Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-072 Palbociclib

Stand: Juni 2018

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

Palbociclib
[zur Behandlung des HR-positiven, HER2-negativen, metastasierten Mammakarzinoms nach endokriner Vortherapie]

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 Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet* Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung: • für das HER2/neu-positive Mammakarzinom • für die initiale endokrin-basierte Therapie
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Operative Resektion • Strahlentherapie • Ovariektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen.	Beschlüsse über die Nutzenbewertungen nach § 35a SGB V: • Palbociclib: Beschluss vom 18. Mai 2017 • Eribulin: Beschluss vom 22. Januar 2015
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:	
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 (zu prüfendes Anwendungsgebiet) Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinizing Hormone-Releasing Hormone) kombiniert werden.
Antiestrogene:	
Tamoxifen L02BA01 Nolvadex®	• Adjuvante Therapie nach Primärbehandlung des Mammakarzinoms. • Metastasierendes Mammakarzinom.
Fulvestrant L02BA03 Faslodex®	Faslodex ist angezeigt 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.
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.

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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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 (zu prüfendes Anwendungsgebiet) Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinizing Hormone-Releasing Hormone) kombiniert werden.
Antikörper	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Paclitaxel zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet. Zu weiteren Informationen wie auch zum humanen epidermalen Wachstumsfaktor-Rezeptor 2 (HER2)-Status siehe Abschnitt 5.1. 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. Zu weiteren Informationen wie auch zum HER2-Status siehe Ab schnitt 5.1.

Zytostatika:	
Cyclophosphamid 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®, Myocet®	Caelyx® ist indiziert: Als Monotherapie bei Patientinnen mit metastasierendem Mammakarzinom mit erhöhtem kardialen Risiko. Myocet® in Kombination mit Cyclophosphamid wird angewendet bei der First-line-Behandlung von metastasiertem Brustkrebs bei erwachsenen Frauen.
Epirubicin L01DB03 Riboepi®	• Mammakarzinom

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

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.
Vindesin L01CA03 Eldisine®	Eindeutiges Ansprechen wurde auch bei folgenden Erkrankungen erzielt, jedoch liegen hierfür erst geringere Erfahrungen vor: […] - 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

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-072 (Palbociclib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. Mai 2018

Gemeinsamer Bundesausschuss, Berlin 2018

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABC/MBC	advanced/metastatic breast cancer
AI	Aromatase-Inhibitoren
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CR	Complete Response
DAHTA	DAHTA Datenbank
ER	Östrogen Rezeptor
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HER	humaner epidermaler Wachstumsfaktor-Rezeptor-2
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PD	Pathomorphologische Diagnostik
PFS	Progresion free survival
QoL	Quality of Life
RCT	Randomisierte kontrollierte Studie
RFI	Rezidivfreies Intervall
RR	Relatives Risiko
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse event
TAM	Tamoxifen

TOR	Toremifen
TRIP	Turn Research into Practice Database
TTF	Time to Failure
TTP	Time to Progression
VEGF	Vascular-endothelial-growth-factor
WHO	World Health Organization

1 Indikation

Zur Behandlung des Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor 2 (HER2)-negativen lokal fortgeschrittenen oder metastasierten Brustkrebs nach vorausgeganger endokriner Therapie

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Brustkrebs* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 20.04.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, 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 2943 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 22 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Hinweis: „Für das vorliegende Anwendungsgebiet wird davon ausgegangen, dass eine weitere endokrine Therapie für die Patientinnen angezeigt ist und keine Indikation für eine Chemotherapie besteht.“

3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2017 [4].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Palbociclib; vom 18. Mai 2017

Siehe auch IQWiG, 2017 [8,10].

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.

Zweckmäßige Vergleichstherapie

a1) Postmenopausale Patientinnen in Erstlinientherapie: Anastrozol oder Letrozol oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind.

a2) Prä-/perimenopausale Patientinnen in Erstlinientherapie: Tamoxifen in Kombination mit einer Ausschaltung der Ovarialfunktion.

b1) Postmenopausale Patientinnen mit Progression nach einer vorange-gangenen endokrinen Therapie: 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.

b2) Prä-/perimenopausale Patientinnen mit Progression nach einer vorangegangenen endokrinen Therapie: Eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligen Zulassung.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a1) Ein Zusatznutzen ist nicht belegt.

a2) Ein Zusatznutzen ist nicht belegt.

b1) Ein Zusatznutzen ist nicht belegt.

b2) Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [6,7].

Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von Strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V: in der Fassung vom 16. Februar 2012; veröffentlicht im Bundesanzeiger (BAnz AT 18. Juli 2012 B3); in Kraft getreten am 19. Juli 2012; zuletzt geändert am 21. Juli 2016; veröffentlicht im Bundesanzeiger (BAnz AT 14. Oktober 2016 B3); in Kraft getreten am 1. Januar 2017

Siehe auch IQWiG, 2014 [11].

Fazit / Ausmaß des Zusatznutzens / Ergebnis

1.4.4 Systemische adjuvante Therapie (endokrine Therapie, Chemotherapie und Antikörpertherapie)

Die Entscheidung über die Notwendigkeit und Art einer adjuvanten Therapie berücksichtigt die Tumorgröße, den Lymphknotenstatus, das Grading, den Hormonrezeptorstatus, den HER2/neu-Status, den Menopausenstatus, weitere Erkrankungen und das Alter als wichtigste Faktoren zur Risikoeinstufung.

Jede Patientin mit positivem Hormonrezeptorstatus soll eine endokrine Therapie erhalten.

Bei Patientinnen mit erhöhtem Risiko und rezeptornegativem Befund sollte eine Chemotherapie in Betracht gezogen werden. Bei Patientinnen mit erhöhtem Risiko und rezeptorpositivem Befund ist entweder die alleinige endokrine Therapie oder die Kombination von Chemotherapie mit endokriner Therapie zu erwägen. Bei Patientinnen mit HER2/neu positiven Tumoren (ab Stadium pT1c und/oder LK Befall) soll eine Behandlung mit Trastuzumab erfolgen.

1.4.5 Primär systemische/neoadjuvante Therapie

Zur Therapieauswahl der primär systemischen Therapie sind die gleichen klinischen und pathomorphologischen Befunde zu erheben (klinische Tumor-größe und Lymphknotenstatus, Grading, Hormonrezeptorstatus, HER2/neu-Status, Menopausenstatus, weitere Erkrankungen und das Alter) wie bei der adjuvanten Therapie. Der Effekt der primär systemischen Therapie ist regelmäßig zu überwachen.

1.4.6.2 Lokal fortgeschrittener Brustkrebs

Essentielle Bestandteile der Therapie des inflammatorischen und/oder primär inoperablen Brustkrebses sind die systemische Therapie, Sekundäroperation und die Strahlentherapie. Die therapeutische Sequenz wird durch die individuellen Gegebenheiten festgelegt.

1.6.1.1 Therapie des Lokalrezidivs

Die Therapie intramammärer Rezidive besteht in der Regel in einer operativen Intervention. Die Mastektomie erzielt hierbei die beste Tumorkontrolle. Ein Thoraxwandrezidiv ist nach Möglichkeit operativ vollständig zu entfernen.

Bei lokoregionärem Rezidiv nach Mastektomie sollte eine postoperative Bestrahlung durchgeführt werden, sofern es auf Grund der bisherigen Strahlenbelastung vertretbar ist. Darüber hinaus soll ergänzend die Notwendigkeit und Möglichkeit zusätzlicher Behandlungen (systemische endokrine und/oder chemotherapeutische Behandlungsverfahren) geprüft werden.

1.6.1.2 Therapie bei metastasierten Erkrankungen

Bei nachgewiesenen Fernmetastasen steht die Lebensqualität der betroffenen Patientin im Vordergrund der therapeutischen Maßnahmen. Diese haben sich darauf auszurichten, eine

Lebensverlängerung unter möglichst langem Erhalt der körperlichen Leistungsfähigkeit, einer akzeptablen Lebensqualität und Linderung tumorbedingter Beschwerden zu erreichen. Die individualisierte Therapiestrategie hat die krankheitsspezifischen Risikofaktoren (viszerale Metastasierung, Knochenmetastasierung, Hirnmetastasierung) sowie die persönliche Situation der Patientin zu beachten. Zur Therapie einer Fernmetastasierung kommen in Abhängigkeit von der individuellen Befundkonstellation medikamentöse, strahlentherapeutische und operative Maßnahmen allein oder in Kombination zum Einsatz. Eine endokrine Therapie ist bei positivem Hormonrezeptorstatus zu empfehlen.

Eine Chemotherapie sollte unter Berücksichtigung der individuellen Risiko-situation und des Therapieziels in Erwägung gezogen werden, insb. bei negativem Rezeptorstatus, Resistenz auf eine endokrine Therapie, schnell progredientem Verlauf, viszeralem Befall und/oder erheblichen Beschwerden. In diesen Situationen kann eine Chemotherapie trotz ihrer Nebenwirkungen die Lebensqualität erhöhen.

G-BA, 2010 [5].

Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie: Anlage VI – Off-Label-Use; Gemcitabin in der Monotherapie beim Mammakarzinom d. Frau vom 20. Mai 2010

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Die Anlage VI wird im Teil B (Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off -Label -Use) nicht verordnungsfähig sind) wie folgt ergänzt: „IV. Gemcitabin in der Monotherapie beim Mammakarzinom der Frau“

IQWiG, 2016 [9].

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Fortgeschrittenes Mammakarzinom

Erstlinientherapie

Für die Erstlinientherapie des fortgeschrittenen Mammakarzinoms sind die Wirkstoffe Anastrozol und Letrozol zugelassen. Für beide Wirkstoffe zeigen die vorliegenden Daten keinen Anhaltspunkt für einen Zusatznutzen gegenüber einer Tamoxifenbehandlung.

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 Zweit-linientherapie 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.

Die Protonentherapie bei der Indikation Mammakarzinom erfüllt derzeit weder alleine noch in Kombination mit einer anderen Therapie die Kriterien des §137 c SGB V (ausreichend, zweckmäßig, wirtschaftlich) und ist damit nicht Leistung im Rahmen der gesetzlichen Krankenversicherung.

3.2 Cochrane Reviews

Lee C et al., 2017 [12].

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).

Endpunkt:

- 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 erfolgte am 7.7.2015
- Cochrane Central Register of Controlled Trials (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 Chi2 test and I2 statistic

- Assessment of the quality of the available evidence by GRADE approach (’Summary of findings’ tables)

Ergebnisse

Anzahl eingeschlossener Studien:

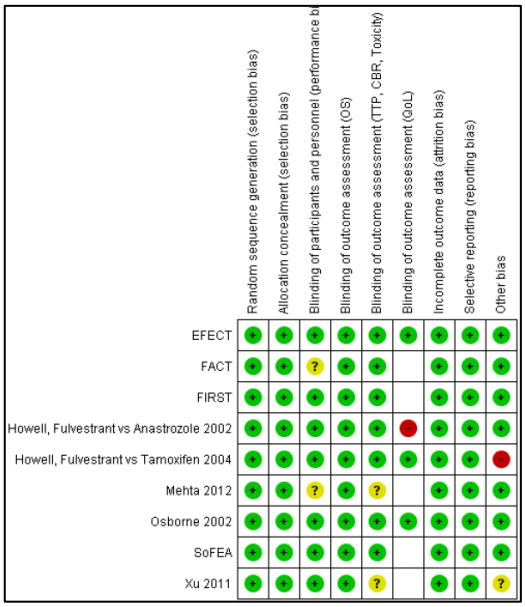
- N=9 (n=4514)

Charakteristika der Population:

- All participants included in the review were **postmenopausal women** with hormone-sensitive breast cancer
- 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
- Four studies included only those 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 treatment for metastatic disease (EFECT; Howell, Fulvestrant vs Anastrozole 2002; Osborne 2002; SoFEA; Xu 2011) → second-line endocrine or more.

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; I2 = 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 (no significant differences):

- 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 (no significant differences):

- 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 that was assessed with 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 (im CR nicht nach first- und secondline differenziert)

- Assessment of three most common toxicities: vasomotor, arthralgia, and gynaecological toxicities.
- Although there was some variation between the individual trials in the three examined toxicities, overall summary statistics were not significantly different between fulvestrant and the comparator drugs.
  - vasomotor toxicity: RR 1.02, 95% CI 0.89 to 1.18; 8 trials, 3544 women; I2 =55%, high-quality evidence,
  - arthralgia: RR 0.96, 95%CI 0.86 to 1.09; 7 trials, 3244 women; I2= 59%; P = 0.02; high-quality evidence
  - Gynaecological toxicity included urinary tract infection, vulvovaginal dryness, vaginal haemorrhage, vaginitis, and pelvic pain: RR 1.22, 95% CI 0.94 to 1.57; 2848 women; I2= 66%; P=0.01; high-quality evidence

Anmerkung/Fazit der Autoren

As evidenced from our pooled data from 4514 women examined in our review, 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

3.3 Systematische Reviews

Wilson FR et al., 2017 [22].

Systematic review and network meta-analysis comparing Palbociclib with chemotherapy agents for the treatment of postmenopausal women with HR-positive and HER2-negative advanced/metastatic breast cancer (ABC).

Fragestellung

Here, we report the results of a systematic literature review (SLR) and network meta-analysis (NMA) that evaluates the efficacy of palbociclib + letrozole and palbociclib + fulvestrant versus chemotherapy agents in postmenopausal women with HR+/HER2- ABC/ MBC who had no prior systemic treatment for advanced disease (first line) or whose disease had progressed after prior endocrine therapy or chemotherapy (second line).

Methodik

Population:

- Postmenopausal women with HR+/HER2- ABC/MBC receiving first- or second-line therapy for their disease.

Intervention:

- First-line: Palbociclib 125 mg daily (3 weeks on and 1 week off) + Letrozole 2.5 mg daily
- Second-line: Palbociclib 125 mg daily (3 weeks on and 1 week off) + Fulvestrant 500 mg (every 14 days for first 3 injections, then every 28 days)

Komperator:

- Endocrine-based therapies, chemotherapy agents, and/or chemotherapy agents + biological therapies:
  - First-line: anastrozole, bevacizumab, capecitabine, carboplatin*, cyclophosphamide, docetaxel, epirubicin, everolimus, exemestane, fluorouracil, gemcitabine, letrozole, liposomal doxorubicin, megestrol acetate*, methotrexate, mitoxantrone*, paclitaxel*, sunitinib, tamoxifen, vinorelbine
  - Second-line: aminoglutethimide, anastrozole, bevacizumab, capecitabine, carboplatin, corticosteroid, cyclophosphamide, docetaxel, doxorubicin, epirubicin, everolimus, exemestane, fluorouracil, fulvestrant, gemcitabine, ixabepilone, letrozole, megestrol acetate, methotrexate, mitoxantrone, motesanib, nab-paclitaxel, paclitaxel, pegylated liposomal doxorubicin, sorafenib, sunitinib, vinorelbine
  - Bendamustine hydrochloride, mutamycin, and vandetanib were also considered as comparators, but did not end up being included in final evidence networks
  - Any combination of the above therapies

Endpunkt:

- PFS, TTP

Recherche/Suchzeitraum:

- Systematische Recherche nach RCTs published from January 2000 to January 2016.

