HR+ HER2- postmenopausal women with ABC because of their more efficacious ORR and TTP/PFS with favorable tolerability profiles. However, direct comparisons among first-line endocrine monotherapies are still required to robustly demonstrate the possible differences among these endocrine agents, especially fulvestrant 500mg and letrozole.

Clinical choices should also depend on the specific disease situation and duration of endocrine therapy.

Kommentare zum Review

- Aussagesicherheit der Netzwerkmetaanalyseergebnisse eingeschränkt; keine Angaben zur Überprüfung der Transitivitätsannahme in der Publikation vorliegend (dh keine Prüfung der Verteilung wichtiger Effektmodifikatoren über die verschiedenen Vergleiche hinweg); Autoren thematisieren die Ähnlichkeitsannahme der Studien nur grob im Diskussionsteil
- Untersuchung der Wirksamkeit basiert nur auf ORR, TTP und PFS

Wang N et al., 2019 [24]. (AWG 2)

Everolimus plus endocrine vs endocrine therapy in treatment advanced ER+, HER2- breast cancer patients: A meta-analysis

Fragestellung

The purpose of this meta-analysis including more randomized trials is to evaluate the efficacy and safety of everolimus combined with endocrine therapy group vs endocrine therapy group for HR + /HER2 −breast cancer.

Methodik

Population:

- advanced HR + , HER2 − breast cancer patients that had recurred or progressed during or after endocrine therapy

Intervention:

- Everolimus plus endocrine therapy (fulvestrant or exemestane or letrozole or anastrozole or tamoxifen or toremifene)

Komparator:

- Endocrine therapy alone

Endpunkte:

- N.a.

Recherche/Suchzeitraum:

- PubMed, The Cochrane Library, EMBASE, Web of Science, Chinese biomedicine literature database, WanFang Data, CNKI, and VIP database up to July 2018

Qualitätsbewertung der Studien:

- Randomization, blinding and allocated concealment was assessed

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs

Charakteristika der Population:

Characteristics of included studies.

Study	Country	Patients (*n*)(E/C)	Mean age (years)	Metastatic site	No. of metastatic sites (%) (≥3)(E/C)	Treatment (E/C)	follow-up (month)
Noguchi[11]	Japan	98/45	59.5/60	CNS Visceral (excluding CNS) Lung Liver Lung and liver Bone Bone only Other	42.8/33.3	EVE + EXE/PBO + EXE	18
Beck[12]	USA	100/37	62/61	Visceral Lung Liver Lung and liver Bone Bone only Other	42/43	EVE + EXE/PBO + EXE	18
Yardley[13]	global	485/239	62/61	Lung Liver Bone	36/37	EVE + EXE/PBO + EXE	18
Baselga[14]	Spain	138/132	68/66.9	Unclear	Unclear	EVE + letrozole/ PBO + letrozole	4
Bachelot[15]	France	54/57	63/66	Bone Bone only Visceral	24/28	EVE + tamoxifen/ tamoxifen	36.2
Guo[16]	China	23/23	57/59.5	Unclear	Unclear	EVE + EXE/EXE	9.5
Guo[17]	China	48/48	51/52	Lung Liver Brain Bone Soft tissue	24/28	EVE + ET/ ET	12

E, experimental group; C, control group.
EVE + EXE/PBO + EXE: everolimus 10 mg/d + exemestane 25 mg/d vs placebo+ exemestane 25 mg/d.
EVE + letrozole/PBO + letrozole: everolimus 10 mg/d + letrozole 2.5 mg/d vs placebo + letrozole2.5 mg/d.
EVE + tamoxifen/tamoxifen: everolimus 10 mg/d + tamoxifen 20 mg/d vs tamoxifen 20 mg/d alone.
EVE + ET/ET: tverolimus 5 mg/d + endocrine therapy vs endocrine therapy (fulvestrant 250 mg/4 week or exemestane 25 mg/d or letrozole 2.5 mg/d or anastrozole 1 mg/d or tamoxifen 20 mg/d or toremifene 60 mg/d).

Qualität der Studien:

Quality assessment of included studies.

Study	Randomization	Blinding	Allocated concealment
Noguchi[11]	Adequate	Adequate	Adequate
Beck[12]	Adequate	Adequate	Adequate
Yardley[13]	Adequate	Adequate	Adequate
Baselga[14]	Adequate	Adequate	Adequate
Bachelot[15]	Adequate	Adequate	Adequate
Guo[16]	Adequate	Adequate	Adequate
Guo[17]	Unclear	Unclear	Unclear

Studienergebnisse:

- PFS:

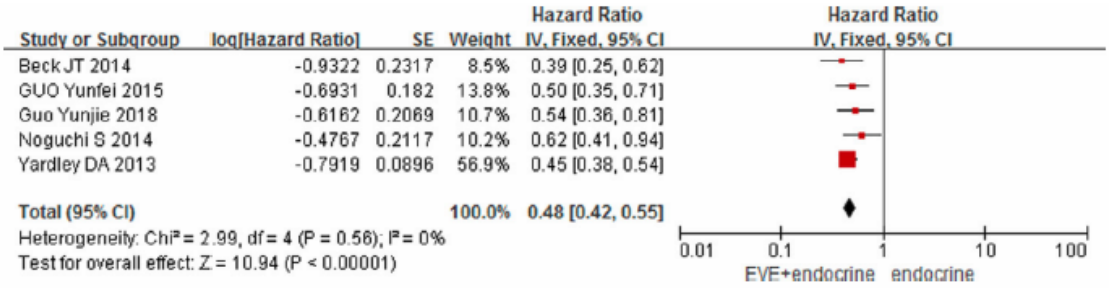

Fig. 1. The PFS of EVE + endocrine group vs endocrine group. EVE, everolimus; progression-free survival.

- CR:

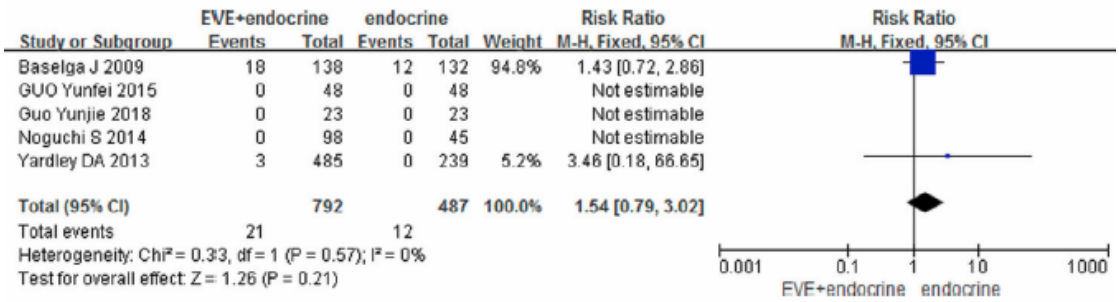

Fig. 2. The CR of EVE + endocrine group vs endocrine group. CR = complete response; EVE, everolimus.

- PR

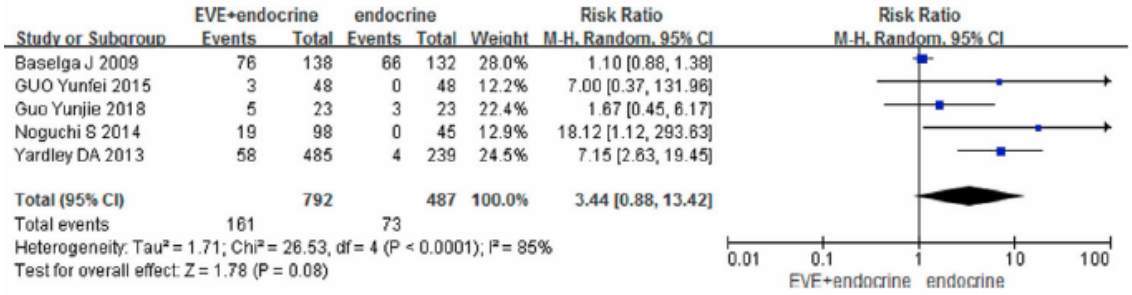

Fig. 3. The PR of EVE + endocrine group vs endocrine group. EVE, everolimus; PR = partial response.

- ORR:

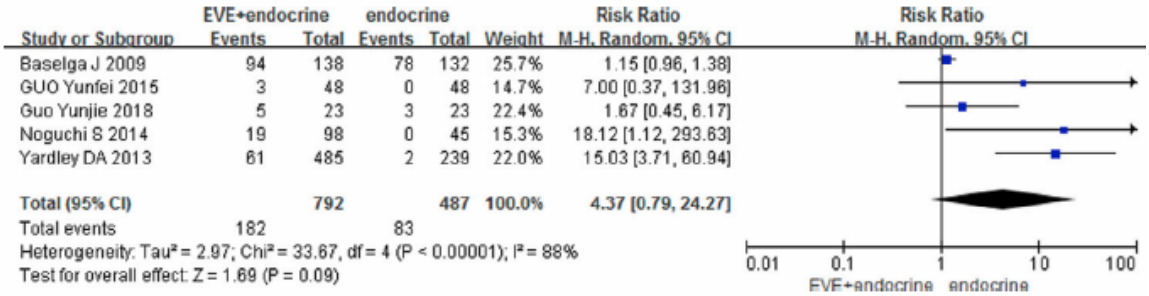

Fig. 4. The ORR of EVE + endocrine group vs endocrine group. ORR = overall response rate.

