Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-166 Abemaciclib

Stand: Oktober 2017

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

Abemaciclib
zur Behandlung des HR-positiven/HER2-negativen, fortgeschrittenen/metastasierten Brustkrebs

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe 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.	Grundsätzlich im Anwendungsgebiet in Betracht kommende nicht-medikamentöse Behandlungen: - Operative Resektion - Strahlentherapie - Ovariektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen.	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: - Palbociclib: Beschluss vom 18. Mai 2017 - Eribulin: Beschluss vom 22. Januar 2015 Beschluss vom 15. Juli 2010 über eine Beauftragung des IQWiG: Nutzenbewertung von Aromatasehemmern zur Behandlung des Mammakarzinoms der Frau. Beschluss vom 20. Mai 2010 über eine Änderung der AM-RL: Anlage VI – Off-Label-Use; Gemcitabin in der Monotherapie beim Mammakarzinom der Frau (nicht verordnungsfähig) Beschluss vom 28. Mai 2009: Protonentherapie beim Mammakarzinom
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche.*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Abemaciclib L01XE50 Verzenios®	Verzenios ist angezeigt zur Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie
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.
Fulvestrant L02BA03 Faslodex®	Faslodex ist angezeigt zur Behandlung von Östrogenrezeptor-positivem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom bei postmenopausalen Frauen: – die keine vorhergehende endokrine Therapie erhalten haben, oder – mit Rezidiv während oder nach adjuvanter Antiöstrogen-Therapie oder bei Progression der Erkrankung unter Antiöstrogen-Therapie.
Aromatase-Inhibitoren (nicht-steroidal):	

II. Zugelassene Arzneimittel im Anwendungsgebiet

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

II. Zugelassene Arzneimittel im Anwendungsgebiet

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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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 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®, Myocet®	– Caelyx® ist indiziert: Als Monotherapie bei Patientinnen mit metastasierendem Mammakarzinom mit erhöhtem kardialen Risiko. – Myocet® in Kombination mit Cyclophosphamid wird angewendet bei der First-line-Behandlung von metastasiertem Brustkrebs bei erwachsenen Frauen.
Epirubicin L01DB03 Riboepi®	– Mammakarzinom
Eribulin L01XX41 Halaven®	Halaven ist indiziert für die Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Brustkrebs, bei denen nach mindestens einer Chemotherapie zur Behandlung einer fortgeschrittenen Brustkrebserkrankung eine weitere Progression eingetreten ist. Die Vortherapien sollen ein Anthrazyklin und ein Taxan entweder als adjuvante Therapie oder im Rahmen der metastasierten Situation enthalten haben, es sei denn, diese Behandlungen waren ungeeignet für den Patienten.
5-Fluorouracil L01BC02 Fluorouracil-GRY®	– fortgeschrittenes und/oder metastasiertes Mammakarzinom
Gemcitabin L01BC05 Gemzar®	Gemcitabin ist angezeigt in Kombination mit Paclitaxel für die Behandlung von Patientinnen mit nicht operablem, lokal rezidiviertem oder metastasiertem Brustkrebs, bei denen es nach einer adjuvanten/neoadjuvanten Chemotherapie zu einem Rezidiv kam. Die vorausgegangene Chemotherapie sollte ein Anthracyclin enthalten haben, sofern dieses nicht klinisch kontraindiziert war.
Ifosfamid L01AA06 Holoxan®	Zur Palliativtherapie bei fortgeschrittenen, therapierefraktären bzw. rezidivierenden Mammakarzinomen.
Methotrexat L01BA01 Methotrexat-GRY®	Mammakarzinome: In Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.
Mitomycin L01DC03 Urocin®	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] – Mammakarzinom
Mitoxantron L01DB07 Onkotrone®	– fortgeschrittenes und/oder metastasiertes Mammakarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet

Paclitaxel L01CD01 Bendatax®	BENDATAX ist zur First-line Chemotherapie bei Patientinnen mit lokal fortgeschrittenem oder metastasierendem Mammakarzinom angezeigt entweder in Kombination mit einem Anthrazyklin bei Patientinnen, bei denen eine Anthrazyklin-Therapie in Betracht kommt, oder in Kombination mit Trastuzumab, bei Patientinnen, die den humanen, epidermalen Wachstumsfactor-Rezeptor 2 (HER-2) – ermittelt durch immunhistochemische Methoden – mit Grad 3+ überexprimieren und für die eine Anthrazyklin-haltige Therapie nicht in Betracht kommt. Als Monotherapie ist BENDATAX für die Behandlung des metastasierenden Mammakarzinoms bei Patientinnen indiziert, bei denen eine Standardtherapie mit Anthrazyklinen erfolglos war oder nicht angezeigt ist.
Paclitaxel Nanopartikel L01CD01 Abraxane®	Abraxane-Monotherapie ist indiziert für die Behandlung des metastasierten Mammakarzinoms bei erwachsenen Patienten, bei denen die Erstlinientherapie der metastasierten Erkrankung fehlgeschlagen ist und für die eine standardmäßige Anthracyclin-enthaltende Therapie nicht angezeigt ist.
Vinblastin L01CA01 Vinblastinsulfat TEVA®	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: - rezidivierendes oder metastasierendes Mammakarzinom (wenn eine Behandlung mit Anthracyclinen nicht erfolgreich war)
Vincristin L01CA02 Vincristinsulfat Teva®	Vincristinsulfat-Teva® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: […] soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom.
Vindesin L01CA03 Eldisine®	Eindeutiges Ansprechen wurde auch bei folgenden Erkrankungen erzielt, jedoch liegen hierfür erst geringere Erfahrungen vor: […] - Mammakarzinom
Vinorelbin L01CA04 Navelbine®	Als Monotherapie bei Patientinnen mit metastasierendem Brustkrebs (Stadium 4), bei denen eine Behandlung mit einer anthrazyklin- und taxanhaltigen Chemotherapie versagt hat oder nicht angezeigt ist.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2017-B-166 (Abemaciclib)

Auftrag von:	Abt. AM
bearbeitet von:	Abt. FB Med
Datum:	05.10.2017

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Mammakarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 02.08.2017 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, Clinical Evidence, 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 2648 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 38 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation

Zur Behandlung des lokal fortgeschrittenen oder metastasierten Hormonrezeptor-positiven (HR+), HER2-negativen Brustkrebs

- als initiale endokrine Therapie (AWG 1) oder

- nach vorangegangener endokriner Therapie (AWG 2) oder
- nach vorangegangener endokriner Therapie und ein oder zwei Chemotherapielinien im metastasierten Stadium (AWG 3)

Abkürzungen:

AI	Aromatase-Inhibitor
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CI	Konfidenzintervall
CR	complete response
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
ER	Östrogen Rezeptor
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HER2	humaner epidermaler Wachstumsfaktor-Rezeptor-2
HR	Hazard Ratio
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCCN	National Comprehensive Cancer Network
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PR	partial response
SIGN	Scottish Intercollegiate Guidelines Network
SD	and stable disease
TAM	Tamoxifen
TOR	Toremifen
TRIP	Turn Research into Practice Database
TTP	time to progression
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

G-BA, 2017 [9]. 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 [15,18].	**Zugelassenes 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. **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** <u>a1) Postmenopausale Patientinnen in Erstlinientherapie:</u> **Zweckmäßige Vergleichstherapie:** Anastrozol oder Letrozol oder ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Letrozol:** Ein Zusatznutzen ist nicht belegt. <u>a2) Prä-/perimenopausale Patientinnen in Erstlinientherapie:</u> **Zweckmäßige Vergleichstherapie:** Tamoxifen in Kombination mit einer Ausschaltung der Ovarialfunktion. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. <u>b1) Postmenopausale Patientinnen mit Progression nach einer vorangegangenen endokrinen Therapie:</u> **Zweckmäßige Vergleichstherapie:** - Tamoxifen oder - Anastrozol oder - Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung, oder - Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung, oder - Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung, oder - Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt. <u>b2) Prä-/perimenopausale Patientinnen mit Progression nach einer</u>

	vorangegangenen endokrinen Therapie: **Zweckmäßige Vergleichstherapie:** Eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligen Zulassung. **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber der zweckmäßigen Vergleichstherapie:** Ein Zusatznutzen ist nicht belegt.
G-BA, 2015 [8]. 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 – Eribulin (neues Anwendungsgebiet) vom 22. Januar 2015 Vgl. IQWiG, 2014 [14,17].	**Zugelassenes Anwendungsgebiet vom 27. Juni 2014:** HALAVEN ist indiziert für die Behandlung von 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 Metastasenbehandlung enthalten haben, es sei denn, diese Behandlungen waren ungeeignet für den Patienten. *[Neues Anwendungsgebiet: Erweiterung des bisherigen Anwendungsgebietes auf Patienten, bei denen nach einer Chemotherapie zur Behandlung einer fortgeschrittenen Brustkrebserkrankung eine weitere Progression eingetreten ist (Anwendung in einer früheren Therapielinie). Der vorliegende Beschluss bezieht sich auf das gesamte Anwendungsgebiet.]* **1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie** a) Patientinnen, die nicht mehr mit Taxanen oder Anthrazyklinen behandelt werden können **Zweckmäßige Vergleichstherapie:** patientenindividuell bestimmte Chemotherapie unter Verwendung der Wirkstoffe als Monotherapie mit Capecitabin, Vinorelbin **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Monotherapie mit Capecitabin, Vinorelbin:** Anhaltspunkt für einen beträchtlichen Zusatznutzen. b) Patientinnen, die für eine erneute Anthrazyklin- oder Taxan-haltige Behandlung infrage kommen **Zweckmäßige Vergleichstherapie:** patientenindividuell bestimmte Chemotherapie mit einer erneuten Anthrazyklin- oder Taxan-haltigen Therapie **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer erneuten Anthrazyklin- oder Taxanhaltigen Therapie:** Ein Zusatznutzen ist nicht belegt. c) Patientinnen mit HER2-positivem Brustkrebs, für die eine Anti-HER2-Therapie angezeigt ist Es wird davon ausgegangen, dass in der Behandlung von Patientinnen mit HER2-positivem Brustkrebs, bei der Therapieentscheidung für eine Behandlung mit Eribulin laut vorliegendem Anwendungsgebiet, die Behandlungsoption einer Anti-HER2-Therapie eingehend berücksichtigt und als nicht angezeigt beurteilt worden ist. Sofern angezeigt: **Zweckmäßige Vergleichstherapie:** Lapatinib in Kombination mit Capecitabin oder Lapatinib in Kombination mit Trastuzumab **Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Lapatinib**

	in Kombination mit Capecitabin oder Lapatinib in Kombination mit Trastuzumab: Ein Zusatznutzen gilt als nicht belegt.
IQWiG, 2016 [16]. Aromatase-hemmer 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 [11]. 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.	**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 Tumorgröße 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**

Juli 2016; veröffentlicht im Bundesanzeiger (BAnz AT 14. Oktober 2016 B3); in Kraft getreten am 1. Januar 2017 Vgl. auch IQWiG, 2014 [19].	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 [10]. Beschluss des G-BA über eine Änderung der Arzneimittel-Richtlinie: Anlage VI – Off-Label-Use; Gemcitabin in der Monotherapie beim Mammakarzinom d. Frau vom 20. Mai 2010	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“
G-BA, 2009 [7]. Beschluss vom 28. Mai 2009: Protonentherapie beim Mammakarzinom	**Fazit:** Die Protonentherapie bei der Indikation Mammakarzinom erfüllt derzeit weder alleine noch in Kombination mit einer anderen Therapie die Kriterien des §137 c SGB V (ausreichend, zweckmäßig, wirtschaftlich) und ist damit nicht Leistung im Rahmen der gesetzlichen Krankenversicherung.