- All references used in two previous NMAs by Generali et al. and Chirila et al. formed the starting point for the current systematic review.
- Literature search was conducted in January 2015 with no date restrictions. An updated literature search was performed by searchingMEDLINE, EMBASE, CochraneCENTRAL, and PubMed from May 2014 (search date of Generali) to January 2016 to identify RCTs that were published since the aforementioned two reviews.

Qualitätsbewertung der Studien:

- Quality assessment for all studies was conducted using the checklist provided in the National Institute for Health and Care Excellence (NICE) single technology appraisal template

Methodik NMA

- Bayesian NMAs and pairwise meta-analyses were conducted to pool RCT results using well-established methods outlined by the NICE
- first line of therapy was defined as having neither previous systemic endocrine therapy nor chemotherapy for ABC/MBC, and
- second line of therapy was defined as having previous systemic endocrine therapy or chemotherapy for ABC/MBC.
- study and patient characteristics were assessed to ensure similarity and to investigate the potential impact of heterogeneity on effect estimates.
- Sensitivity analyses were conducted to include both the palbociclib phase 2 and 3 studies, and to adjust for heterogeneity in median PFS/TTP values.
- NMA results were qualitatively compared with pairwise estimates generated from traditional frequentist meta-analyses of direct evidence. Inconsistency in the networks was assessed by comparing deviance and deviance information criterion (DIC) statistics in fitted consistency and inconsistency models

Ergebnisse

Anzahl eingeschlossener Studien:

- Sixty RCTs met eligibility criteria and were stratified by line of therapy (57 von 60 RCTs wurden in die NMA eingeschlossen)

Charakteristika der Population:

- percentage of HR+ patients was reported in 56 of the 57 trials and ranged from about 15 to 100%, and the proportion of patients receiving prior metastatic endocrine therapy or chemotherapy ranged from 0 to 100%.
- Based on this high level of heterogeneity, trials were stratified by line of therapy based on prior neoadjuvant/adjuvant and advanced/metastatic therapy received by patients
- Firstline: 22 studies were included that enrolled a total of 8152 patients
- Secondline: 44 studies were included that enrolled a total of 14,708 patients
- head-to-head trials were available for 45 of the pairwise comparisons in the network, with single studies informing 35 of these comparisons.

Qualität der Studien:

- the studies included in the NMA had a low risk of bias

Studienergebnisse (secondline):

- palbociclib + fulvestrant → showed statistically significant improvements in PFS/TTP relative to capecitabine [intermittent: HR 0.28 (95% CrI 0.13–0.65); continuous: HR 0.24 (0.11–0.56)], mitoxantrone [HR 0.26 (0.12–0.53)], and pegylated liposomal doxorubicin [HR 0.19 (0.07–0.50)], and trended toward improvements (not statistically significant) versus paclitaxel [HR 0.48 (0.16–1.44)], docetaxel [HR 0.71 (0.24–2.13)], and other monotherapy or combination chemotherapy agents (HRs ranging from 0.23 to 0.89; Table 2).
- Palbociclib + fulvestrant ranked more favorably than all chemotherapy comparators for PFS/TTP in terms of SUCRA, probability best, andmean rank. Palbociclib + fulvestrantwas associated with the highest SUCRA value among all treatments (97.20%), and an 18.90% probability of being the best treatment.

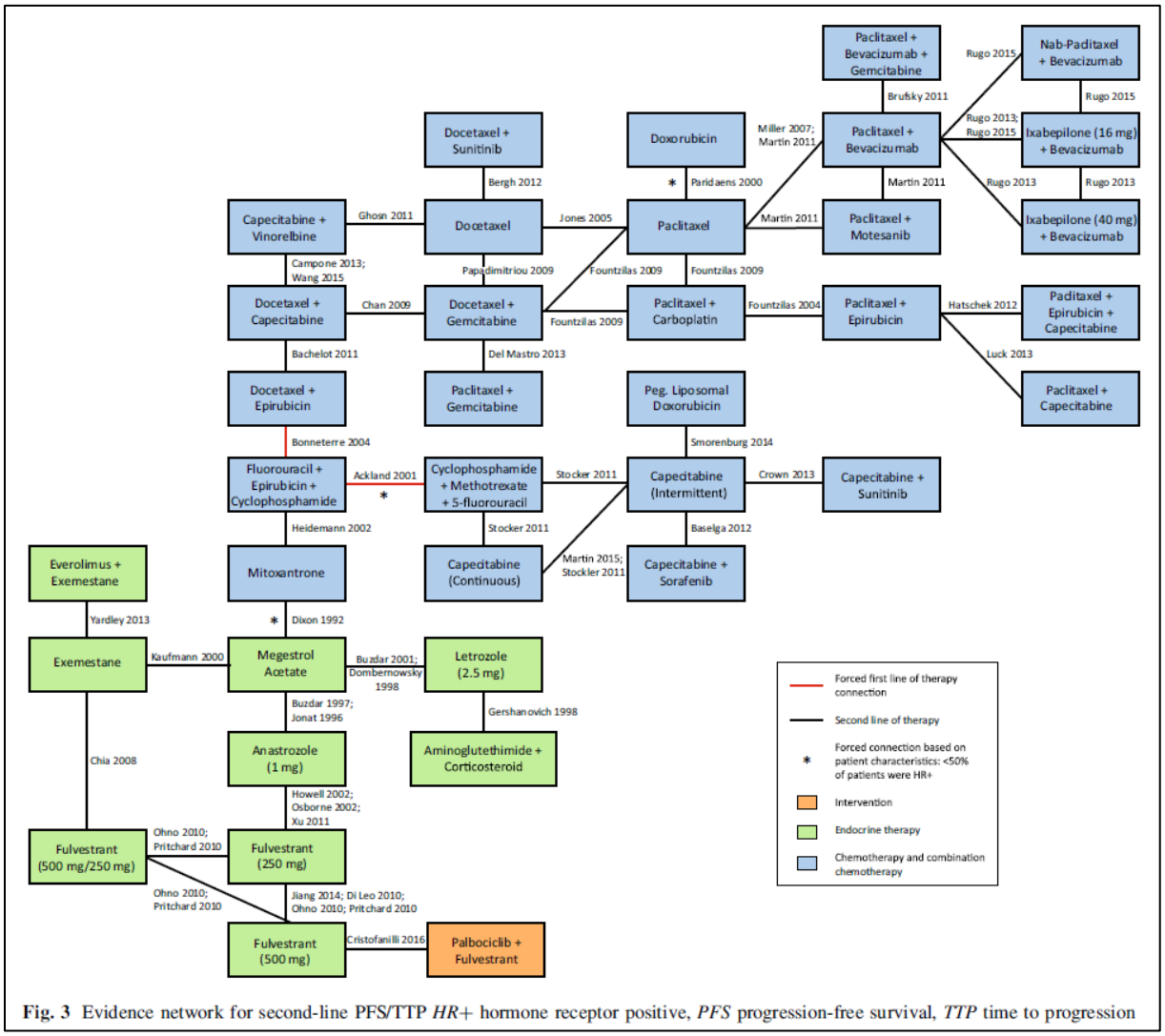


Fig. 3 Evidence network for second-line PFS/TTP *HR+* hormone receptor positive, *PFS* progression-free survival, *TTP* time to progression

- In the second-line random-effects model using vague priors, palbociclib + fulvestrant showed statistically significant improvements versus capecitabine [intermittent: HR 0.29 (95% CrIR 0.10–0.81); continuous: HR 0.25 (0.09–0.70)], mitoxantrone [HR 0.26 (0.11–0.60)], and pegylated liposomal doxorubicin [HR 0.2 (0.06–0.64)] and trended toward improvements versus paclitaxel [HR 0.49 (0.14–1.74)], docetaxel [HR 0.69 (0.2–2.57)], and other monotherapy or combination chemotherapy agents (HRs ranging from 0.23 to 0.89). Similar

results and statistical significance were obtained from the randomeffects model using informative priors. Model fit statistics were favorable from both random-effects models

Table 2 Second-line therapy NMA results for PFS/TTP: palbociclib + fulvestrant versus comparators

Comparisons	HR (95% CrI) Fixed-effects model	HR (95% CrI) Random-effects model: vague priors	HR (95% CrI) Random-effects model: informative priors
Palbociclib + Fulvestrant	1	1	1
Single chemotherapy agents			
Doxorubicin	0.80 (0.27–2.44)	0.81 (0.22–3.02)	0.82 (0.19–3.40)
Docetaxel	0.71 (0.24–2.13)	0.69 (0.20–2.57)	0.70 (0.17–2.76)
Paclitaxel	0.48 (0.16–1.44)	0.49 (0.14–1.74)	0.49 (0.12–1.98)
Capecitabine (intermittent)	**0.28 (0.13–0.65)**	**0.29 (0.10–0.81)**	**0.29 (0.10–0.89)**
Mitoxantrone	**0.26 (0.12–0.53)**	**0.26 (0.11–0.60)**	**0.26 (0.11–0.65)**
Capecitabine (continuous)	**0.24 (0.11–0.56)**	**0.25 (0.09–0.70)**	**0.25 (0.09–0.78)**
Pegylated liposomal doxorubicin	**0.19 (0.07–0.50)**	**0.20 (0.06–0.64)**	**0.19 (0.06–0.67)**
Combination chemotherapy agents			
Paclitaxel + bevacizumab + gemcitabine	0.89 (0.28–2.82)	0.89 (0.23–3.49)	0.91 (0.20–3.95)
Docetaxel + sunitinib	0.77 (0.26–2.36)	0.75 (0.21–2.81)	0.76 (0.18–3.12)
Paclitaxel + bevacizumab	0.72 (0.24–2.20)	0.73 (0.20–2.68)	0.74 (0.17–3.11)
Paclitaxel + gemcitabine	0.64 (0.22–1.94)	0.67 (0.19–2.45)	0.67 (0.16–2.77)
Ixabepilone 40 mg + bevacizumab	0.61 (0.18–2.05)	0.62 (0.15–2.53)	0.62 (0.13–2.84)
Nab-paclitaxel + bevacizumab	0.60 (0.20–1.87)	0.60 (0.16–2.27)	0.61 (0.13–2.61)
Docetaxel + gemcitabine	0.55 (0.19–1.61)	0.57 (0.17–1.99)	0.58 (0.15–2.29)
Paclitaxel + motesanib	0.51 (0.16–1.61)	0.53 (0.14–2.13)	0.53 (0.12–2.33)
Docetaxel + capecitabine	0.49 (0.17–1.38)	0.51 (0.16–1.70)	0.51 (0.14–1.96)
Docetaxel + epirubicin	0.45 (0.19–1.06)	0.46 (0.17–1.28)	0.47 (0.16–1.44)
Paclitaxel + carboplatin	0.44 (0.14–1.38)	0.46 (0.13–1.67)	0.46 (0.11–1.94)
Ixabepilone 16 mg + bevacizumab	0.45 (0.15–1.39)	0.45 (0.12–1.71)	0.46 (0.10–1.93)
Capecitabine + sorafenib	0.44 (0.17–1.14)	0.45 (0.14–1.49)	0.44 (0.14–1.54)
Capecitabine + vinorelbine	0.44 (0.15–1.28)	0.47 (0.14–1.62)	0.47 (0.13–1.85)
Paclitaxel + epirubicin	0.35 (0.11–1.16)	0.36 (0.09–1.44)	0.31 (0.07–1.37)
Fluorouracil + epirubicin + cyclophosphamide	**0.31 (0.14–0.67)**	**0.32 (0.13–0.78)**	**0.31 (0.12–0.87)**
Paclitaxel + capecitabine	**0.3 (0.09–0.98)**	**0.31 (0.08–1.23)**	0.31 (0.07–1.44)
Paclitaxel + epirubicin + capecitabine	**0.29 (0.09–0.95)**	**0.31 (0.08–1.16)**	0.37 (0.08–1.70)
Capecitabine + sunitinib	**0.23 (0.1–0.56)**	**0.24 (0.08–0.71)**	**0.23 (0.08–0.78)**
Cyclophosphamide + methotrexate + 5-fluorouracil	**0.23 (0.1–0.51)**	**0.23 (0.09–0.61)**	**0.23 (0.09–0.68)**
Model fit statistics	Residual deviance = 58.12 vs. 51 DIC = −4.11	Residual deviance = 52.50 vs. 51 DIC = −4.36 Heterogeneity (SD) = 0.11 (0.01–0.26)	Residual deviance = 52.11 vs. 51 DIC = −4.63 Heterogeneity (SD) = 0.11 (0.01–0.26)

Analyses use data from PALOMA-3 [6]. Statistically significant differences are shown in ***bold***. Endocrine therapies have been excluded from this table, given that the focus is on chemotherapy agents. For vague priors in the random-effects model, a uniform distribution for between-study variance was assumed, as recommended by the National Institute for Health and Care Excellence [9]. Informative priors were based on an estimate of between-study variance using data from previous Cochrane systematic reviews [12]

CrI credible interval, *DIC* deviance information criterion, *HR* hazard ratio, *SD* standard deviation

- After adjusting for heterogeneity in median PFS/TTP values in the second-line analysis, palbociclib + fulvestrant was associated with improved PFS/TTP relative to all chemotherapy comparators. Model fit was favorable across all sensitivity analyses.

Anmerkung/Fazit der Autoren

- The second-line NMA results suggest that palbociclib + fulvestrant is associated with improved PFS/TTP relative to all other chemotherapy treatments. In the fixed effects model, statistically significant improvements in PFS/TTP were observed in favor of palbociclib + fulvestrant relative to capecitabine (intermittent and continuous), mitoxantrone, and

pegylated liposomal doxorubicin, and trended toward improvements versus paclitaxel, docetaxel, and other monotherapy or combination chemotherapy agents. Results from the random-effects models aligned closely with those of the fixed-effects model.

- Limitations: heterogeneity in patient and study characteristics, introduced primarily by the fact that the included studies span several decades

Kommentare zum Review

- Ergebnisse zu Firstline nicht berichet, da dies nicht das AWG umfasst.
- HER2-Status in Studien unterschiedlich

Lin W.Z. et al., 2017 [14].

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

this meta-analysis aimed 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:

- combination of targeted therapy with fulvestrant

Komperator:

- fulvestrant plus placebo

Endpunkt:

- partial response (PR), complete response (CR), and stable disease (SD), and progression free survival (PFS),

Recherche/Suchzeitraum:

- The PubMed and Embase databases and the Cochrane Central Register of Controlled Trials were searched using the terms ‘‘breast cancer’’, ‘‘metastatic’’, ‘‘advanced’’, ‘‘fulvestrant’’, ‘‘endocrine therapy’’ and ‘‘randomized trial’’. The search was limited to articles published between January 2000 and June 2016. Abstracts presented at the annual meetings of the European Society of Medical Oncology and the American Society of Clinical Oncology between 2000 and 2016 were also analyzed.

