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-120-Ribociclib

Stand: August 2018

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

Ribociclib
zur Behandlung des HR-positiven/HER2-negativen, fortgeschrittenen/metastasierten Brustkrebs in Kombination mit einem Aromatasehemmer oder Fulvestrant

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
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: • Ribociclib: Beschluss vom 16. März 2018 • 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:	
Ribociclib L01XE42 Kisqali®	Geplantes neues Anwendungsgebiet laut Beratungsanforderung: „Kisqali wird in Kombination mit einem Aromatasehemmer oder Fulvestrant zur Behandlung von Patienten mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom angewendet. 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.
Toremifen L02BA02 Fareston®	First-line Behandlung des hormonabhängigen metastasierenden Mammakarzinoms bei postmenopausalen Patientinnen. Fareston kann bei Patientinnen mit Östrogenrezeptor-negativen Tumoren nicht empfohlen werden.
Fulvestrant L02BA03 Faslodex®	Faslodex® ist angezeigt als Monotherapie zur Behandlung von Östrogenrezeptor-positivem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom bei postmenopausalen Frauen: • die keine vorhergehende endokrine Therapie erhalten haben, oder • mit Rezidiv während oder nach adjuvanter Antiöstrogen-Therapie oder bei Progression der Erkrankung unter Antiöstrogen-Therapie. -in Kombination mit Palbociclib zur Behandlung des Hormonrezeptor-(HR)-positiven humanen Wachstumsfaktor-Rezeptor-2-(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinoms bei Frauen, die eine vorhergehende endokrine Therapie erhalten haben

II. Zugelassene Arzneimittel im Anwendungsgebiet

Aromatase-Inhibitoren (nicht-steroidal):	
Anastrozol L02BG03 Arimidex®	Arimidex® ist angezeigt für die: • Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen. • Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen. • Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen, die bereits 2 bis 3 Jahre adjuvant Tamoxifen erhalten haben.
Letrozol L02BG04 Femara®	• Adjuvante Therapie postmenopausaler Frauen mit hormonrezeptor-positivem primärem Mammakarzinom. • Erweiterte adjuvante Therapie des hormonabhängigen primären Mammakarzinoms bei postmenopausalen Frauen nach vor-heriger adjuvanter Standardtherapie mit Tamoxifen über 5 Jahre. • First-Line-Therapie des hormonabhängigen fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen. • Behandlung des Mammakarzinoms im fortgeschrittenen Stadium nach Rezidiv oder Progression der Erkrankung bei Frauen, die sich physiologisch oder nach einem künstlichen Eingriff in der Postmenopause befinden und die zuvor mit Antiöstrogenen 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

II. Zugelassene Arzneimittel im Anwendungsgebiet

Medroxyproges-teronacetat L02AB02 MPA Hexal®	Zur palliativen Behandlung bei folgenden hormonabhängigen Tumoren: • metastasierendes Mammakarzinom • […].
Gonadotropin-Releasing-Hormon-Analoga:	
Leuprorelin L02AE02 Enantone-Gyn®	Mammakarzinom prä- und perimenopausaler Frauen, sofern eine endokrine Behandlung angezeigt ist.
Goserelin L02AE03 Zoladex®	Behandlung von Patientinnen mit Mammakarzinom (prä- und perimenopausale Frauen), bei denen eine endokrine Behandlung angezeigt ist.
Proteinkinase-Inhibitoren:	
Everolimus L01XE10 Afinitor®	Hormonrezeptor-positives, fortgeschrittenes Mammakarzinom: Afinitor wird in Kombination mit Exemestan zur Therapie des Hormonrezeptor-positiven, HER2/neu-negativen, fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen ohne symptomatische viszerale Metastasierung angewendet, nachdem es zu einem Rezidiv oder einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.
Palbociclib L01XE33 IBRANCE®	IBRANCE ist angezeigt zur Behandlung von Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen lokal fortgeschrittenen oder metastasierten Brustkrebs: • in Kombination mit einem Aromatasehemmer • in Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinizing Hormone-Releasing Hormone) kombiniert werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Monoklonale Antikörper:	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Paclitaxel zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet. Bevacizumab wird in Kombination mit Capecitabin zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet, bei denen eine Behandlung mit anderen Chemotherapie-Optionen, einschließlich Taxanen oder Anthracyclinen, als nicht geeignet angesehen wird. Patienten, die innerhalb der letzten 12 Monate Taxan- und Anthracyclin-haltige Therapieregime im Rahmen der adjuvanten Behandlung erhalten haben, sollten nicht mit Avastin in Kombination mit Capecitabin therapiert werden.
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Liposomales Doxorubicin L01DB01 Caelyx®	Caelyx® ist indiziert: Als Monotherapie bei Patientinnen mit metastasierendem Mammakarzinom mit erhöhtem kardialen Risiko.
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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

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Abkürzungsverzeichnis

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

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

1 Indikation

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

Hinweis

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

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.

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3 Ergebnisse

3.1 IQWiG Berichte/G-BA Beschlüsse

G-BA, 2017 [5].

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

Vgl. auch IQWiG, 2017 [8,10].

Anwendungsgebiet (laut Zulassung vom 09. November 2016):

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 vorangegangenen 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.

Ausmaß des Zusatznutzens

Für a1, a2, b1, b2:

Ein Zusatznutzen ist nicht belegt.

IQWiG, 2016 [9].

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

Fazit

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 Zweitlinientherapie des fortgeschrittenen Mammakarzinoms mit Aromatasehemmern.

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

Drittlinientherapie

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

G-BA, 2016 [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

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 Risikosituation 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 [6]

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

Fazit

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“

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).

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

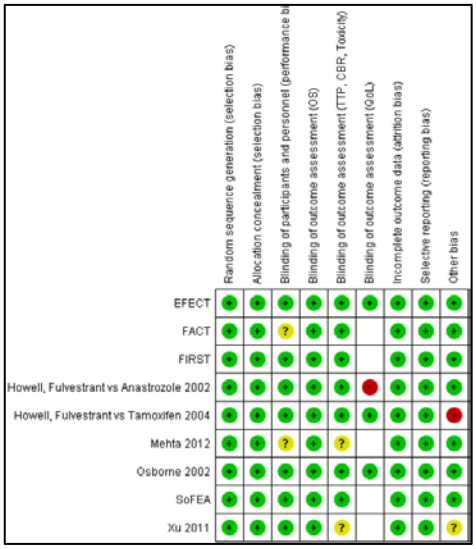
Anzahl eingeschlossener Studien: N=9 (n=4514)

Charakteristika der Population /der Studien:

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

Qualität der Studien:

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



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

OS:

- Overall: HR 0.97, 95% CI 0.87 to 1.09; (p=0.62; 2480 women; I^2=66%; high quality evidence) → no sign. difference

- Subgroup with approved dose (FIRST): HR 0.70, 95%CI 0.50 to 0.98 → superiority of fulvestrant (=firstline)

PFS:

- Overall: HR 0.95; 95%CI 0.89 to1.02 (4258 women; 9 studies; moderate-quality evidence)→ no significant differences
- Subgroup with approved dose (FIRST): HR of 0.66 (95% CI 0.47 to 0.93) 205 women
- first-line treatment: HR 0.93, 95%CI 0.84 to 1.03; 1996 women; 4 studies
- second-line treatment: HR 0.96, 95% CI 0.88 to 1.04; 2255 women; 5 studies

Clinical benefit rate:

- Overall: RR 1.03 (95% CI 0.97 to 1.10); 4105 women; high-quality evidence
- Firstline: RR 1.00, 95% CI 0.94 to 1.07; 1999 women; 4 studies)
- Secondline: RR 1.03, 95% CI 0.92 to 1.15; 2105 women, 5 studies)

Quality of life:

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

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

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

HER2 Status der eingeschlossenen Studien unklar

3.3 Systematische Reviews

Beith J et al., 2016 [2].