Cochrane Reviews

Mao, C et al., 2012 [23]. Toremifene versus tamoxifen for advanced breast cancer.	1. Fragestellung (AWG 1) To compare the efficacy and safety of toremifene (TOR) with tamoxifen (TAM) in patients with advanced breast cancer.
	2. Methodik **Population**: women with a diagnosis of advanced breast cancer (histologically verified inoperable primary, metastatic, or recurrent breast cancer; measurable or evaluable disease according to WHO criteria) **Intervention/Komparator**: TOR with TAM, other therapies allowed as long as participants randomised to receive TOR or TAM, doses of TOR ranged from 40 to 240 mg/day, doses of TAM ranged from 20 to 40 mg/day **Endpunkte:** • Primärer Endpunkt: Overall survival (OS) • Sekundäre Endpunkte: Objective response rate (ORR); time to progression (TTP); Adverse events **Recherche:** until 1 July 2011, reference lists of relevant trials or reviews screened **Anzahl eingeschlossene Studien/**Patienten (Gesamt): 7 RCTs/2 061 patients, 1226 patients in the TOR group, 835 patients in the TAM group Subgroup analyses on the following: • effect of menopausal status on outcome measures; • effect of hormone receptor status on outcome measures; • effect of agent doses on outcome measures; • impact of line of treatment on outcome measures; and • impact of study quality on outcome measures. Heterogenität • Chi2 Test: Heterogenität bei $P < 0.10$ • I^2 Statistik: Heterogenität bei $I^2 > 50\%$ Sensitivity analysis with the following adjustments: • repeating the analysis excluding studies with high risk of bias; • repeating the analysis each time excluding a single study to determine the influence of the individual data set on the pooled results …. We also tested the robustness of the results by repeating the analysis using different measures of effect size (risk ratio, odds ratio etc) and different statistical models (fixed-effect and random-effects models). Qualitätsbewertung der Studien: Cochrane risk of bias tool Assessment of reporting biases: Funnel plot
	3. Ergebnisse

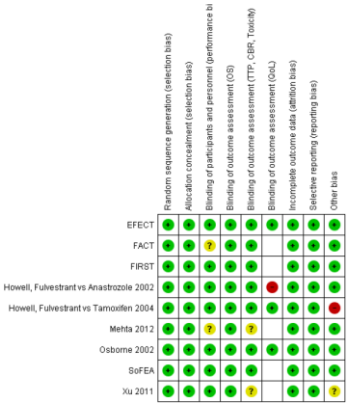
	Study characteristics • median or mean age of patients: 60 to 65 years • 5 studies performed in post-menopausal women,1 study performed in pre- or post-menopausal women • majority of patients either ER-positive or of unknown status • TOR or TAM was given as first-line treatment for advance breast cancer in 6 studies, in 1 study (Nomura 1993) line of treatment unclear due to absence of full report • dosage of TOR: 40 mg/day, 60mg/day, 200 mg/day or 240 mg/day dosage of TAM: 20 mg/day, 30 mg/day or 40 mg/day • median length of follow up (reported in 3 studies: Gershanovich 1997; Pyrhonen 1997; Stenbygaard 1993: 20.5, 25.2, and 19months, respectively • most studies considered as “low or unclear risk” of bias: baseline characteristics homogeneous between treatment arms, outcomes objective indicators, relevant data reported completely, data analysis done in ITT manner • *Results* <u>ORR, TTP und OS</u> • keine statistisch signifikanten Unterschiede zwischen den Gruppen in den Wirksamkeitsendpunkten: ORR, TTP und OS • keine Subgruppenanalysen: … we could not divide the eligible studies into clinically relevant subgroups according to these factors to examine their effect on outcome measures. Thus, no subgroup analyses were actually conducted • The frequencies of most adverse events were also similar in the two groups, while headache seemed to occur less in the TOR group than in the TAM group (RR 0.14, 95% CI 0.03 to 0.74, P = 0.02). • There was no significant heterogeneity Sensitivity analysis did not alter the results.
	4. Fazit der Autoren TOR and TAM are equally effective and the safety profile of the former is at least not worse than the latter in the first-line treatment of patients with advanced breast cancer. Thus, TOR may serve as a reasonable alternative to TAM when anti-oestrogens are applicable but TAM is not the preferred choice for some reason. *5. Kommentare zum Review* • HER-2 Status nicht thematisiert • meist Erstlinie
Lee C et al., 2017 [20]. Fulvestrant for hormone-sensitive metastatic breast	1. Fragestellung (AWG 1/2) 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.
	2. Methodik

cancer	**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:** 1. any standard endocrine agents (tamoxifen and aromatase inhibitors) not containing fulvestrant 2. any other anticancer treatment (e.g.chemotherapy). **Endpunkte:** • PFS, TTP, TTF • OS • Clinical benefit rate: defined as the proportion of women with an objective response or a best overall tumour assessment of stable disease • Quality of life • Tolerability **Recherche:** am 7.7.2015 • Cochrane Central Register of Controlled Trials (CENTRAL) (via the Cochrane Library, Issue 6, 2015 • MEDLINE and EMBASE from 2008 to 7 July 2015 • WHO ICTRP for all prospectively registered and ongoing trials • major conference proceedings (ASCO and San Antonio Breast Cancer Symposium) and practice guidelines from major oncology groups (ASCO, ESMO,NCCN and Cancer Care Ontario). • Handsearch in reference lists from relevant studies **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 9 (n=4514) **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool, Assessment of heterogeneity by using Chi^2 test and I^2 statistic Assessment of the quality of the available evidence by GRADE approach ('Summary of findings' tables)
	3. Ergebnisse *Study characteristics:* • 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 • 5 studies with 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 • Hormone positive women with exception in 1 study: In Howell, Fulvestrant vs Tamoxifen 2004,less than 80% of women in both arms had oestrogen receptor -positive tumours.

- 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

Risk of bias

- 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



Results for fulvestrant vs. comparators (other endocrine therapy)

<u>OS</u>

- 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)

<u>PFS:</u>

- 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)

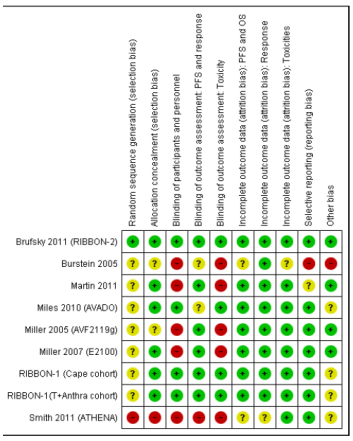
<u>Clinical benefit rate</u> →no significant differences:

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

<u>Quality of life</u>

- 4 studies reported quality of life that was assessed with Functional Assessment of Cancer Therapy-Breast (FACT-B) or Functional Assessment of Cancer Therapy-Endocrine Symptoms (FACT-ES) questionnaires with follow-up ranging from 8.9 months to 38 months.

	• None of the studies reported a difference in quality of life as per their analyses between participants receiving fulvestrant and other endocrine treatments but numerical data were not presented. <u>Toxicity</u> Assessment of three most common toxicities: vasomotor, arthralgia, and gynaecological toxicities. Although there was some variation between the individual trials in the three examined toxicities, overall summary statistics were not significantly different between fulvestrant and the comparator drugs. • vasomotor toxicity: RR 1.02, 95% CI 0.89 to 1.18; 8 trials, 3544 women; I^2 =55%, high-quality evidence, • arthralgia: RR 0.96, 95%CI 0.86 to 1.09; 7 trials, 3244 women; I^2= 59%; P = 0.02; high-quality evidence • Gynaecological toxicity included urinary tract infection, vulvovaginal dryness, vaginal haemorrhage, vaginitis, and pelvic pain: RR 1.22, 95% CI 0.94 to 1.57; 2848 women; I^2= 66%; P=0.01; high-quality evidence
	4. Fazit der Autoren As evidenced from our pooled data from 4514 women examined in our review, fulvestrant (mostly administered at the anachronistic dose of 250 mg) was as effective as other standard endocrine therapies with respect to efficacy (measured by PFS, CBR, overall survival), toxicity, and quality of life. It is important to highlight that even at this inferior dose, fulvestrant was as effective and well tolerated as other comparator endocrine therapies. In our one included study of fulvestrant at the 500 mg dose level, fulvestrant was superior to anastrozole (FIRST).
Wagner AD et al., 2012 [35]. Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer (Review)	1. Fragestellung (AWG 3) To evaluate the benefits in progression-free survival, overall survival and harms of VEGF-targeting therapies in patients with hormone-refractory or hormone-receptor negative metastatic breast cancer.
	2. Methodik **Population:** Women with histologically or cytologically confirmed, endocrine refractory or resistant, locally advanced or metastatic breast cancer **Intervention:** systemic, oral or intravenous, VEGF-targeting therapies, in combination with chemotherapy, with or without trastuzumab. **Komparator:** systemic chemotherapy, with or without trastuzumab, in the same dose, route and schedule of administration as in the experimental intervention. **Endpunkte**: PFS, OS, TTP, Tumor response, Toxicity, QoL **Recherche:** Searches of CENTRAL, MEDLINE, EMBASE, the Cochrane Breast Cancer Group's Specialised Register, registers of ongoing trials + proceedings of conferences in January and September 2011, starting in

	2000. Reference lists were scanned and members of the Cochrane Breast Cancer Group, experts and manufacturers of relevant drug were contacted to obtain further information. **Anzahl eingeschlossene Studien**: 7 RCT, 1 non-RCT, 5 ongoing trials **Qualitätsbewertung der Studien:** Cochrane risk of bias tool.
	3. Ergebnisse *Study characteristics* • trials on VEGF-targeting therapies for metastatic breast cancer are limited to bevacizumab • All trials used bevacizumab in combination with established chemotherapy regimens. • first-line setting: 4 trials; second-line setting:3 RCTs • additionally, 1 register study for harm evaluation (ATHENA, Smith 2011) Risk of bias: In general, the methodological quality of the included trials can be considered as appropriate.  *Results* PFS • First-line (4 trials): HR 0.67 (95% CI 0.61 to 0.73), I^2=51% • Second-line (2 trials): HR 0.85 (95%CI 0.73 to 0.98), I^2=55% OS • First-line (3 trials): HR 0.93 (95% CI 0.84 to 1.04);I^2 = 0% • Second-line (2 trials): HR 0.98 (95% CI 0.83 to 1.16); I^2 = 5% Tumor response • First-line: OR 1.96; 95% CI 1.64 to 2.34, I^2=56% • Second-line: OR 1.87; 95% CI 1.37 to 2.54. I^2=25% Toxicity • data from RCTs and registry data were consistent and in line with the known toxicity profile of bevacizumab. • significantly higher rates of AEs grade III/IV (OR 1.77; 95% CI 1.44 to

	2.18) and SAEs (OR 1.41; 95% CI 1.13 to 1.75) in patients treated with bevacizumab • rates of treatment-related deaths were lower in patients treated with bevacizumab (OR 0.60; 95% CI 0.36 to 0.99). <u>QoL</u> • was evaluated in four trials but results were published for only two. • A significant benefit in the quality of life (QoL) or other patients-related outcomes has not been observed in any of the included trials. Even in the trial which noted the greatest impact on bevacizumab on PFS (Miller 2007, E2100)), no impact on the QoL could be observed
	4. Fazit der Autoren: The overall patient benefit from adding bevacizumab to first- and second-line chemotherapy in metastatic breast cancer can at best be considered as modest. It is dependent on the type of chemotherapy used and limited to a prolongation of PFS and response rates in both first- and second-line therapy, both surrogate parameters. In contrast, bevacizumab has no significant impact on the patient related secondary outcomes of OS or QoL, which indicate a direct patient benefit. For this reason, the clinical value of bevacizumab for metastatic breast cancer remains controversial. 5. *Kommentar zum Review:* • Mind. 62% Patienten in allen Studien mit HR+Status, Ausnahme 1 Studie (47%)
Ghersi, D et al., 2015 [12]. Taxane-containing regimens for metastatic breast cancer**.**	1. Fragestellung (AWG 3) To compare taxane-containing chemotherapy regimens with regimens not containing a taxane in the management of women with metastatic breast cancer. Subquestions within the review were: • subquestion A: regimen A plus taxane versus regimen A (e.g. doxorubicin plus docetaxel versus doxorubicin alone) • subquestion B: regimen A plus taxane versus regimen B (e.g. doxorubicin plus docetaxel versus doxorubicin plus cyclophosphamide) • subquestion C: single-agent taxane versus regimen C (e.g. docetaxel versus doxorubicin plus cyclophosphamide)
	2. Methodik **Population:** Women with advanced (metastatic) breast cancer, either newly diagnosed or recurrent **Intervention:** Any chemotherapy regimen containing a taxane **Komparator:** Any chemotherapy regimen not containing a taxane. **Endpunkte:** Primary outcomes o Overall survival

	○ Time to progression Secondary outcomes ○ Time to treatment failure ○ Objective tumour response rate ○ Toxicity ○ Health related quality of life **Recherche:** • Cochrane Breast Cancer Group (CBCG) Specialised Register on 14 February 2013. • MEDLINE and EMBASE from 2008 to February 2013 • WHO International Clinical Trials Registry Platform search for prospectively registered and ongoing trials on 14 February 2013 • ClinicalTrials.gov register on 14 February 2013 for additional unpublished and ongoing studies, **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 28 (n=6871) • subquestion A: 2 studies • subquestion B: 14 studies • subquestion C: 13 studies **Qualitätsbewertung der Studien:** Cochrane Risk of bias tool Assessment of heterogeneity by using Chi^2 test and I^2 statistic
	3. Ergebnisse *Study characteristics* <u>Question A: regimen A plus taxane versus regimen A (2 trials)</u> • Population: anthracycline naïve women receiving <u>first-line chemotherapy</u> for metastatic breast cancer. • Taxene used: ○ Paclitacel in 1 trials ○ Docetaxel in 1 trial <u>Question B: regimen A plus taxane versus regimen B (14 trials)</u> • Population: ○ =women who were receiving <u>first-line chemotherapy</u> for metastatic breast cancer, ○ majority of participants in all of these trials were anthracycline naïve in the metastatic setting. • Taxene used: ○ Paclitaxel in 7 studies ○ docetaxel in 6 studies ○ paclitaxel or docetaxel at investigatior's choice in 1 study <u>Question C: single-agent taxane versus regimen C (12 trials)</u> • Population: ○ in 5 <u>of the 13 i</u>ncluded studies the majority of participants received <u>first-line</u> chemotherapy; in 7 trials the majority of participants received <u>>firstline</u> chemotherapy ○ 6 of the 13 studies were anthracycline naïve • Taxene used:

	○ Paclitaxel in 6 studies ○ docetaxel in 7 studies *Risk of bias:* Of the 28 included studies, we considered 19 studies to be at low risk of bias overall; however, some studies failed to report details on allocation concealment and methods of outcome assessment for those outcomes that are more likely to be influenced by a lack of blinding (for example tumour response rate). *Results* **Overall survival** <u>Overall effect: taxane-containing versus non-taxane containing regimens</u> • Stat. sign. improvement in OS in favour of taxane containing regimens (HR of 0.93 (95% CI 0.88 to 0.99; P=0.002; participants = 6008; treatment comparisons = 23, I^2=52%;) • First-line trials only (overall): HR 0.93; 95% CI 0.87 to 0.99; P = 0.03; participants = 4439; treatment comparisons = 16; I^2 = 55%; Subgroup analysis: type of taxane • "docetaxel vs non taxane": HR 0.87 (95% CI 0.80 to 0.94; P=0.0008; 13 trials (n=3174); I2=2%)→sign. difference • "paclitaxel vs. non-taxane": HR of 1.01 (95% CI 0.93 to 1.10; P=0.84; 9 trials (n=2834); I2=67%)→ n.s. • Although the test for differences between type of taxane subgroups was statistically significant (P = 0.01), this was considered weak evidence given the variability in the comparator arms and taxane schedules (weekly versus three weekly) in these studies. Subgroup analysis: prior anthracyclines • 6 trials with women who had received previous anthracyclines for advanced disease: no difference in OS (HR 0.97; 95%CI 0.85 to 1.11; P = 0.66, 6 trials (n=1243); I2=58%) • 17 trials with anthracycline-naive women: HR for OS 0.93; 95% CI 0.87 to 0.99; P = 0.02, I^2=52% • A test of differences between prior and no prior exposure to anthracyclines revealed no significant interaction (P = 0.51). <u>Question A: regimen A plus taxane versus regimen A</u> • No stat. sign. difference in OS (HR 1.00 (95% CI 0.84 to 1.18; P=0.97; 2 trials (n=630), I^2 = 0%) <u>Question B: regimen A plus taxane versus regimen B</u> • No stat. sign. difference (HR 0.92 (95% CI 0.84 to 1.00; P=0.05;9 trials (n=2645) (I^2 = 70%) <u>Question C: single-agent taxane versus regimen C</u> • No stat. sign. difference (HR 0.95 (95% CI 0.87 to 1.03; P=0.19; 12 trials (n=2957) , I^2 = 42%) **PFS** <u>Overall effect: taxane-containing versus non-taxane containing regimens</u> • Stat. sign. difference in favour of taxane containing regimens (HR of

	0.92 (95%CI 0.87 to 0.97; P =0.002, n=5960, 22 treatment comparisons, I^2=73%) • First-line trials only (15 trials): HR 0.96; 95%CI 0.90 to 1.02; P=0.22, I2=62%) → n.s. Subgroup analysis: type of taxane • docetaxel vs non taxane: →sign. difference (HR 0.80; 95% CI 0.74 to 0.86; P <0.00001) • paclitaxel vs. non-taxane: →n.s. (HR 1.04; CI 0.96 to 1.12) • significant interaction, but there was significant and substantial heterogeneity (I2 = 95.5%; P < 0.00001) in both docetaxel and paclitaxel studies, and variability may relate to the differences in the comparator arms and taxane schedule (that is weekly versus three weekly) in these studies. Subgroup analysis: prior anthracyclines • 5 studies included women who had had prior anthracyclines in the advanced setting: HR for PFS 0.76; 95% CI 0.67 to 0.86; P < 0.0001; 5 trials; I^2=85% • 17 trials with anthracycline-naive women: PFS n.s. **Toxicity** <u>Overall effect: taxane-containing versus non-taxane containing regimens</u> Treatment-related death: →n.s. • (RR 1.00; 95% CI 0.63 to 1.57; =0.99;I2=0) Grade 3/4 leukopaenia: →n.s. • RR1.07; 95%CI 0.97 to 1.17; P=0.16; n= 6564; I2 = 90% Grade 3/4 nausea or vomiting: superiority • RR 0.62; 95% CI 0.46 to 0.83; P=0.001; n= 6245) I2 = 46% Grade 3/4 neurotoxicity:→ inferiority • RR 4.84; 95%CI 3.18 to 7.35; P<0.00001; n=5783, I2=8% Grade 3/4 alopecia:→ inferiority • RR 2.37; 95% CI 1.45 to 3.87; P=0.0006; n= 2437, I2 = 94% **Quality of life** • Compliance with completion of baseline and follow-up quality of life instruments varied across studies, ranging from 61% to 99% for baseline and approximately 30% to 87% for follow-up. • Some studies reported problems with participants in poorer health not completing questionnaires (for example 304 Study Group). None of the individual studies reported a statistically significant difference in overall quality of life or in any of the subscales between taxane-containing and non-taxane-containing chemotherapy regimens.
	4. Fazit der Autoren When we consider all trials, we have sufficient evidence to determine the effects of taxane-containing chemotherapy regimens in women with metastatic breast cancer. Taxane-containing regimens appear to improve overall survival, time to progression, and overall response in women with metastatic breast cancer. The degree of heterogeneity encountered indicates

	that taxane-containing regimens are more effective than some, but not all, non-taxane-containing regimens. Thus the results of this review, which was confined to trials of chemotherapy alone, are unlikely to change, and further updates are not planned. However, if future trials examine either the role of taxanes in specific subtypes of breast cancer, or the role of taxanes together with or versus targeted therapies, then a new review would be warranted.

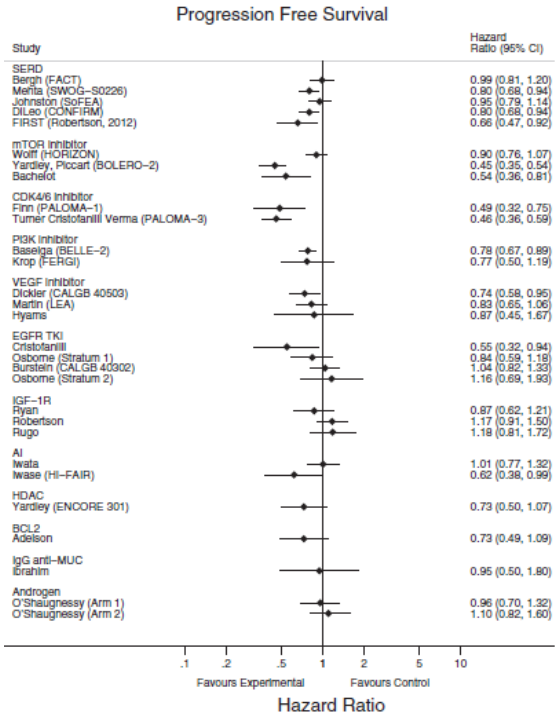
Systematische Reviews

Beith, J et al., 2016 [2]. Hormone receptor positive, HER2 negative metastatic breast cancer: A systematic review of the current treatment landscape.	1. Fragestellung (AWG 1 / 2) 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
	2. Methodik (Review protocol registered on PROSPERO) **Population:** women with hormone receptor positive, HER2 negative metastatic breast cancer **Intervention/Komparator:** (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. **Endpunkte:** PFS; OS, clinical benefit rate, AEs on grade 3 or 4 events **Recherche:** 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 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 32 studies **Qualitätsbewertung der Studien:** using the MERGE criteria for evaluating the quality of studies and assessing the effect of interventions
	3. Ergebnisse *Study characteristics* • Interventions: addition of a trial agent to standard treatment (n=24), optimization strategies (n=8) • 12 studies in the first line only setting, 5 in first or second line and 9 studies of second or later lines of treatment, 6 trials without specification

- 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
- 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.

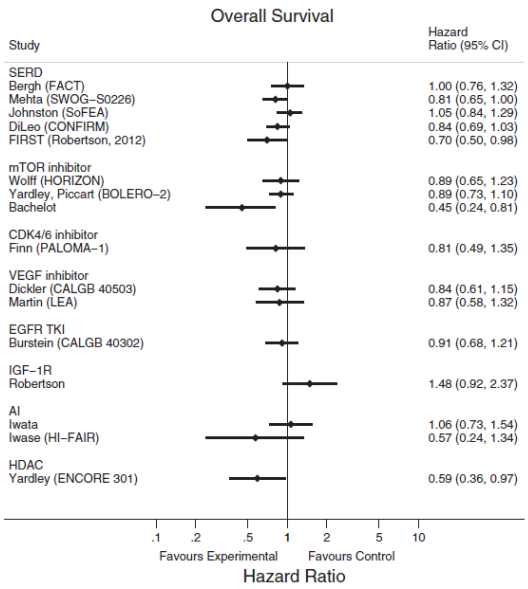
Results (→ Anhang: Table 2 Efficacy result by study)

<u>Progression-free survival</u>



- 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.

<u>Overall survival</u>



- 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.
	4. 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. *5. Kommentare zum Review* • 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.
Bachelot, T et al., 2014 [1]. Comparative efficacy of everolimus plus exemestane versus fulvestrant for hormone-receptor-positive advanced breast cancer following progression/ recurrence	1. Fragestellung (AWG 1 / 2) This network analysis was conducted to compare the efficacy of everolimus plus exemestane versus fulvestrant in patients with advanced breast cancer who are eligible for further endocrine therapies.
	2. Methodik **Population:** patients with advanced breast cancer who are eligible for further endocrine therapies **Intervention:** Everolimus plus Exemestane **Komparator:** Fulvestrant **Endpunkte**: PFS und TTP **Recherche** in 2012 in Cochrane Library (CDSR, DARE, and HTA, 2010–2012), EMBASE, and MEDLINE **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 7/k.A. **Qualitätsbewertung der Studien**: assessment for quality based on seven items (appropriate randomization; adequate concealment of treatment allocation; groups

after endocrine therapy: a network meta-analysis	similar at the onset of the study in terms of prognostic factors, care providers, participants, and outcome assessors blind to treatment allocation; unexpected imbalances in dropouts between groups; evidence to suggest that more outcomes were measured than reported; intent-to-treat analysis; and appropriate methods used to account for missing data)
Vgl. Qiao L et al., 2014 [33].	3. Ergebnisse • 7 studies identified that could be used in a network analysis • 6 used to form the basis of a network analysis, the seventh used as an alternative for an additional sensitivity analysis BOLERO 2 (doppelblind) 4. Baselga J, et al. (2012) Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 366(6):520–529. 7. Piccart M, et al. (2012) Final progression-free survival analysis of BOLERO-2: a phase III trial of everolimus for postmenopausal women with advanced breast cancer. Presented at CTRC-AACR San Antonio Breast Cancer Symposium, San Antonio, TX, 4–8 December 2012. Poster P6-04-02 CONFIRM (doppelblind) 9. Di Leo A, et al. (2010) Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol 28(30):4594–4600. EFECT (doppelblind) 8. 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 receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 26(10):1664–1670. Parideans et al. (offen) 15. Paridaens RJ, et al. (2008) Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol 26(30): 4883–4890. SoFEA (doppelblind) Johnston SR, et al. (2013) Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol 14(10):989–998. 18. Fulvestrant with or without anastrozole or exemestane alone in treating postmenopausal women with locally advanced or metastatic breast cancer (2013). http://www.clinicaltrials.gov/ct2/show/NCT00253422?term=sofea&rank=1. Accessed 25 Oct 2013 TAMRAD (doppelblind) 19. Bachelot T, et al. (2012) Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECOstudy. J Clin Oncol 30(22):2718–2724. Howell et al. (doppelblind) 14. Howell A, et al. (2004) Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. J Clin Oncol 22(9):1605–1613. – Fulvestrantdosierung 250mg/Monat nicht zulassungskonform

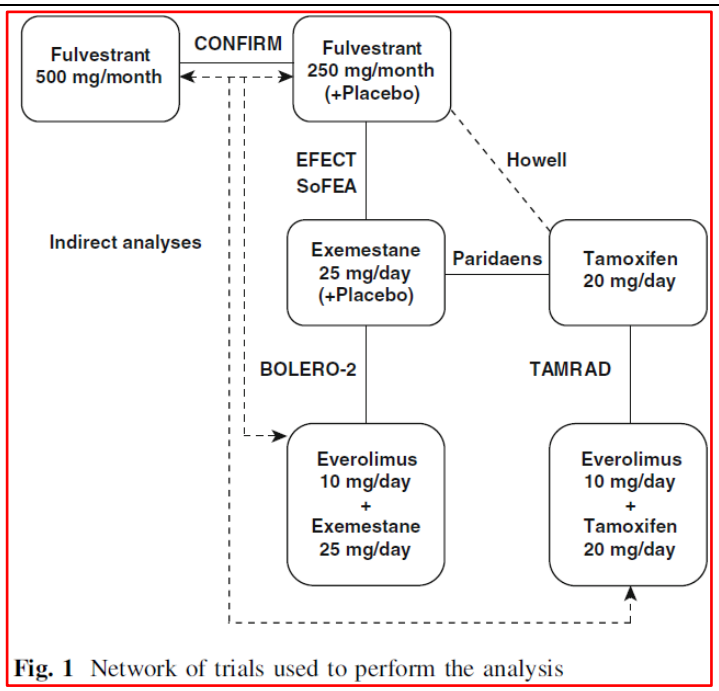


Fig. 1 Network of trials used to perform the analysis

In the primary analysis, the results suggest that everolimus plus exemestane is more efficacious for PFS/TTP than both fulvestrant 250 (HR = 0.47; 95 % CrI 0.38–0.58) and 500 mg (HR = 0.59; 95 % CrI 0.45–0.77)

Prior aromatase inhibitor therapy

- based on local assessment of PFS from BOLERO-2
- everolimus plus exemestane more efficacious for PFS/TTP than fulvestrant 250 and 500 mg (HR = 0.47; 95 % CrI 0.38–0.58 and HR = 0.55; 95 % CrI 0.40–0.76, respectively)
- centrally reviewed PFS data of BOLERO-2 did not substantially change the results: everolimus plus exemestane remained more efficacious for PFS/TTP than fulvestrant 250 and 500 mg

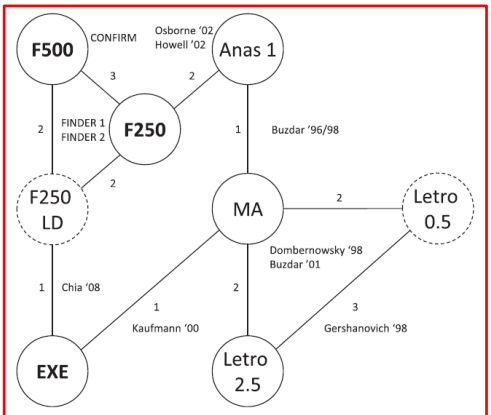
4. Fazit der Autoren

These results suggest that everolimus plus exemestane may be more efficacious than fulvestrant in patients with advanced breast cancer who progress on or after adjuvant or first-line therapy with a nonsteroidal aromatase inhibitor.