- The clinical benefit rate (CBR):

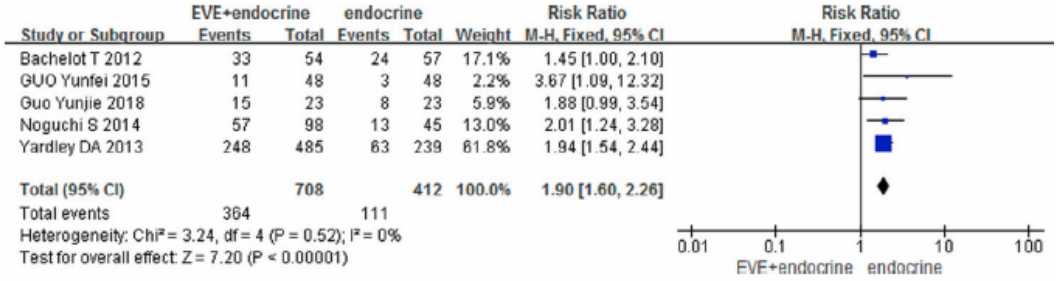

Fig. 5. The CBR of EVE + endocrine group vs endocrine group. CBR = clinical benefit rate; EVE, everolimus.

- The time to definitive deterioration (TTD)

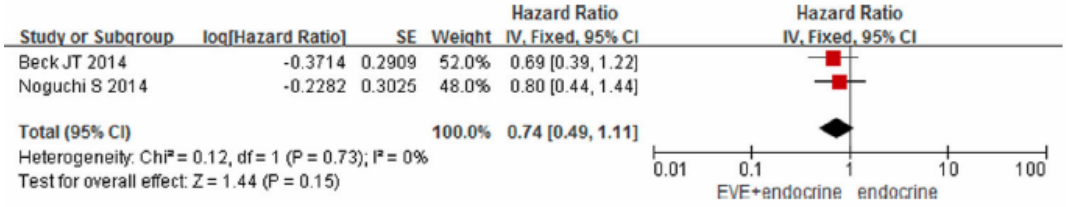

Fig. 6. The TTD of EVE + endocrine group vs endocrine group. EVE, everolimus; TTD, time to definitive deterioration.

- Adverse Events:

Table 3
Most common adverse events (all grades).

Adverse event	I^2(%)	*P*	Statistical method	Effect estimate	Z(*P*)
Stomatitis	0	0.61	RR(fixed effects model)	4.98[3.89,6.36]	12.8($P < 0.00001$)
Rash	57	0.04	RR(random effects model)	3.76[2.23,6.34]	4.95($P < 0.00001$)
Fatigue	0	0.57	RR(fixed effects model)	1.46[1.22,1.74]	4.12($P < 0.0001$)
Diarrhea	0	0.58	RR(fixed effects model)	1.92[1.51,2.43]	5.37($P < 0.00001$)
Decreased appetite	0	0.66	RR(fixed effects model)	2.28[1.69,3.09]	5.34($P < 0.00001$)
Nausea	0	0.85	RR(fixed effects model)	1.04[0.84,1.28]	0.33($P = 0.74$)
Cough	0	0.70	RR(fixed effects model)	2.32[1.65,3.26]	4.86($P < 0.00001$)
Pneumonitis	19	0.29	RR(fixed effects model)	20.45[7.07,59.12]	5.57($P < 0.00001$)
Decreased weight	0	0.81	RR(fixed effects model)	3.66[2.45,5.48]	6.32($P < 0.00001$)
Dyspnea	1	0.37	RR(fixed effects model)	2.28[1.56,3.34]	4.25($P < 0.00001$)
Anemia	72	0.01	RR(random effects model)	3.55[1.11,11.36]	2.14($P = 0.03$)
Hyperglycemia	0	0.59	RR(fixed effects model)	5.16[2.85,9.34]	5.42($P < 0.00001$)

RR, risk ratio.

Table 4
Most common adverse events (grades 3-4).

Adverse event (grade 3-4)	I^2(%)	*P*	Statistical method	Effect estimate	Z(*P*)
Stomatitis	0	0.76	RR(fixed effects model)	14.32[3.99.51.47]	4.08($P < 0.0001$)
Rash	0	0.95	RR(fixed effects model)	4.60[0.80,26.57]	1.71($P = 0.09$)
Fatigue	0	0.83	RR(fixed effects model)	3.03[1.33,6.88]	2.65($P = 0.008$)
Diarrhea	0	0.80	RR(fixed effects model)	5.81[1.06,31.97]	2.02($P = 0.04$)
Pneumonitis	33	0.22	RR(fixed effects model)	5.61[1.69,18.58]	2.82($P = 0.005$)
Decreased weight	0	0.58	RR(fixed effects model)	5.35[1.03,27.67]	2.00($P = 0.05$)
Dyspnea	0	0.45	RR(fixed effects model)	10.67[1.97.57.70]	2.75($P = 0.006$)
Anemia	56	0.13	RR(random effects model)	8.99[0.68,119.25]	1.66($P = 0.10$)
Hyperglycemia	10	0.35	RR(fixed effects model)	7.57[2.43,23.63]	3.49($P = 0.0005$)

RR, risk ratio.

Anmerkung/Fazit der Autoren

In conclusion, everolimus combined with endocrine may be more efficacious in patients with HR +, HER2 −advanced breast cancer. However, combination therapy was associated with a higher risk of adverse events than with endocrine therapy alone. Therefore, we need to carefully select suitable patients and observe their adverse reactions. If well tolerated, combination therapy with everolimus and endocrine therapy may be a useful treatment option in patients with HR +, HER2 −advanced breast cancer refractory to nonsteroidal AIs.

Kommentare zum Review

- In dem Review ist nicht spezifiziert, ob sich die endokrine Vortherapie eventuell auf das adjuvante Setting bezieht.
- Untersuchung der Wirksamkeit basiert nur auf CR, PR, ORR, PFS, clinical benefit rate und time to definitive deterioration.

Lin WZ et al., 2017 [14]. (AWG 2)

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 (Palbociclib) im AWG zugelassen und relevant
- Untersuchung der Wirksamkeit basiert nur auf PR, CR, SD und PFS

Wang J et al., 2018 [23]. (AWG 1/AWG 2)

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 (AI; 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:

- 7 RCT, 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 AI had similar time to progression/progression-free survival; however, time to progression/progression-free survival for fulvestrant 500 mg was significantly longer compared with AI (HR 0.75; 95% CI 0.62–0.91, P=0.003).
- Subgroup analysis revealed significant prolongation of time to progression/progression-free survival with fulvestrant compared with AI in the patients of estrogen and progesterone receptor-positive (HR 0.86; 95% CI, 0.75–0.98, P= 0.022) and patients aged ≥ 65 years (HR 0.81; 95% CI 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 AI, which was not seen with fulvestrant 250 mg. When

compared with AI, fulvestrant prolonged time to progression/progression-free survival in the subgroups including estrogen and progesterone-positive patients and those aged ≥ 65 years

Kommentare zum Review

- Einschluss von Studien zu 1line und 2nd line endocrine therapy, Analysen nicht getrennt nach Setting durchgeführt

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Messina C et al., 2018 [15]. (AWG 1/ AWG2)

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: Patients with metastatic HR+/HER2− breast cancer

Intervention: CDK4/6 inhibitors plus ET

Komparator: ET

Endpunkte: PFS, ORR, Safety

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs with 4.578 patients

Charakteristika der Population:

- 5 RCTs first-line
- 2 RCTs second-line
- 1 RCT first and second-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:
  - One phase II trial [7] and five phase III trials [8, 9, 12–14] assessed the efficacy of CDKi plus ET versus ET alone in endocrine sensitive setting; 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: (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).

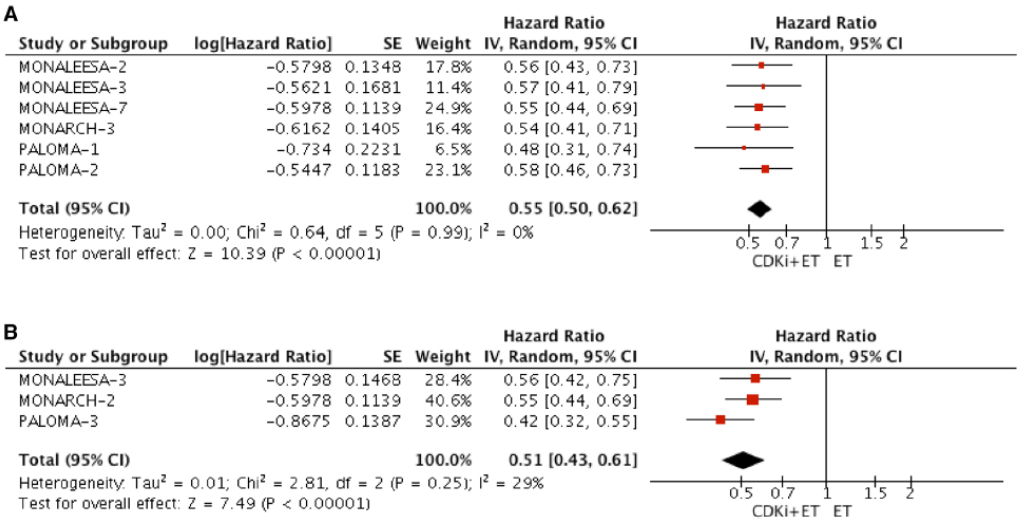

Fig. 2 Forest plot of hazard ratios (HRs) for progression-free survival (PFS) in eight randomized trials of CDK inhibitors plus endocrine therapy compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**) advanced HR+ HER2− breast cancer women. Pooling HRs were computed using random-effects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

- Response:
  - o 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).
  - o Two phase III trials [10, 11] reported the OR events occurring in the CDKi plus ET arm and in the ET alone arm, respectively, in endocrine-resistant setting: (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).