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

Fragestellung

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

Methodik

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

Intervention/ Komperator (exclusion of adjuvant therapy):

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

Endpunkt:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

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

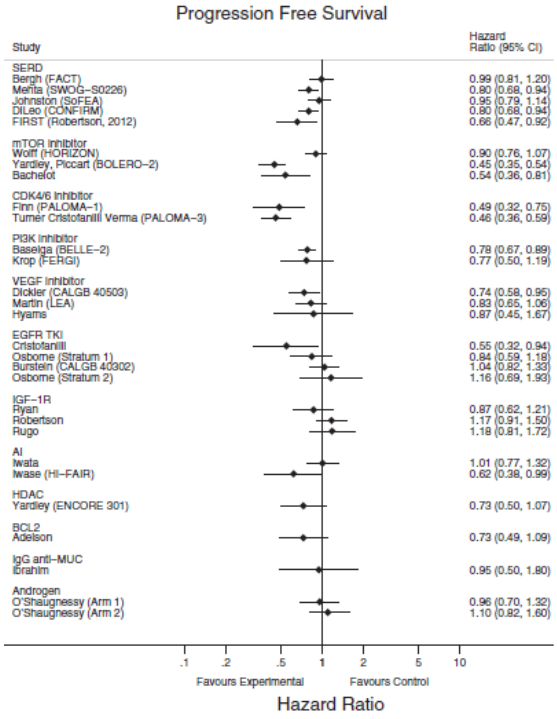
Charakteristika der Population:

- 555 (5%) had HER2 positive metastatic breast cancer.
- Interventions: addition of a trial agent to standard treatment (n=24), optimization strategies (n=8)
- 12 Studien=Firstline; 5 Studien= First- oder 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

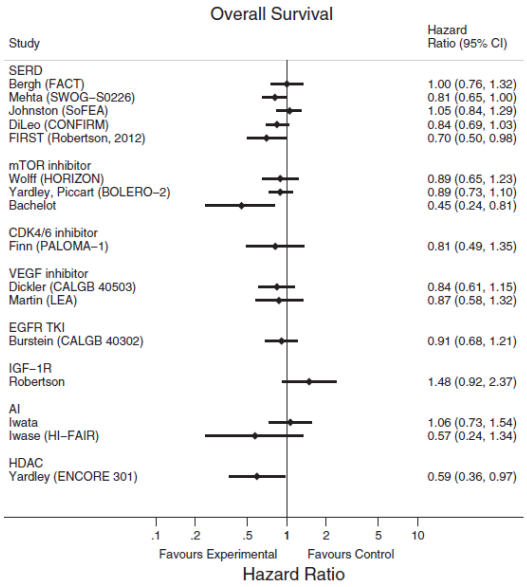
Studienergebnisse (**Anhang 1**: Charakteristik und Studienergebnisse auf Einzelstudienbasis)



- 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.

Lin WZ 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

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

Methodik

Population: metastatic breast cancer patients progressed on previous endocrine treatment

Intervention: targeted therapy plus fulvestrant

Komparator: fulvestrant plus placebo

Endpunkt:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien: Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien: N=8

Charakteristika der Studien/Population:

Table 2 Characteristics of studies in the meta-analysis

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

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

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

Studienergebnisse:

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

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

Fazit der Autoren

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

Kommentare zum Review

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

Ramos-Esquivel A et al., 2018 [19].

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

Fragestellung

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

Methodik

Population: metastatic HR-positive, HER2-negative breast cancer

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

Komparator: AI as first-line treatment

Endpunkte:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool: Risk of bias was categorized as ‘low risk’, ‘high risk’, or as ‘unclear risk

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

Ergebnisse

Anzahl eingeschlossener Studien: N=3

- Nur 1 Studie mit im AWG zugelassenen Medikament: PALOMA-2 (Ergebnisdarstellung auf diese Studie beschränkt)

Charakteristika der Population: PALOMA-2

- Postmenopausal women with locoregionally recurrent or metastatic disease
- No prior systemic anti-cancer therapy for advanced ER+ disease

Qualität der Studien:

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

Studienergebnisse:

Results of PALOMA-2 (Palbociclib + Letrozole vs Letrozole)

- PFS HR 0,58 (95% CI 0,46; 0,73)
- ORR: RR 1,55 (95% CI 1,07; 2,24)
- Clinical benefit rate: RR 2,2 (95% CI 1,43; 3,45)
- Treatment related side effects (grade 3-4): RR 9,68 (95% CI 6,65; 14,09)

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

- Nur 1 der im Review untersuchten Medikamente im AWG zugelassen (Palbociclib), Ergebnisdarstellung auf Palbociclib-Studie PALOMA-2 beschränkt
- Patientenrelevanz der Wirksamkeits-EP unklar

Zhang J et al. 2017 [22]

Efficacy and safety of endocrine monotherapy as first-line treatment for hormone-sensitive advanced breast cancer: A network meta-analysis

Fragestellung

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

Methodik

Population:

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

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

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

Komparator: k. A.

Endpunkte: ORR, TTP, PFS, AE

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien: Cochrane Collaboration Risk of Bias tool

Statistische Methoden:

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

Ergebnisse

Anzahl eingeschlossener Studien: N=8

Charakteristika der Studien

Characteristics of included studies.

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

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

Qualität der Studien:

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

Ergebnisse:

Direct pairwise metaanalyses

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

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

Meta-analysis of direct comparisons for safety

Comparisons	Hot flashes			Weight gain			Nausea			Bone pain		
	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P	OR (95% CI)	I^2	P
Tamoxifen vs Anastrozole	1.25 (0.77,2.04)	64.2	0.095	1.40 (0.56,3.49)	0.2	0.317	0.89 (0.65,1.22)	0.0	0.802	0.97 (0.52,1.83)	-	-
Exemestane vs Anastrozole	1.64 (0.91,2.98)	-	-	2.29 (0.78,6.78)	-	-	-	-	-	0.49 (0.09,2.80)	-	-

Fulvestrant 250 vs Tamoxifen	**0.66 (0.44,0.98)**	-	-	1.54 (0.45,5.33)	-	-	0.55 (0.28,1.07)	-	-	-	-	-
Letrozole vs Tamoxifen	1.19 (0.84,1.69)	-	-	-	-	-	0.90 (0.63,1.30)	-	-	1.09 (0.78,1.52)	-	-
Exemestane vs Tamoxifen	0.88 (0.58,1.35)	-	-	1.58 (0.90-2.79)	-	-	0.84 (0.50,1.43)	-	-	0.92 (0.60,1.41)	-	-
Fulvestrant 500 vs Anastrozole	0.94 (0.42,2.11)	-	-	-	-	-	-	-	-	-	-	-

Direct MA results suggested that

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

Network meta-analysis

Netzwerkgeometrie:

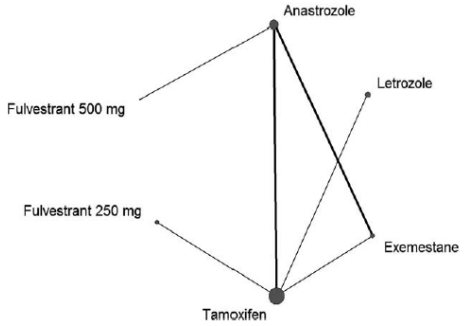


Figure 2. Network of eligible comparisons for the network meta-analysis for efficacy. The size of the nodes is proportional to the number of randomized participants (sample size), and the width of the lines is proportional to the number of trials comparing each pair of treatments.