5. Kommentare zum Review

- Research was funded by Novartis Pharmaceuticals Corporation (pU für Everolimus);Conflict of interests:
  - TB and GJ: Advisor for Novartis Pharmaceuticals Corporation, received research support and speaker honoraria from Novartis.
  - RMcC, SD, JG, DV KF: Received research support from Novartis Pharmaceuticals Corporation.
  - JZ: Employee of Novartis Pharmaceuticals Corporation.
- Suche und Auswahl der Literatur nicht vollständig transparent, Ergebnis der Qualitätsbewertung der eingeschlossenen Studien liegt nicht vor
- Empfohlene Dosis von Fulvestrant beträgt 500 mg; Everolimus nur in

	Kombination mit Exemestan zugelassen • Endpunkte PFS/TTP nicht per se patientenrelevant • Siehe auch: System. Review zu Everolimus der Canadian Agency for Drugs and Technologies in Health, 2013: 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.
Cope S et al., 2013 [5]. Progression-Free Survival with Fulvestrant 500mg and Alternative Endocrine Therapies as Second-Line Treatment for Advanced Breast Cancer: A Network Meta-Analysis with Parametric Survival Models	1. Fragestellung (AWG 2) To estimate the expected PFS for fulvestrant 500 mg versus alternative hormonal therapies for postmenopausal women with advanced breast cancer who relapsed previously by means of a network meta-analysis of currently available randomized controlled trials using alternative underlying survival functions.
	2. Methodik **Population:** Postmenopausal ER+ advanced breast cancer (stage III or IV) who relapsed on prior endocrine therapy. **Intervention/Komparator:** fulvestrant 500 mg, letrozole, anastrozole, exemestane, and megestrol acetate vs. Placebo or one of the regimens (Hinweis: Comparisons of the same intervention with different background treatments were excluded) **Recherche):** in January 2010 **Endpunkte:** PFS, TTP **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 11 RCTs **Qualitätsbewertung der Studien:** Instrument nicht genannt
	3. Ergebnisse • 11 RCTs with fulvestrant 500mg (n=3), fulvestrant 250mg (n=5), fulvestrant 250mg loading dose (n=3), anastrozole 1mg (n=3), megestrol acetate (n=4), letrozole 2.5mg (n=3), letrozole 0.5mg (n=3), and exemestane (n=2) • studies were of high quality, although some potential limitations were identified in terms of blinding for 3 studies, most studies phase III, some phase II studies also included (siehe auch “Table 1” im Anhang) • generalizability of results may be limited to North America and Europe

	 **Fig. 2 – Network of randomized controlled trials. ANAS1, anastrozole 1 mg; EXE, exemestane 1 mg; F250, fulvestrant 250 mg; F250LD, fulvestrant 250 mg loading dose; F500, fulvestrant 500 mg; LETRO 0.5, letrozole 0.5 mg; LETRO2.5, letrozole 2.5 mg; MA, megestrol acetate 160 mg OD or 40 mg QID; OD, once daily; QID, four times daily. *Data for F250 LD and Letro 0.5 were included in the current network meta-analysis, but results are not presented for these treatments as they do not reflect approved doses.** The log-normal distribution provided the best fit, suggesting that the proportional hazard assumption was not valid. Based on the difference in expected PFS, it was found that fulvestrant 500mg is more efficacious than fulvestrant 250mg, megestrol acetate, and anastrozole (-5.73 months; 95% CrI:-10.67,-1.67). Expected PFS for fulvestrant 500mg ranged from 10.87 (95% CrI 9.21, 13.07) to 17.02 (95% CrI 13.33, 22.02) months for the Weibull versus log-logistic distribution.
	4. Fazit der Autoren Fulvestrant 500 mg is expected to be more efficacious than fulvestrant 250 mg, megestrol acetate, and anastrozole 1 mg and at least as efficacious as exemestane and letrozole 2.5 mg in terms of PFS among postmenopausal women with advanced breast cancer after failure on endocrine therapy. The findings were not sensitive to the distribution, although the expected PFS varied substantially, emphasizing the importance of performing sensitivity analyses. *5. Kommentare zum Review* • The research conducted in this analysis was commissioned by AstraZeneca. The MAPI Consultancy authors received compensation fees for services in relation to conducting the research and preparing the article. Source of financial support: This study was funded by Astra- Zeneca (Macclesfield, UK) (pU für Fulvestrant) • study documents for fulvestrant were made available by AstraZeneca • Empfohlene Dosis von Fulvestrant beträgt 500 mg • Megestrolacetat in der pallitiven Therapiesituation zugelassen • Alle eingeschlossenen Studien untersuchten Therapiearme mit Dosierungen und/oder Wirkstoffen außerhalb der Zulassung. • Endpunkte PFS/TTP nicht per se patientenrelevant
Lin WZ et al., 2017 [22]. Fulvestrant	1. Fragestellung (AWG 2) to evaluate the efficacy and toxicity of adding targeted agents to fulvestrant (combination therapy) compared with fulvestrant alone in metastatic breast cancer

<table>
<tr><td rowspan="4">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.</td><td>patients progressed on previous endocrine treatment.</td></tr>
<tr><td>2. Methodik
Population: metastatic breast cancer patients progressed on previous endocrine treatment.
Intervention: targeted therapy plus fulvestrant
Komparator: fulvestrant plus placebo
Endpunkte: partial response (PR), complete response (CR), and stable disease (SD), PFS, toxicity
Recherche: Medline, Embase, Cochrane Central Register of Controlled Trials: between 2000- June 2016
Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 trials

Qualitätsbewertung der Studien: Jaded scale</td></tr>
<tr><td>3. Ergebnisse

Study characteristics
Table 2 Characteristics of studies in the meta-analysis
<table>
<tr><th>Author year</th><th>Targeted agent</th><th>Pathway inhibited</th><th>HER2 expression</th><th>Postmenopausal status (%)</th><th>Prior endocrine therapy</th></tr>
<tr><td>Hyams DM21 2013</td><td>Cediranib</td><td>VEGF</td><td>−/+</td><td>100</td><td>Tam/AIs</td></tr>
<tr><td>Robertson JFR22 2013</td><td>Ganitumab</td><td>IGF</td><td>−/+ (7%)</td><td>100</td><td>Tam/AIs</td></tr>
<tr><td>Burstein HJ23 2014</td><td>Lapatinib</td><td>EGFR</td><td>−/+ (16%)</td><td>100</td><td>AIs</td></tr>
<tr><td>Clemons MJ24 2014</td><td>Vandetanib</td><td>VEGF</td><td>−/+ (5%)</td><td>100</td><td>Tam/AIs</td></tr>
<tr><td>Zaman K25 2015</td><td>Selumetinib</td><td>MAPK</td><td>–</td><td>100</td><td>AIs</td></tr>
<tr><td>Baselga J20 2015</td><td>Buparlisib</td><td>PI3K-mTOR</td><td>–</td><td>100</td><td>AIs</td></tr>
<tr><td>Cristofanilli M26 2016</td><td>Palbociclib</td><td>CDK4/CDK6</td><td>–</td><td>80</td><td>Tam/AIs</td></tr>
<tr><td>Krop IE27 2016</td><td>Pictilisib</td><td>PI3K-mTOR</td><td>–</td><td>100</td><td>AIs</td></tr>
</table>

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

The quality was high in all studies (Jadad score >=3).

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]</td></tr>
<tr><td>4. Fazit der Autoren

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

5. Kommentare zum Review
• Nur 1 der untersuchten Medikamente im AWG zugelassen und relevant
• Patientenrelevanz der Wirksamkeits-EP unklar</td></tr>
<tr><td>Xu L et al., 2016 [37].

A meta-</td><td>1. Fragestellung (AWG 3)

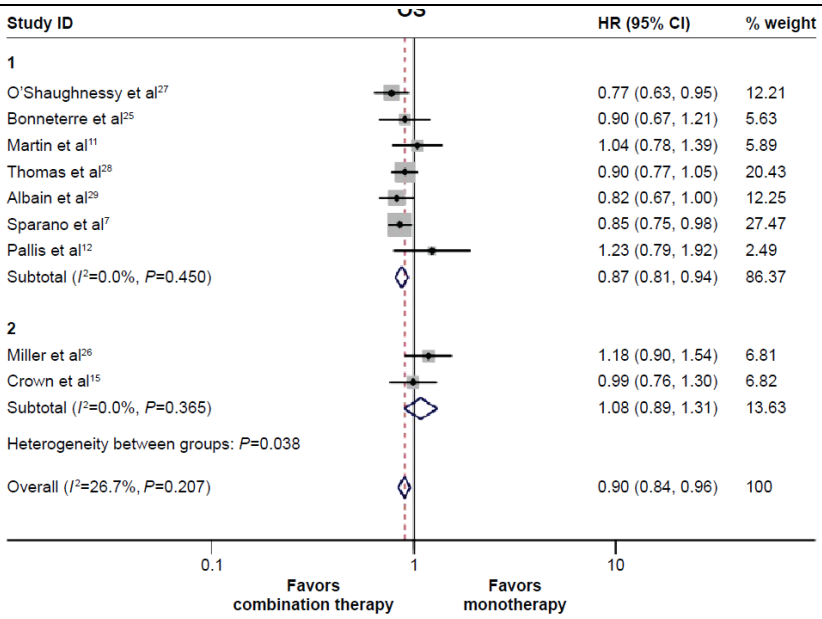
A meta-analysis of Phase III randomized clinical trials (RCTs) comparing the efficacy and toxicity of combination therapy with single-agent therapy in those MBC</td></tr>
</table>

analysis of combination therapy versus single-agent therapy in anthracycline- and taxane-pretreated metastatic breast cancer: results from nine randomized Phase III trials	patients who had been heavily pretreated with anthracyclines and taxanes.
	2. Methodik **Population**: adults with MBC pretreated with an anthracycline and/or a taxane as adjuvant or palliative treatment **Intervention:** combination therapy **Komparator:** single agent **Endpunkte:** efficacy and toxicity **Recherche:** in PubMed, EMBASE, and Cochrane library until 01/08/2015; search for onging trials (ClinicalTrials.gov); screening of references lists, conference proceedings **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 9 trials (n= 4641) **Qualitätsbewertung der Studien:** Jadad scale
Vgl. auch Qi et al., 2013 [32]; Zhang et al., 2016 [38]:	• Ergebnisse *Study characteristics* **Table 1** Characteristics of nine trials eligible for meta-analysis

Author	Martin et al[11]	Sparano et al[7]	Pallis et al[12]	Crown et al[15]	Miller et al[26]	Thomas et al[28]	O'Shaughnessy et al[27]	Bonneterre et al[25]	Albain et al[29]
Year	2007	2010	2012	2013	2005	2007	2002	2002	2008
Country	Spain	USA	Greece	Ireland	USA	USA	USA	France	USA
Patients (n)	252	1,221	148	442	462	752	511	176	529
Age, years, median (range)									
Combination	58 (28–82)	53 (23–78)	60 (32–82)	52 (27–79)	51 (29–78)	53 (25–76)	52 (26–79)	Not reported	53 (26–83)
Single agent	57 (35–80)	53 (24–81)	60 (34–82)	54 (31–77)	52 (30–77)	52 (25–79)	51 (25–75)	Not reported	53 (27–75)
Regimens	GEM + NVB/NVB	IXA + CAP/CAP	NVB + GEM/CAP	Sunitinib + GEM/CAP	Bevacizumab + CAP/CAP	Ixabepilone + CAP/CAP	DOC + CAP/CAP	5-FU + vinorelbine/ DOC	GEM + paclitaxcel paclitaxcel
Metastatic or recurrent (%)	Metastatic (100)	Metastatic (100)	Metastatic (100)	Metastatic (94), recurrent (6)	Metastatic (100)	Metastatic (100)	Metastatic (97), recurrent (3)	Metastatic (100)	Metastatic (97), recurrent (3)
Jadad score	3	3	3	3	3	3	3	3	3
Line of therapy	First to third line	Any line	≥2nd line	Not reported	Any line	Any line	First to third line	Not reported	Not reported
HER-2 positive (%)									
Combination	15	14	14.9	13	26.3	16	Not reported	Not reported	Not reported
Single agent	15	16	12.2	11	20.4	14	Not reported	Not reported	Not reported

Abbreviations: GEM, gemcitabine; NVB, vinorelbine; IXA, ixabepilone; CAP, capecitabine; DOC, docetaxel; 5-FU, 5-fluorouracil.