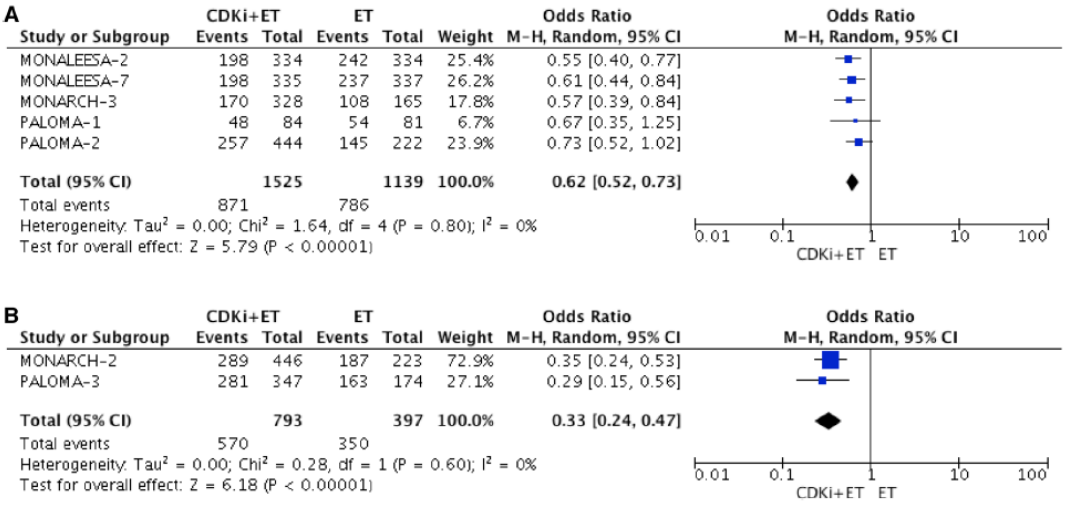

Fig. 4 Forest plot of Odds ratios (ORs) objective response rate (ORR) in seven randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive disease (**a**), endocrine-resistant disease (**b**) in advanced or metastatic HR+ HER2− breast cancer women. Pooling 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 reported G3–G4 AEs occurring in the CDKi plus ET arm and in the ET alone arm (Fig. 5a).
  - o 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%).
  - o 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:. 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%).
  - o All 8 RCTs 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).

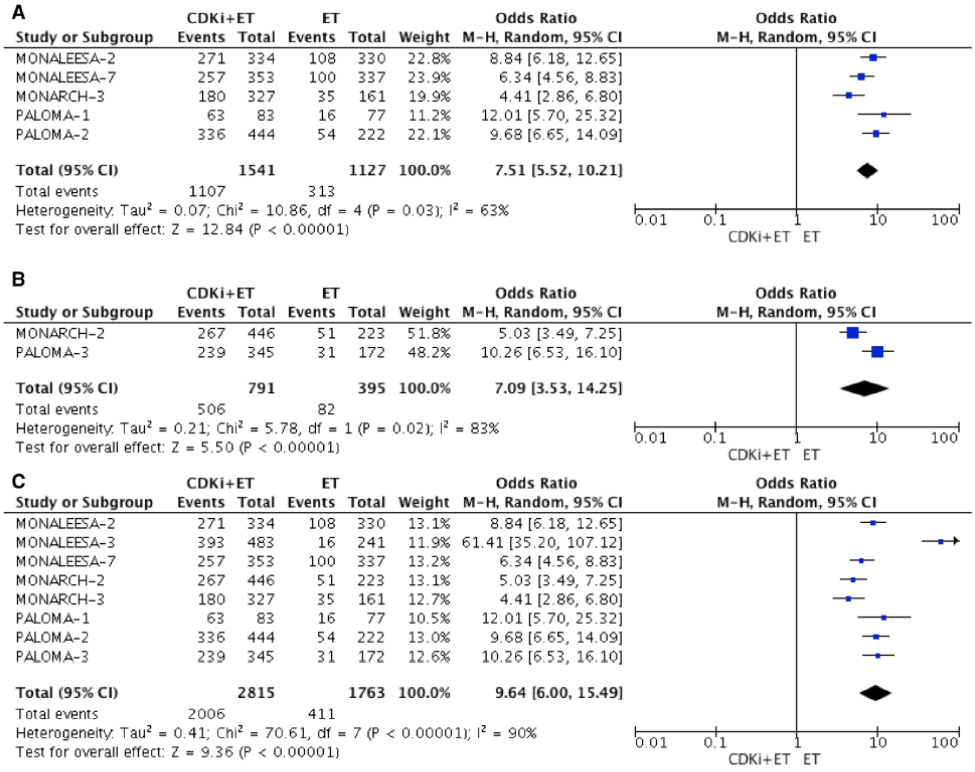

Fig. 5 Forest plot of odds ratios (ORs) for ≥G3–G4 AE in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population in advanced HR+ HER2− breast cancer women. Pooling ORs were computed using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

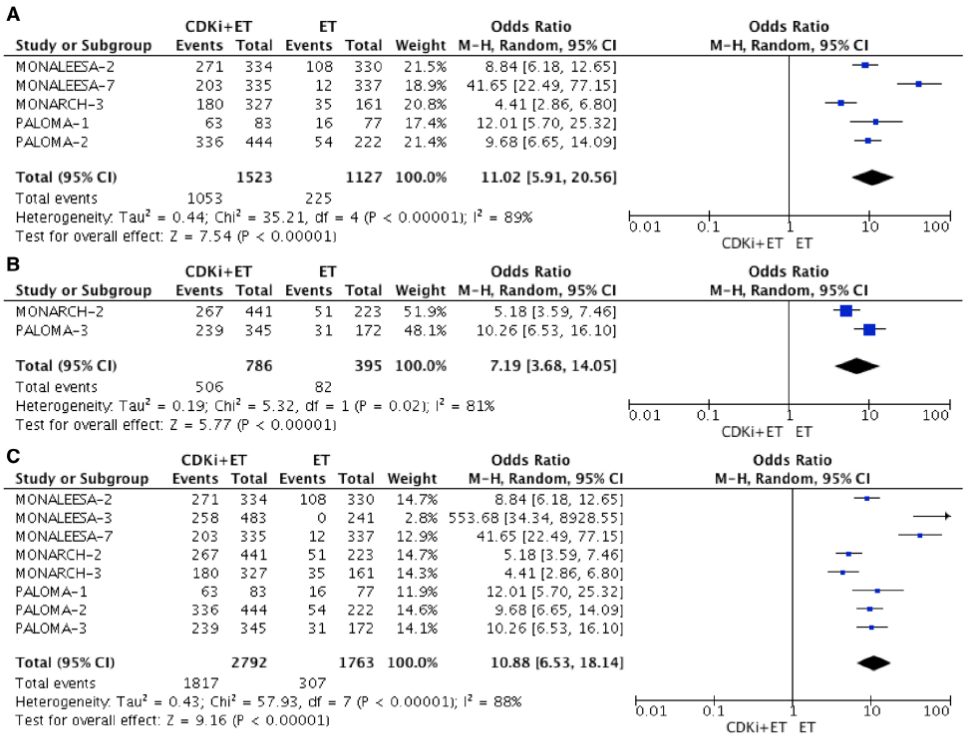

Fig. 6 Forest plot of odds ratios (ORs) for ≥G3–G4 neutropenia in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population (**c**) in advanced HR+ HER2− breast cancer women. Pooling ORs 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

- Untersuchung der Wirksamkeit basiert nur auf PFS und ORR
- Eingeschlossene Studien umfassen firstline und/oder secondline endocrine therapy, Analysen getrennt nach setting
- Weitere Reviews zu dem Thema:
  - SR von Shohdy et al. 2017 [21] 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)

Ding W et al., 2018 [4]. (AWG 1/ AWG2)

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: siehe ,,Charakteristika der Studien‘‘

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 (2x Palbociclib, 2x Ribociclib, 2 Abemaciclib) containing 3182 patients

Charakteristika der Studien:

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:

- CDK4/6 inhibitor group had a longer PFS (HR 0.51; 95% CI, 0.46–0.57, P< 0.00001), a better objective response (risk rate=1.53; 95% CI, 1.35–1.74, P < 0.00001), as well as a better clinical benefit response (risk rate=1.29; 95% CI, 1.13–1.47, P=.0001).
- subgroup analyses of PFS according to stratification factors and other baseline characteristics confirmed a great performance of CDK4/6 inhibitors across the all subgroups (-> Tab.)
- 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

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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

- Untersuchung der Wirksamkeit basiert nur auf PFS und Response
- Eingeschlossene Studien umfassen first- oder secondline endocrine setting, Subgruppenanalyse nach Setting durchgeführt

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Petrelli F et al., 2019 [18]. (AWG 1 / AWG2)

Comparative efficacy of palbociclib, ribociclib and abemaciclib for ER+ metastatic breast cancer: an adjusted indirect analysis of randomized controlled trials

Fragestellung

a systematic literature review to identify the published RCTs in advanced ER + BC, including these 3 CDK4–6 inhibitors evaluating efficacy in first- or further line settings; an indirect adjusted meta-analysis to synthesize the efficacy (PFS, ORR) and toxicity (grade [G]3–4 toxicities occurring in at least 5% of patients in experimental arms) of each regimen over the others.