Assessment of Consistency:

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

Results of NMA:

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

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

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

Ranking for efficacy with fixed-effects model:

Ranking for ORR

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

Probability of treatment rankings for TTP/PFS

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

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

Anmerkung/Fazit der Autoren

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

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

Kommentare zum Review

- Aussagesicherheit der Netzwerkmetaanalyseergebnisse eingeschränkt; keine Angaben zur Überprüfung der Transitivitätsannahme in der Publikation vorliegend (Prüfung der Verteilung wichtiger Effektmodifikatoren über die verschiedenen Vergleiche)

Ayyagari R. et al., 2018 [1]

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

Fragestellung

To quantitatively synthesize the available evidence on progression-free survival (PFS) associated with endocrine therapies first-line treatments for HR+/HER2– mBC among postmenopausal women,

To evaluate the efficacy of these agents in pre-identified patient populations in an effort to identify subsets of patients most likely to benefit from novel targeted therapies (TT) as well as to explore comparative efficacy in more homogeneous settings

Methodik

Population:

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

Intervention:/Komparator:

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

Endpunkte: PFS

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien: Cochrane Risk of Bias tool

Statistische Analysen: Network Meta-analysis

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

Ergebnisse

Anzahl eingeschlossener Studien: N=5

Charakteristika der Studien

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

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

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

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

Qualität der Studien

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

Supplementary Table 4. Risk of bias assessment table.

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

Ergebnisse

PFS - Direkte Vergleiche:

Table III. Summary of trial-level treatment effects.

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

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

Netzwerkgeometrie:

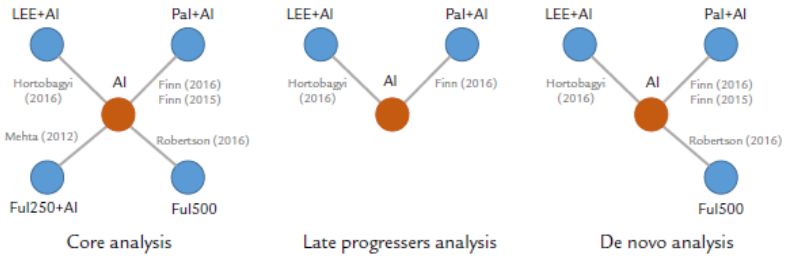


Figure 2. Evidence network according to type of analysis. AI = aromatase inhibitor; Ful250 = fulvestrant 250 mg; Ful500 = fulvestrant 500 mg; LEE = ribociclib; Pal = palbociclib. The references in the figure are: Hortobagyi (2016)[17], Finn (2015)[15], Finn (2016)[16], Mehta (2012)[13], Robertson (2016)[12].

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

Treatment Comparisons for Core Analysis:

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

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

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

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

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

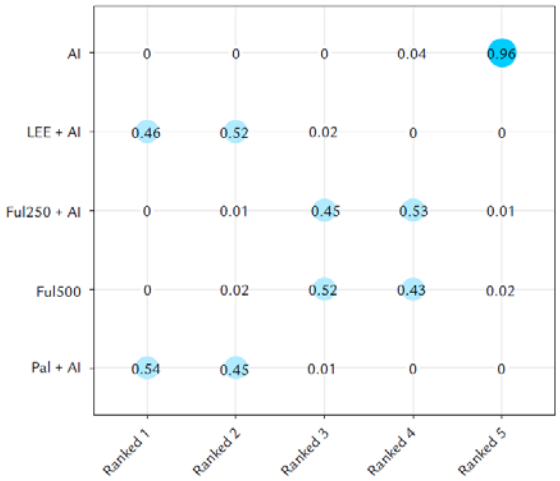


Figure 3. Ranking probabilities according to treatment, core analysis. AI = aromatase inhibitor; Ful250 = fulvestrant 250 mg; Ful500 = fulvestrant 500 mg; LEE = ribociclib; Pal = palbociclib.

Subgroup analyses:

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

Anmerkung/Fazit der Autoren

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

Kommentare zum Review

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

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

Fragestellung

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

Methodik

Grundlage der Leitlinie

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

Systematische Recherche, Auswahl und Bewertung von bestehenden Leitlinien:

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

Systematische Recherche, Auswahl und Bewertung der Primärliteratur und SR:

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

LoE

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

Formulierung der Empfehlungen und formale Konsensusfindung

- Entwurferstellung und Diskussion der Empfehlungen durch Arbeitsgruppen (nach Regeln des nominalen Gruppenprozesses)

- Konsentierung der Empfehlungen und der dazu gehörigen Empfehlungsgrade durch Leitliniengruppe im moderierten, formalen Konsensusverfahren (Nominaler Gruppenprozess).

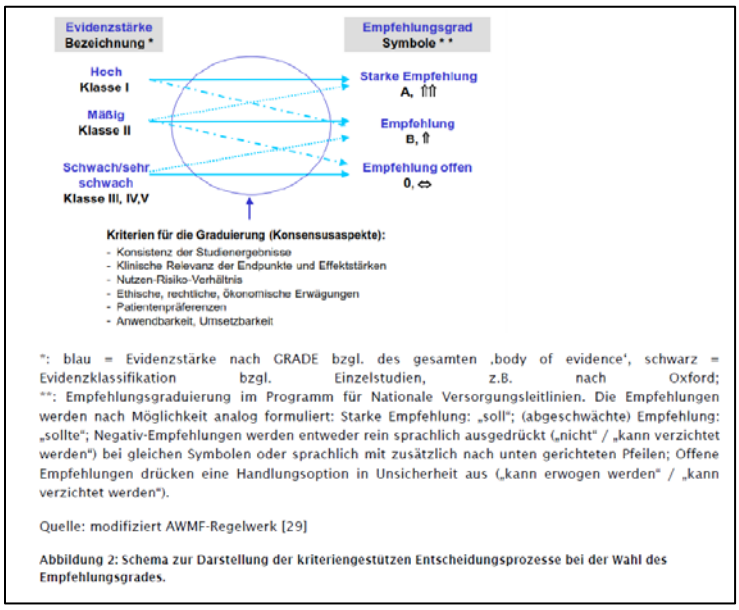
  GoR:

Tabelle 9: verwendete Empfehlungsgrade

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

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

Festlegung des Empfehlungsgrades



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

Quelle: modifiziert AWMF-Regelwerk [29]

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

Tabelle 10: Festlegungen hinsichtlich der Konsensstärke

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

Sonstige methodische Hinweise

Stand der LL: 01.12.2017, gültig bis 30.11.2022

Empfehlungen

Lokal fortgeschrittenes Mammakarzinom

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

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

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

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

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

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

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

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

5. Das rezidivierte oder metastasierte Mammakarzinom

5.4 Fernmetastasen

5.4.1. Systemische Therapie des metastasierten Mammakarzinoms

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

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

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

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

5.15.	Evidenzbasierte Empfehlung
	Ovarialsuppression und Tamoxifen bei prämenopausalen Patientinnen
Empfehlungsgrad A	Bei prämenopausalen Patientinnen ist die Ausschaltung der Ovarialfunktion (GnRH-Analoga, Ovarektomie) in Kombination mit Tamoxifen die Therapie der ersten Wahl, wenn die Therapie mit Tamoxifen nicht vor weniger als 12 Monaten beendet wurde. Alternativ kann unter Ausschaltung der Ovarfunktion wie bei postmenopausalen Patientinnen vorgegangen werden und die endokrine Therapie mit CDK 4/6 Inhibitoren kombiniert werden.
Level of Evidence 1b	Quellen: [29, 989, 1006, 1007]
	Starker Konsens

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

5.16.	Evidenz- /konsensbasierte Empfehlung
	Weitere Therapien bei prämenopausalen Patientinnen
Empfehlungsgrad 0	In der Folge kann in der Prämenopause eine Ovarialsuppression in Kombination z.B. mit einem Aromatasehemmer oder Fulvestrant ggf. in Kombination mit Palbociclib zum Einsatz kommen. Die Therapie kann somit unter Beibehaltung der ovariellen Suppression in Analogie zu der Behandlung postmenopausaler Patientinnen durchgeführt werden.
2c/EK	Quellen: [29, 1008, 1009]
	Starker Konsens

Quellen:
29. NICE. The National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009 [addendum 2014]; Available from: https://www.nice.org.uk/guidance/cg81/evidence/addendum-242246990
1008. Taylor, C.W., et al., Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol, 1998. 16(3): p. 994-9.
1009. Loibl, S., et al., Palbociclib (PAL) in combination with fulvestrant (F) in pre-/peri-menopausal (PreM) women with metastatic breast cancer (MBC) and prior progression on endocrine therapy–results from Paloma-3. J Clin Oncol, 2016. 34(suppl): p. abstr 524.