• 7trials with combination chemotherapy vs. single-agent therapy; 2 trials with chemotherapy plus targeted therapy (sunitinib or bevacizumab) vs. single-agent therapy. • Line of therapy: mixed (→ tab 1) • Hinweis: 3 Studien mit nicht im AWG zugelassenen Arzneimitteln (Sparano et al., Thomas et al., Crown et al.) *Results* OS (→ figure) • Overall: Superiority of combination therapy (HR 0.90 [95% CI 0.84; 0.96]) • two chemotherapy agents combination vs single-agent therapy: HR 0.87 [94% CI 0.81; 0.94] • targeted drug plus chemotherapy vs single drug: HR =1.08 [95% CI 0.89–1.31] → n.s



PFS

- two chemotherapy agents combination v single-agent therapy: HR 0.77 [94% CI 0.70; 084]
- targeted drug plus chemotherapy vs single drug: HR =0.85 [95% CI 0.74–0.97]

Safety

- Concerning the grade 3 or 4 hematological toxicities, leukopenia, anemia, neutropenia, thrombocytopenia, and febrile leukopenia were more frequent in the doublet agents group
- doublet agents produced significantly increased gastrointestinal toxicities including nausea, stomatitis, and pharyngitis than did single agent, whereas the incidence of diarrhea and anorexia in the doublet agents did not differ from the single agent

3. Fazit der Autoren

When compared with single-agent therapy, doublet agents should be considered a treatment option because of the superior efficacy and the manageable safety profile for the prior anthracycline- and taxane-treated MBC patients.

4. Kommentare zum Review

- Quality assessment of included studies: results not reported
- 3 von 9 Studien mit nicht im AWG zugelassenen Arzneimitteln
- funding from National Natural Science Foundation of China
- Syst. Reviews mit ähnlichen Fragestellungen erzielen vergleichbare Schlussfolgerungen:

  Zhang et al. 2016 [38]: „Currently available clinical evidence for MBC patients pretreated with anthracyclines and taxanes indicates that doublet chemotherapy may be a more efficient regimen for MBC patients in terms of ORR and PFS, but with more frequencies of grade 3 and 4 myelosuppression toxicities compared with a single agent. The addition of a targeted agent to chemotherapy significantly improve ORR, but not PFS

	or OS. However, data about targeted agent containing regimens in this setting is too immature to come to an exact conclusion, and more RCTs are needed to appraise the therapeutic effect of specific targeted agent containing doublet therapy for MBC patients in this setting." **Qi et al**. **2013 [32]** : "In conclusion, our meta-analysis showed that doublet agents offered a significant improvement in PFS and ORR in patients with MBC pre-treated with an anthracycline and a taxane but did not benefit OS, but they also produced more toxicity. Due to the highly heterogeneous nature of this disease and limitations of the study, we were still unable to clearly set the role of combination therapy in the treatment of MBC pre-treated with an anthracycline and a taxane with available data from randomised clinical trial; more high-quality RCTs were needed to investigate the issue:"
Puglisi F et al., 2016 [30]. Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review	1. Fragestellung (AWG 3) To assess single-agent therapy for HER2-negative MBC second-line treatment
	2. Methodik **Population:** HER2-negative advanced or metastatic breast cancer who had received one prior line of chemotherapy treatment in the advanced or metastatic setting. **Intervention:** single-agent chemotherapy as a second-line treatment: • taxanes (paclitaxel, nab-paclitaxel, docetaxel), • vinca alkaloids (vinorelbine, vinblastine, vincristine), • platinum-based treatments (cisplatin, carboplatin), • anthracyclines (doxorubicin, pegylated liposomal doxorubicin [PLD], epirubicin) • and other monotherapy (capecitabine, gemcitabine, eribulin, melphelan or cyclophosphamide) **Komparator**: any comparator **Endpunkte**: OS, PFS; TTP; QoL, toxicity outcomes **Recherche:** in MEDLINE, Embase and The Cochrane Library up to 10/ 2013; update search in Pubmed 10/2013-11/2014 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 53 RCT of which **14** reported data specifically for second- and/or later-line treatment within the metastatic setting. **Qualitätsbewertung der Studien:** Quality appraisal of the elements of selection, attrition, detection, and performance bias was performed in accordance with the NICE Guidelines Manual 2009
	3. Ergebnisse *Study and patient level characteristics of trials enrolling second- and/or later-line patients* (n = 14)

- 5 trials reported data for a purely second-line patient population,
- 3 trials reported data from mixed-line treatment but provided results for the second-line subgroup separately,
- 3 trials had unclear second-line status (i.e. it was unclear whether the previous therapy had been given in the adjuvant or metastatic setting),
- 2 trials reported data from second- or later-line patients,
- 1 trial reported data from a second- or later-line subgroup separately.

Further 39 RCTs as first- or later-line (mixed) patients (no focus in this review)

Risk of bias (13 were full papers + could be assessed for quality):

- 7 reported efficacy data on an intention-to-treat basis
- randomisation was carried out appropriately in 5 but concealment of treatment allocation was unclear in most trials.
- 1 trial was double blinded and almost all trials did not have blinded outcome assessors.
- In terms of the distribution of patient characteristics between treatment groups, slight imbalances in potential prognostic factors were noted in 6 trials
- Few trials reported confidence intervals around point estimates
- only 3 confirmed HER2-negative status at enrolment; No trial assessed or commented on discordant HER2 status between the primary tumour and metastases.

Results

Overall Survival (12 studies)

Table 3
Overall survival in second- and/or later-line setting.

Line of therapy within metastatic setting	First author, year	Treatment arms	*N*	Median OS, months (95% CIs)	HR (95% CIs), *p*-value
2nd line	Gasparini, 1991	Epirubicin	22	12	–
		Doxorubicin	21	11	
	Dieras, 1995	Paclitaxel 175 mg/m^2, q3w	41	12.7	$p = 0.15$
		Mitomycin	40	8.4	
	Venturino, 2000	Vinorelbine	33	9.5	–
		Leucovorin then 5-fluorouracil	33	9	
		Mitoxantrone + leucovorin then 5-fluorouracil	33	9	
	Papadimitriou, 2009	DTX weekly	34	28 (15.7, 40.3)	$p = 0.41$
		DTX + gemcitabine	41	14 (3, 25)	
	Von Minckwitz, 2014/TANIA	Bevacizumab + chemotherapy	247	NR: OS data immature, data to be reported in	
		Single-agent chemotherapy (investigator's choice)	247	future publication	
2nd line (subgroup)	Nielsen, 1990	Epirubicin	42	12	–
		Epirubicin + vindesine	33	12	
	Joensuu, 1998	Epirubicin then mitomycin	74	10	Non-significant
		CEF then mitomycin + vinblastine	88	8	
	Norris, 2000	Doxorubicin + vinorelbine	NR	9.4	–
		Doxorubicin	NR	11.3	
Unclear if 2nd line	Baselga, 2012	CAPE + sorafenib	65	19	1.08 (0.65, 1.78)
		CAPE + placebo	51	23.4	
	Sato, 2012	DTX 60 q3w + CAPE	82	NR. OS data immature	
		Sequential DTX 70 q3w until progression, then CAPE	81		
2nd line or later	Keller, 2004	Pegylated liposomal doxorubicin	150	10.4	1.07 (0.79, 1.45), $p = 0.57$
		Control: vinorelbine OR mitomycin C + vinblastine	151	9	
	Palmieri, 2012	DTX q3w	16	7.8 (4.8, 11)††	$p = 0.388$
		Vinorelbine	18	4.9 (3.9, 5.8)††	
2nd line or later (subgroup)	Gradishar, 2005	ABI-007 (nab-paclitaxel)	131	13.0††	0.73, $p = 0.024$
		Paclitaxel 175 mg/m^2, 3 weekly	136	10.7††	

Abbreviations: CAPE, capecitabine; CEF, cyclophosphamide, epirubicin and 5-fluorouracil; CI, confidence interval; DTX, docetaxel; HR, hazard ratio; NR, not reported; OS overall survival; q3w, three-weekly.
N.B. OS data not reported in Ahmad 2013.
†† Calculated (converted from weeks to months).

- Median overall survival (OS) in most trials was 8–13 months.
- Only 1 trial reported a sign. difference between interventions in the 2nd-line metastatic setting: nab-paclitaxel (n =131) conferred a statistically significant OS advantage vs. three-weekly paclitaxel (n = 136) (median OS

	13.0 vs. 10.7 months, respectively; HR 0.73, p = 0.024) PFS (4 studies) • 3 trials demonstrated significantly longer PFS: o capecitabine + sorafenib (6.4 months) vs. capecitabine (4.1 months), HR 0.58 (95% CI: 0.41,0.81), p = 0.001; o capecitabine + low dose DTX (10.5 months)vs. DTX monotherapy before having sequential capecitabine (9.8 months), HR 0.62 (95% CI: 0.40, 0.97), p = 0.0342; o bevacizumab + chemotherapy (6.3 months, 95% CI: 5.4, 7.2) vs. single-agent treatment of physician's choice (TPC) (approx. 60% capecitabine) (4.2 months, 95% CI: 3.9, 4.7), HR 0.75 (95% CI: 0.61, 0.93), p = 0.0068 • pegylated liposomal doxorubicin showed no benefit over control therapy of either vinorelbine or mitomycinC + vinblastine (PFS 2.9 and 2.5 months, respectively; HR 1.26 (95% CI: 0.98, 1.62); p = 0.11 Time to Progression (7 studies) • 3 trials showed a significantly longer TTP: o 3-weekly paclitaxel showed benefit over mitomycin (median TTP 3.5 vs. 1.6 months, respectively; p = 0.026) o capecitabine + sorafenib was superior to capecitabine alone (median TTP 6.8 vs. 4.1 months, respectively; HR 0.56 [95% CI: 0.39, 0.8]; p = 0.001) o nab-paclitaxel was associated with significantly greater TTP vs. standard paclitaxel q3w (median TTP 4.8 vs. 3.7 months, respectively; HR 0.73; p = 0.02) o No benefit in terms of TTP was demonstrated for • doxorubicin + vinorelbine vs. doxorubicin monotherapy (TTP 4.3 vs. 5.3 months, respectively) • pegylated liposomal doxorubicin vs. vinorelbine or mitomycin C + vinblastine (p > 0.05) • 3-weekly docetaxel vs. vinorelbine (2.4 vs. 1.7 months, respectively; p = 0.82) or • epirubicin vs. epirubicin + vindesine (TTP 6 months in both treatment arms) Grade ≥3 adverse events, discontinuation and safety summary • Table 5 (Anhang)
	4. Fazit der Autoren There are few RCTs conducted specifically in the second-line HER2-negative MBC setting. Nab-paclitaxel was the only single agent that demonstrated a survival advantage at the second-line and beyond. Few treatment options provide clinical benefit without adversely influencing tolerability. Given that MBC is an incurable disease and that an equally important aim of treatment at this stage is to enhance QoL and enable patients to be at home with their families, it is vital that trial

	investigators and clinicians set standards for the design and conduct of clinical trials with this aim in mind, with patients enrolled according to the treatment line received within the metastatic setting, with sufficient sample size to enable outcomes to be estimated with greater precision, with HER2-negative status and any discordant status established, a non-invasive method that has recently been tested in phase I and with PROs recorded. This would contribute to physicians being able to more reliably inform patients regarding the likely range of treatment outcomes, and thereby help patients reach the treatment decision that is right for them. *5. Kommentare zum Review* • Conflict of interest reported
Fang Y et al., 2015 [6]. The efficacy and safety of bevacizumab combined with chemotherapy in treatment of HER2-negative metastatic breast cancer: a meta-analysis based on published phase III trials	1. Fragestellung (AWG 3) To evaluate the efficacy and safety of Bev + standard chemotherapy for HER2-negative MBC
	2. Methodik **Population:** predominantly patients with HER2-negative MBC **Intervention:** Bevacizumab + chemotherapy **Komparator:** chemotherapy alone **Endpunkte:** PFS (primary endpoint); OS, toxicity **Recherche:** Cochrane Central Register of Controlled Trials, the Cochrane databases, EMBASE, MEDLINE, and ClinicalTrials.gov from the first available year until May 2014. **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 4 RCT consisting of 3082 patients. **Qualitätsbewertung der Studien:** seven-point Jadad ranking system
	3. Ergebnisse *Study characteristics* • 3 Trials (E2100, AVADO, and RIBBON-1) investigated Bev + chemotherapy as a first-line treatment for HER2-negative MBC, • 1 trial (RIBBON-2) evaluated it as a second-line treatment for HER2-negative MBC patients that had received one previous cytotoxic treatment:

Table 1 Characteristics of the included four RCTs

	E2100	AVADO[a]	RIBBON-1[b]	RIBBON-2
First author	Miller, K.	Miles, D. W.	Robert, N. J.	Brufsky, A. M.
Year	2007	2010	2011	2011
Treatment line	First	First	First	Second
Patients (treatment/control)	347/326	247/241	824/413	459/225
Treatment in experimental arm(s)	Paclitaxel 90 mg/m^2 d1,8,15,q4w; Bevacizumab 10 mg/kg q2w	Docetaxel 100 mg/m^2 d1, q3w; Bevacizumab 15 mg/kg d1 q3w	Capecitabine 1000 mg/m^2 bid, d1 to d14, q3w or taxane/anthracycline q3w; Bevacizumab 15 mg/kg q3w	Chemotherapy (capecitabine, paclitaxel, nab-paclitaxel, docetaxel, gemcitabine, or vinorelbine); Bevacizumab 10 mg/kg q2w or 15 mg/kg q3w
Treatment in control arm(s)	Paclitaxel 90 mg/m^2 d1,8,15,q4w	Docetaxel 100 mg/m^2 d1,q3w; Placebo d1,q3w	Capecitabine 1000 mg/m^2 bid d1 to d14, q3w or taxane/anthracycline q3w; placebo, q3w	Chemotherapy (capecitabine, paclitaxel, nab-paclitaxel, docetaxel, gemcitabine, or vinorelbine); placebo, q2w or q3w
Primary end point	PFS	PFS	PFS	PFS
Secondary end point	OS, ORR, toxic effects, QoL	OS, BOR, DoR, time to treatment failure, safety	OS, 1-year survival rate, ORR, DoOR, safety	OS, ORR, DoOR, 1-year survival rate, safety
PFS	11.8 vs 5.9 months (HR 0.60, CI 0.51 to 0.70)	10.0 vs 8.1 months (HR 0.77, CI 0.64 to 0.93)	8.6 vs 5.7 months (HR 0.68, CI 0.54 to 0.86)[c]; 9.2 vs 8.0 months (HR 0.77, CI 0.60 to 0.99)[d]	7.2 vs 5.1 months (HR 0.78, CI 0.64 to 0.93)
OS	26.7 vs 25.2 months (HR 0.88, CI 0.74 to 1.05)	30.2 vs 31.9 months (HR 1.03, CI 0.70 to 1.33)	29.0 vs 21.2 months (HR 0.85, CI 0.63 to 1.14)[c]; 25.2 vs 23.8 months (HR 1.03, CI 0.77 to 1.38)[d]	18.0 vs 16.4 months (HR 0.90, CI 0.71 to 1.14)

PFS progression-free survival, *OS* overall survival, *ORR* objective response rate, *BOR* best overall response, *QoL* quality of life, *DoR* duration of response, *DoOR* duration of objective response, *HR* hazard ratios, *CI* confidence interval

[a] The 7.5 mg/kg bevacizumab arm was excluded

[b] The population of capecitabine arm is 615 (treatment/control=409/206); The population of taxane/anthracycline arm is 622 (treatment/control=415/207)

[c] The capecitabine arm

[d] The taxane/anthracycline arm

Qualität der Studien: The Jadad scores of the RCTs were 4–7, which is indicative of a high-quality report

Results

Pooled results

(The docetaxel + Bev (7.5 mg/kg) arm of AVADO trial was excluded from the combined analysis because its dosage was not approved for MBC treatment.)

- Bev + standard chemotherapy improved PFS (HR 0.70, CI 0.64–0.77, P=0.000) but had no effect on OS (HR 0.92, CI 0.82–1.02, P=0.119).
- Bev + chemotherapy increased the incidence of febrile neutropenia (RR 1.45, CI 1.00 to 2.09, P=0.048), proteinuria (RR 11.68, CI 3.72–36.70, P=0.000), sensory neuropathy (RR 1.33, CI 1.05–1.70, P=0.020), and grade ≥3 hypertension (RR 13.94, CI 7.06–27.55, P=0.000).
- No differences in efficacy were observed between Bev + paclitaxel and Bev + capecitabine (Cape), but Bev + Cape increased the incidence of neutropenia.
- Bev + standard chemotherapy improved PFS in HER2-negative MBC patients. No benefit in OS was observed.
- Bev + Cape and Bev + paclitaxel had similar treatment efficacy, but Bev + Cape had a higher incidence of neutropenia.

Subgroup analysis

- Whether the clinical benefits of Bev + standard chemotherapy for HER2-negative MBC were affected by different prognostic factors such as hormone receptor status, patient age, number of metastatic sites, tumor grade, prior taxane therapy, or visceral disease was investigated.
- The addition of Bev to standard chemotherapy was consistently beneficial in terms of PFS in all of the subgroups analysed.

Second-line Chemotherapy : RIBBON-2-Trial

Chemotherapy (capecitabine, paclitaxel, nab-paclitaxel, docetaxel, gemcitabine, or vinorelbine) plus Bevacizumab 10 mg/kg q2w or 15 mg/kg q3w vs Chemotherapy plus placebo:

- PFS: 7.2 vs 5.1 months (HR 0.78, CI 0.64 to 0.93)

	• OS: 18.0 vs 16.4 months (HR 0.90, CI 0.71 to 1.14)
	4. Fazit der Autoren: Bev + standard chemotherapy improves PFS significantly in HER2-negativeMBC patients. However, the addition of Bev was associated with more toxicities including febrile neutropenia, proteinuria, sensory neuropathy, and grade ≥3 hypertension. We also found that Bev + paclitaxel and Bev + Cape had similar therapeutic efficacy. Based on the data, we conclude Bev + Cape had a higher incidence of neutropenia than Bev + paclitaxel. 5. Kommentar zu Review • 3 von 4 RCTs untersuchten First-line Chemotherapy, 1 RCT Second-line • Siehe auch CR von Wagner et al. 2012 [35]
Hu Q et al., 2014 [13]. A systematic review of gemcitabine and taxanes combination therapy randomized trials for metastatic breast cancer	1. Fragestellung (AWG3) To compare the efficacy and toxicity for patients receiving chemotherapy with or without GT-based regimens.
	2. Methodik **Population:** Patients with MBC (Trials with first-line and second-line metastatic or advanced breast cancer patients were accepted) **Intervention**: gemcitabine -based chemotherapy **Komparator:** chemotherapy regimen without gemcitabine (all cytotoxic chemotherapy regimens were considered eligible, and new targeted drugs such as bevacizumab were included) **Endpunkte:** time to progression (TTP), progression-free survival (PFS), overall survival (OS) and the drug toxicity. **Recherche:** Pubmed, MEDLINE, EMBASE, and conference proceedings. Manual search in several oncology journals that publish clinical trials. The latest search was performed on September 31, 2013. **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 8 studies (n=2234) **Qualitätsbewertung der Studien**: Jadad scale
	3. Ergebnisse *Study characteristics* Treatment lines: 4 studies with first-line, 2 studies with second-line, 2 studies with first- or second-line

Table 1 Characteristics of included studies

Study ID	Arms	Patients	Treatments (cycle)	Endpoints	Study design	Lose	Treatment lines	Jada scale
Dorte L. Nielsen 2011	Gemcitabine + Docetaxel	170	G 1,000 mg/m2 d1,8 + D 75 mg/m2 d8(21d)	OS.ORR.TTP. toxicity	phase3, random, open-label	6	First or second-line	3
	Docetaxel	167	D 100 mg/m2 d1(21d)					
Kathy S. Albain 2008	Gemcitabin + Paclitaxel	266	G 1,250 mg/m2 d1,8 + P 175 mg/m2 d1(21d)	OS.TTP.ORR. toxicity	phase3, random, unclear	8	first-line	3
	Paclitaxel	263	P 175 mg/m2 d1(21d)					
H. Joensuu 2010	Docetaxel + Gemcitabin(alternating)	122	D l100 mg/m2 d1 + G 1000 mg/m2 d1,8(21d)	TTP.OS.ORR. toxicity	phase3, random, open-label	3	first-line	3
	Docetaxel	115	D l100 mg/m2 d1(21d)					
Christos A. Papadimitriou 2009	Gemcitabin + Docetaxel	41	D 35 mg/m2 + G 600 mg/m2(7d)	ORR.OS.TTP. toxicity	phase2, random, unclear	13	second-line	2
	Docetaxel	34	D 40 mg/m2(7d)					
Adam Brufsky 2011	Gemcitabin + Paclitaxel + Bevacizumab	93	P 90 mg/m2 d1, 8, 15 + B 10 mg/kg d1,15 + G 1500 mg/m2 d1, 15(28d)	ORR.PFS.OS. toxicity	phase2, random, open-label	28	first-line	3
	Paclitaxel + Bevacizumab	94	P 90 mg/m2 d1, 8, 15 + B 10 mg/kg d1, 15(28d)					
	Vinorelbine	127	V 30 mg/m2 d1,8(21d)					
C. Levy 2005	Gemcitabin + Docetaxel	153	D 75 mg/m2 d1 + G 1000 mg/m2 d1, 8(21d)	ORR.PFS.TTP. toxicity	Phase3,random, unclear	Unknown	second-line	2
	Capecitabine + Docetaxel	152	D 75 mg/m2 d1 + C 1250 mg/m2 bid d1-14(21d)					
Zielinski 2005	Gemcitabine + epirubicin + and paclitaxel(GET)	124	G 1,000 mg/m2 d1, 4 + E 90 mg/m2 d1+ P 175 mg/m2 d1(21d)	TTP.ORR. toxicity	Phase3,random, unclear	Unknown	first-line	3
	Fluorouracil + Epirubicin + Cyclophosphamide(FEC)	135	F 500 mg/m2 d1 + E 90 mg/m2 d1 + C 500 mg/m2 d1(21d)					
Stephen Chan 2009	Gemcitabin + Docetaxel	153	G 1000 mg/m2 d1,8 + D 75 mg/m2 d1(21d)	PFS.ORR.OS. toxicity	Phase3,random, unclear	8 + 3	first + second-line	3
	Capecitabine + Docetaxel	152	C 1,250 mg/m2 bid d1-14 + D 75 mg/m2 d1(21d)					

G = gemcitabine, D = docetaxel, C = capecitabine, F = flurouracil, C = cyclophospham, E = epirubicin, P = paditaxel, V = vinorelbine, B = bevacizumab, OS = overall survival, ORR = objective response rates, PFS = progression-free survival, TTP = time to progression.

Risk of bias: All studies reviewed were considered high quality (Jadad=3)

Results

ORR: 8 studies

- GT-based therapy increases ORR (OR = 1.28, 1.07 to 1.53, P = 0.006), there was no evidence of heterogeneity among trials.
- first-line (5 studies): GT-based regimen superior (OR = 1.47, 1.17 to 1.83, P = 0.0007).
- second-line (2 studies): no significant difference (OR = 0.91, 0.51 to 1.63, P = 0.76)
- first-and second- line (2 studies): no sign. difference
- results showed there was benefit for GT-based chemotherapy on ORR (OR = 1.37, 1.09 to 1.73, P = 0.008; 1.17, 0.88 to 1.55, P = 0.29) in “gemcitabine additional roles to taxanes” and “gemcitabine replacement to other non-taxane drugs” subgroups.

PFS: 2 studies

- PFS was not significantly improved (HR = 1.01, 0.7 to 1.46, P = 0.47).
- significant heterogeneity found in the data (P = 0.05, I2 = 74%). Heterogeneity may be caused by a few trial numbers or small samples, which were not eliminated.

TTP: 5 studies

- GT-based treatment prolong TTP (HR = 0.80, 0.71 to 0.89, P < 0.0001), no evidence of heterogeneity among trials.
- first-line subgroup (3 studies) GT- based treatment prolong TTP (HR = 0.79, 0.69 to 0.92, P = 0.0003).
- second-line (1 study): no sign. difference
- first-and second-line (1 study): no sign. difference

	OS: 7 studies • Overall: GT-based chemotherapy had no significant difference compared to other regimens; no statistically significant heterogeneity. • first-line (3 studies): GT-based combination was superior(HR = 0.84, 0.71 to 0.99, P =0.04). • second-line (1 study): no difference between groups • first-and second-line (2 studies): no difference between groups Toxicity Anemia grade 3–4 • overall (7 studies): inferiority of GT (OR 3.09 [1.85; 5.18]) • first-line (4 studies): inferiority of GT (OR 3.15 [1.75; 5.66]). • second-line (1 study): no sign. difference between groups (OR 4.07 [0.19; 87.93] • first-and second-line (2 studies): no sign. difference between groups Neutropenia grade 3–4 • overall (8 studies): inferiority of GT (OR 2.16 [1.05; 4.42]; I^2= 87%) • first-line (4 studies): no sign. difference between groups • second-line (2 studies): no sign. difference between groups • first-and second-line (2 studies): no sign. difference between groups thrombocytopenia grade 3–4 • overall (7 studies): inferiority of GT (OR 8.57 [4.81; 15.27]; I^2= 46%) • first-line (4 studies): inferiority of GT (OR 13.97 [5.66; 34.50]; I2=0%) • second-line (1 study): no sign. difference between groups • first-and second-line (2 studies): inferiority of GT (OR 6.15 [2.73; 13.87], I2=83%) Sensitivity analysis: Due to the high heterogeneity in the above analysis, we performed subgroup analysis in the meta-analysis. A sensitivity analysis was also conducted by removing one study at a time and calculating the pooled HRs for the remaining studies. We found that no article substantially influenced the pooled result in this analysis.
	4. Fazit der Autoren: Gemcitabine/taxanes-treated patients with metastatic breast cancer showed a significant improvement in the ORR, TTP and OS (first-line background) compared to patients not treated with the combination regimen. GTbased regimens led to more serious hematologic toxicity. Limitations: • Heterogeneity in the length of follow up in the long-term mortality studies • Some of the selected studies are not blinded • the number of trials is quite small *5. Kommentar zum Review:* • SR mit gleicher Fragestellung: Li et al. 2013 [21], siehe unten: Einschluss von 6