Methodik

Population: ER + metastatic BC

Intervention/Komparator: palbociclib, ribociclib, and abemaciclib

Endpunkte:

- efficacy (OS and/or PFS and/or overall response rate [ORR]
- safety outcomes (G3–4 toxicities of any treatment arms))

Recherche/Suchzeitraum:

- We searched Pubmed, EMBASE, and the Cochrane Library up to 14th October 2018

Qualitätsbewertung der Studien: Jadad Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs with 3743 participants (1827 in first-line studies and 1916 in second-line studies)
- 3 trials included patients with not previously treated advanced ER + BC, and three included patients with pretreated advanced ER + BC and progressing while receiving adjuvant treatment or first-line therapy for metastatic disease.

Charakteristika der Studien und Quality assessment:

Author/year	Type of study	Primary endpoint	N° pts Exp/ctr	Median age Exp/ctr	Median follow up (months)	Previous endocrine therapy %	De novo/ recurrent Exp/ctr (%)	Jadad scale

						Exp/ctr		
1st line studies								
Palbociclib + letrozole Finn/2016	Phase 3	PFS	444/222	62/61	15.3	56.1/56.8	37.6/62.4	5
Ribociclib + letrozole Hortobagyi /2016	Phase 3	PFS	334/334	62/63	23	52.4/51.2	34.1/65.9	5
Abemaciclib + letrozole Goetz/2017	Phase 3	PFS	328/165	63/63	17.8	45.7/48.5	41.2/58.8	5
2nd line studies							**Previous adjuvant/1st line**	
Palbociclib + faslodex Cristofanilli/ 2016	Phase 3	PFS	347/174	57/56	8.9	100/100	21/79* vs 21/78	5
Ribociclib + faslodex Sledge/2018	Phase 3	PFS	484/282	63/63	Not reported	80/82.6	59.7/22.7 vs 58.7/16.5	5
Abemaciclib + faslodex Sledge/2017	Phase 3	PFS	446/223	59/62	19.5	100/100	59/38.3 vs 59.6/38.1	5

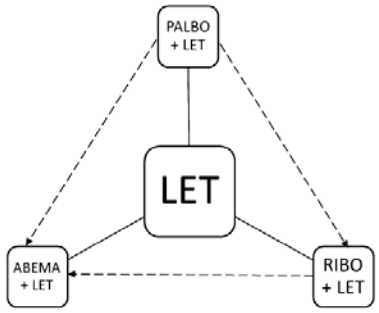

Fig. 2 Direct and indirect first line treatment comparison diagram. *LET* letrozole, *PALBO* palbociclib, *RIBO* ribociclib, *ABEMA* abemaciclib

Studienergebnisse:

First line endocrine therapy

Direkte Vergleiche

- Hazard ratios for PFS were respectively 0.58 (95% CI 0.46–0.72), 0.56 (95% CI 0.43–0.72) and 0.54 (95% CI 0.41–0.72) for the three main direct comparisons of palbociclib, ribociclib, and abemaciclib

Indirekte Vergleiche

- Palbociclib vs ribociclib

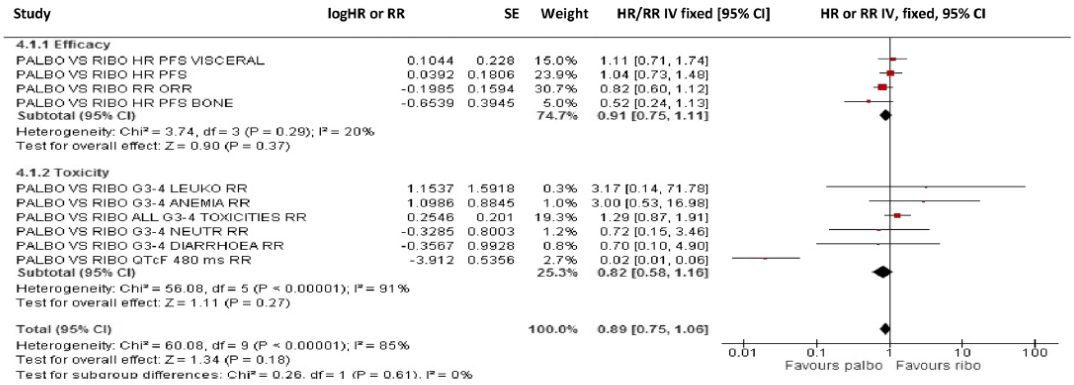

Fig. 3 Forest plots for all indirect comparisons among CDK4–6 inhibitors in first-line trials for advanced ER + BC patients: palbociclib versus ribociclib

- palbociclib versus abemaciclib

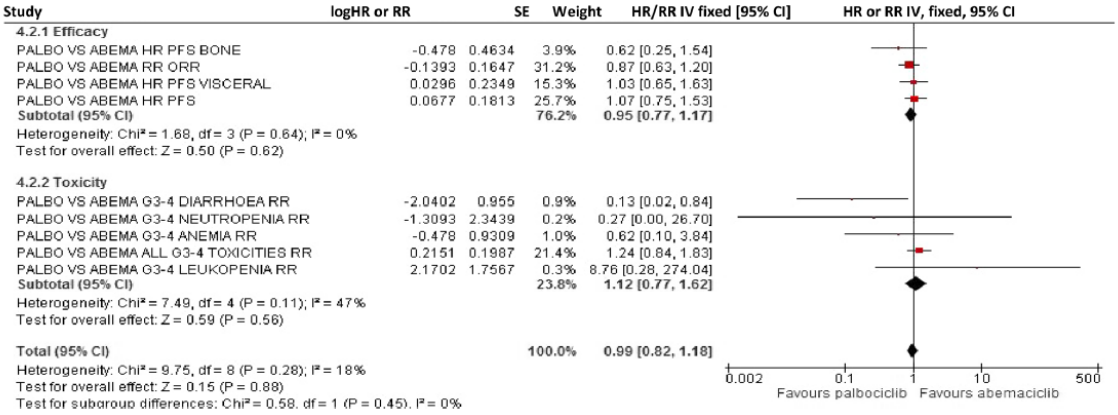

Fig. 4 Forest plots for all indirect comparisons among CDK4–6 inhibitors in first-line trials for advanced ER + BC patients: palbociclib versus abemaciclib

- ribociclib versus abemaciclib

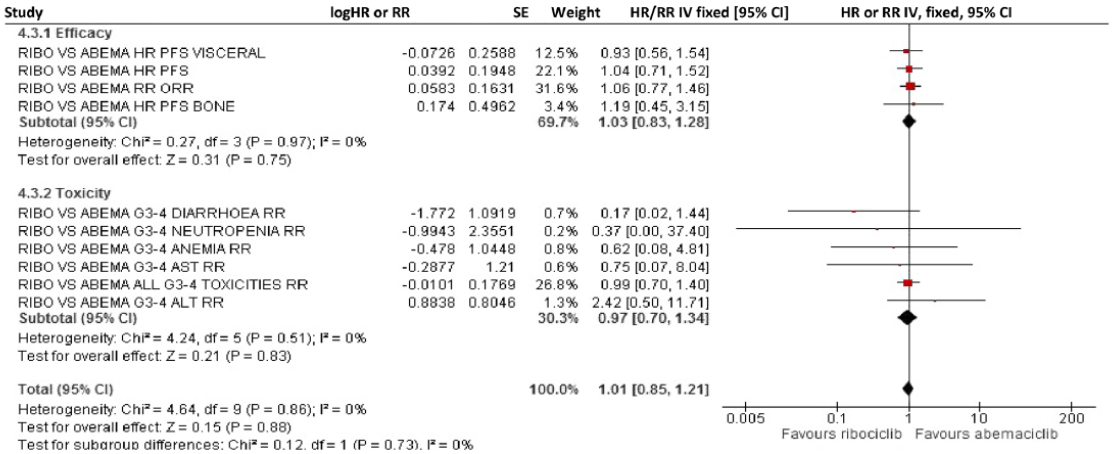

Fig. 5 Forest plots for all indirect comparisons among CDK4–6 inhibitors in first-line trials for advanced ER + BC patients: ribociclib versus abemaciclib

Second-line endocrine therapy

Direkte Vergleiche:

- PFS and ORR: Hazard ratios for PFS were respectively 0.46 (95% CI 0.36–0.59), 0.59 (95% CI 0.48–0.73) and 0.55 (95% CI 0.44–0.78) for the 3 main direct comparisons of palbociclib, ribociclib, and abemaciclib in second-line settings.