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

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

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

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

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

5.4.2. Chemotherapie des metastasierten Mammakarzinoms

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

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

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

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

Quellen:

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

Hintergrund:

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

- Cochrane Review von Dear et al. 2013:

- o keine signifikanten Unterschiede im Gesamtüberleben und progressionsfreien Überleben zwischen Kombinationstherapie und einer sequentiellen Monochemotherapie (OS HR 1,04 95% CI 0,93-1,16; p=0,45 / PFS HR1,11 95% CI 0,99-1,25; p=0,08).
- o signifikant höheres Ansprechen durch Kombi-Chemotherapie
- o höhere Toxizität durch Kombinationschemotherapie (febrile Neutropenien)
- o viele v.a. nicht hämatologische Nebenwirkungen in dieser Metaanalyse nicht beschrieben.
- o In CR betrachtete Szenarien einer sequentiellen Monochemotherapie: a) Wechsel der Monochemotherapie bei Progression oder b) festgelegter Wechsel der Monochemotherapien ohne Progression nach einigen Zyklen; Ergebnisse für beide Szenarien ähnlich

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

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

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

Bevacizumab beim metastasierten Mammakarzinom (1. Linie)

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

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

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

Rugo HS et al. 2016

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

Leitlinienorganisation/Fragestellung

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

1. Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for hormone receptor (HR) –positive metastatic breast cancer (MBC)?
    1.1 For postmenopausal women: What are the optimal sequence and duration?
    1.2 Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?
    1.3 For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?

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

2. Is there an optimal second- or later-line endocrine therapy for HR-positive MBC?
    2.1 Should other treatment or disease-free interval play a role in treatment selection?
    2.2 Which hormone therapy should be offered?
    2.3 What are the optimal timing, dose, and schedule of treatment?

3. How or should endocrine therapies be used in combination or sequence with:
    3.1 Mammalian target of rapamycin inhibitors (everolimus)?
    3.2 Cyclin-dependent kinase 4/6 inhibitors (palbociclib)?

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

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

6. In which patients or settings is hormone therapy recommended over chemotherapy?
    6.1 Is there a role for combined cytotoxic and endocrine therapies?
    6.2 What is the optimal duration of treatment with hormonal therapy?

7. Is there a role for additional biomarkers in the selection of treatment for patients with HR-positive disease?
    7.1 What is the role of genomic profiling or intrinsic subtypes in this population?

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

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

Methodik

<u>Grundlage der Leitlinie</u>

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

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

Recherche/Suchzeitraum:

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

LoE/ GoR

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

Sonstige methodische Hinweise

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

Empfehlungen

ASCO Key Guideline Recommendations for HR-positive MBC

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

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

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

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

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

First-line therapy for HR-positive metastatic breast cancer

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

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

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

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

Second-line therapy for HR-positive MBC

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

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

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

Targeted Therapy

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

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

Postmenopausal women

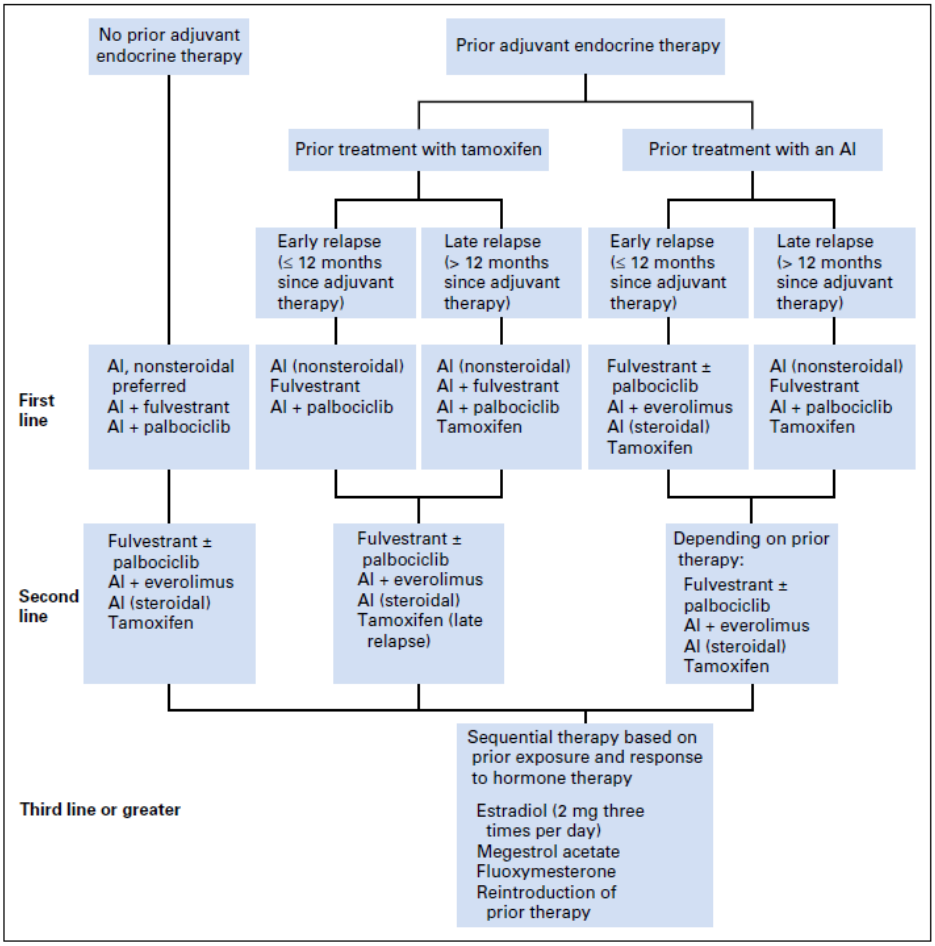


Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered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