	von 8 Studien, die hier berücksichtigt wurden, plus 3 weitere, die hier nicht eingeschlossen wurden.
Li W et al., 2013 [21]. Efficacy of gemcitabine-based chemo-therapy in metastatic breast cancer: a meta-analysis of randomized controlled trials	1. Fragestellung (AWG 3) To compare the effects of gemcitabine-based chemotherapy and gemcitabine-free regimens.
	2. Methodik **Population:** Patients with advanced or metastatic breast cancer **Intervention:** gemcitabine-based therapy (in combination or sequential) **Komparator:** gemcitabine-free therapy **Endpunkte:** partial response (PR), complete response (CR), TTP and OS **Recherche**: PubMed and Embase databases were searched between January 1990 and December 2012. **Anzahl eingeschlossene Studien** (Gesamt): 9 (n=2651) **Qualitätsbewertung der Studien:** Jadad scale
	3. Ergebnisse *Study characteristics* • 4 study on first-line treatment, 3 with pretreated patients, 2 mixed pop. (→ Tab. 1) Table 1. Relevant randomized trials included in this meta-analysis ($N = 2651$). First Author Year Trial Phase / Prior Treatment / Regimens / No. of Patients / No. of Overall Response / TTP (months) / Median OS (months) Zielinski[13] 2005 / First line / GET / 124 / 71 / 9.1 / 29.5 vs / $P = 0.093$ / $P = 0.557$ / $P = 0.61$ FEC / 135 / 66 / 9.0 / 24.9 Feher[12] 2005 / First line / Gem / 198 / 30 / 3.4 / 11.8 vs / $P < 0.001$ / $P = 0.0001$ / $P = 0.0004$ Epi / 199 / 75 / 6.1 / 19.1 Martin[14] 2007 / Anthracycline and Taxane / Gem + Vin / 125 / 45 / 6.0 / 15.9 vs / $P = 0.093$ / $P = 0.0028$ / $P = 0.8046$ Vin / 127 / 33 / 4.0 / 16.4 Albain[15] 2008 / Anthracycline / Gem + Pac / 266 / 110 / 6.14 / 18.6 vs / $P = 0.0002$ / $P = 0.0002$ / $P = 0.0489$ Pac / 263 / 69 / 3.98 / 15.8 Chan[16] 2009 / First line or Anthracycline / Gem + Doc / 153 / 49 / 8.05 / 19.29 vs / $P = 0.931$ / $P = 0.121$ / $P = 0.983$ Cap + Doc / 152 / 48 / 7.98 / 21.45 Joensuu[17] 2010 / First line / Doc→Gem / 122 / 67 / 11.3 / 27 vs / $P = 0.15$ / $P = 0.72$ / $P = 0.60$ Doc / 115 / 69 / 11.7 / 28 Nielsen[18] 2011 / First line or Anthracycline / Gem + Doc / 170 / 41 / 10.3 / 19.7 vs / $P = 0.78$ / $P = 0.06$ / $P = 0.57$ Doc / 167 / 36 / 8.3 / 17.9 Brufsky[19] 2011 / First line / Gem + Pac + B / 93 / 54 / 11.3 / 24.3 vs / $P = 0.117$ / $P = 0.247$ / $P = 0.475$ Pac + B / 94 / 46 / 8.8 / 25.0 Pallis[20] 2012 / Anthracycline and Taxane / Gem + Vin / 74 / 21 / 5.4 / 20.4 vs / $P = 0.576$ / $P = 0.736$ / $P = 0.319$ Cap / 74 / 18 / 5.2 / 22.4 GET, gemcitabine, epirubicin, paclitaxel; FEC, fluorouracil, epirubicin, paclitaxel; Gem, gemcitabine; Vin, vinorelbine; Pac, paclitaxel; Doc, docetaxel; Cap, capecitabine; B, Bevacizumab; Epi, epirubicin; TTP, time to progression; OS, overall survival. Risk of bias • Inspection of the funnel plot did not suggest potential publication bias. • quality was high in 7 phase III studies (Jadad score ≥3). Two trials were of

	low quality (Jadad score ≤2) including one phase II trial and one phase III trial.
	
	Results
	
	Overall Effect: gemcitabine-based therapy vs gemcitabine-free chemotherapy
	
	• CR (9 trials): HR 1.40, 95% CI 0.98–2.00
	• PR (9 trials): HR 1.02, 95% CI 0.70–1.50
	• ORR (9 trials): HR 1.09, 95% CI 0.73–1.62
	• TTP (7 trials): HR 0.91, 95% CI 0.72–1.15
	• OS (8 trials): HR 1.05, 95% CI 0.88–1.25
	➔ No stat. sign. difference
	
	Exclusion of 1 study with only in postmenopausal women aged > 59–91 years from meta-analysis resulted in an improvement in PR and ORR
	
	Toxicity
	
	• grade 3 and 4 anemia: HR 2.02, 95% CI 1.35–3.02; P=0.006
	• neutropenia: HR 2.33, 95% CI 1.37–3.63; P=0.01
	• thrombocytopenia: HR 8.31, 95% CI 5.00–13.82; P<0.0001
	➔ significantly higher AE rates in the gemcitabine-based arm
	
	Subgroup: gemcitabine-based doublet versus single agent (3 trials, n=1118 pts)
	
	• Gemcitabine-based doublets were superior to monotherapy in
	  ○ ORR (HR 1.64, 95% CI 1.26–2.12; P=0.0002)
	  ○ TTP (HR 0.71, 95% CI 0.62–0.81; P<0.00001).
	• No difference in OS (HR 0.90, 95% CI 0.79–1.03; P=0.14),
	• higher frequencies of grade 3 to 4 hematological toxic effects in the doublets arm

	4. Fazit der Autoren In conclusion, our study suggests that a gemcitabine-based regimen is as effective as a gemcitabine-free regimen, and that adding gemcitabine to monotherapy may enhance efficacy, although a possible increase in toxicity should be considered. *5. Kommentare zum Review* • CoI: The authors received no payment in preparation of this manuscript; and they have disclosed that they have no significant relationships with or financial interests in any commercial companies related to this study or article • Keine Subgruppenanalysen in Bezug auf Vorbehandlung/Therapielinie • Ähnliche Fragestellung wie SR von Hu et al. 2014 [13], der 6 der 9 Studien ebenfalls eingeschlossen hat.
Qi W et al., 2013 [31]. Paclitaxel-	1. Fragestellung (AWG 3) To examine whether a paclitaxel-based regimen is more effective than a docetaxel-based regimen for MBC patients.

based versus docetaxel-based regimens in metastatic breast cancer: a systematic review and meta-analysis of randomized controlled trials	2. Methodik **Population:** patients with pathologically confirmed metastatic breast cancer **Intervention:** paclitaxel-based regimens **Komparator:** docetaxel-based regimens **Endpunkte:** OS, PFS, TTP, ORR, AEs **Recherche:** PubMed (up to January 2012), Embase (1980 to January 2012), and the Cochrane Register of Controlled Trials (up to January 2012). **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 7 trials(n=1694) **Qualitätsbewertung der Studien:** 5-point Jadad scale
	3. Ergebnisse *Study characteristics* • 3 trials with patients received taxane-based regimens as first-line treatment; 4 trials with 45.6% to 62.2% of patients previously received anthracycline-based regimens for MBC • 1 trial was conducted in elderly or frail patients with MBC • Risk of bias: Jadad scores all trials were 3 points. *Results* OS • 5 trials: HR of 0.87 (95% CI: 0.60–1.27; I^2= 81.3%): → no sign. difference • subgroup first-line treatment (2 trials): paclitaxel-based regimen significantly improved OS compared with a docetaxel-based regimen (HR: 0.73, 95% CI: 0.56–0.94, p=0.014). PFS (2 trials): HR: 0.76, [95% CI: 0.58–1.00], I2=65%→ no sig. difference Time to Progression (3 trials): HR: 1.13 [95% CI: 0.81–1.58], I2=74% → no sig. difference ORR (7 studies) RR: 1.01 [95% CI: 0.88–1.15], → no sig. difference Toxicity: paclitaxel-based regimen superior to docetaxel based regimen: • anemia grade 3 or 4: RR 0.64, 95% CI: 0.44–0.94, p=0.023), • neutropenia grade 3 or 4: RR 0.74, 95% CI: 0.58–0.93, p=0.011, • neutropenia grade 3 or 4: RR: 0.74, 95% CI: 0.58–0.93, p=0.011 • febrile neutropenia grade 3 or 4: RR: 0.38, 95% CI: 0.15–0.96, p=0.041 • thrombopenia grade 3 or 4: RR: 0.62, 95% CI: 0.41–0.96, p=0.033 • mucositis grade 3 or 4: RR: 0.082, 95% CI: 0.025–0.27, p<0.001 • diarrhea grade 3 or 4: RR 0.19, 95% CI: 0.081–0.47, p<0.001 • fatigue grade 3 or 4: RR: 0.43, 95% CI: 0.20–0.96, p=0.03
	4. Fazit der Autoren Our meta-analysis confirmed that the efficacy of the paclitaxel-based regimen was

	comparable to the docetaxel-based regimen for patients with MBC, and the paclitaxel-based regimen was associated with less toxicity and better tolerability, especially in older patients and when used in weekly regimens 5. *Kommentar zum Review:* • significant heterogeneity among included trials

Leitlinien

Rugo HS et al., 2016 [34]. Endocrine Therapy for Hormone Receptor-Positive Metastatic Breast Cancer: American Society of Clinical Oncology Guideline.	ASCO Guidelines: Endocrine therapy for women with hormone receptor (HR) –positive metastatic breast cancer (MBC).
	Methodik/ Grundlage der Leitlinie **Expert Panel** was convened with multidisciplinary representation in medical oncology, radiation oncology, psycho-oncology, patient advocacy, and guideline methodology. All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests... In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy. **ASCO guidelines are based on systematic reviews**: • 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 • **Literature search**: in Medline to 4/2014; Cochrane Library databases to Issue 3 of March 2013; Antonio Breast Cancer Symposium (2011 to 2014) and ASCO abstracts (2012 to 2014); targeted literature search update was performed in June 2015 to obtain the most recent evidence • Formal assessment of Study Quality (*Detaillierte Informationen + Bewertungsergebnisse zu finden im METHODOLOGY SUPPLEMENT*) **LoE /GoR** • Definitions for Types of recommendation, Strengths of evidence Strengths of recommendation→ Anhang • Recommendations reflect high, moderate or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. Sonstige methodische Hinweise • Revision Dates: The co-chairs determine the need for guideline updates or revisions on the basis of periodic review and consideration of the literature. If new and compelling data are identified, the Expert Panel or an update committee is reconvened to discuss revisions to the document • Evidenzgrundlage im Anhang abgebildet
	Empfehlungen **ASCO Key Guideline Recommendations for HR-positive MBC**

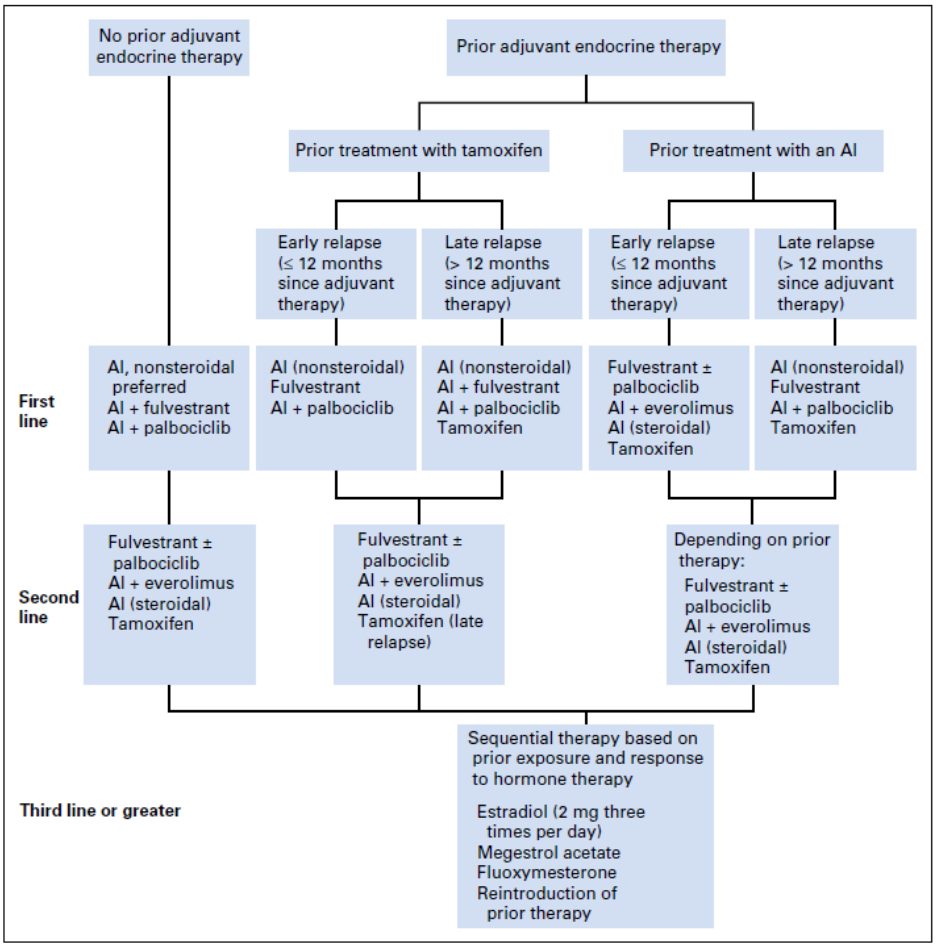


Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered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