Indirekte Vergleiche

- In indirect comparisons, all three second-line agents (CDK4–6 + fulvestrant) were similar in term of PFS: HR_{ind} 0.78 (95% CI 0.57–1.07), 0.84 (95% CI 0.61–1.14) and 1.07 (95% CI 0.81–1.43) for palbociclib versus ribociclib, palbociclib versus abemaciclib and ribociclib versus abemaciclib comparisons. (The treatment inconsistency was low: P for heterogeneity 0.29, I2 = 19%). Similarly, ORR was not significantly different among the three comparisons: RRind 1.21 (95% CI 0.66–2.22), 1.04 (95% CI 0.57–1.91), and 1.26 (95% CI 0.8–1.98)
- All G3–4 toxicities (only for palbociclib and ribociclib comparison), G3–4 leukopenia, neutropenia, anemia, and diarrhea were analyzed. No differences among agents were found, except less G3–4 diarrhea with palbociclib and ribociclib compared with abemaciclib (RR_{ind} 0 [95% CI 0–0.15], P = 0.002 and 0.02 [95% CI 0–0.36], P = 0.007) and less G3–4 anemia with ribociclib compared to abemaciclib (RR_{ind} 0.18 [95% CI 0.03–1.04], P = 0.05)

Anmerkung/Fazit der Autoren

According to these data, based on similar effect on PFS and ORR and despite a different toxicity profile, there is still no clinical tool aiding decision-making for first-line and subsequent therapies for the treatment of advanced ER + BC. Ongoing biomarker studies will elucidate the best strategy in the whole ER + BC population and subgroups (luminal A vs. B disease)

Kommentare zum Review

- Eingeschlossene Studien umfassen first- oder secondline endocrine setting; Analysen getrennt nach Therapielinie
- Transitivitäts-, Homogenitäts- und Konsistenzannahmen im Review überprüft bzw. diskutiert
- keine Daten zu OS, Wirksamkeitsuntersuchung basiert auf PFS und ORR

Bottcher TM et al., 2019 [3]. (AWG 1/ AWG2)

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 RCT 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 ETs in HR+/HER2 MBC regarding efficacy, tolerability and safety.

Methodik

Population: HR+/HER2- MBC

Intervention: everolimus, abemaciclib, ribociclib or palbociclib in combination with ET

Komparator: ET

Endpunkte: OS, PFS, ORR, AE

Recherche/Suchzeitraum: Pubmed search on the 2 November 2017

Qualitätsbewertung der Studien:

randomization of patients (risk of selection bias), blinding (risk of performance bias), lost to follow- up and whether the results were analyzed in accordance with the intention to treat (ITT) principle or per protocol. Additionally, unequal attritions and whether outcomes were assessed by blinded investigators (risk of detection bias)

Ergebnisse

Anzahl eingeschlossener Studien:8 RCTs

- 4 Studies Patients received treatments as first-line metastatic treatment (27-29, 32)
- 2 Studies previously treated for metastatic disease (25, 30)
- 2 Studies: Mixed population (26, 31)

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 (HR for disease progression or death was 0.49; 95% CI 0.32–0.75; one-sided p<.0001) [28], and 30.5 versus 19.3 months (HR 0.65; 95% CI 0.51–0.84; p=.001) [29]. 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)	–	–	10.6[b]	4.1[b]	NR	14.7	20.2	10.2	30.5[b]	19.3[b]	9.5	4.6	22.4[b]	10.2[b]	NR[b]	19.2[b]
(95% CI)			(9.5–NR)	(2.8–5.8)	(19.3–NR)	(13–16.5)	(13.8–27.5)	(5.7–12.6)	(24.7–NR)	(16.4–30.6)	(9.2–11)	(3.5–5.6)				
Med. TTP (mo)	8.6	4.5	–	–	–	–	–	–	–	–	–	–	–	–	–	–
(95% CI)	(6 –14)	(3.6–8.7)														
HR (95% CI;	0.54 (0.36–81;		0.36[b] (0.27–0.47;		0.59[b] (0.43–0.72;		0.49 (0.32–0.75;		0.65[b] (0.51–0.84;		0.46 (0.36–0.59;		0.46[b] (0.36–0.58;		0.51[b] (0.36–0.72;	
p-value)	$p = .0021$)		$p < .001$)		$p = .002$)		one-sided		$p = .001$)		$p < .0001$)		$p < .001$)		$p = .000102$)	
							$p < .0001$)									
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	0.4	40.7	27.5	43	33	42.1	34.7	19	9	35.2	16.1	48.2	34.5
			(4.9–9.7)	(0.0–2.3)	(35.4–46.0)	(22.8–32.3)	(32–54)	(23–45)	(37.5–46.9)	(28.4–41.3)	(15.0–23.6)	(4.9–13.8)	(30.8–39.6)	(11.3–21.0)	(42.8–53.6)	(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 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 HRþ/ 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

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Beith J et al., 2016 [2]. (AWG 1/ AWG2)

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)

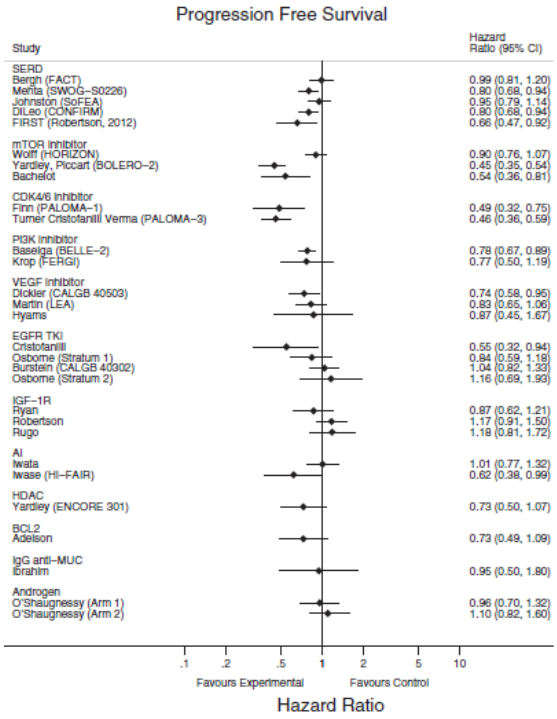
Charakteristika der Population:

- 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 Seconline; 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

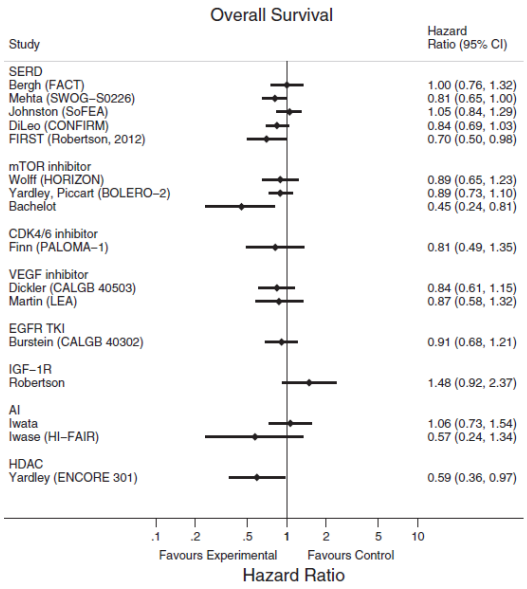
Studienergebnisse (**Anhang 1**: Charakteristik und Studienergebnisse auf Einzelstudienbasis)



- 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

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Patterson-Lomba O et al., 2019 [17]. (AWG 1/ AWG 2)

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:

- Efficacy outcomes: OS, PFS, Time to progression (TTP),ORR
- Safety outcomes: AE, SAE, 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 “Systematic reviews: CRD's guidance for undertaking reviews in health care”

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs

Charakteristika der Studien:

- 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

Characteristics[a]	PALOMA-3*		MONARCH-2		KCSG BR10-04*			MONALEESA-7*	
	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:
  - 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 3 trials, partly due to the former trial being in the first-line setting.
- 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.