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs (5 Phase II-Studien, 3 Phase III-Studien) [n=2470 Patienten]

Charakteristika der Population:

Table 1 Randomized trials included in this meta-analysis

Author year, phase	Treatment	No. of patients
Hyams DM21	Fulv + cediranib	31
2013, II	Fulv + placebo	31
Robertson JFR22	Fulv + ganitumab	72
2013, II	Fulv + placebo	34
Burstein HJ23	Fulv + lapatinib	146
2014, III	Fulv + placebo	145
Clemons MJ24	Fulv + vandetanib	61
2014, II	Fulv + placebo	68
Zaman K 25	Fulv + selumetinib	23
2015, II	Fulv + placebo	23
Baselga J 20	Fulv + buparlisib	576
2015, III	Fulv + placebo	571
Cristofanilli M26	Fulv + palbociclib	347
2016, III	Fulv + placebo	174
Krop IE27	Fulv + pictilisib	89
2016, II	Fulv + placebo	79

Fulv = fulvestrant

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

Qualität der Studien:

- The results of the funnel plot and the Egger's test (P = 0.75) showed no potential publication bias. The quality was high in all studies (Jadad score ≥ 3).

Studienergebnisse:

PFS

- data were available in 7 trials including 2,368 patients
- Since between-study heterogeneity was observed, a random-effect model was used (I2 = 79.6%, P = 0.00).
- Combination therapy was associated with a reduction of 21% in the risk of progression (HR = 0.79; 95% CI 0.72–0.87; P = 0.00)

Objective response rate and disease control rate

- A fixed-effect model was used for ORR (I2 = 11.7%, P = 0.34), and a random-effect model was chosen for DCR (I2 = 58.5%, P = 0.03). The combination arm resulted in a significant improvement in ORR (RR = 1.70; 95% CI 1.30–2.21; P = 0.00) and a trend of increase in DCR (RR = 1.27; 95% CI 0.96–1.69, P = 0.09)

Toxicity

- Overall, combination arm was associated with a greater incidence of drug-related grade 3 or higher toxic effects (RR = 1.24; 95% CI 1.13–1.36; P = 0.00). Based on meta-analysis of four studies [21, 22, 25, 26], more patients in the combination arm discontinued treatment due to toxicity than those in fulvestrant monotherapy (RR = 4.58; 95% CI 2.53–8.29; P = 0.00).

Anmerkung/Fazit der Autoren

- In summary, adding targeted agents with fulvestrant showed ORR and PFS benefit in patients with advanced breast cancer compared with fulvestrant alone. It is urgent to identify biomarkers which could be routinely used to stratify patients.

Kommentare zum Review

- Ergebnisse der Netzwerk-Meta-Analyse aufgrund methodischer Limitationen nicht berichtet
- HER2-Status in Studien unterschiedlich

Beith J et al., 2016 [1].

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)

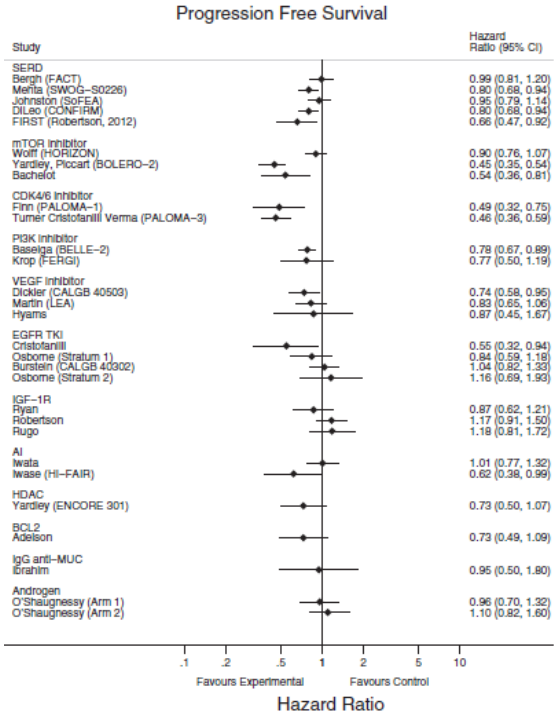
Charakteristika der Population:

- 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:

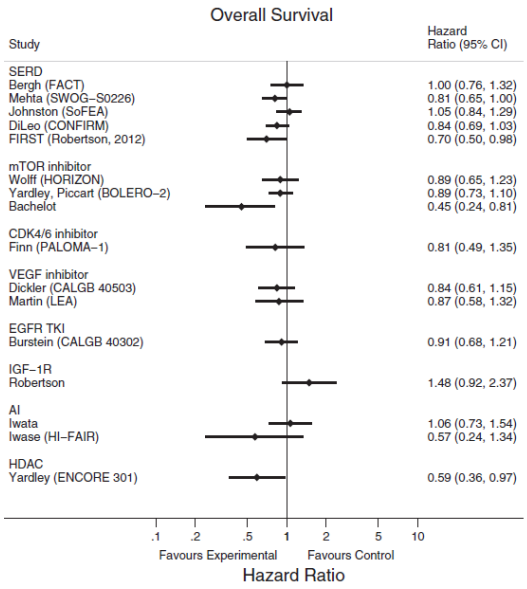
- MERGE assessment: 15 studies had a low risk of bias, 13 had low to moderate risk of bias and 7 had moderate to high risk of bias

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.

Qiao L et al., 2014 [19].

Mammalian target of rapamycin (mTOR) inhibitors and combined chemotherapy in breast cancer: a meta-analysis of randomized controlled trials

Fragestellung

we performed a meta-analysis to determine the efficacy and safety of mTOR inhibitors combined chemotherapy (with steroidal or nonsteroidal aromatase inhibitors) in treatment of breast cancer, such that more reliable and evidence-based medicine to guide clinical practice may be achieved.

Methodik

Population:

- breast cancer patients undergoing chemotherapy using steroid (exemestane) or nonsteroid (letrozole) aromatase inhibitors with or without mTOR inhibitors (everolimus)

Intervention:

- mTOR inhibitors everolimus, temsrrolimus, or sirolimus

Komperator

- Placebo

Endpunkt:

- overall response rate (ORR), progression-free survival (PFS), clinical benefit rate

Recherche/Suchzeitraum:

- Durchgeführt Ende 2013
- Medline (nicht näher ausgeführt)

Qualitätsbewertung der Studien:

- Jaded Scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 Studien:
  - 6 Studien evaluated everolimus plus endocrine therapy [17-21, 31], including 5 studies that described the results of phase III trials, while the remaining one study described the results of phase II trials. All these studies were conducted on postmenopausal women with advanced breast cancer who are hormone receptor (HR) positive and human epidermal growth factor receptor-2 (HER2) negative.
  - 3 other studies evaluated everolimus in combination with neoadjuvant chemotherapy [22, 23, 32]. There were 2 studies that evaluated temsirolimus plus letrozole [24, 25], while the last one was a phase II study about sirolimus that were conducted in patients with metastatic breast cancer [26].

Charakteristika der Population:

Table 1. Summary of everolimus plus endocrine therapy in HR+, HER2- advanced breast cancer (6 studies)

Author/phase	Patients	N	Chemotherapy regimens	Efficacy
Mario Campone et al., 2013/BOLERO-2	with HR+, HER2- visceral metastases	271	Everolimus + exemestane	PFS: 6.8 vs 2.8 months HR: 0.47; 95% CI 0.37-0.60
		135	Placebo + exemestane	CBR: 44.6% vs 22.2%
	without visceral metastases	214	Everolimus + exemestane	PFS: 9.9 vs 4.2 months; HR: 0.41; 95% CI 0.31-0.55;
		104	Placebo + exemestane	CBR: 59.8% vs 31.7%
José Baselga, M.D et al., 2012/BOLERO-2	Postmenopausal advanced BC	485	Exemestane + everolimus	PFS: 6.9 vs 2.8 months HR: 0.43; 95% CI: 0.35-0.54
		239	Exemestane + placebo	ORR: 9.5% vs 0.4%
G. N. Hortobagyi et al., 2011/BOLERO-2	Postmenopausal advanced BC	485	Exemestane + everolimus	PFS: 7.4 vs 3.2 months HR: 0.44; 95% CI: 0.36-0.53
		239	Exemestane + placebo	ORR: 12.0% vs 1.3% CBR: 50.5% vs 25.5%
Shinzaburo Noguchi et al., 2013/BOLERO-2	metastatic Asian	98	Exemestane+everolimus	PFS: 8.48 vs 4.14 months HR: 0.62; 95% CI 0.41-0.94 CBR: 58.2 vs 28.9% ORR: 19.4% vs 0
		45	Exemestane + placebo	
	Non-Asian	387	Exemestane + everolimus	PFS: 7.33 vs 2.83 months HR: 0.41; 95% CI, 0.33-0.50
		194	Exemestane + placebo	CBR: 49.6% vs 25.8% ORR: 10.9% vs 2.1%
Novartis Pharmaceuticals Corporation/BOLERO-2	HR+, HER2- metastatic	485	Exemestane+everolimus	PFS: 7.8 vs 3.2 months HR: 0.45; ORR: 12.6% vs 1.7%
		239	Exemestane + placebo	
Thomas Bachelot et al., 2012/Phase II	HR+, HER2- metastatic	54	Tamoxifen + everolimus	PFS: 8.6 vs 4.5 months HR: 0.54; 95% CI, 0.36-0.81 CBR: 61% vs 42% ORR: 14% vs 13%
		57	Tamoxifen	

Table 3. Summary of combined everolimus with neoadjuvant chemotherapy in breast cancer (3 studies)

Author/phase	N	Chemotherapy regimens	RR	Grades 3 to 4
Baselga et al 2009/Phase II	138	Everolimus + Letrozole	36.2%	Stomatitis (2.2%) Rash (0.7%) Asthenia (0%) Hypercholesterolemia (0.7%) Fatigue (1.5%) Anorexia (0%) Hyperglycemia (5.1%)
	132	Letrozole	39.4%	Stomatitis (0%) Rash (0%) Asthenia (0.8%) Hypercholesterolemia (0%) Fatigue (0%) Anorexia (0%) Hyperglycemia (0%)
Jens Huober et al 2013/Phase II	197	Paclitaxel + everolimus	52.2%	Anaemia (1%) Leukopaenia (12.3%) Neutropenia (17.8%) Nausea (0%) Diarrhoea (1%)
	198	Paclitaxel	61.7%	Anaemia (1.5%) Leukopaenia (7.7%) Neutropenia (9.5%) Nausea (0%) Diarrhoea (0.5%)
Gonzalez et al 2011/Phase II	23	Paclitaxel + everolimus-5FU + epirubicin + cyclophosphamide	47.8%	Anemia (13%) Leukopenia (17%) Rash/Desquamation (9%) Vomiting (13%)
	27	Paclitaxel-5FU + epirubicin + cyclophosphamide	29.6%	Anemia (4%) Leukopenia (11%) Rash/Desquamation (7%) Vomiting (4%)

Table 4. summary of temsirolimus plus letrozole in postmenopausal breast cancer (2 studies)

Author/phase	N	Chemotherapy regimens	Efficacy	Gradt 3 and 4 toxicities
Antonio C. Wolff et al., 2013/Phase III	556	Letrozole + Temsirolimus	PFS: 8.9 vs 9.0 months HR: 0.90	Asthenia (3%) Diarrhea (2%) Rash (1%) Fever (1%) Pruritus (1%) Stomatitis (1%) Nausea (1%) Anorexia (1%) Hyperlipemia (2%) Anemia (1%) Dyspnea (3%)
	556	Letrozole + Placebo		Asthenia (2%) Diarrhea (1%) Rash (< 0.5%) Fever (1%) Pruritus (0) Stomatitis (< 0.5%) Nausea (1%) Anorexia (1%) Hyperlipemia (< 0.5%) Anemia (1%) Dyspnea (3%)
Chow, et al., 2006/Phase III	493	Letrozole + Temsirolimus	PFS: 9.2 vs 9.2 months ORR: 24% vs 24% CBR: 40% vs 43%	grade 3-5 AEs neutropenia (3%) hyperglycemia (4%) dyspnea (3%),
	499	Letrozole + Placebo		dyspnea (3%) asthenia (1%)

Qualität der Studien:

Table 5. Quality of reports of 12 clinical trials using the Jadad assessment scale

Trials	Randomization (range: 0-2)	Blindness (range: 0-2)	Withdrawals/dropouts (range: 0-1)	Total score (range: 0-5)
Campone 2013	1	2	1	4
Baselga 2012	1	2	0	3
Hortobagyi 2011	1	0	0	1
Noguchi 2013	1	2	1	4
Novartis 2012	1	2	0	3
Bachelot 2012	1	0	1	2
Huober 2013	1	0	1	2
Gonzalez 2011	1	0	0	1
Baselga 2009	1	2	1	4
Antonio 2013	1	2	1	4
Chow 2006	1	0	0	1
Bhattacharyya 2011	1	0	0	1

Studienergebnisse:

Efficacy and safety comparison between endocrine therapy with everolimus and with placebo

Everolimus plus exemestane significantly increased PFS (pooled HR for PFS, HR 0.44, 95% CI 0.41-0.48), CBR (pooled RR for CBR, RR 1.92, 95% CI 1.69-2.17) and ORR (pooled RR for ORR, RR 9.18, 95% CI 5.21-16.15). There was no significant heterogeneity both for PFS (p = 0.71) and for CBR (p = 0.8). The heterogeneity of ORR was significant (p = 0.009). However, when one of the study, which is out of range [21], was removed from the analysis, the heterogeneity showed no significance (p = 0.699). All the pooled HR for PFS, the pooled RR for CBR, and the pooled RR for overall response were performed using the fixed-effect model.

Adverse events

The meta-analyses of any adverse events showed that the risks of stomatitis (5.44, 95% CI, 4.63-6.38), rash (6.30, 95% CI, 5.04-7.86), hyperglycemia (6.68, 95% CI, 4.48-9.96), diarrhea (1.85, 95% CI, 1.62-2.11), fatigue (1.34, 95% CI, 1.21-1.49), anorexia (2.47, 95% CI, 2.11-2.89) and pneumonitis (47.36, 95% CI, 17.74-126.39) were higher in patients treated with everolimus plus exemestane than in those treated with placebo plus endocrine therapy. The risk of nausea was comparable between two groups (OR = 1.05, 95% CI = 0.94-1.16).

We also analyzed the Grade 3 or 4 adverse events and the result showed that the risks of stomatitis (9.28, 95% CI, 4.77-18.08), rash (6.07, 95% CI, 1.65-22.39), hyperglycemia (8.38, 95% CI, 3.82-18.39), diarrhea (3.34, 95% CI, 1.63-6.86), nausea (2.43, 95% CI, 1.26-4.71), fatigue (4.03, 95% CI, 2.13-7.62), and pneumonia (13.34, 95% CI, 3.79-46.91) were higher in patients receiving everolimus plus exemestane than in those receiving placebo plus exemestane. The risk of anorexia were comparable between two groups (1.91 95% CI, 0.89-4.09).

efficacy of everolimus and other mTOR inhibitors

We have analyzed the efficacy of everolimus in combination with neoadjuvant chemotherapy. The result showed that the pooled RR for ORR of everolimus in combination with neoadjuvant

chemotherapy significantly improved the ORR (RR = 0.9, 95% CI = 0.77-1.05; Figure 3A), while there was no significant heterogeneity (p = 0.22). We also analyzed the efficacy of endocrine therapy by adding temsirolimus to letrozole in postmenopausal breast cancer. The result suggested that the pooled RR for ORR of temsirolimus plus letrozole did not improve the ORR (RR = 1.0, 95% CI = 0.86-1.15; Figure 3B). The heterogeneity did not show significant difference either (p = 0.97). Meanwhile, analysis of the pooled RR for CBR showed that temsirolimus plus letrozole did not improved the CBR (RR = 0.94, 95% CI = 0.86-1.04; Figure 3C), while there was no significant heterogeneity (p = 0.75). All the pooled RR for ORR and CBR were performed using the fixed-effect model.