Premenopausal women

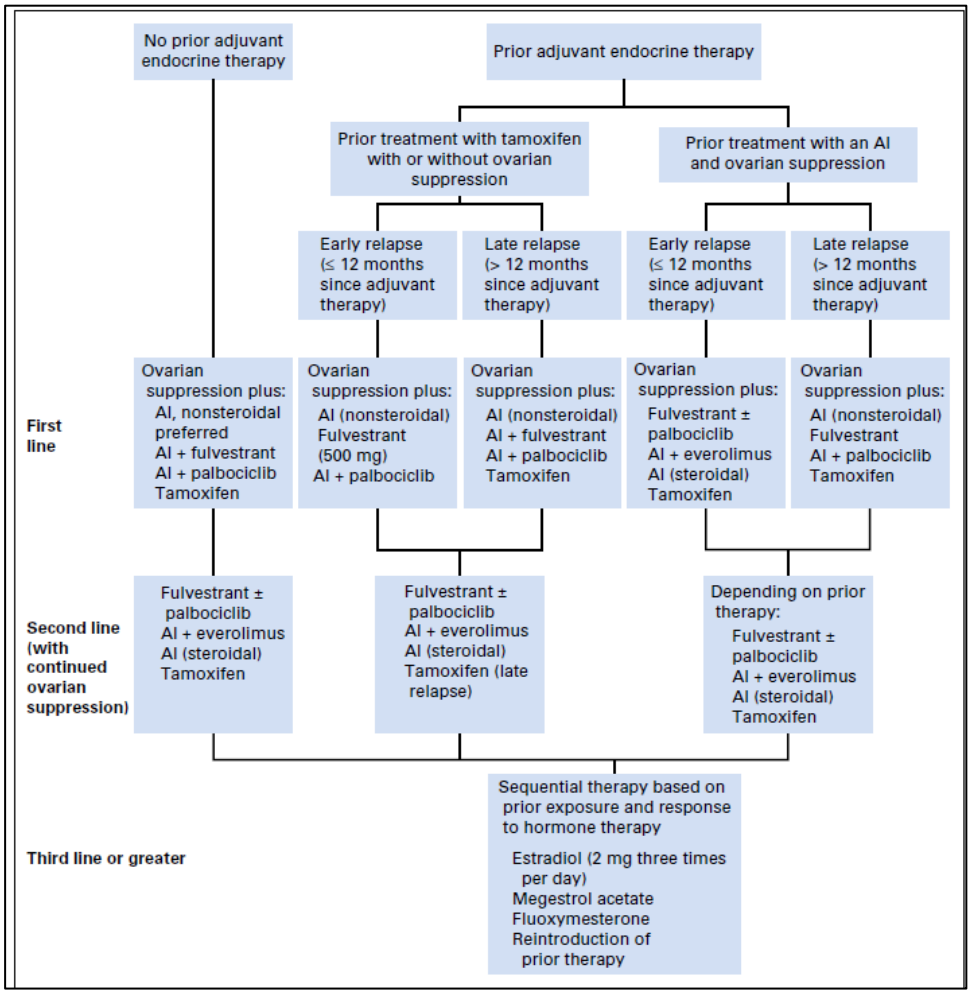


Fig 2. Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered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

Wildiers H et al., 2013 [21].

Belgian Health Care Knowledge Centre (KCE)

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

Leitlinienorganisation/Fragestellung

- collaboration between the College of Oncology and the KCE
- 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))

Empfehlungen

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.

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Chemotherapy

- Chemotherapy for patients with metastatic breast cancer is indicated for the following conditions **(expert opinion)**:
  - hormone-refractory or HR– tumours
  - rapidly progressive disease or symptomatic disease
  - life-threatening disease (e.g. diffuse lung or liver metastases, massive bone marrow metastases with pancytopenia)
- The choice between polychemotherapy and sequential single-agent chemotherapy should take into account the prognosis, performance status, need for rapid symptom control and toxicity profiles, with the ultimate goal of optimizing quality and quantity of life **(expert opinion)**.
- Anthracycline- and/or taxane-based regimens are to be preferred as first-line treatment **(1A evidence)**.
- In patients with anthracycline resistance or failure and who are taxane-naive, and are considered for further chemotherapy, taxane-based treatment (monotherapy or combination of a taxane with gemcitabine or capecitabine) should be used, taking into account quality of life, toxicity, characteristics of the disease and the ease of administration **(1A evidence)**.

Clinical evidence:

Multiple systematic reviews exist evaluating different chemotherapy regimens for women with metastatic breast cancer [175, 220-222]

A systematic review of 43 randomized trials (n = 9 742 women) suggests that polychemotherapy is associated with higher response rates and longer progression-free survival and a modest improvement in overall survival compared to single-agent treatment, but produces more adverse events including a decrease in white blood cell count, increased hair loss and nausea and vomiting [220]. On the other hand, the only major RCT [223] comparing sequential monotherapies with combined anthracyclines and taxanes did not demonstrate improved survival or quality of life with the latter approach, despite increased response rates [204].

The combined use of anthracyclines and taxanes increased objective response rate and time-to-progression in some trials. Moreover, overall survival was improved in two RCTs [225, 226]

Polychemotherapy compared to single-agent therapy obtained slightly superior results in overall survival in metastatic breast cancer women pretreated with anthracycline. In one phase III trial [227], the combination of capecitabine plus docetaxel resulted in significantly superior efficacy in time-to-disease progression (HR 0.65; 95%CI 0.54-0.78; median, 6.1 vs. 4.2 months), overall survival (HR 0.77; 95%CI 0.63-0.94; median, 14.5 vs.11.5 months), and objective tumour response rate (42% vs. 30%, p=0.006) compared with docetaxel. The combination resulted in significantly increased hematologic and non-hematologic toxicity. Another randomized phase III trial compared paclitaxel plus gemcitabine with paclitaxel [228]. The combination regimen was associated with an improved overall survival (18.6 months versus 15.8 months; log-rank p = 0.0489, with an adjusted Cox hazard ratio of 0.78 [95% CI 0.64-0.96; p = 0.0187]), a longer time-to-progression (6.14 vs. 3.98 months; log-rank p = 0.0002) and a better response rate (41.4% vs. 26.2%; p = 0.0002). The gemcitabine/paclitaxel arm was also associated with increased pain relief and better quality of life. However, there was more grade 3 to 4 neutropenia on combined therapy and grade 2 to 4 fatigue and neuropathy were slightly more prevalent. Data from these two RCTs demonstrated that the combination of a taxane with capecitabine or gemcitabine is superior to taxane alone in increasing overall survival in patients with metastatic breast cancer [204].

A randomized phase III trial compared docetaxel plus gemcitabine with docetaxel plus capecitabine and showed similar efficacy in terms of progression-free survival (median PFS was 8.05 months [95% CI, 6.60 to 8.71] for docetaxel plus gemcitabine and 7.98 [95% CI, 6.93 to 8.77] for docetaxel plus capecitabine), tumour response rate (32% in both arms) and overall survival. Time-to-failure was longer and non-hematologic toxicity was significantly lower in the docetaxel plus gemcitabine arm [229]. However, severe hematologic toxicity rates (grades 3 to 4 leukopenia) were higher in docetaxel plus gemcitabine group (78% vs. 66%; p=0.025), as was the transfusion rate (docetaxel plus gemcitabine, 17%; docetaxel plus capecitabine, 7%; p=0.0051).

References:

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Biological therapy

Bevacizumab:

- In women with metastatic breast cancer, adding bevacizumab to a systemic chemotherapy, either in first-line or in second-line therapy, cannot be recommended (**weak recommendation**).

Clinical Evidence: Wagner et al

- evaluated OS, PFS and harms of VEGF-targeting therapies in patients with hormone-refractory or hormone-receptor negative metastatic breast cancer
- search of the electronic databases until September 8, 2011.
- overall risk of bias of this review was considered as low
- total number of seven RCTs, data from one register, and five ongoing trials examining the effect of bevacizumab in combination with chemotherapy
- Five of the included RCTs addressed (predominantly) HER-2 negative patients (with a maximum of 4% HER-2 positive patients)
- Overall survival did not differ significantly between the groups with and without bevacizumab, neither in first-line chemotherapy (HR=0.93; 95%CI 0.84-1.04), nor in second-line chemotherapy (HR=0.90; 95%CI 0.71-1.14) in HER-2 negative patients.
- Progression-free-survival was significantly better after treatment with bevacizumab in both first-line (HR=0.67; 95%CI 0.61-0.73) and second-line chemotherapy (HR=0.78; 95%CI 0.64-0.93).
- Significantly higher rates of grade 3/4 adverse events (OR=1.77; 95%CI 1.44-2.18) and serious adverse events (OR=1.41; 95%CI 1.13-1.75) were observed in patients treated with bevacizumab.