TABLE 3 Outcomes in the premenopausal populations

	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
PFS hazard ratio	0.50	NA	0.45	NA	0.61	0.98	NA	0.55	NA
95% CI	(0.29-0.87)	NA	(0.26-0.75)	NA	(0.37-1.00)	(0.62-1.55)	NA	(0.44-0.69)	NA
Median PFS (mo)	9.5	5.6	Not reached	10.5	NR	NR	NR	23.8	13.0
95% CI	NR	NR	NR	NR	NR	NR	NR	(19.2-not reached)	(11.0-16.4)
TTP hazard ratio	NR	NR	NR	NR	NR	NR	NR	NR	NR
95% CI	NR	NR	NR	NR	NR	NR	NR	NR	NR
Median TTP (mo)	NR	NR	NR	NR	16.3	14.5	13.5	NR	NR
95% CI	NR	NR	NR	NR	(7.5-25.1)	(11.0-18.0)	(10.3-16.8)	NR	NR
OS hazard ratio	NR	NR	NR	NR	0.60	0.52	NR	0.92	NA
95% CI	NR	NR	NR	NR	(0.28-1.32)	(0.23-1.19)	NR	(0.6-1.4)	NA
Median OS (mo)	NR	NR	NR	NR	Not reached[b]	Not reached[b]	53.5	Not Reached[b]	29.4
95% CI	NR	NR	NR	NR	NR	NR	NR	NR	(28.2, NE)
ORR, N (%)	18 (25.0)	4 (11.1)	31 (43.1)[d]	8 (19.0)[d]	NR[c]	NR[c]	NR[c]	137 (40.9)	100 (29.7)
CBR, N (%)	50 (69.4)	16 (44.4)	56 (77.8)[d]	29 (69.0)[d]	NR[c]	NR[c]	NR[c]	265 (79.1)	235 (69.7)
Overall AEs, N (%)	71 (98.6)	35 (97.2)	70 (98.6)	40 (95.2)	NR	NR	NR	329 (98.2)	317 (94.1)
Overall SAEs, N (%)	10 (14.1)	7 (19.4)	8 (11.3)	2 (4.8)	NR	NR	NR	60 (17.9)	39 (11.6)
Discontinuation due to AE, N (%)	4 (5.6)	0 (0.0)	4 (5.6)	0 (0.0)	NR	NR	NR	21 (6.3)	12 (3.6)
All-cause discontinuation, N (%)	NR	NR	NR	NR	NR	NR	NR	161 (48.1)	216 (64.1)
EORTC QLQ-C30 hazard ratio	NR	NR	NR	NR	NR	NR	NR	0.7[e]	NA[e]
EORTC QLQ-B23 hazard ratio	NR	NR	NR	NR	NR	NR	NR	0.68[e]	NA[e]
FACT-B hazard ratio	NR	NR	NR	NR	NR	NR	NR	NR	NR
EQ-5D	NR	NR	NR	NR	NR	NR	NR	0.68[e]	NA[e]

Abbreviation(s): AE, adverse event; CBR, clinical benefit rate; GnRHa, gonadotropin-releasing hormone agonist (eg, goserelin); NA, not applicable; NE, not estimable; NR, not reported; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SAE, serious AE; TTP, time to progression.
[a]Sample size and outcomes correspond to the pre- or peri-menopausal population.
[b]Median OS was not reached.
[c]The poster has information for partial response and stable response, but not for complete response. Therefore we cannot derive ORR and CBR values.
[d]The reported ORR and CBR values pertain to the ITT population.

- No NMA conducted due to lack of clinical similarity of the studies (different endocrine therapies, first-line vs second line setting)

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)
- Zu OS und PRO wenig Daten verfügbar

3.4 Leitlinien

AWMF, 2017 [13].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.2, 08.2019 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 SR 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 identifizierten 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 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).

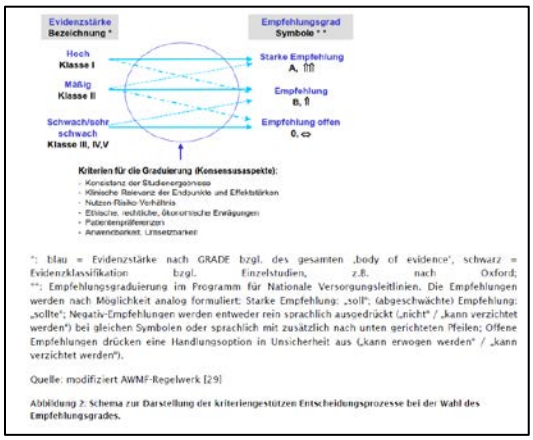
  GoR:

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 zum lokal fortgeschrittenen Mammakarzinom:

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

Empfehlungen zum lokal fortgeschrittenen Mammakarzinom:

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.

5.15.	Evidenzbasierte Empfehlung
	Ovarialsuppression und Tamoxifen bei prämenopausalen Patientinnen
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 CDK 4/6 Inhibitoren kombiniert werden.
Level of Evidence 1b	Quellen: [29, 989, 1006, 1007]
	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

5.16.	Evidenz- /konsensbasierte Empfehlung
	Weitere Therapien bei prämenopausalen Patientinnen
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, 1008, 1009]
	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
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.
1009. Loibl, S., et al., Palbociclib (PAL) in combination with fulvestrant (F) in pre-/peri-menopausal (PreM) women with metastatic breast cancer (MBC) and prior progression on endocrine therapy–results from Paloma-3. J Clin Oncol, 2016. 34(suppl): p. abstr 524.

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 Aromata-sehemmer 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

5.4.2. Chemotherapie des metastasierten Mammakarzinoms

5.21.	Konsensbasierte Empfehlung
	Kriterien vor einer Chemotherapie
EK	Vor Durchführung einer Chemotherapie sollen der Allgemeinzustand und die Komorbidität, die Vortherapien der Patientin erhoben und die Compliance abgeschätzt werden.
	Starker Konsens

5.22.	Konsensbasierte Empfehlung
	Toxizitätsbeurteilung
EK	Während der Therapie soll eine regelmäßige Toxizitätsbeurteilung (subjektiv und objektiv) erfolgen. Die Dosierung soll ebenso wie die angestrebten Zeitintervalle gemäß generell akzeptiertem Standard- bzw. aktuell publizierter Therapieregime erfolgen. Nach Bestimmung eines geeigneten und repräsentativen Messparameters (Symptome, Tumormarker, Bildgebung) vor Therapiebeginn soll eine Evaluation des Therapieeffektes mindestens alle 6–12 Wochen entsprechend der klinischen Erfordernisse erfolgen. Im Verlauf können bei anhaltender Remission und guter klinischer und laborchemischer Beurteilbarkeit des Erkrankungsstatus die bildgebenden Intervalle verlängert werden.
	Starker Konsens

5.23.	Konsensbasierte Empfehlung
	Modifikation der Chemotherapie
EK	Eine Unterbrechung der Therapie sollte bei klinisch relevanter Progression oder nicht tolerabler Toxizität erfolgen. Ein Wechsel auf eine andere Chemotherapie sollte ohne nachgewiesene Progression oder ohne nicht tolerable Toxizität nicht erfolgen.
	Starker Konsens

5.24.	Evidenzbasierte Empfehlungen
	Polychemotherapie/Kombinationstherapie
Empfehlungsgrad B	a.) Bei Indikation zu einer Chemotherapie sollten Patientinnen ohne hohen Remissionsdruck eine sequentielle Chemotherapie erhalten.
Level of Evidence 1a	De novo-Recherche: [1033, 1034]
	Starker Konsens
Empfehlungsgrad 0	b.) Die Kombinationstherapie aus Chemotherapie und Bevacizumab kann in der Erstlinientherapie das progressionsfreie Überleben verbessern, allerdings mit erhöhter Nebenwirkungsrate und ohne Einfluss auf das Gesamtüberleben.
Level of Evidence 1a	Quellen: [1035, 1036] [1037-1040]
	Starker Konsens
Empfehlungsgrad 0	c.) Bei stärkeren Beschwerden und raschem Wachstum bzw. aggressivem Tumorverhalten, d.h. bei hohem Remissionsdruck, kann eine Polychemotherapie oder eine Chemotherapie + Bevacizumab durchgeführt werden.
Level of Evidence 1a	Quellen: [1004], [1033]
	Starker Konsens

Quellen:

1004. Carrick, S., et al., Single agent versus combination chemotherapy for metastatic breast cancer. 51 Cochrane Database Syst Rev, 2005(2): p. Cd003372.
1033. Dear, R.F., et al., Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev, 2013(12): p. Cd008792.
1034. Sledge, G.W., et al., Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). J Clin Oncol, 2003. 21(4): p. 588-92.
1035. Miller, K., et al., Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med, 2007. 357(26): p. 2666-76.
1036. Gray, R., et al., Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol, 2009. 27(30): p. 4966-72.
1037. Robert, N.J., et al., RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2–negative, locally recurrent or metastatic breast cancer. Journal of Clinical Oncology, 2011. 29(10): p. 1252-1260.
1038. Welt, A., et al., Capecitabine and bevacizumab with or without vinorelbine in first-line treatment of HER2/neu-negative metastatic or locally advanced breast cancer: final efficacy and safety data of the randomised, open-label superiority phase 3 CARIN trial. Breast Cancer Res Treat, 2016. 156(1): p. 97-107.
1039. Lang, I., et al., Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer: interim efficacy results of the randomised, open-label, non-inferiority, phase 3 TURANDOT trial. Lancet Oncol, 2013. 14(2): p. 125-33.
1040. Zielinski, C., et al., Bevacizumab plus paclitaxel versus bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer (TURANDOT): primary endpoint results of a randomised, open-label, non-inferiority, phase 3 trial. Lancet Oncol, 2016. 17(9): p. 1230-9.
1041. Ghersi, D., et al., Taxane-containing regimens for metastatic breast cancer. Cochrane Database Syst Rev, 2015(6): p. Cd003366

Hintergrund:

keine einheitliche Therapiestrategieempfehlung aufgrund der Heterogenität der Metastasen und der individuellen Krankheitsverläufe

- Cochrane Review von Dear et al. 2013:
  - o keine signifikanten Unterschiede im Gesamtüberleben und progressionsfreien Überleben zwischen Kombinationstherapie und einer sequentiellen Monochemotherapie (OS HR 1,04 95% CI 0,93-1,16; p=0,45 / PFS HR1,11 95% CI 0,99-1,25; p=0,08).