Anmerkung/Fazit der Autoren

The results showed that everolimus plus exemestane significantly increased the ORR relative risk (relative risk = 9.18, 95% CI = 5.21-16.15), PFS hazard ratio (hazard ratio = 0.44, 95% CI = 0.41-0.48), and clinical benefit rate (relative risk = 1.92, 95% CI 1.69-2.17) compared to placebo control, while the risks of stomatitis, rash, hyperglycemia, diarrhea, fatigue, anorexia and pneumonitis also increased. Three studies that enrolled 715 women who received everolimus as neoadjuvant therapy were analyzed. Compared to chemotherapy with placebo, chemotherapy plus everolimus did not increase the ORR relative risk (relative risk = 0.90, 95% CI = 0.77-1.05). Meanwhile, two other studies that enrolled 2104 women examined the efficacy of temsirolimus (or placebo control) plus letrozole. The results indicated that emsirolimus plus letrozole did not increase the ORR relative risk and clinical benefit rate (p > 0.05). Together, these data suggest that the combined mTOR inhibitor (everolimus) plus endocrine therapy (exemestane) is superior to endocrine therapy alone. As a neoadjuvant, everolimus did not increase the ORR, while temsirolimus plus letrozole treatment has limited effect on the ORR and the CBR of breast cancer patients.

Based on the results of our meta-analysis, mTOR inhibitiors in combination with endocrine therapy is likely to be considered as a new therapeutic strategy for women with advanced breast cancer that were previously treated with aromatose inhibitor [27]. A better understanding is needed regarding which patients will most likely benefit from these therapies and have limited potential to develop resistance to mTOR agents.

3.4 Leitlinien

AWMF, 2017 [13].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.0, 2017 AWMF Registernummer: 032-045OL,

Leitlinienorganisation/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

- Basis dieser LL ist ein Aktualisierungsantrag
- Aktualisierung erfolgte auf 2 Wegen: (1) Formulierung einer Schlüsselfrage auf Basis von Empfehlungen und einer sich daran anschließenden systematischen Primärliteraturrecherche inkl. methodischen Literatur-Selektionsprozess (Festlegung: nur für 17 Schlüsselfragen durchgeführt); (2) LL-Adaption (Empfehlungen aus LL werden übernommen

Systematische Recherche Auswahl und Bewertung von Leitlinien

- Recherche nach LL, die nach 2013 veröffentlicht wurden (inkl. Abgleich mit LL-Bericht des IQWiG)
- Festlegung von Ein- und Ausschlusskriterien
- LL wurden eingeschlossen, wenn sie mindestens 50% der Domäne 3 (Rigour of Development) des AGREE II Instruments erfüllten (Bewertung durch 2 Begutachter)
- Systematische Recherche in LL-Datenbanken im Juni 2015 und im Oktober 2015 wiederholt; weitere n=8 LL wurden im Anschluss an die Recherche durch die einzelnen Arbeitsgruppen und n=2 LL durch das Methodenteam identifiziert (berücksichtigt wurden n=23 LL) → methodische Bewertung mittels AGREE II

Primärliteraturrecherche

- nach PICO-Schema in verschiedenen Datenbanken
- Zeitraum: 06. April – 2. November 2016
- Methodische Bewertung: SIGN-Checklisten für Systematic Reviews, RCT, Observational Studies (jeweils Version 2004) sowie Studies of Diagnostic Accuracy (Version 2006)

Formulierung der Empfehlungen und formale Konsensusfindung

- Arbeitsgruppen erarbeiteten zunächst themenbezogen entsprechende Statements und Empfehlungen. In Telefonkonferenzen, in welchen immer mindestens ein Methodiker der AWMF oder des OL anwesend war, wurden diese nach den Regeln des nominalen Gruppenprozesses diskutiert, falls nötig angepasst und schließlich innerhalb der AG als Vorlage für die Konsensuskonferenz verabschiedet.
- **Empfehlungen** Empfehlungen sind thematisch bezogene handlungsleitende Kernsätze der Leitlinie. Die Abstimmung des Empfehlungstextes und des dazugehörigenen Empfehlungsgrades durch die Leitlinien-Gruppe erfolgte im Rahmen eines moderierten, formalen Konsensusverfahrens (Nominaler Gruppenprozess).
- **Expertenkonsens (EK)** Als EK werden Empfehlungen bezeichnet, zu denen keine ausreichende Evidenz aus Studien, Leitlinien oder anderer aggregierter Literatur gefunden werden konnte. In der Regel adressieren diese Empfehlungen Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können.
- In der LL wird zu allen Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in der LL drei Empfehlungsgrade unterschieden (siehe Tabelle 9), die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.

- 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.

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

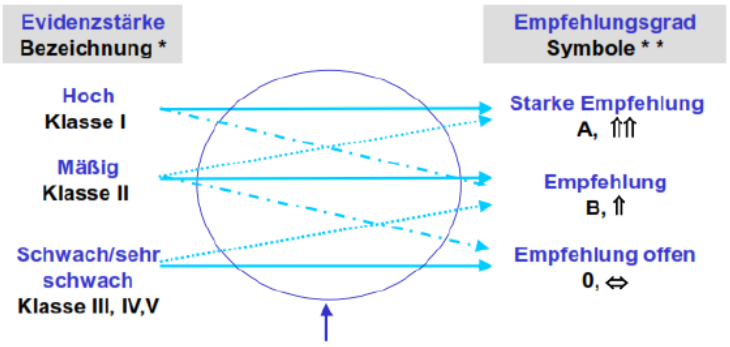
LoE

Als Schema der Evidenzgraduierung wurde die Klassifikation des Oxford Centre for Evidence-based Medicine (Version 2009) verwendet.

GoR

Tabelle 9: verwendete Empfehlungsgrade

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



Kriterien für die Graduierung (Konsensusaspekte):

- Konsistenz der Studienergebnisse
- Klinische Relevanz der Endpunkte und Effektstärken
- Nutzen-Risiko-Verhältnis
- Ethische, rechtliche, ökonomische Erwägungen
- Patientenpräferenzen
- Anwendbarkeit, Umsetzbarkeit

*: 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.

Sonstige methodische Hinweise

Stand der LL: 01.12.2017, gültig bis 30.11.2022

Systemische adjuvante Therapie (endokrine, Chemo-, Antikörpertherapie)

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

Adjuvante endokrine Therapien wie Tamoxifen und Aromatasehemmer reduzieren signifikant die Wahrscheinlichkeit eines Rezidivs um relativ ca. 40% und die Wahrscheinlichkeit des Versterbens um relativ ca. 30% [227, 363, 727, 730].

Daten einiger Studien (wie Tam-02, [734, 735]) weisen darauf hin, dass ein späterer Beginn (bis zu 5 Jahre nach abgeschlossener Lokaltherapie und/oder Chemotherapie) mit einer adjuvanten endokrinen Therapie besser ist, als ganz auf diese endokrine Therapie zu verzichten. Auch dieser spätere Beginn der endokrinen Therapie verlängerte das DFS und das OS bzw. DDFS. Die MA.17-Studie [736], die auch ein längeres therapiefreies Intervall zwischen Tamoxifen und Letrozol zuließ, zeigte ähnliche Ergebnisse. Das sind Hinweise darauf, dass bei Nebenwirkungen eine Therapiepause einem generellen Abbruch vorzuziehen ist.

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

Die endokrine adjuvante Behandlung des frühen Mammakarzinoms gehört zu den effektivsten Therapiemöglichkeiten. Aktuelle Publikationen belegen dies für ein Zeitintervall von bis zu 15 Jahren. Dabei unterschied man die initiale adjuvante Therapie (IAT, Jahr 0-5) und die erweiterte adjuvante Therapie (EAT: Jahr 6-10).

Nach 5 Jahren Tamoxifen reduzieren weitere 5 Jahre adjuvant Tamoxifen bei Patientinnen mit hormonrezeptor-positiven Mammakarzinomen die Rezidivrate (absolut -2,8% in der ATLAS-Studie) und das Gesamtüberleben (absolut -2,48% in der ATLAS-Studie, [738-740]) unabhängig vom

Menopausenstatus (allerdings waren nur 9% der Patientinnen in der ATLAS-Studie prämenopausal). Die Häufigkeit einer Lungenembolie und eines Endometriumkarzinoms waren nach 10 Jahren Tamoxifen signifikant erhöht im Vergleich zu 5 Jahren Tamoxifen ohne Einfluss auf die Mortalität. Eine ischämische Herzkrankheit und Herzinfarkte waren nach 10 Jahren signifikant seltener als nach 5 Jahren Tamoxifen.

Wurden die Patientinnen nach 5 Jahren adjuvant Tamoxifen postmenopausal, verbesserte die nachfolgende Gaben von Letrozol für 5 Jahre adjuvant das DFS und das OS, besonders bei Frauen, die vor dem Letrozol prämenopausal waren oder Lymphknotenmetastasen hatten [736]. Zugelassen für diese EAT in Deutschland nach 5 Jahren Tamoxifen sind Tamoxifen und Letrozol.

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

Wenn die Gabe des Tamoxifens von 5 auf 10 Jahre verlängert wird, werden die ipsi- und kontralateralen Rezidivhäufigkeiten reduziert und in der ATLAS-Studie das Gesamtüberleben. Allerdings sind die Raten an Lungenembolien und Endometriumkarzinomen erhöht, ohne Einfluss auf die Mortalität [738-740]. Die risikoadaptierte Dauer der Tamoxifen-Gabe (längere Gabe bei erhöhtem Rezidivrisiko) wird von der ASCO empfohlen [737].

4.53.	Evidenz- /konsensbasierte Empfehlungen
	Endokrine Therapie
EK	a.) Für Patientinnen mit einem ER+ Mammakarzinom und erhöhtem Risiko, die nach abgeschlossener Chemotherapie noch prämenopausal sind, kann unter Ausschaltung der Ovarfunktion ein Aromatasehemmer eingesetzt werden.
	Konsens
Level of Evidence **LL-Adapt.**	b.) Die alleinige Ovarialsuppression kann entweder durch Gabe eines GnRHa oder durch eine bilaterale Ovarektomie für prämenopausale Frauen mit einem ER+ Mammakarzinom erwogen werden, die kein Tamoxifen erhalten können oder wollen.
	Leitlinienadaptation: [730]
	Starker Konsens
Empfehlungsgrad **A**	c.) Die Ovarialsuppression (GnRHa oder bilaterale Ovarektomie) zusätzlich zu Tamoxifen oder einem Aromatasehemmer soll nur bei hohem Rezidivrisiko und prämenopausaler Situation nach adjuvanter Chemotherapie erwogen werden. Bei Einsatz eines Aromatasehemmers soll eine Ovarialsuppression obligat erfolgen.
Level of Evidence **LL-Adapt.**	Leitlinienadaptation: [730]
	Starker Konsens

In verschiedenen Studien (z.B. SOFT, TEXT, [742]) wurde der Effekt der Unterdrückung der Ovarialfunktion von bis zu 5 Jahren zusammen mit der Gabe von Exemestan oder zusammen mit Tamoxifen vs. der alleinigen Tamoxifen-Gabe in der adjuvanten Therapie von Frauen mit einem

hormonrezeptor-positiven Mammakarzinom untersucht, die prämenopausal waren oder innerhalb von 8 Monaten nach Abschluss der adjuvanten Chemotherapie wieder prämenopausal wurden. Nach der Einzelanalyse jeder dieser Studien und nach der kombinierten Analyse von zwei dieser Studien (SOFT, TEXT) zeigte sich eine erhöhte Effektivität der zusätzlichen Ausschaltung der Ovarialfunktion nur in der Gruppe der unter 35-jährigen Patientinnen, die ein hohes Rezidivrisiko hatten (und deshalb eine Chemotherapie erhielten). In einer Metaanalyse aller dieser Studien [743] zeigten sich eine höhere Wirksamkeit in Bezug auf das DFS aber eine erhöhte Nebenwirkungsrate bis hin zu mehr Todesfällen für die Kombination der Unterdrückung der Ovarialfunktion mit einem Aromatasehemmer als für die Kombination der Unterdrückung der Ovarialfunktion zusammen mit Tamoxifen. Die höhere Nebenwirkungsrate bedingt ein Risiko für eine verminderte Therapieadhärenz.

Die Gabe eines GnRHa-Analogons ist entsprechend der Ergebnisse verschiedener Studien (z.B. ZIPP-Studie, [744]) und Metaanalysen der alleinigen Tamoxifengabe äquivalent, allerdings mit einer erhöhten Nebenwirkungsrate und damit Abbruchrate im Vergleich mit Tamoxifen verbunden. Obgleich verlässliche Daten fehlen, kann ebenfalls mit einer erhöhten Spättoxizität (z.B. Koronarerkrankungen, Osteoporose, Demenz) gerechnet werden.

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

In den Metaanalysen [363, 726, 727, 745] zeigen sich in Bezug auf das OS und das DFS eine Überlegenheit der adjuvanten Aromatasegabe (AI) allein oder in Sequenz mit Tamoxifen im Vergleich zum Tamoxifen allein bei postmenopausalen Patientinnen mit einem hormonrezeptor-positiven Mammakarzinom. In der EBCTCG-Metaanalyse wurden 2 Kohorten gebildet:

Kohorte 1 als Vergleich zwischen 5 Jahren AI vs. 5 Jahren Tamoxifen und Kohorte 2 mit der Gaben AI nach 2-3 Jahren Tamoxifen für insgesamt 5 Jahre. Die Gaben von 5 Jahren AI nach 5 Jahren Tamoxifen wurden nicht in diese Metaanalyse einbezogen. Da die Analyse nur Daten bis 2006 einschloss, wurden die Studien ABCSG 12 und die Switch-Arme der BIG 1-98 Studie nicht in diese Metaanalyse eingeschlossen. In Kohorte 1 wurde die signifikante Überlegenheit der AI-Gabe gegenüber Tamoxifen in Bezug auf das DFS aber nicht in Bezug auf die Mortalität nachgewiesen. In Kohorte 2 zeigte sich der signifikante Vorteil der zusätzlichen AI-Gabe in Bezug auf DFS und Überleben im Vergleich zur alleinigen Tamoxifen-Gabe.

Die alleinige Gabe des Aromatasehemmers über 5 Jahre reduziert die Rezidivrate besonders wirksam bei high-risk Mammakarzinomen und/oder lobulären invasiven Mammakarzinomen.