Conclusions

- Among women with HER-2 negative metastatic breast cancer, treated with bevacizumab in combination with chemotherapy versus chemotherapy alone:
- A difference in overall survival between bevacizumab in combination with first-line chemotherapy and first-line chemotherapy alone could neither be demonstrated nor refuted (Wagner 2012; **low level of evidence**).
- A difference in overall survival between bevacizumab in combination with second-line chemotherapy and second-line chemotherapy alone could neither be demonstrated nor refuted (Wagner 2012; **moderate level of evidence**).
- It is plausible that bevacizumab in combination with first-line chemotherapy has a positive effect on progression free survival as compared to first-line chemotherapy alone (Wagner 2012; **moderate level of evidence**).
- It is demonstrated that bevacizumab in combination with second-line chemotherapy has a positive effect on progression free survival in women with HER-2 negative metastatic breast cancer as compared to second-line chemotherapy alone (Wagner 2012; **high level of evidence**)
- It is plausible that bevacizumab in combination with first-line chemotherapy leads to more grade 3 or higher adverse events as compared to first-line chemotherapy alone (Wagner 2012; **moderate level of evidence**)
- There are indications that bevacizumab in combination with first or second-line chemotherapy leads to more serious adverse events as compared to first or second-line chemotherapy alone (Wagner 2012; **low level of evidence**)

References: Wagner et al. Vascularendothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database Syst Rev. 2012;7:CD008941.

Treatment of locoregional relapse

- A local recurrence in the thoracic wall should be treated preferentially with surgery and adjuvant radiotherapy whenever possible (1C evidence).
- A local recurrence after breast-conserving treatment should be treated by mastectomy (1C evidence).
- Systemic treatment for a completely excised locoregional recurrence should be discussed on a case by case basis in the multidisciplinary team meeting (expert opinion).

Clinical Evidence: Few trials exist on the use of systemic treatment for a locoregional recurrence that has been completely excised [66].
References: [66] Kwaliteitsinstituut voor de Gezondheidszorg (CBO) en Vereniging van Integrale Kankercentra (VIKC), V. Zuiden (Eds). Richtlijn Behandeling van het mamma-carcinoom 2005. Alphen aan den Rijn: 2005.

Partridge, AH et al., 2014 [18].

Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline

Leitlinienorganisation/Fragestellung

- American Society of Clinical Oncology (ASCO) Clinical Practice Guideline
- To identify optimal chemo- and targeted therapy for women with human epidermal growth factor 2 (HER2)– negative (or unknown) advanced breast cancer

Methodik

Grundlage der Leitlinie

- Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.
- Author's disclosure of potential conflict of interest available

Target Population :

- Women with advanced breast cancer (locally advanced/ nonresectable or metastatic disease treated with noncurative intent).
- HER2-negative status is not an eligibility criterion for the systematic review, and for many patients in the trials reviewed, HER2 status was not given.

Primary outcome measures:

- overall survival, progression-free survival, overall response, Clinical Benefit Rate, quality of life, and/or adverse events.

Recherche/Suchzeitraum:

- MEDLINE (Ovid):2009 through to May 2013 for first-line trials; 1993 through to May 2013 for second-line trials.
- Cochrane Library: 2009 through to current.
- Graue Literatur: annual meeting proceedings of ASCO (2012, 2013), San Antonio Breast Cancer Symposium (SABCS) (2011, 2012)

LoE/GoR

Study Quality Assessment:

- design aspects related to individual study quality were assessed by 1 reviewer (blinding, allocation concealment, placebo control, intention to treat, funding sources, etc)
- risk of bias is assessed as "low," "intermediate," or "high" for the identified evidence.

Definitions for Types of recommendation, Strengths of evidence Strengths of recommendation→ Anhang

Sonstige methodische Hinweise

- Keine direkte Verknüpfung der Empfehlungen mit der Literatur.
- Aus der Literaturübersicht wurde die Beschreibung der relevante systematische Reviews zu den jeweiligen Empfehlungen extrahiert und unter der Überschrift „Clinical Evidence" hinzugefügt.

Empfehlungen

RECOMMENDATIONS FOR CHEMOTHERAPY AND TARGETED THERAPY FOR WOMEN WITH HER2-NEGATIVE (OR UNKNOWN) ADVANCED BREAST CANCERBASED ON STANDARDIZED RATINGS OF CLINICAL BENEFITS + HARMS (A), EVIDENCE STRENGTH (B), AND RECOMMENDATION STRENGTH (C)

Empfehlung 1

Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for patients with hormone receptor–positive advanced/metastatic breast cancer, except for immediately life threatening disease or if there is concern regarding endocrine resistance.

A. The main benefit is less toxicity and better quality of life for the patient associated with endocrine therapy compared with chemotherapy (**potential benefit: high**). The harm is that metastatic disease could progress rapidly and prove fatal if there is no response, but the risk of this is low (**potential harm: low**).
B. The quality of the evidence is intermediate, and is based on the NCCC systematic review.
C. The **strength of this recommendation is strong** and is supported by the evidence and expert consensus.
Qualifying statement: It should be noted that the basis for this recommendation is the relative likelihood of response to chemotherapy versus endocrine therapy and not the rapidity of response, for which there are no good data.

Clinical Evidence:
The prior systematic review[3] addressed the role of endocrine therapy compared with CT as first-line treatment for advanced hormone receptor–positive breast cancer. One high-quality systematic review[4] was used to form recommendations, which entailed an analysis of 10 randomized controlled trials (RCTs) comparing CT with endocrine treatments. In that review, no difference was found in OS, and no data were available on QoL or AEs, but the authors report that CT was associated with higher levels of toxicity, especially nausea, vomiting, and alopecia. They recommended endocrine therapy first unless disease was rapidly progressing, in which case CT was appropriate, as a fast response was medically necessary.

Empfehlung 2

Sequential single-agent chemotherapy rather than combination therapy should be offered, although combination regimens may be considered for immediately life-threatening disease for which time may allow only one potential chance for therapy.

A. The benefit is less toxicity and better quality of life (**potential benefit: high**). The potential harm is for rapidly progressing, life-threatening disease to escape control if response to a single agent isn't achieved (**potential harm: high**). The main benefit is there is less toxicity and better quality of life for the patient associated with sequential single agent chemotherapy compared with combination chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly if there is no response, but the risk of this is low (potential harm: low).
B. The evidence quality is high, and includes a large RCT.
C. The strength of this recommendation is strong.

Clinical Evidence from RCTs:
An RCT comparing first-line sequential single-agent vs combination treatment reported by Sledge et al,[5] included a total of 731 patients randomly assigned to one of three arms: doxorubicin and paclitaxel together, doxorubicin until progression then paclitaxel, or paclitaxel until disease progression then doxorubicin. Tumor response rate and time to treatment failure (TTF) were significantly lower in either of the two sequential arms when compared with the combined therapy, but they did not differ from each other. There were, however, no significant differences between the duration of OS between arms, and the combination arm was associated with more severe adverse effects.

The NCCC review[3] also reported that combination regimens were associated with a survival benefit compared with single-agent regimens in the first-line setting, but noted that these conclusions were limited by lack of control for subsequent treatments and lack of QoL data. There is evidence from a pivotal trial reported by O'Shaughnessy et al,[6] as well as the two follow-up articles reported by Leonard et al[7] and Miles et al[8] that single-agent sequential therapy is likely no different from combination regimens, although combination regimens are associated with greater, and more severe, AEs.

Clinical Evidence from SR:

Combination therapy has demonstrated increases in treatment response rates,[15,16] but not in OS, compared with single agent regimens.

Table 1. Main Findings From Systematic Reviews and/or Meta-Analyses (continued)

Study	Publication Type	Evidence Base	Main Findings
Butters et al, 2010[15]	Systematic review	17 trials including 2,674 patients	• In comparisons between two-drug combinations and three or more drug combinations, no differences were detected for OS or TTP, although differences were detected in ORR. • An increase in the number of drugs was associated with an increase in the incidence of adverse effects.
Carrick et al, 2009[16]	Systematic review	43 trial including 9,742 patients	• When comparing single-agent regimens with combination regimens, significant differences were detected in favor of combination regimens for OS, TTP, and ORR. • Combination regimens were associated with increases in adverse effects in white cell count, alopecia, nausea, and vomiting.