- o signifikant höheres Ansprechen durch Kombi-Chemotherapie
- o höhere Toxizität durch Kombinationschemotherapie (febrile Neutropenien)
- o viele v.a. nicht hämatologische Nebenwirkungen in dieser Metaanalyse nicht beschrieben.
- o In CR betrachtete Szenarien einer sequentiellen Monochemotherapie: a) Wechsel der Monochemotherapie bei Progression oder b) festgelegter Wechsel der Monochemotherapien ohne Progression nach einigen Zyklen; Ergebnisse für beide Szenarien ähnlich

Ergebnisse dieser Metaanalyse unterstützen Empfehlungen einer sequentiellen Monotherapie im Vergleich zu einer Kombinationschemotherapie bis auf die Fälle mit schneller Tumorprogression und hohem Remissionsdruck.

Hat die Patientin in der adjuvanten Therapie noch keine Anthrazykline/Taxane erhalten, so können diese primär eingesetzt werden.

- Cochrane Review von Ghersi et al. 2015: Taxan-haltige Chemotherapien
  - o Verbesserung des PFS und Gesamtüberleben sowie Tumoransprechen
  - o Erhöhung des Risiko für Neuropathie und verringern Risiko für Übelkeit und Erbrechen im Vergleich zu nicht-Taxan-haltigen Regimen

Bevacizumab beim metastasierten Mammakarzinom (1. Linie)

- Paclitaxel plus Bevacizumab vs. Paclitaxel-Monotherapie: Phase-3-Studie (E2100) [1035, 1036].
  - o Verdopplung der ORR (unabhängig des Hormonrezeptorstatus)
  - o Sig. Verlängerung des PFS
  - o OS: n.s. (median: 26.7 vs. 25.2 Monate; HR 0.88; p=0.16)
  - o UE signifikant erhöht
- Capecitabin plus Bevacizumab (3 Phase-3-Studien) [1037-1039].

Zusammenfassend zeigten sich in der Bevacizumab –Kombination erhöhte Remissionsraten und verbesserte PFS (allerdings ohne OS-Vorteil).

5.25.	Konsensbasierte Empfehlung
	Monotherapie
EK	Als Monotherapie können z. B. folgende Substanzen zum Einsatz kommen: Alkylanzien, Anthrachinone, Anthrazykline (auch in liposomaler Form), Eribulin, Fluorpyrimidine, Platinkomplexe, Taxane, und Vinorelbin. Bei einer Polychemotherapie können diese Substanzen untereinander bzw. mit weiteren Substanzen kombiniert werden. Es sollten allerdings nur in Studien überprüfte Kombinationen eingesetzt werden.
	Starker Konsens

Rugo HS et al., 2016 [20].

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 3
- 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 4 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)

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

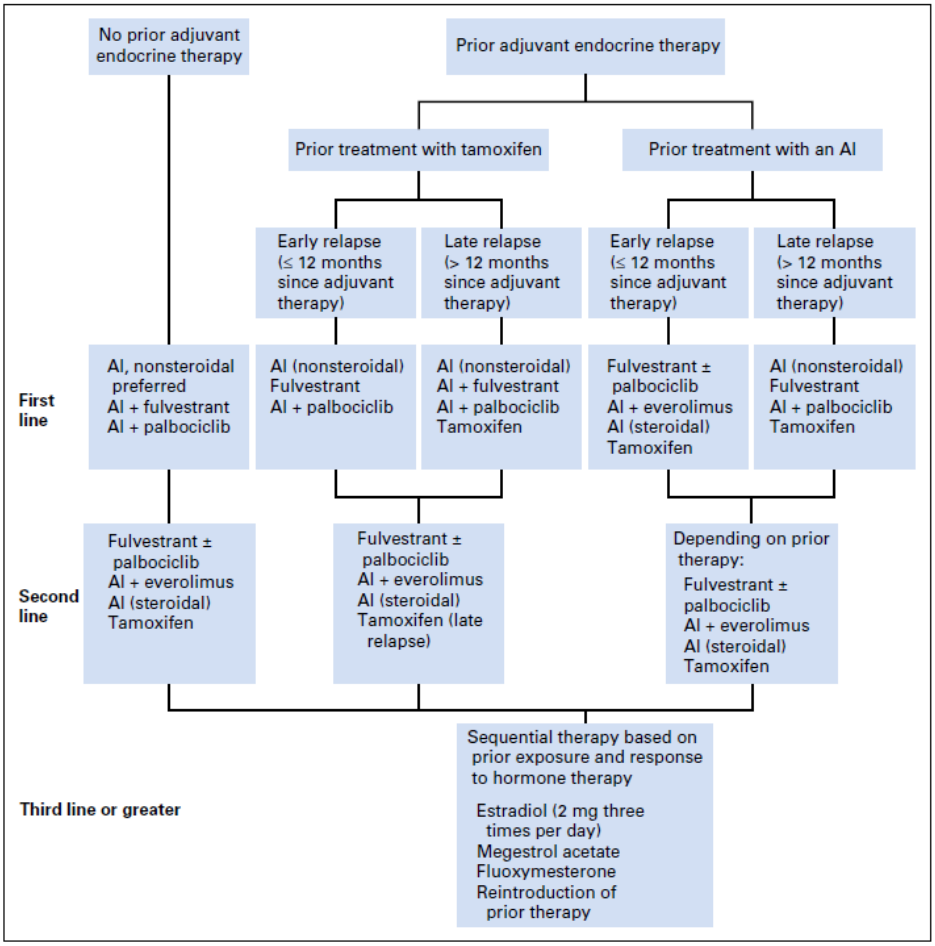


Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered 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

Premenopausal women

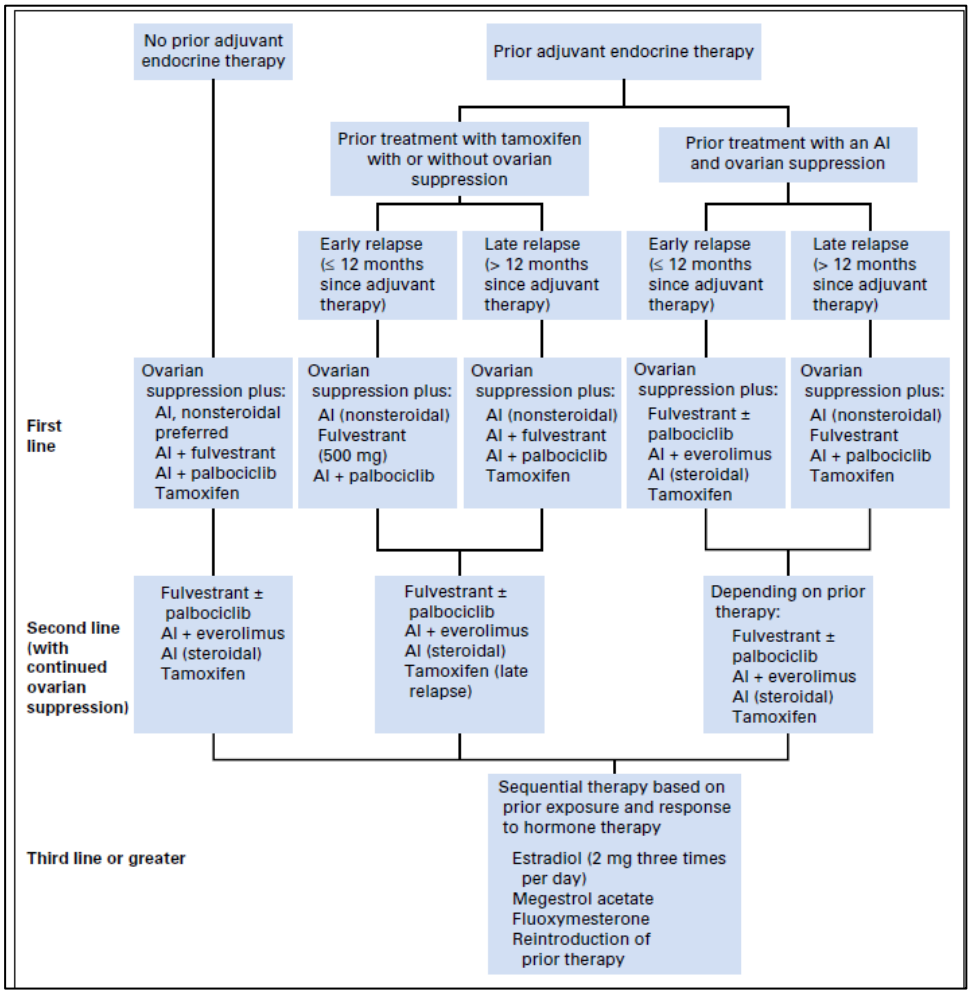


Fig 2. Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered 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.