Wenn nach 5 Jahren Tamoxifen die Patientin postmenopausal geworden ist und ein erhöhtes Rezidivrisiko hat, wird entsprechend der MA.17-Studie die Gabe von Letrozol für weitere 5 Jahre empfohlen [736]. Dieses Vorgehen wird auch von der ASCO [746] nach ihrer Metaanalyse aller bis 2013 abgeschlossenen Studien empfohlen.

Auf dem SABCS 2016 wurden weitere Studien zur verlängerten (EAT) Gabe eines Aromatasehemmers nach bereits 5 Jahren vorgestellt, z.B. NSABP B-42 (10 vs. 5 Jahre AI, [747]) oder IDEAL trial (5 Jahre AI nach 5 Jahren einer adjuvanten endokrinen Therapie mit Tamoxifen

und/oder AI) [748]. In keiner dieser Studien konnte eine signifikante Verlängerung des Überlebens oder eine signifikante Reduktion der Mortalität durch diese verlängerte AI-Gabe gezeigt werden, allenfalls eine Reduktion der ipislateralen und kontralateralen Rezidivrate (Zusammenfassung durch Gnant 2016). Zu gleichen Ergebnissen kam auch die MA.17R-Studie, die bereits publiziert ist [749].

Mit jüngeren postmenopausalen Patientinnen, die bereits eine endokrine Therapie mit einem AI in den ersten 5 Jahren erhalten und gut vertragen hatten, kann eine erweiterte endokrine Therapie mit einem AI unter bestimmten Umständen (erhöhtes Rezidivrisiko z.B. bei positivem Nodalstatus, keine Osteopenie/ Osteoporose) diskutiert werden [750].

227. Department of Health, National Clinical Guideline - Diagnosis, staging and treatment of patients with Breast Cancer. National Clinical Guideline No. 7. 2015.
363. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet, 2005. **365**(9472): p. 1687-717.
726. Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet, 1998. **352**(9132): p. 930-42.
727. Davies, C., et al., Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet, 2011. **378**(9793): p. 771-84.
730. Eisen, A., et al., Optimal Systemic Therapy for Early Female Breast Cancer. Evidence-based series, 2014: p. 1-21.
734. Delozier, T., et al., Delayed adjuvant tamoxifen: ten-year results of a collaborative randomized controlled trial in early breast cancer (TAM-02 trial). Ann Oncol, 2000. **11**(5): p. 515-9.
735. Veronesi, A., et al., Late tamoxifen in patients previously operated for breast cancer without postoperative tamoxifen: 5-year results of a single institution randomised study. BMC Cancer, 2010. **10**: p. 205.
736. Goss, P.E., et al., Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst, 2005. **97**(17): p. 1262-71.
737. Burstein, H.J., et al., Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: american society of clinical oncology clinical practice guideline focused update. J Clin Oncol, 2014. **32**(21): p. 2255-69.
738. Davies, C., et al., Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet, 2013. **381**(9869): p. 805-16.
739. Gray, R.G., et al., aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. 2013, American Society of Clinical Oncology.
740. Petrelli, F., et al., Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials. Breast Cancer Res Treat, 2013. **140**(2): p. 233-40.
743. Chlebowski, R.T., K. Pan, and N.F. Col, Ovarian suppression in combination endocrine adjuvant therapy in premenopausal women with early breast cancer. Breast Cancer Res Treat, 2017. **161**(2): p. 185-190.
744. Hackshaw, A., et al., Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer. J Natl Cancer Inst, 2009. **101**(5): p. 341-9.
745. Ryden, L., et al., Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials. Breast, 2016. **26**: p. 106-14.
747. Mamounas, E., et al., Abstract S1-05: A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): Results from NRG Oncology/NSABP B-42. 2017, AACR.
748. Van de Velde, C., et al., Optimal duration of extended letrozole treatment after 5 years of adjuvant endocrine therapy; results of the randomized phase III IDEAL trial (BOOG 2006–05). European Journal of Cancer, 2017. **72**: p. S9.
749. Goss, P.E., et al., Extending Aromatase-Inhibitor Adjuvant Therapy to 10 Years. N Engl J Med, 2016. **375**(3): p. 209-19.
750. Gnant, M. Discussion. in San Antonio Breast Cancer Symposium. 2016.

Rugo HS et al., 2016 [20].

ASCO Guidelines

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

Leitlinienorganisation/Fragestellung

To develop recommendations about endocrine therapy for women with hormone receptor (HR) –positive metastatic breast cancer (MBC).

Guideline Questions:

1. Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for hormone receptor (HR) –positive metastatic breast cancer (MBC)?

1.1 For postmenopausal women: What are the optimal sequence and duration?

1.2 Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?

1.3 For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?

1.4 Are there demonstrated differences between pre- and postmenopausal patients?

2. Is there an optimal second- or later-line endocrine therapy for HR-positive MBC?

2.1 Should other treatment or disease-free interval play a role in treatment selection?

2.2 Which hormone therapy should be offered?

2.3 What are the optimal timing, dose, and schedule of treatment?

3. How or should endocrine therapies be used in combination or sequence with:

3.1 Mammalian target of rapamycin inhibitors (everolimus)?

3.2 Cyclin-dependent kinase 4/6 inhibitors (palbociclib)?

4. Does estrogen or progesterone expression (high v low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women?

5. How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting?

6. In which patients or settings is hormone therapy recommended over chemotherapy?

6.1 Is there a role for combined cytotoxic and endocrine therapies?

6.2 What is the optimal duration of treatment with hormonal therapy?

7. Is there a role for additional biomarkers in the selection of treatment for patients with HR-positive disease?

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

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

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

Methodik

<u>Grundlage der Leitlinie</u>

- Zielpopulation: Women with HR-positive MBC.
- Expert Panel was convened with multidisciplinary representation in 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:

- o 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
- o Formal assessment of Study Quality (Detaillierte Informationen + Bewertungsergebnisse zu finden im METHODOLOGY SUPPLEMENT)

Recherche/Suchzeitraum:

- The ASCO Expert Panel was convened to conduct a systematic review of evidence from 2008 through 2015 to create recommendations informed by that evidence. Outcomes of interest included sequencing of hormonal agents, hormonal agents compared with chemotherapy, targeted biologic therapy, and treatment of premenopausal women.
- 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 was performed in June 2015 to obtain the most recent evidence

LoE/ GoR

- Definitions for Types of recommendation, Strengths of evidence Strengths of recommendation

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.

- 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 2 abgebildet

ASCO Key Guideline Recommendations for HR-positive MBC

Postmenopausal women

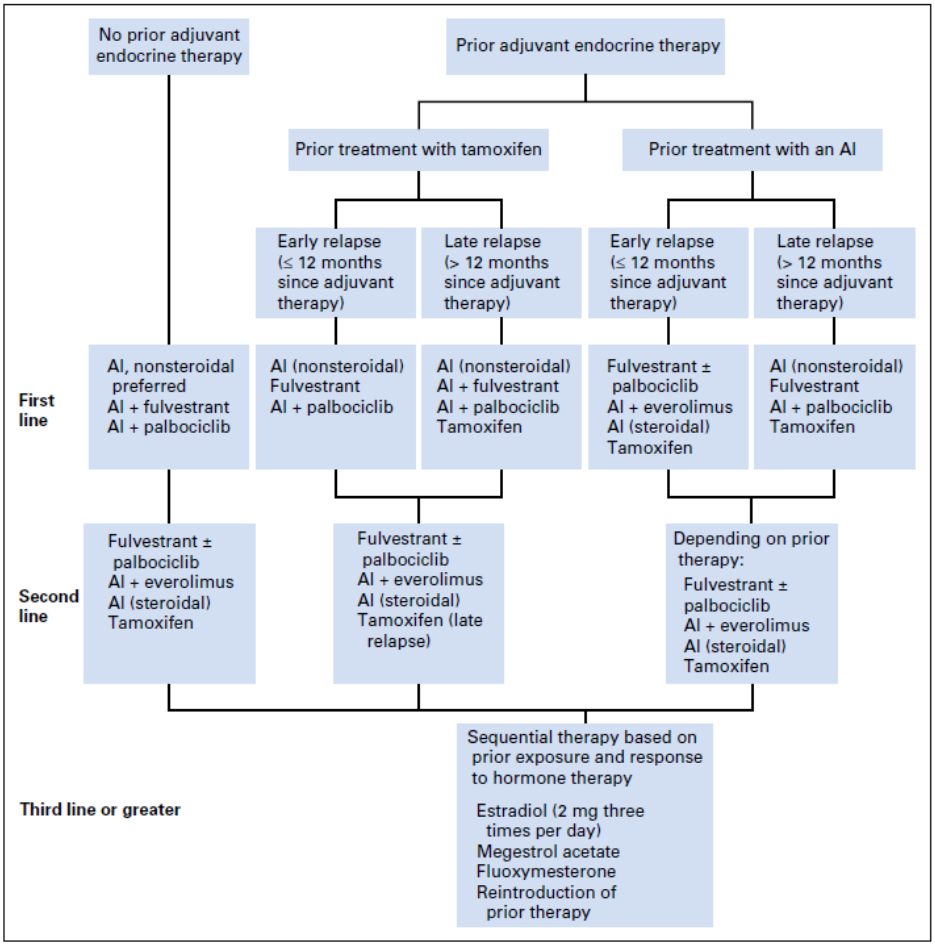


Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered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

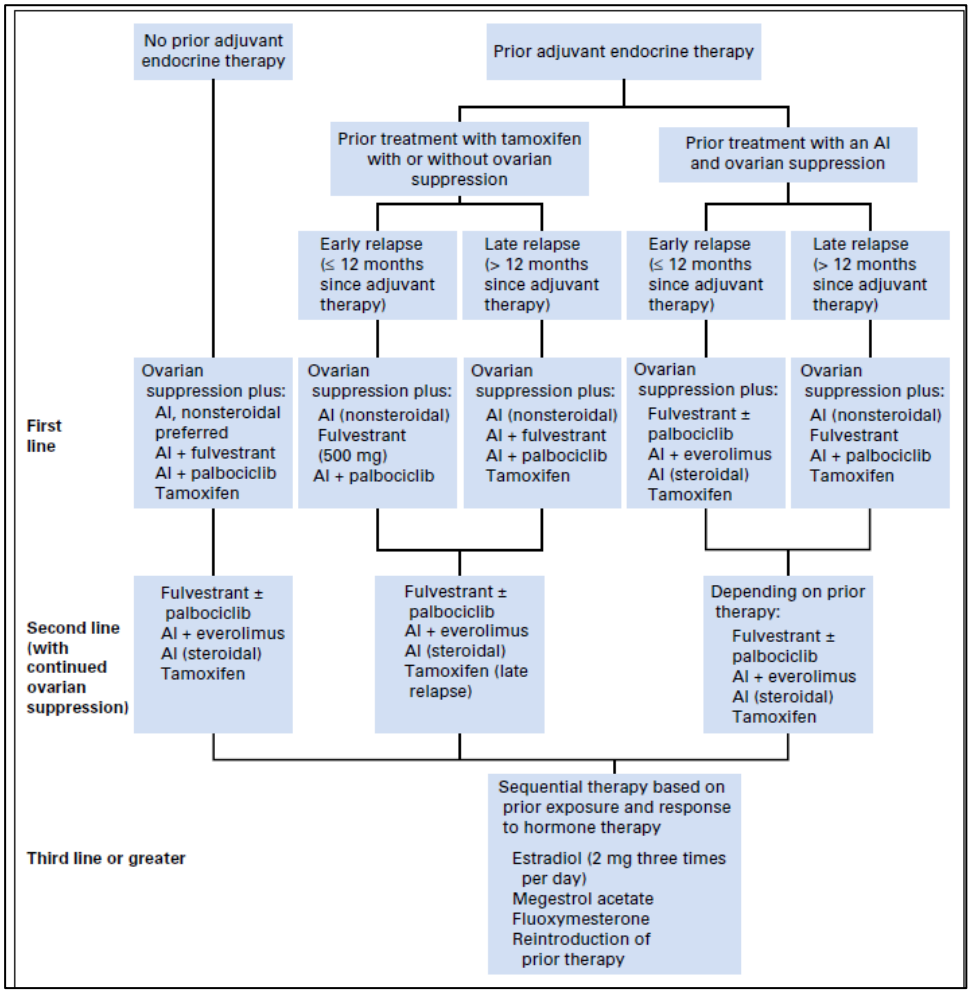


Fig 2. Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered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

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*).

NICE, 2009 [17].

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
- 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.“

Regelmäßige Überprüfung der Aktualität der Empfehlungen: letzter Surveillance Report vom November 2015: 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.

Recherche/Suchzeitraum:

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

LoE/ GoR

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).

Systemic disease-modifying therapy

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

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

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.

Breast cancer in women: diagnosis, treatment and follow-up (KCE Reports 143 – 3rd EDITION)

Leitlinienorganisation/Fragestellung

- This guideline was the result of collaboration between the College of Oncology and the KCE and covered a broad range of topics: diagnosis, staging, treatment, reconstructive surgery, supportive therapy and follow up. It primarily concerned women with invasive early or advanced breast cancer.
- The KCE is a federal institution which is financed for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, food chain safety and environment, and Federal Public Service of social security. The development of clinical practice guidelines is part of the legal mission of the KCE.
- A clinical practice guideline (CPG) on the management of breast cancer was firstly published in 2007[1], and completely updated in 2010[2].

[1] Christiaens et al. Support scientifique du Collège d'Oncologie: un guideline pour la prise en charge du cancer du sein. Brussels: Centre fédéral d'expertise des soins de santé; 2007. Good Clinical Practices (GCP) 63B
[2] Cardoso et al. Soutien scientifique au Collège d'Oncologie: mise à jour des recommandations de bonne pratique pour la prise en charge du cancer du sein. Brussels: Centre Fédéral d'expertise des Soins de santé; 2010. Good Clinical Practices (GCP) KCE report 143

Methodik

Grundlage der Leitlinie

- quality appraisal: AGREE for clinical practice guidelines, checklists of the Dutch Cochrane Centre for original studies

LoE/ GoR

Table 7 - GRADE levels of evidence quality and strength of recommendations (version applicable to the 2010 KCE guideline).

Grade	Description
1A	Strong recommendation based on high level of evidence
1B	Strong recommendation based on moderate level of evidence
1C	Strong recommendation based on low or very low level of evidence
2A	Weak recommendation based on high level of evidence
2B	Weak recommendation based on moderate level of evidence
2C	Weak recommendation based on low or very low level of evidence

Table 8 - Strength of recommendations according to the GRADE system (version applicable to the 2013 KCE guideline update).

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Table 9 - Factors that influence the strength of a recommendation.

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted

Funding and declaration of interest: Although the development of the guidelines is paid by KCE budget, the sole mission of the KCE is providing scientifically valid information. The KCE has no interest in companies (commercial or not, e.g. hospital, university), associations (e.g. professional association, syndicate), individuals or organisations (e.g. lobby group) on which the guidelines could have a positive or negative impact (financial or other). All clinicians involved in the GDG or the peer-review process completed a declaration of interest form.