Empfehlung 3

With regard to targeted agents, the role of bevacizumab is controversial, and this therapy should be considered (where available) with single-agent chemotherapy only when there is immediately life-threatening disease or severe symptoms, in view of improved response rates (similar to Recommendation 2 regarding the use of combination chemotherapy). It is recognized that there is not currently an approved indication for bevacizumab in the United States because the weight of evidence shows no significant survival benefit. Other targeted agents should not be used either in addition to, or as a replacement for, chemotherapy in this setting outside of a trial

A. The benefit is improved disease control (**potential benefit: moderate**). The potential harms are unique toxicity, increased costs, and barriers to access (**potential harm: high**)
B. The quality of the evidence is high and is supported by multiple trials.
C. The strength of the recommendation is moderate and is based on both evidence and expert consensus.
Qualifying statement: Bevacizumab added to single-agent chemotherapy improves response and progression-free survival but not overall survival

Clinical Evidence from SR:
The addition of bevacizumab to CT has demonstrated improvements in objective response rate (ORR) and PFS[17,26,28] but not in duration of response[17,26,28] or OS. One study reported no differences in AEs associated with the addition of bevacizumab,[26] whereas another reported increased rates of hypertension.[17]

Table 1. Main Findings From Systematic Reviews and/or Meta-Analyses

Study	Publication Type	Evidence Base	Main Findings
Petrelli et al, 2012[26]	Meta-analysis	Two studies including 1,003 patients,	• Addition of bevacizumab to CT regimens resulted in significant increases in ORR and PFS. • No differences detected in duration of responses. • Addition of bevacizumab did not increase adverse events (in particular febrile neutropenia). • Bevacizumab should be investigated further in the second-line setting.
Cuppone et al, 2011[17]	Meta-analysis	Five RCTs including 3,841 patients	• Adding bevacizumab to first-line combination regimens significantly improved PFS but at a cost of significantly higher incidences of hypertension.
Valachis et al, 2010[28]	Meta-analysis	Five RCTs including 3,163 patients	• Adding bevacizumab to first-line combination regimens significantly improved PFS and ORR

Empfehlung 4

No single agent has demonstrated superiority in the treatment of patients with advanced breast cancer, and there are several active agents appropriate for first-line chemotherapy. The evidence for efficacy is strongest for taxanes and anthracyclines. Other options include capecitabine, gemcitabine, platinum-based compounds, vinorelbine, and ixabepilone. Treatment selection should be based on previous therapy, differential toxicity, comorbid conditions, and patient preferences. Specifically, drugs for which clinical resistance has already been shown should not be reused

A. The benefit is a patient-tailored approach with potential improvements in disease control and quality of life (**potential benefit: high**). The harm is the potential use of a less active agent (**potential harm: low**)
B. The evidence quality supporting the activity of a number of single agents is high, but there is insufficient evidence to support superiority of any single agent.
C. The strength of the recommendation is strong and is based on the available evidence and expert consensus

Clinical Evidence from SR:
Anthracyclines plus taxanes are no more effective than anthracyclines plus cyclophosphamides for any outcomes.[29]
Capecitabine has demonstrated superior median survival compared with cyclophosphamide-methotrexate-fluorouracil(CMF), with an acceptable toxicity profile,[25] and further benefits have been found when combining capecitabine with bevacizumab.[19]
Taxane combination regimens were superior to taxane monotherapy for TTP,[13] PFS,[30] and partial response[30] rates but not for OS. Furthermore, taxane monotherapy was associated with significantly fewer AEs, especially grade 3 and higher stomatitis and diarrhea.[13,27,30]

Table 1. Main Findings From Systematic Reviews and/or Meta-Analyses

Study	Publication Type	Evidence Base	Main Findings
O'Shaughnessy et al, 2012[25]	Systematic review	Seven prospective studies including 1,813 patients and four retrospective studies including 1,087 patients	• First-line capecitabine monotherapy demonstrated superior median survival compared with CMF combination therapy; all other comparisons for efficacy were nonsignificant. • Capecitabine monotherapy (1,000 mg/m^2 twice daily, for 14 d of a 21-d cycle) has proven efficacy in the first-line setting with acceptable adverse effects (lower myelosuppression), allowing for further cycles.
Belfiglio et al, 2012[13]	Meta-analysis	Three RCTs including 1,313 patients	• Comparisons made between docetaxel monotherapy and combinations including docetaxel detected superior TTP with the combination arms, but no differences in ORR or OS. • Combination docetaxel treatment was associated with higher incidences of grade 3 diarrhea and stomatitis.
Xu et al, 2011[30]	Meta-analysis	Four RCTs including 2,343 patients	• Comparisons made between taxane monotherapy and combinations including taxanes detected superior PFS and PR with the combination arms, but no differences were detected in 1-yr survival, clinical benefit rate, or CR. • Monotherapy was associated with significantly lower stomatitis and diarrhea.
Vriens et al, 2011 (SABCS abstract)[29]	Meta-analysis	Five RCTs in the metastatic setting (of 10 RCTs total), No. of patients NR.	• Pooling five RCTs that compared an anthracycline plus a taxane with an anthracycline plus a cyclophosphamide detected no difference in OS. • No difference in efficacy was detected between taxanes and cyclophosphamide.
Piccart-Gebhart et al, 2008[27]	Systematic review with meta-analysis	11 RCTs including 3,953 patients	Pooling trials comparing taxanes against combinations of taxanes plus anthracyclines found: • Single-agent taxane regimens were superior to single-agent anthracycline regimens for OS and ORR, but demonstrated inferior PFS. • Combination regimens with taxanes demonstrated superior ORR and PFS, but inferior OS.
Jassem et al, 2009[19]	Systematic review	Five RCTs including 1,178 patients	• No RCT reported an OS difference between arms. • Gemcitabine plus vinorelbine demonstrated superior PFS compared with vinorelbine alone. • Capecitabine plus bevacizumab demonstrated superior ORR compared with capecitabine alone. • Median OS for these patients typically remained < 16 mo.

Empfehlung 5

Chemotherapy regimens should not be specifically tailored to different breast cancer subtypes (eg, triple negative, lobular) at the present time due to the absence of evidence proving differential efficacies. In addition, in vitro chemoresistance assays should not be used to select treatment

A. The benefits are not omitting potentially efficacious treatment and cost-saving on in vitro assays (**potential benefit: high**)
B. Current evidence shows no convincing basis for either of these approaches
C. The strength of this recommendation is moderate, and is supported by expert consensus

Qualifying statement: This recommendation will need to be modified if ongoing or future research addressing this important issue suggests benefits of tailoring

Empfehlung 6

Second- and later-line therapy may be of clinical benefit and should be offered as determined by previous treatments, toxicity, coexisting medical conditions, and patient choice. As with first-line treatment, no clear evidence exists for the superiority of one specific drug or regimen. Active agents include those active in first-line treatment.

A. The benefit is further chance of disease control and symptomatic improvement (potential benefit: high). The harm is toxicity (potential harm: high).
B. The quality of the evidence ranges from high to low as reported in multiple randomized trials.
C. The strength of the recommendation is strong and is based on expert consensus

Qualifying statement: The most convincing data are for eribulin based on survival superiority against best standard treatment in a recent large RCT, but there is a lack of good comparative data between these various agents.

Empfehlung 7

Palliative care should be offered throughout the continuum of care. As there are diminishing returns with later lines of chemotherapy, clinicians should also offer best supportive care without further chemotherapy as an option.