NICE, 2009 [16].

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.

Chemotherapy

Recommendation

1.3.8 On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy. [2009]

Qualifying statement: These recommendations are based on limited randomised trial evidence and GDG consensus

1.3.9 Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. [2009]

Qualifying statement: This recommendation is based on randomised trial evidence confirming increased response rate and toxicity from combination chemotherapy and uncertainty over overall survival benefit compared with sequential single agent chemotherapy.

Clinical evidence

Combination versus sequential chemotherapy

Evidence for comparing single chemotherapy with sequential chemotherapy comprised five RCTs (Creech et al. 1979; Chlebowski et al. 1979; Sledge et al. 2003; Smalley et al. 1976 and Baker et al. 1974) and one observational study (Chlebowski et al. 1989). The older studies were not always very stringently reported. Two small, poor quality trials (Baker et al. 1974 and Creech et al. 1979) found no significant difference in tumour response, response duration, time to progression or overall survival when chemotherapy agents were given together or sequentially (on disease progression).

Two other studies (Chlebowski et al. 1979 and Smalley et al. 1976) and a retrospective analysis of their data (Chlebowski et al. 1989) showed that whilst combined therapy resulted in superior tumour response and apparently significantly longer median overall survival, follow-up revealed that long term survival was no different between study arms.

One large RCT (Sledge et al. 2003) demonstrated that combining anthracycline and taxane, rather than giving the drugs sequentially in either order, resulted in a better tumour response and superior time to progression but did not improve median overall survival.

Consistently, adverse events due to combined therapy were reported as being more numerous or of greater severity than those experienced with single agents.

Combined versus single chemotherapy regimes

Evidence for comparing single chemotherapy with combined chemotherapy comprised one very high quality systematic review (n > 7,000 study participants) (Carrick et al. 2005) a more modest systematic review (Takeda et al. 2007) three RCTs (Eijertsen et al. 2004; Pacilio et al. 2006 and Martin et al. 2007) and two post-study papers published from the pivotal trial by O'Shaughnessy et al. 2002 (Leonard et al. 2006 and Miles et al. 2004).

Good evidence suggests that the relative risk of death was significantly reduced for patients given combined chemotherapy agents compared with single drugs as first- or second-line treatment. The advantage was greatest for combinations which did not include their comparator. Combined therapies containing anthracyclines or alkylating agents were significantly better at reducing the relative risk of death whereas taxanes did not improve survival as part of a combined therapy.

RCT evidence from three trials showed that first-line treatment with combined therapies including an anthracycline and/or taxane compared with the same anthracycline or taxane, provided no survival advantages but were associated with higher levels of adverse events.

Quality of life outcomes were equivocal. Similarly, a small RCT compared second-line (or higher) combined therapy of vinorelbine and gemcitabine with vinorelbine alone and reported no significant difference in overall survival between arms but more adverse events with combined therapy. In contrast, a post-study analyses of long term patient outcomes from a trial of capecitabine (CAP) and docetaxel (DOC) vs DOC alone showed that either combined or sequential therapy with the two agents was significantly better in terms of survival than receiving DOC alone.

Although considerable data were published within systematic reviews about comparison of adverse events and quality of life between combined and single agent regimes the findings were equivocal across studies

Hinweis: Die folgende Empfehlung zur Therapiesequenz basiert auf gesundheitsökonomischer Evidenz (siehe qualifying statement):

1.3.10 For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine (whichever was not used as secondline treatment). [2009]

Qualifying statement: This recommendation was based on the findings of a health economic analysis that compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens, for patients who are anthracycline resistant or for whom anthracycline therapy is contraindicated….

Clinical evidence

Vinorelbine

The level of evidence on the use of vinorelbine (VIN) as a monotherapy or in combination with other agents is generally of very poor quality consisting mainly of low patient number, non-comparative phase II trials or small RCTs.

Vinorelbine monotherapy

One small, statistically underpowered RCT (Pajk et al. 2008) compared VIN with capecitabine (CAP) in a small number of heavily pre-treated women and reported no significant difference in response or survival outcomes but more adverse events (particularly neutro-penia) in the VIN group. Two poor quality phase II studies evaluated VIN for women with metastatic disease (Udom et al. 2000 and Zelek et al. 2001) finding that as second- or thirdline treatment response rates of up to 41%, response duration of 4 months and time to progression of ~2.75 months were reported.

Vinorelbine combined therapy

Two poor to moderate quality RCTs tested VIN in combination with 5'-fluorouracil (5´-FU) vs docetaxel (DOC) (Bonneterre et al. 2002) or gemcitabine (GEM) vs VIN (Martin et al. 2007). VIN and 5´-FU combined resulted in similar treatment outcomes as DOC monotherapy but with a higher incidence of neutropenia. VIN and GEM resulted in superior progression-free survival, but not significantly different overall survival or response duration, compared with VIN alone. Thirteen poor to moderate quality phase II, non-comparative, studies described VIN combined with: trastuzumab (TRZ) (Burstein et al. 2003; Chan et al. 2006; Jahanzeb et al. 2002; Bartsch et al. 2007; De Maio et al. 2007 and Catania et al. 2007b), CAP (Ghosn et al. 2006 and Davis 2007), DOC (Mayordomo et al. 2004), GEM (Ardavanis et al. 2007 and Colomer et al. 2006), 5'-FU (Stuart 2008), mitozantrone (Onyenadum et al. 2007), cisplatin followed by DOC (Shamseddine et al. 2006) and CAP followed by DOC (Ghosn et al. 2008). For all phase II combination studies, the overall tumour response rates ranged from 33-75%, median overall survival from 13-35.8 months, median response duration from 2.6-17.5 months, median time to progression (reported in two studies) from 6.6-8.6 months and median progression-free survival (reported in two studies) from 9.6-9.9 months. The most commonly reported adverse events attributed to VIN were neutropenia, nausea and vomiting and alopecia.

Taxanes

There was good quality evidence on the use of taxanes as first- or second-line monotherapy or in combination, comprising a high quality Cancer Care Ontario guideline (Verma et al. 2003), two good systematic reviews (Ghersi et al. 2005 and Bria et al. 2005) and four RCTs (Lin et al. 2007; Cassier et al.2008; Bontenbal et al.2005 and Jones et al. 2005). The total patient number exceeded 15,000.

Anthracycline naïve women did not derive any benefit from paclitaxel (PAC) as first line monotherapy compared with controls. A large systematic review (Verma et al. 2003) found that for anthracycline naïve patients, when taxanes were added to anthracycline based regimes, there were no significant differences in time to progression (TTP) or overall survival (OS) but tumour response was significantly improved. However, PAC and doxorubicin (DOX) combined therapy resulted in superior median OS and TTP compared with 5´-FU, DOX and cyclophosphamide (FAC) combined. There was no evidence to suggest a significant difference in quality of life between DOC and PAC when either was combined with anthracycline as first-line therapy. One moderate RCT (Bontenbal et al.2005) demonstrated that DOX and DOC combined therapy in first line treatment of advanced disease resulted in superior tumour response and clinical benefit, when

compared with FAC. Time to event analyses also showed significant reductions in the risk of death and time to progression with AT therapy compared to FAC but there were more reports of febrile neutropenia with FAC.

Meta-analysis demonstrated significant improvements in TTP, tumour response and time to treatment failure in favour of taxane containing regimes compared with non-taxane containing regimes and a borderline advantage in OS. However, statistical significance for OS and TTP was lost when only first-line therapy with taxanes was considered. Taxanes and taxane-containing regimes were reported to have a higher incidence of neurotoxicity and leukopenia but fewer cases of nausea and vomiting than controls.

PAC monotherapy was preferable to mitomycin in terms of TTP but not other outcomes. DOC monotherapy correlated with improved OS (compared with combined mitomycin and vinblastine) and improved TTP and tumour response compared with several other multi-agent therapies. Good RCT data (Jones et al. 2005) demonstrated a significant advantage in OS, TTP and response duration for patients on DOC versus PAC monotherapy although the tumour responses were similar. Another RCT (Cassier et al. 2008) found no significant differences in efficacy or survival outcomes between PAC and DOC as first-line therapy combined with DOX then given as monotherapy

1.3.11 Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate[4]. [2009]

Qualifying statement: This recommendation is from ‘Gemcitabine for the treatment of metastatic breast cancer’, NICE technology appraisal guidance 116 (2007). It was formulated by the technology appraisal and not by the guideline developers It has been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendation can be found at www.nice.org.uk/TA116.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2019) am 02.09.2019

#	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	(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 Sep 2014 to present

Systematic Reviews in Medline (PubMed) am 02.09.2019

#	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 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]))
8	#3 OR #7
9	(#8) 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 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]))))))
10	((#9) AND ("2014/09/01"[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 02.09.2019

#	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 ("2014/09/01"[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

1. Beith et al. 2016

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. Characteristics of RCTs included in the meta-analysis Messina C et al., 2018

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* = 0·13 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

Gemeinsamer Bundesausschuss

3. 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.

4. Rugo et al. 2016

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.