Recherche/Suchzeitraum:

- A broad search of electronic databases (Medline, PreMedline, EMBASE), specific guideline websites and websites of organisations in oncology … was conducted. (until 2010, update einiger Fragestellungen in 2013))

Systemic treatment

Endocrine therapy and ER antagonists

- In premenopausal women with hormone receptor-positive or hormone receptor-unknown metastatic breast cancer, suppression of ovarian function in combination with tamoxifen is the first-line hormonal therapy of choice (**1A evidence**).
- In postmenopausal women with hormone receptor-positive or hormone receptor-unknown metastatic breast cancer, first-line treatment consists of third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) or Tamoxifen. In the choice of the agent, the adjuvant endocrine therapy received should be taken into consideration. As second-line treatment, a third generation aromatase inhibitor or Fulvestrant is recommended (**1A evidence**).
- Fulvestrant may be considered as an alternative to third generation aromatase inhibitors for metastatic breast cancer in postmenopausal women with hormone receptor-positive (ER+ and/or PgR+) breast cancer that has recurred after prior adjuvant tamoxifen therapy or progressed during prior tamoxifen therapy for advanced disease (**1B evidence**).

Clinical evidence:

A meta-analysis of 4 RCTs found a significant survival benefit (HR 0.78, p=0.02) and progression-free survival benefit (HR 0.70, p=0.0003) in favour of the combined treatment [214].

In a recent systematic review including 6 RCTs, aromatase inhibitors were found to have a clear advantage in overall response rate, clinical benefit, and time to progression over tamoxifen as first-line hormonal treatment in postmenopausal patients with metastatic breast cancer [215].

Overall survival did not differ significantly. These results confirm the recommendations of CBO [66], the German Cancer Society [17], Cancer Care Ontario [216] and the Central European Cooperative Oncology Group [204]. However, tamoxifen remains an acceptable alternative as first-line treatment. Based on data from RCTs, following tamoxifen failure, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) or fulvestrant are recommended for second-line treatment for post-menopausal patients with HR-positive metastatic breast cancer based upon the more favourable side-effect profile [204, 216].

Flemming et al. [217, 218] reported results from two phase III, multicentre RCTs comparing fulvestrant versus anastrozole in patients with prior metastatic or adjuvant endocrine therapy. No significant differences were observed between fulvestrant and anastrozole therapy arms for time-to-progression (primary endpoint), objective response rate, time-to-treatment failure, clinical benefit, and overall survival (median follow-up ranging from 15.1 to 27.0 months). No significant differences in tolerability measures were identified between therapy arms with the exception of a higher incidence of joint disorders (including arthralgia, arthrosis, and arthritis) for patients treated with anastrozole (12.8% vs. 8.3%, p = 0.0234).

Flemming et al. [217, 218] also reported the results of the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) (n = 693) [219] comparing fulvestrant with exemestane in women with HR-positive breast cancer recurring after prior adjuvant non-steroidal aromatase inhibitor (NSAI) therapy (during or within 6 months of discontinuation) or progressing during prior NSAI therapy for advanced disease. At a median follow-up of 13 months, there were no significant differences for median time-to-progression (primary endpoint), objective response rate, clinical benefit rate, or duration of response. Fulvestrant and exemestane were both well tolerated, with no significant differences noted across any adverse events.

References:

[204]. Beslija S et al. Second consensus on medical treatment of metastatic breast cancer. Annals of Oncology. 2007;18(2):215-25.
[214]. Klijn JG et al. Combined tamoxifen and luteinizing hormonereleasing 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):343-53.
[215]. Ferretti G et al. Second- and third-generation aromatase inhibitors as first-line endocrine therapy in postmenopausal metastatic breast cancer patients: a pooled analysis of the randomised trials. Br J Cancer. 2006;94(12):1789-96.
[216]. Eisen A, Prichard K, Johnston M, Oliver T, Breast Cancer Disease Site Group. Role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Toronto: Cancer Care Ontario; 2003.
[217]. Flemming J, Madarnas Y, Franek JA. Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations. Toronto: Cancer Care Ontario; 2008. Evidence-based Series #1-13: Section 1
[218]. Flemming J, Madarnas Y, Franek JA. Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: a systematic review. Breast Cancer Research & Treatment. 2009;115(2):255-68.
[219]. Chia S, Gradishar W. Fulvestrant vs exemestane following nonsteroidal aromatase inhibitor failure: first overall survival data from the EFECT trial. Breast Cancer Res Treat. 2007;106(Suppl 1):S115, A2091.

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Gradishar W.J. et al., 2018 [16].

NCCN Clinical Practice Guidelines in Oncology

Breast Cancer, Version 1.2018 (März 20, 2018).

Siehe auch: Gradishar W.J. et al. 2018 [15].

Leitlinienorganisation/Fragestellung

Nicht spezifiziert

Methodik

Grundlage der Leitlinie

- Update
- “Recommendations within the NCCN Guidelines are derived from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts and researchers in those situations where high-level evidence does not exist. “
- Regelmäßiges Update einer bestehenden Leitlinie
- Prior to the annual update of the Guidelines, an electronic search of the PubMed database, provided by the U.S. National Library of Medicine, is performed to obtain key literature published since the previous Guidelines update. Suchzeitraum: 06/19/14 and 06/29/15

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 was performed in June 2015 to obtain the most recent evidence

LoE/ GoR

- The level of evidence depends upon the following factors, which are considered during the deliberation process by the Panel: extent of data (e.g., number of trials, size of trials, clinical observations only), consistency of data (e.g., similar or conflicting results across available studies or observations), and quality of data based on trial design and how the results/observations were derived (e.g., RCTs, non-RCTs, meta-analyses or systematic reviews, clinical case reports, case series). The degree of consensus within the Panel is based on the percentage of Panel votes, as shown in the Definitions for NCCN Categories section below. The NCCN does not formally consider cost of an intervention in its assessment; however, in some situations, Panels may consider the overall value of a treatment, especially when robust data from pharmacoeconomics studies are available for specific interventions.
- Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

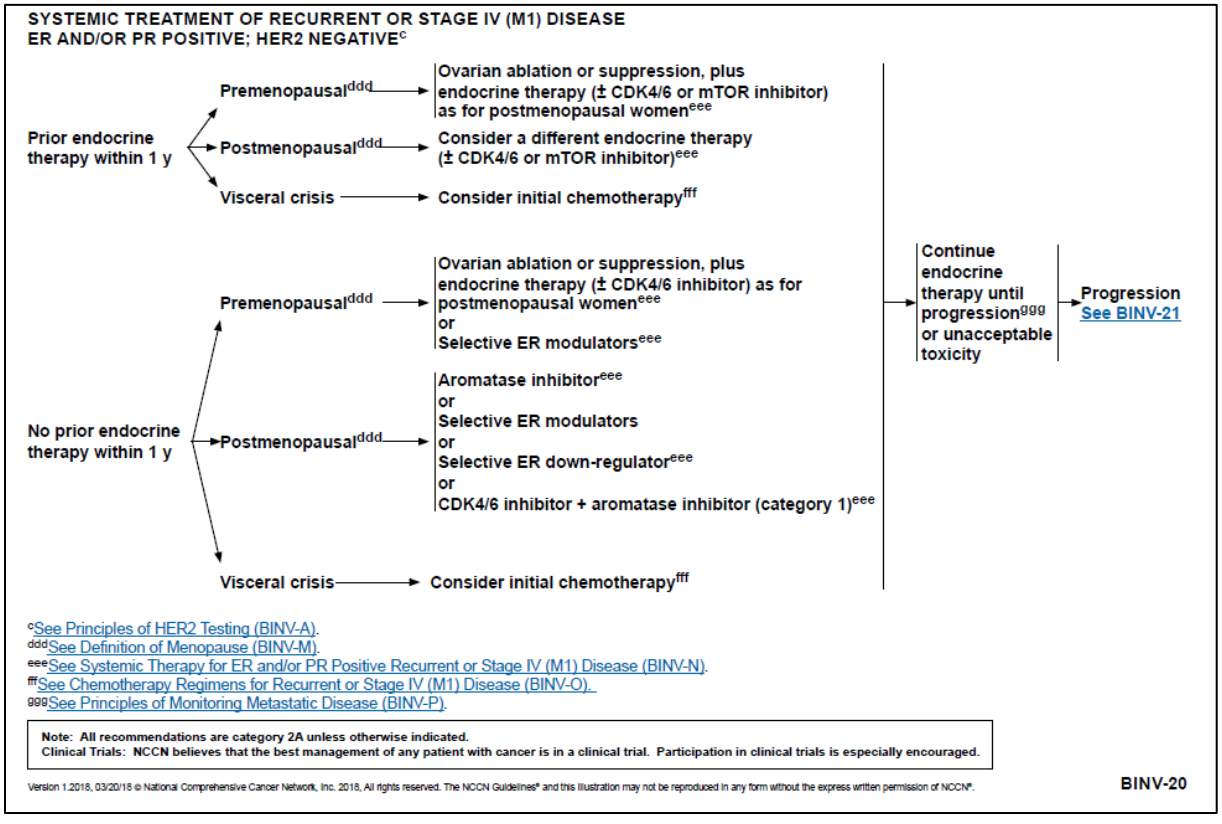
All recommendations are category 2A unless otherwise noted.

NCCN Guidelines finanziert durch NCCN Member Institution (Kliniken und Universitäten), Interessenkonflikte sind veröffentlicht

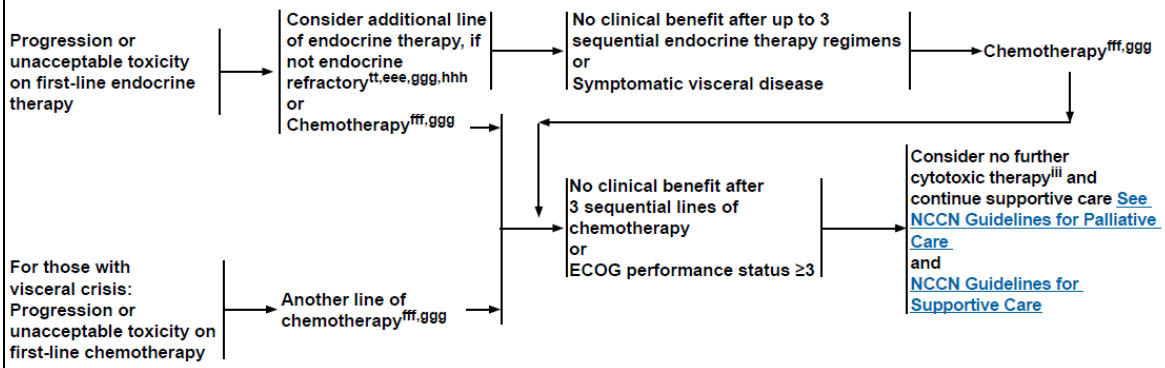
Sonstige methodische Hinweise

„discussion update in progress„

Leitlinie entspricht nicht einer S3-Leitlinie, (z.B. fehlt eine formelle Bewertung der Primärliteratur)



SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE
ER AND/OR PR POSITIVE; HER2 NEGATIVE[c]



[c]See Principles of HER2 Testing (BINV-A).

[tt]False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).

[eee]See Systemic Therapy for ER and/or PR Positive Recurrent or Stage IV (M1) Disease (BINV-N).

[fff]See Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-O).

[ggg]See Principles of Monitoring Metastatic Disease (BINV-P).

[hhh]If there is disease progression while on CDK4/6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

[iii]The potential side effects of additional chemotherapy may outweigh any clinical benefit in a patient who has a compromised performance status.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

SYSTEMIC THERAPY FOR ER AND/OR PR-POSITIVE RECURRENT OR STAGE IV (M1) DISEASE

HER2-Negative and Premenopausal
See Systemic Treatment of Stage IV (M1) Disease (BINV-20)

HER2-Positive and Premenopausal
See Systemic Treatment of Stage IV (M1) Disease (BINV-22)

HER2-Negative and Postmenopausal

Preferred regimens:
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Selective ER down-regulator (fulvestrant, category 1)[1]
- Tamoxifen or toremifene
- Steroidal aromatase inactivator (exemestane)
- Palbociclib + aromatase inhibitor (category 1)[2,3]
- Palbociclib + fulvestrant (category 1)[2,4]
- Ribociclib + aromatase inhibitor (category 1)[2,3]
- Abemaciclib + aromatase inhibitor (category 1)[2,3]
- Abemaciclib + fulvestrant (category 1)[2,5]
- Exemestane + everolimus[2,6]
- Fulvestrant + everolimus
- Tamoxifen + everolimus
- Ribociclib + tamoxifen (category 1)[2,7]

Useful in certain circumstances:
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol
- Abemaciclib[2,8]

HER2-Positive and Postmenopausal
- Aromatase inhibitor ± trastuzumab
- Aromatase inhibitor ± lapatinib
- Aromatase inhibitor ± lapatinib + trastuzumab
- Fulvestrant ± trastuzumab
- Tamoxifen ± trastuzumab

[1]A single study (S0226) in women with hormone receptor-positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole.

[2]If there is disease progression while on CDK4/6 inhibitor therapy, there are no data to support an additional line of therapy with another CDK4/6-containing regimen. Likewise, if there is disease progression while on a everolimus-containing regimen, there are no data to support an additional line of therapy with another everolimus regimen.

[3]CDK4/6 inhibitor in combination with an aromatase inhibitor (anastrozole, letrozole, or exemestane) may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

[4]For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive and HER2-negative metastatic breast cancer that has progressed on or after prior adjuvant or metastatic endocrine therapy.

[5]Indicated after progression on prior endocrine therapy.

[6]A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on non-steroidal AI).

[7]May be considered as a treatment option for first-line therapy with ovarian suppression or ablation for premenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.

[8]Indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Endocrine Therapy for Stage IV or Recurrent Metastatic Disease

Women with recurrent or metastatic disease characterized by tumors that are ER- and/or PR-positive are appropriate candidates for initial endocrine therapy.

In premenopausal women without previous exposure to an antiestrogen, initial treatment is with selective ER modulator alone or ovarian suppression/ablation plus endocrine therapy as for postmenopausal women.[522] In premenopausal women who received a prior endocrine therapy within 12 months, the preferred second-line therapy is ovarian ablation or suppression followed by endocrine therapy as for postmenopausal women.

Endocrine therapies for recurrent/stage IV disease in postmenopausal women include nonsteroidal aromatase inhibitors (anastrozole and letrozole); steroidal aromatase inhibitors (exemestane); serum ER modulators (tamoxifen or toremifene); ER down-regulators (fulvestrant); progestin (megestrol acetate); androgens (fluoxymesterone); and high-dose estrogen (ethinyl estradiol) and recently several new combination therapies with novel agents have become available such as exemestane with everolimus, palbociclib in combination with fulvestrant, and palbociclib with letrozole.