A. The benefits include a patient-centered approach emphasizing quality of life (**potential benefit: high**). The main harm is fear of abandonment and giving up hope, which can be addressed by effective communication and appropriate end-of-life planning (**potential harm: moderate**).
B. The quality of the evidence is intermediate and is supported by several RCTs in patients with advanced cancer.
C. The strength of the recommendation is strong and is supported by evidence, expert consensus, and another independent expert consensus.[9]

Qualifying statement: Evidence suggests that response to second and subsequent lines of chemotherapy is strongly influenced by response to earlier treatment; patients whose disease has failed to respond to up to two initial lines of treatment are less likely to respond to a third or subsequent line.[10]

Empehlung 8

As there is no cure yet for patients with advanced breast cancer, clinicians should encourage all eligible patients to enroll onto clinical trials. This should include the option of phase II and even targeted phase I trials before all standard lines of therapy have been used, in the absence of immediately life-threatening disease.

A. The benefits are more patients will be directed to clinical studies providing treatment benefits to them, and the medical community will benefit from more research to improve treatments available and on which to base treatment decisions. The potential harm is patients will receive inferior treatment.
B. There is no strong evidence to suggest this approach might impair outcome.
C. The strength of this recommendation Is strong and based on expert consensus.

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Advanced breast cancer (update) Diagnosis and treatment; Issued: February 2009,

last modified: August 2017. NICE (CG81)

Leitlinienorganisation/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

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

LoE

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

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

GoR

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

Sonstige methodische Hinweise

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

Aktualisierungen:

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

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

Empfehlungen

Systemic disease-modifying therapy

Recommendations

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

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

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

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

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

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

Endocrine Therapy

Recommendation

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Chemotherapy

Recommendation

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

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

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

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

Clinical evidence

Combination versus sequential chemotherapy

Evidence for comparing single chemotherapy with sequential chemotherapy comprised five RCTs (Creech et al. 1979; Chlebowski et al. 1979; Sledge et al. 2003; Smalley et al. 1976 and Baker et al. 1974) and one observational study

(Chlebowski et al. 1989). The older studies were not always very stringently reported. Two small, poor quality trials (Baker et al. 1974 and Creech et al. 1979) found no significant difference in tumour response, response duration, time to progression or overall survival when chemotherapy agents were given together or sequentially (on disease progression).

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

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

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

Combined versus single chemotherapy regimes

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

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

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

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

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

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

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

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

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

Clinical evidence

Vinorelbine

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

Vinorelbine monotherapy

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

Vinorelbine combined therapy

Two poor to moderate quality RCTs tested VIN in combination with 5'-fluorouracil (5´-FU) vs docetaxel (DOC) (Bonneterre et al. 2002) or gemcitabine (GEM) vs VIN (Martin et al. 2007). VIN and 5´-FU combined resulted in similar treatment

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

Taxanes

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

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

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

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

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

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

3.5 Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

CADTH, 2013 [3].

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, 2016 [4].

Canadian Agency for Drugs and Technologies in Health (CADTH)

Pan-Canadian Oncology Drug Review Final Clinical Guidance Report: Palbociclib (Ibrance) for Advanced Breast Cancer.

Conclusion

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to the combination of palbociclib and letrozole compared with letrozole alone in the treatment of postmenopausal women with ER+, HER2-, metastatic breast cancer who have not received any prior treatment for metastatic disease. This was based on the PALOMA-1 clinical trial, which was a small open-label phase 2 RCT. The study demonstrated a statistically significant improvement in PFS. With an absolute improvement in PFS of 10 months, the magnitude of benefit is both statistically and clinically meaningful. There was no significant difference in median OS, but the study was underpowered for this endpoint. Despite the higher incidence of AEs seen in the combination group, there were only 13% who discontinued therapy due to AEs compared to 2% in the letrozole alone group. Although the most common side effects experienced with palbociclib and letrozole in this trial are not life threatening, they do require monitoring by an experienced health care team familiar with the toxicities associated with this combination, as a higher incidence of AEs (e.g., grade 3/4 neutropenia potentially leading to febrile neutropenia) may occur in an unselected non-clinical trial population. The only patient-reported outcome was pain and there was no difference observed between the two groups. There were no reported quality of life parameters in this trial. The Clinical Guidance Panel also considered that from a clinical perspective:

- •The Clinical Guidance Panel had concerns about the internal validity and thus quality of the PALOMA-1 trial given that it was a small phase 2 study with many protocol amendments/deviations and skewed population (many de novo metastatic cases).
- The results of PALOMA-2, a large, ongoing, double-blinded phase 3 RCT of palbociclib and letrozole versus letrozole alone for ER+/HER2- ABC as first-line therapy will provide additional data on PFS and OS outcomes, and further information on the safety of this combination therapy. This intended confirmatory trial will provide more robust data and certainty in the magnitude of effect with palbociclib in combination with letrozole compared to letrozole alone, as well as more information about the toxicity profile and use of palbociclib in patients with an ECOG PS of 2. Results are anticipated in June 2016.
- The study design of PALOMA-1 also did not explore the role of combining palbociclib with other endocrine therapies.

NICE, 2016 [17].

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

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NICE, 2012 [16].

Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer. Technology appraisal guidance TA 263.

Key conclusion

1.1 Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast cancer, that is, when treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate,

or when taxanes or anthracyclines have been used as part of adjuvant treatment within the past 12 months.

Evidence for clinical effectiveness

4.5 Data from the capecitabine cohort of the RIBBON-1 trial formed the clinical-effectiveness evidence in the manufacturer's submission.

The Committee noted that no quality of life data had been collected in the trial. The Committee considered quality of life to be an important outcome measure in advanced cancer and that this was an omission from the trial.

The Committee was aware that patients from both arms of the trial could receive treatment with bevacizumab after disease progression as well as other subsequent treatments and that all these subsequent therapies could have confounded the relative treatment effect in terms of overall survival. …The Committee concluded that bevacizumab plus capecitabine improved progression-free survival relative to capecitabine plus placebo, but that there was no robust evidence that it improved overall survival and that its effects on health-related quality of life had not been captured.

Hinweis:

Review of the evidence in August 2015: We found nothing new that affects the recommendations in this guidance.

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

#	Suchfrage
1	"breast neoplasms/drug therapy" OR "breast neoplasms/radiotherapy" OR "breast neoplasms/therapy" OR "breast neoplasms/treatment"
2	((breast[ti]) OR mamma*[ti]) AND ("neoplasm metastasis/drug therapy" OR "neoplasm metastasis/radiotherapy" OR "neoplasm metastasis/therapy") OR ("neoplasm recurrence, local/drug therapy" OR "neoplasm recurrence, local/radiotherapy" OR "neoplasm recurrence, local/therapy")
3	(#1) OR #2
4	(breast[ti]) OR mamma*[ti]
5	(#4) AND (((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR malignan*[tiab])
6	(#5) AND (((((((advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab]) OR relaps*[tiab]) OR progression*[tiab]) OR progressive*[tiab]) OR disseminat*[tiab])
7	(#6) AND ((((((((((((treatment*[tiab]) OR therapy[tiab]) OR therapies[tiab]) OR therapeutic[tiab]) OR monotherap*[tiab]) OR polytherap*[tiab]) OR pharmacotherap*[tiab]) OR effect*[tiab]) OR efficacy[tiab]) OR treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]) or chemotherapy*[tiab])
8	#3 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
10	((#9) AND ("2013/04/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 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]))

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Anhang

1. Beith et al. 2016 [2]

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

Guide for Rating of Potential for Bias

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

Definitions for Types of recommendations

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

Definitions for Strengths of evidence

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

Definitions for Strengths of recommendation

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

3. Rugo et al. 2016 [20]

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

Ergebnisse der syst. Literaturauswertung: Systematic reviews:

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

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

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