According to some studies, in postmenopausal women, aromatase inhibitors appear to have superior outcome compared with tamoxifen, although the differences are modest.[523-526] A Cochrane review has also suggested a survival benefit favoring the aromatase inhibitors over other endocrine therapies, although the advantage is small.[527] A randomized phase III trial comparing tamoxifen with exemestane as first-line endocrine therapy for postmenopausal women with metastatic breast cancer showed no significant differences in progression-free survival (PFS) or OS between the two arms.[525]

Fulvestrant appears to be at least as effective as anastrozole in patients whose disease progressed on previous tamoxifen.[528,529] A randomized phase II study compared anastrozole versus fulvestrant in over 200 patients with advanced breast cancer.[530,531] In the initial analysis, fulvestrant was as effective as anastrozole in terms of overall response (36.0% vs. 35.5%; odds ratio, 1.02; 95% CI, 0.56 –1.87; *P* = .947) in evaluable patients (n = 89 for fulvestrant and n = 93 for anastrozole).[530] An improved time to progression was seen with fulvestrant compared to anastrazole (median time to progression was 23.4 months for fulvestrant vs. 13.1 months for anastrozole; HR, 0.63; 95% CI, 0.39–1.00; *P* = .0496).[531] This study used a higher 500 mg loading dose every 2 weeks for 3 doses and then 500 mg monthly.[530] The median OS was observed to be longer in the fulvestrant group than in the anastrozole group (54.1 months vs. 48.4 months; HR, 0.70; *P* = .041).[532] These findings are currently being studied in a prospective phase III trial (ClinicalTrials.gov identifier: NCT01602380).

A phase II study of fulvestrant in postmenopausal women with advanced breast cancer and disease progression following aromatase inhibitor therapy documented a partial response rate of 14.3% with an additional 20.8% of patients achieving stable disease for at least 6 months.[533] The clinical benefit rates of exemestane and fulvestrant observed in a phase III trial of postmenopausal women with hormone receptor-positive advanced breast cancer who experienced disease progression on prior nonsteroidal aromatase inhibitor therapy were comparable (32.2% vs. 31.5%; *P* = .853).[534] In that study, fulvestrant was administered as a 500 mg loading dose followed by doses of 250 mg on day 14, day 28, and then monthly.

A separate phase III randomized study in postmenopausal women with metastatic ER-positive breast cancer compared fulvestrant 500 mg every 2 weeks for 3 doses followed by 500 mg monthly versus fulvestrant 250 mg monthly. The PFS was superior with the fulvestrant 500 mg regimen (HR, 0.80; 95% CI, 0.68–0.94; *P* = .006),[535] indicating an increased duration of response with the higher dose of fulvestrant. The final analyses demonstrated an increase in median OS (4.1 months) and reduced risk of death (19%) with a dose of 500 mg compared with 250 mg. Median OS was 26.4 versus 22.3 months (HR, 0.81; 95% CI, 0.69–0.96; *P* = .02).[536]

Combination endocrine therapy in postmenopausal women with hormone receptor-positive, previously *untreated* metastatic breast cancer has been reported from two studies comparing single-agent anastrozole versus anastrozole plus fulvestrant.

In one study (FACT), combination endocrine therapy was not superior to single-agent anastrozole (time to progression HR, 0.99; 95% CI, 0.81–1.20; *P* = .91).[537] In the second study (S0226), PFS (HR, 0.80; 95% CI, 0.68–0.94; stratified log-rank *P* = .007) and OS (HR, 0.81; 95% CI, 0.65–1.00; stratified *P* = .049) were superior with combination anastrozole plus fulvestrant.[538] An unplanned subset analysis in this trial suggested that patients without prior adjuvant tamoxifen experienced the greatest benefit. The reason for the divergent outcomes in these two studies is not known.

A phase III trial studied the effect of fulvestrant alone or in combination with anastrozole or exemestane in patients with advanced breast cancer and an acquired non-steroidal aromatase inhibitor-resistant disease.[539] An aromatase inhibitor had been given as adjuvant treatment to 18% of patients for a median of 27.9 months, and to 82% of patients for locally advanced/metastatic disease for a median of 19.3 months. Median PFS was 4.8 months, 4.4 months, and 3.4 months for patients treated with fulvestrant alone, anastrazole plus fulvestrant, and fulvestrant plus exemestane, respectively. No differences were observed for overall response rate, clinical benefit rate, and OS. This trial provides no evidence that adding an aromatase inhibitor to fulvestrant in patients with non-steroidal aromatase inhibitor-resistant disease improves the results achieved with fulvestrant alone. In postmenopausal women who have received previous antiestrogen therapy and are within one year of antiestrogen exposure, there is evidence supporting the use of a selective aromatase inhibitor as the preferred first-line therapy for their recurrent disease.[540,541]

Palbociclib, a highly selective inhibitor of CDK 4/6 kinase activity, has a role in treating women with ER-positive metastatic breast cancer in combination with endocrine therapy. A phase II, open-label, randomized, multicenter trial evaluated the safety and efficacy of palbociclib in combination with letrozole versus letrozole alone as first-line treatment for patients with advanced ER-positive, HER2- negative breast cancer.[542] Median PFS reported was double with the combination regimen compared to letrozole alone (20.2 months for the palbociclib plus letrozole group and 10.2 months for the letrozole alone group; HR, 0.488; 95% CI, 0.319–0.748).[542] Grade 3/4 adverse reactions reported at a higher incidence in the palbociclib plus letrozole versus letrozole alone group included neutropenia (54% vs. 1%) and leukopenia (19% vs. 0%). Based on this study, the FDA approved palbociclib in combination with letrozole for the treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

The phase III trial (PALOMA-3) compared the combination of palbociclib and fulvestrant to fulvestrant in pre- or post-menopausal hormone receptor-positive, HER2-negative advanced breast cancer patients, whose disease progressed on prior endocrine therapy. Pre- or peri-menopausal patients also received goserelin. The median PFS was 9.2 months for the combination compared to 3.8 months for fulvestrant (HR 0.42, P < .000001) with similar discontinuation rates because of adverse effects (2.6% and 1.7%, respectively).[543] Grade 3/4 adverse events of palbociclib and fulvestrant were mainly confined to neutropenia with the same low incidence (0.6%) of febrile neutropenia in both arms. OS data from this trial are immature.[543]

The NCCN Panel has included the combination of palbociclib with letrozole as a first-line endocrine therapy option for postmenopausal patients with hormone receptor-positive, HER2-negative metastatic breast cancer. In addition, the recently updated version includes palbociclib with fulvestrant as a category 1 option for women with hormone receptor-positive (post-menopausal or premenopausal women receiving ovarian suppression with an LHRH agonist), HER2-negative metastatic breast cancer who have progressed on endocrine therapy.

Limited studies document a PFS advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal women with hormone receptor-positive metastatic breast cancer that is HER2-positive.[544,545]

Resistance to endocrine therapy in women with hormone receptor-positive disease is frequent. One mechanism of resistance to endocrine therapy is activation of the mammalian target of rapamycin (mTOR) signal transduction pathway. Several randomized studies have investigated the use of aromatase inhibition in combination with inhibitors of the mTOR pathway.

A randomized phase II study estimated the efficacy of tamoxifen alone versus tamoxifen combined with everolimus, an oral inhibitor of mTOR, in women with hormone receptor-positive, HER2-negative metastatic breast cancer previously treated with an aromatase inhibitor.[546] After a

median follow-up of 13 months, an intent-to-treat analysis showed that the clinical benefit was 42.1% (95% CI, 29.1–55.9) with tamoxifen alone and 61.1% (95% CI, 46.9–74.1) with tamoxifen plus everolimus. An improvement in median time to progression was seen when everolimus was combined with tamoxifen compared with tamoxifen alone. Median time to progression was 4.5 months (95% CI, 3.7–8.7) with tamoxifen alone versus 8.5 months (95% CI, 6.01–13.9) with everolimus and tamoxifen.[546]

A phase III trial in postmenopausal women with advanced, hormone receptor-positive breast cancer with no prior endocrine therapy for advanced disease, randomized subjects to letrozole with or without the mTOR inhibitor temsirolimus has been reported.[547] In this study, PFS was not different between the treatment arms (HR, 0.89; 95% CI, 0.75–1.05; long-rank $P = .18$).

The results of this trial differ from that of the BOLERO-2 trial (described below). The reasons for the differences in the outcomes of these two randomized phase III studies[547,548] is uncertain, but may be related to the issues of patient selection and extent of prior endocrine therapy.

A phase III study (BOLERO-2) randomized postmenopausal women with hormone receptor-positive advanced breast cancer that had progressed or recurred during treatment with a nonsteroidal aromatase inhibitor to exemestane with or without the mTOR inhibitor everolimus.[549] Final results reported after median 18-month follow-up show that median PFS (by central review) remained significantly longer with everolimus plus exemestane versus placebo plus exemestane at 11.0 versus 4.1 months, respectively; (HR, 0.38; 95% CI, 0.31–0.48; $P < .0001$).[548] The adverse events (all grades) that occurred more frequently in those receiving everolimus included stomatitis, infections, rash, pneumonitis, and hyperglycemia.[548,549] Analysis of safety and efficacy in the elderly patients enrolled in this trial showed that elderly patients treated with an everolimus-containing regimen had similar incidences of these adverse events, but the younger patients had more on-treatment deaths.[550] Based on the evidence from the BOLERO-2 trial, the NCCN Panel has included everolimus plus exemestane as an option for women who fulfill the entry criteria for BOLERO-2.

Many premenopausal and postmenopausal women with hormone-responsive breast cancer benefit from sequential use of endocrine therapies at disease progression. Therefore, women with breast cancers who respond to an endocrine maneuver with either shrinkage of the tumor or long-term disease stabilization (clinical benefit) should receive additional endocrine therapy at disease progression. After second-line endocrine therapy, little high-level evidence exists to assist in selecting the optimal sequence of endocrine therapy. Additional endocrine therapies for second-line and subsequent therapy are listed in the NCCN Guidelines for Breast Cancer.

Endocrine therapy may be active in patients with negative ER and PR determinations, especially on the primary tumor and in soft tissue disease and/or bone-dominant disease.[551-553] Endocrine therapy is associated with relatively low toxicity. Further false-negative determinations of ER and PR tumor status are not unusual and the hormone receptor status of primary and metastatic sites of disease may differ. Therefore, the NCCN Breast Cancer Panel recommends consideration of a trial of endocrine therapy for patients with disease characterized as hormone receptor-negative with disease localized to the bone or soft tissue only or with asymptomatic visceral disease, irrespective of HER2 tumor status.

CADTH, 2013 [2].

Pan-Canadian Oncology Drug Review Final Clinical Guidance Report: Everolimus (Afinitor) for Advanced Breast Cancer

Conclusion: The Clinical Guidance Panel concluded that there is a net overall clinical benefit to the combination of everolimus and exemestane in the treatment of postmenopausal women with hormone receptor positive , HER 2 negative, metastatic breast cancer who have previously been exposed to a non-steroidal aromatase inhibitor (e.g anastrazole, letrozole) and who have a good performance status (0-2. This recommendation is based on a planned interim analysis of a single phase III randomized placebo-controlled international study (BOLERO-2). While there was a statistically and clinically significant improvement in progression free survival (the primary endpoint of this study), the data are too immature to report on overall survival. The clinical panel acknowledges this recommendation is based on statistical and clinical benefit of PFS and delay in deterioration of QOL. There was however more toxicity associated with the combination of everolimus and exemestane although this did not appear to have a negative impact on quality of life as measured in this study. Patients receiving this therapy should be monitored closely by a health care team familiar with the toxicity profile these agents.

CADTH, 2012 [3].

Pan-Canadian Oncology Drug Review Final Clinical Guidance Report: Eribulin (Halaven) for Metastatic Breast Cancer.

Conclusion: The pCODR Breast Clinical Guidance Panel concluded that there is a net overall clinical benefit to eribulin in the 3rd line or greater treatment of women with incurable locally advanced/ metastatic breast cancer previously exposed to anthracyclines and taxanes, based on a single high-quality randomized controlled trial (EMBRACE)1 that demonstrated a clinically and

statistically significant benefit in overall survival for women treated with eribulin compared with those treated with physician's choice.

NICE, 2013 [18].

Everolimus with exemestane for treating advanced breast cancer after endocrine therapy;

Technology appraisal guidance [TA421] Published date: 21 December 2016

This guidance replaces TA295 [Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy]

Recommendations

1.1 Everolimus, in combination with exemestane, is recommended within its marketing authorisation, as an option for treating advanced human epidermal growth factor receptor 2 (HER2)-negative, hormone-receptor-positive breast cancer in postmenopausal women without symptomatic visceral disease that has recurred or progressed after a non-steroidal aromatase inhibitor. Everolimus is recommended only if the company provides it with the discount agreed in the patient access scheme.

Evidence for clinical effectiveness

The committee noted that the company had submitted more mature evidence for overall survival in its Cancer Drugs Fund reconsideration submission than it had originally. The committee was aware that the company and ERG used different methods to model the same progression-free survival data in this reconsideration compared with the original appraisal. Noting that the hazard ratio changed from 0.77 to 0.89 in the analyses, the committee highlighted that the more mature overall survival data suggested everolimus plus exemestane compared with exemestane alone was less clinically effective than it appeared in the company's original submission.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 17.04.2018

#	Suchfrage
1	[mh “Breast Neoplasms”]
2	(breast or mamma*):ti,ab,kw
3	(cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplas* or lesions* or mass*):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 Publication Year from 2013 to 2018

SR, HTAs in Medline (PubMed) am 17.04.2018

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Leitlinien in Medline (PubMed) am 17.04.2018

#	Suchfrage
1	"breast neoplasms"[majr]
2	((breast[ti]) OR mamma*[ti]) 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])
3	#1 OR #2
4	(#3) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))

5	(((#4) AND ("2013/04/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

Referenzen

1. **Beith J, Burslem K, Bell R, Woodward N, McCarthy N, De Boer R, et al.** Hormone receptor positive, HER2 negative metastatic breast cancer: A systematic review of the current treatment landscape. Asia Pac J Clin Oncol 2016;12 Suppl 1:3-18.

2. **Canadian Agency for Drugs and Technologies in Health (CADTH).** Everolimus (Afinitor) for Advanced Breast Cancer [online]. Toronto (CAN): CADTH; 2013. [Zugriff: 20.04.2018]. (Pan-Canadian Oncology Drug Review Final Clinical Guidance Report). URL: https://www.cadth.ca/sites/default/files/pcodr/pcodr-afinitorab-fn-cgr.pdf.

3. **Canadian Agency for Drugs and Technologies in Health (CADTH).** Pan-Canadian Oncology Drug Review Final Clinical Guidance Report: Eribulin (Halaven) for Metastatic Breast Cancer [online]. Toronto (CAN): CADTH; 2012. [Zugriff: 20.04.2018]. URL: https://www.cadth.ca/sites/default/files/pcodr/pcodr-halavenmb-fn-cgr.pdf.

4. **Gemeinsamer Bundesausschuss (G-BA).** 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 – Palbociclib vom 18. Mai 2017 [online]. Berlin (GER): G-BA; 2017. [Zugriff: 20.04.2018]. URL: https://www.g-ba.de/downloads/39-261-2947/2017-05-18_AM-RL-XII_Palbociclib_D-264_BAnz.pdf.

5. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage VI – Off-Label-Use; Gemcitabin in der Monotherapie beim Mammakarzinom der Frau; vom 20. Mai 2010 [online]. Berlin (GER): G-BA; 2010. [Zugriff: 20.04.2018]. URL: https://www.g-ba.de/downloads/39-261-1129/2009-12-17-AMR6-SN-Gemcitabin_BAnz.pdf.

6. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über Empfehlungen zur Aktualisierung der Anforderungen an strukturierte Behandlungsprogramme für Patientinnen mit Brustkrebs und zur Aktualisierung der Anforderungen an die Dokumentation an strukturierte Behandlungsprogramme für Patientinnen mit Brustkrebs vom 17. März 2011 [online]. Berlin (GER): G-BA; 2011. [Zugriff: 20.04.2018]. URL: https://www.g-ba.de/downloads/39-261-1309/2011-03-17-DMP-Brustkrebs-Empfehlungen%20zur%20Aktualisierung.pdf.

7. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von Strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V: in der Fassung vom 16. Februar 2012; veröffentlicht im Bundesanzeiger (BAnz AT 18. Juli 2012 B3); in Kraft getreten am 19. Juli 2012; zuletzt geändert am 21. Juli 2016; veröffentlicht im Bundesanzeiger (BAnz AT 14. Oktober 2016 B3); in Kraft getreten am 1. Januar 2017 [online]. Berlin (GER): G-BA; 2017. [Zugriff: 20.04.2018]. URL: https://www.g-ba.de/downloads/62-492-1274/DMP-RL_2016-07-21_iK-2017-01-01.pdf.

8. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Addendum zum Auftrag A16-74 (Palbociclib); Addendum; Auftrag A17-15 [online]. Köln (GER): IQWiG; 2017. [Zugriff: 20.04.2018]. (IQWiG-Berichte; Band 508). URL: https://www.iqwig.de/download/A17-15_Palbociclib_Addendum-zum-Auftrag-A16-74_V1-0.pdf.

9. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Aromatasehemmer beim Mammakarzinom der Frau ; Abschlussbericht; Auftrag A10-03 [online]. Köln (GER): IQWiG; 2016. [Zugriff: 20.04.2018]. (IQWiG-Berichte; Band 437). URL:

https://www.iqwig.de/download/A10-03_Abschlussbericht_Aromatasehemmer-beim-Mammakarzinom.pdf.

10. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Palbociclib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A16-74 [online]. Köln (GER): IQWiG; 2017. [Zugriff: 20.04.2018]. (IQWiG-Berichte; Band 491). URL: https://www.iqwig.de/download/A16-74_Palbociclib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

11. **Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG).** Systematische Leitlinienrecherche und -bewertung sowie Extraktion relevanter Empfehlungen für das DMP Brustkrebs; Abschlussbericht; Auftrag V12-02 [online]. Köln (GER): IQWiG; 2014. [Zugriff: 20.04.2018]. (IQWiG-Berichte; Band 224). URL: https://www.iqwig.de/download/V12-02_Abschlussbericht_Leitlinienrecherche-und-bewertung-fuer-das-DMP-Brustkrebs.pdf.

12. **Lee CI, Goodwin A, Wilcken N.** Fulvestrant for hormone-sensitive metastatic breast cancer. Cochrane Database of Systematic Reviews [online]. 2017(1):Cd011093. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011093.pub2/abstract.

13. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften).** Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 4.0 [online]. AWMF-Register-Nr. 032-045OL. Berlin (GER): Deutsche Krebsgesellschaft; 2017. [Zugriff: 20.04.2018]. URL: http://www.awmf.org/uploads/tx_szleitlinien/032-045OLl_S3_Mammakarzinom_2017-12.pdf.

14. **Lin WZ, Xu QN, Wang HB, Li XY.** 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. Breast Cancer 2017;24(3):345-352.

15. **National Comprehensive Cancer Network (NCCN).** Breast Cancer: NCCN Evidence Blocks; Version 4.2017 [online]. Fort Washington (USA): NCCN; 2018. [Zugriff: 20.04.2018]. URL: https://www.nccn.org/professionals/physician_gls/pdf/breast_blocks.pdf.

16. **National Comprehensive Cancer Network (NCCN).** Breast Cancer; Version 1.2018 [online]. Fort Washington (USA): NCCN; 2018. [Zugriff: 20.04.2018]. (NCCN Clinical Practice Guidelines in Oncology). URL: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

17. **National Institute for Health and Care Excellence (NICE).** Advanced breast cancer: diagnosis and treatment [online]. 08.2017. London (GBR): 2009. [Zugriff: 20.04.2018]. (NICE Clinical guideline; Band 81). URL: https://www.nice.org.uk/guidance/cg81/evidence/full-guideline-pdf-242246993.

18. **National Institute for Health and Care Excellence (NICE).** Everolimus with exemestane for treating advanced breast cancer after endocrine therapy [online]. 12.2016. London (GBR): NICE; 2016. [Zugriff: 20.04.2018]. (NICE Technology appraisal guidance; Band 421). URL: https://www.nice.org.uk/guidance/TA421.

19. **Qiao L, Liang Y, Mira RR, Lu Y, Gu J, Zheng Q.** Mammalian target of rapamycin (mTOR) inhibitors and combined chemotherapy in breast cancer: a meta-analysis of randomized controlled trials. Int J Clin Exp Med 2014;7(10):3333-3343.

20. **Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, et al.** Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016;34(25):3069-3103.

21. **Wildiers H, Stordeur S, Vlayen J, Scholten R, Wetering F, Bourgain C, et al.** Breast cancer in women: diagnosis, treatment and follow-up; 3rd Ed. [online]. Belgian Health Care Knowledge Centre (KCE); 2013. [Zugriff: 20.04.2018]. (KCE Report; Band 143). URL: http://kce.fgov.be/sites/default/files/page_documents/KCE_143_Breast_cancer_0.pdf.

22. **Wilson FR, Varu A, Mitra D, Cameron C, Iyer S.** Systematic review and network meta-analysis comparing palbociclib with chemotherapy agents for the treatment of postmenopausal women with HR-positive and HER2-negative advanced/metastatic breast cancer. Breast Cancer Res Treat 2017;166(1):167-177.

Anhang

1. Beith et al. 2016 [1]

Studiencharakteristik

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

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

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

*Year of publication or conference.

Studienergebnisse der Einzelstudien

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

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

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

2. Rugo et al. 2016 [20]

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.

Single studies:

Table 3. Efficacy Outcomes

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Survival (months)		CBR (%)*	Time to Initiation of Chemotherapy
				OS	PFS or TTP		
Single-agent v single-agent hormone therapies							
Phase II							
Lombart-Cussac[23]; SBCG 2001/03	Exemestane	First	47	Median, 19.9	Median TTP, 6.1	59.6	NR
	Anastrozole		50	48.3	12.1	68	NR
P				NS	NS		
Robertson[14,15]; FIRST	Fulvestrant	First	102	Median, 54.1 (*n* = 86)	Median TTP, 23.4	72.5	NR
	Anastrozole		103	48.4 (*n* = 84)	13.1	67.0	NR
P				**.041**	**.01**	.386 (primary end point)	
Ohno[24]; FINDER-1	Fulvestrant (250 mg/month)	Second	45	NR	Median TTP, 6.0	42.2	NR
	Fulvestrant (250 mg + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		51	NR	7.5	54.9	NR
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		47	NR	6.0	46.8	NR
Pritchard[25]; FINDER-2	Fulvestrant (250 mg per month)	Second	47	NR	Median TTP, 3.1	31.9	NR
	Fulvestrant (250 mg + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		50	NR	6.1	47.1	NR
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		46	NR	6.0	47.8	NR
Phase III							
Di Leo[21,26]; CONFIRM	Fulvestrant 250 mg	Second	374	**Median, 22.03**	**Median PFS, 5.5**	39.6	NR
	Fulvestrant 500 mg		362	**26.4**	**6.5**	45.6	NR
P				**< .05**	**< .05**	NS	
Iwata[22]	Exemestane	First	147	Median, not reached	Median, 13.8 (range, 10.8-16.5)	75 (range, 66.7-82.1)	NR
	Anastrozole		145	60.1	11.1 (range, 10.8-16.6)	77.3 (range, 69.1-84.3)	NR
P				NS	NS		
Xu[26]	Fulvestrant	Second	121	NR	Median TTP, 3.6	48.2	NR
	Anastrozole		113	NR	5.2	36.1	NR
P					NS		
Chia[20]; EFECT	Fulvestrant	Second	351	NR	Median PFS, 3.7	32.2	NR
	Exemestane		342	NR	3.7	31.5	NR
P					NS	NS	
Paridaens[27]	Exemestane	First	182	1 year, 86%; Median, 37.2	1-year PFS, 41.7%; Median, 9.9	NR	NR
	Tamoxifen		189	82%; 43.3	31.2%; 5.8	NR	NR
P				NS	NS		
Single-agent v combination endocrine therapies							
Phase II							
Johnston[30]; SoFEA	Fulvestrant + placebo	Second	231	19.4 (A *v* B)	4.8 (A *v* B)	NR	NR
	Fulvestrant + anastrozole		243	Median, 20.2	Median PFS, 4.4	NR	NR
P				NS	NS		
	Exemestane		249	21.6 (B *v* C)	3.4 (B *v* C)	NR	NR
P				NS	NS		

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Table 3. Efficacy Outcomes (continued)

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Survival (months)		CBR (%)*	Time to Initiation of Chemotherapy
				OS	PFS or TTP		
Phase III							
Bergh[13]; FACT	Anastrozole alone	First	256	38.2	10.2	NR	NR
	Fulvestrant + anastrozole		258	Median, 37.8	Median TTP, 10.8	NR	NR
P				NS	NS		
Mehta[12]; SWOG 0226	Anastrozole alone → fulvestrant	First	345	**Median, 41.3**	**PFS, 13.5**	70	NR
	Anastrozole + fulvestrant		349	**47.7**	**15**	73	NR
P				**.05**	**.05**		
Endocrine therapy ± HER2-targeted therapies							
Phase II							
Johnston[39]; MINT	Placebo	First	121	90%	14.0	NR	NR
	Anastrozole + AZD8931 20 mg		118	83%	10.9	NR	NR
	Anastrozole + AZD8931 40 mg		120	87%	13.8	NR	NR
P				NS	NS		
Phase III							
Burstein[40]; CALGB 40302	Fulvestrant + placebo	First	145	Median, 26.4	Median, 3.8	NR	NR
	Fulvestrant + lapatinib		146	30	4.7	NR	NR
P				NS	NS		
Huober[41]; eLEcTRA	Letrozole alone	First	31	NR	3.3	39	NR
	Letrozole + trastuzumab		26	NR	TTP, 14.1	65	NR
P				NS	NS	.06	
Schwarzberg[42] Johnston[5]	Letrozole + placebo	First	108	Median, 32.3	**Median PFS, 3.0**	**29**	NR
	Letrozole + lapatinib		111	33.3	**8.2**	**48**	NR
P				NS	**< .05**	**< .05**	
Kaufman[6]; TAnDEM	Anastrozole alone	First	104	Median, 23.9	**PFS, 2.4 (range, 2-4.6)**	**27.9 (range, 19.5-37.5)**	NR
	Trastuzumab + anastrozole		103	28.5	**4.8 (range, 3.7-7.0)**	**42.7 (range, 33-52.9)**	NR
P				NS	**< .05**	**< .05**	
Endocrine therapy ± mTOR inhibitors							
Phase II							
Bachelot[43]; GINECO	Tamoxifen	First	57	**Median not yet reached**	**Median TTP, 4.5**	**42**	NR
	Tamoxifen + everolimus		54	**32.9**	**8.6**	**61**	NR
P				**< .05**	**< .05**	**< .05**	
Phase III							
Wolff[44]; HORIZON	Letrozole + placebo	First	555	NR	Median, 9.0	NR	NR
	Letrozole + temsirolimus		555	Median, NR	8.9	NR	NR
P				NS	NS		
Piccart[45] Yardley[50] Baselga[4]; BOLERO-2	Exemestane + placebo	Second	239	26.2	**Median PFS, 3.2**	**25.5**	NR
	Everolimus + exemestane		485	31.0	**7.4**	**50.5**	NR
P				.14	**< .05**	**< .05**	
Endocrine therapy ± CDK 4/6 inhibitor							
Phase II							
Finn[7]; PALOMA-1	Letrozole alone	First	81	33.3	10.2	58	NR
	Letrozole + palbociclib		84	37.5	20.2	81	NR
P				.42	**< .001**	**< .001**	

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Table 3. Efficacy Outcomes (continued)

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Survival (months)		CBR (%)*	Time to Initiation of Chemotherapy
				OS	PFS or TTP		
Phase III							
Turner[17]; PALOMA-3	Fulvestrant + placebo	≥ Second	171	NR	3.8	19	NR
	Fulvestrant + palbociclib		347	NR	9.2	34	NR
P					**< .001**	**< .001**	
Endocrine therapy ± novel agents							
Endocrine therapy ± RET, VEGFR, and EGFR TKI							
Phase II							
Clemons[46]; OCOG-Zamboney	Fulvestrant + placebo	First	68	69.1%	4.8	NR	NR
	Fulvestrant + vandetanib		61	73.7%	6	NR	NR
P				NS	NS		
Endocrine therapy ± IGFR antibody							
Phase II							
Robertson[47]	Placebo + fulvestrant or exemestane	Second	50	Not reached	5.7	NR	NR
	Ganitumab + fulvestrant or exemestane		106	22.2 months	Median PFS, 3.9	NR	NR
P				**.025** (favors placebo)	NS		
Endocrine therapy ± VEGF antibody							
Phase III							
Martin[48]; LEA	Letrozole or fulvestrant	First	184	51.8	14.4	67.4	NR
	Letrozole or fulvestrant + bevacizumab		190	52.1	19.3	76.8	NR
P				NS	NS	**.041**	
Dickler[49]; CALGB 40503	Letrozole	First	170	44	16	62	NR
	Letrozole + bevacizumab		173	47	20	80	NR
P				NS	**.016**	**.005**	
Endocrine therapy ± HDAC inhibitor							
Phase II							
Yardley[50]; ENCORE	Exemestane + placebo	Second	66	**Median PFS, 19.8**	Median, 2.3	25.8	NR
	Exemestane + entinostat		64	**28.1**	4.3	28.1	NR
P				**< .05**	NS	NS	
Endocrine therapy ± pan-PI3K inhibitor							
Phase II							
Krop[51]	Fulvestrant + placebo	Second	79	NR	5.1	6.3 (ORR)	NR
	Fulvestrant + pictilisib		89	NR	6.6	7.9	NR
P					NS		
Phase III							
Baselga[52]	Fulvestrant + placebo	Second	571	NR	**5.0 (range, 4.0-5.2)**	7.7 months (ORR)	NR
	Fulvestrant + buparlisib		576	NR	**6.9 (range, 6.8-7.8)**	11.8 months	NR
P					**< .001**		

Abbreviations: CBR, clinical benefit rate; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; GINECO, Groupe d'Investigateurs Nationaux pour l'Étude des Cancers Ovariens; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2HR, hormone receptor; IGFR, insulin-like growth factor receptor; mTOR, mammalian target of rapamycin; NR, not reported; NS, not significant; ORR, overall response rate; OS, overall survival PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; RET, rearranged during transfection; TKI, tyrosine kinase inhibitor; TTP, time to progression; VEGFR, vascular endothelial growth factor receptor.

*CBR is defined as the number of patients with complete response, partial response, and stable disease.