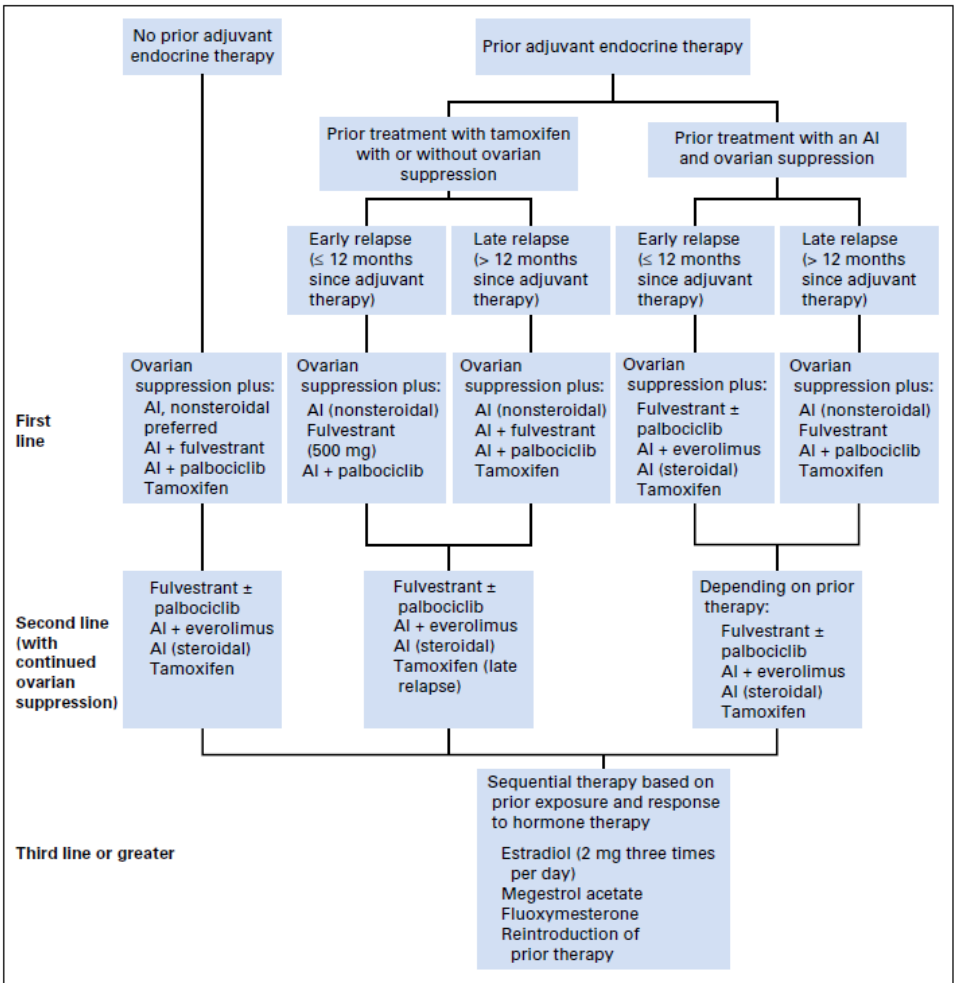


Fig 2. Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered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

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

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

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

Treatment should be administered until there is unequivocal evidence of disease

	progression as documented by imaging, clinical examination, or disease-related symptoms. (*Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong*) The use of combined endocrine therapy and chemotherapy is not recommended. (*Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong*) **First-line therapy for HR-positive metastatic breast cancer** Postmenopausal women with HR-positive MBC should be offered aromatase inhibitors (AIs) as first-line endocrine therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*). Combination hormone therapy with fulvestrant, with a loading dose followed by 500 mg every 28 days, plus a nonsteroidal AI may be offered to patients with MBC without prior exposure to adjuvant endocrine therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate*). Premenopausal women with HR-positive MBC should be offered ovarian suppression or ablation in combination with hormone therapy because contemporary hormonal agents have only been studied among postmenopausal women. (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*) Treatment should take into account the biology of the tumor and the menopausal status of the patient with careful attention paid to ovarian production of estrogen. (*Type: Evidence and Consensus-based; benefits outweigh harms; Evidence quality: Intermediate; Strength of Recommendation: Moderate*) **Second-line therapy for HR-positive MBC** The choice of second-line hormone therapy should take into account prior treatment exposure and response to previous endocrine therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*). Sequential hormone therapy should be offered to patients with endocrine-responsive disease. except in the case of rapid progression with organ dysfunction; no specific order of agents is recommended. (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*). When fulvestrant is administered, it should be administered using the 500-mg dose and with a loading schedule (treatment start, day 15, day 28, then once per month). (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*). **Targeted Therapy** A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-naıve HR-positive MBC, because PFS but not OS was improved compared with the nonsteroidal AI letrozole alone. Palbociclib may also be offered in combination with fulvestrant in patients exposed to prior hormone therapy and up to one line of chemotherapy, on the

	basis of data from the phase III PALOMA-3 trial. PFS was improved compared with fulvestrant alone; OS data are immature (*Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: intermediate*). Exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC who experience progression during prior treatment with nonsteroidal AIs, with or without one line of prior chemotherapy, either before or after treatment with fulvestrant, because PFS but not OS was improved compared with exemestane alone. This combination should not be offered as first-line therapy for patients who experience relapse 12 months from prior nonsteroidal AI therapy or for those who are naıve to hormone therapy (*Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*). **HER2$^+$ HR$^+$ MBC:** The addition of HER2 targeted therapy to first-line AIs should be offered to patients with hormone receptor positive, HER2 positive metastatic breast cancer in whom chemotherapy is not immediately indicated..(*Type: Evidence and Consensus-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong*)
NCCN, 2017 [24]. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 2.2017.	Fragestellung: nicht spezifiziert
	Methodik/Grundlage der Leitlinie “Recommendations within the NCCN Guidelines are derived from critical evaluation of evidence, integrated with the clinical expertise and consensus of a multidisciplinary panel of cancer specialists, clinical experts and researchers in those situations where high-level evidence does not exist. “ Regelmäßiges Update einer bestehenden Leitlinie Prior to the annual update of the Guidelines, an electronic search of the PubMed database, provided by the U.S. National Library of Medicine, is performed to obtain key literature published since the previous Guidelines update. Suchzeitraum: 06/19/14 and 06/29/15 **LoE** The level of evidence depends upon the following factors, which are considered during the deliberation process by the Panel: extent of data (e.g., number of trials, size of trials, clinical observations only), consistency of data (e.g., similar or conflicting results across available studies or observations), and quality of data based on trial design and how the results/observations were derived (e.g., RCTs, non-RCTs, meta-analyses or systematic reviews, clinical case reports, case series). The degree of consensus within the Panel is based on the percentage of Panel votes, as shown in the Definitions for NCCN Categories section below. The NCCN does not formally consider cost of an intervention in its assessment; however, in some situations, Panels may consider the overall value of a treatment, especially when robust data from pharmacoeconomics

studies are available for specific interventions.

Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert.

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

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

Sonstige methodische Hinweise

- *„discussion update in progress„*
- Leitlinie entspricht nicht einer S3-Leitlinie, (z.B. fehlt eine formelle Bewertung der Primärliteratur) und wurde nur ergänzend dargestellt.

Empfehlungen

<u>Endocrine Therapy for recurrent or stage IV disease</u>

Premenopausal patients

- Selective ER modulators (tamoxifen or toremifene) or ovarian ablation or suppression plus endocrine therapy as for postmenopausal women

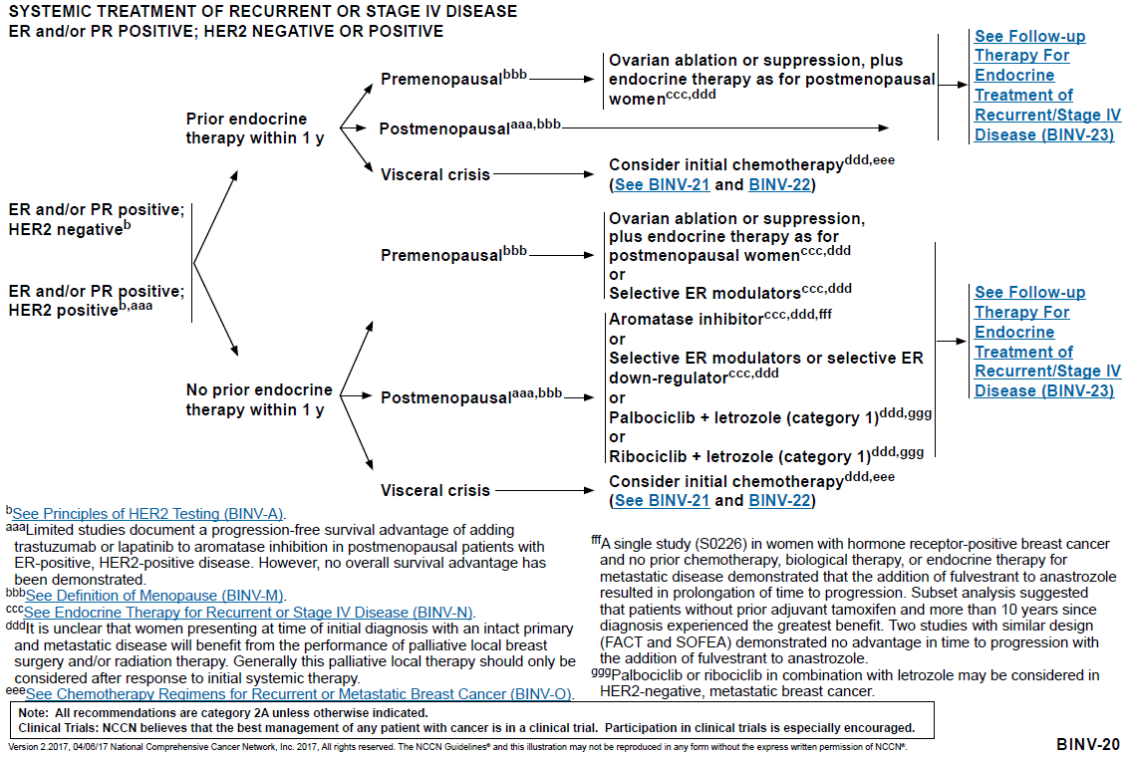
Postmenopausal Patients

- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator (exemestane)
- Exemestane + everolismus[1,2]
- Palbociclib + letrozole (category 1)[2,3]
- Palbociclib + fulvestrant (category 1)[2,4]
- Ribociclib + letrozole (category 1)[2,3]
- Fulestrant[5]
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

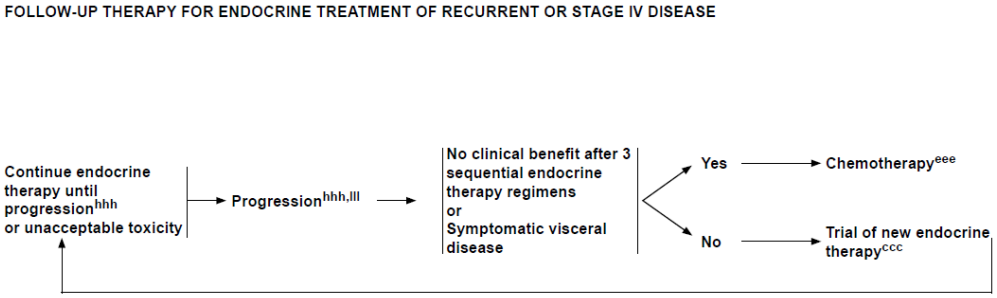
[1] A combination of exemestane with everolimus can be considered for patients who meet the eligibility criteria for BOLERO-2 (progressed within 12 mo or on no-steroidal AI).
[2] If there is disease progression while on a CDK4/6 inhibitor + letrozole, there are no data to support an additional line of therapy with another palbociclip regimen.
[3] Palbociclib or ribociclib in combination with letrozole may be considered as a treatment option for first-line therapy for postmenopausal patients with hormone-receptor positive, HER2-negative metastatic breast cancer.
[4] For postmenopausal women or for premenopausal women receiving ovarian suppression with an LHRH agonist, with hormone-receptor positive, HER2-negative metastatic breast cancer that has progressed on or after prior adjuvant or metastatic

	endocrine therapy. [5] A single study (S0226) in women with hormone-receptor positive breast cancer and no prior chemotherapy, biological therapy, or endocrine therapy for metastatic disease demonstrated that the addition of fulvestrant to anastrozole resulted in prolongation of time to progression. Subset analysis suggested that patients without prior adjuvant tamoxifen and more than 10 years since diagnosis experienced the greatest benefit. Two studies with similar design (FACT and SOFEA) demonstrated no advantage in time to progression with the addition of fulvestrant to anastrozole. <u>Chemotherapy Regimens for Recurrent or Metastatic Disease</u> There is no compelling evidence that combination regimens are superior to sequential single agents. **Preferred single agents:** anthracyclines, • doxorubicin, • pegylated liposomal doxorubicin taxanes, • paclitaxel anti-metabolites, • capecitabine • gemcitabine; non-taxane microtubule inhibitors, • eribulin • vinorelbine **Other single agents:** • cyclophosphamide, • carboplatin, • docetaxel, • albumin-bound paclitaxel, • cisplatin, epirubicin • ixabepilone, **Combination Regimens** • CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil) • FEC (fluorouracil/epirubicin/cyclophosphamide) • AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Paclitaxel/bevacizumab[3] [3]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

	Algorithmus: Systemic treatment of recurrent or stage IV disease [BINV-20]:



BINV-23:



Patridge AH et al., 2014 [29]. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American	ASCO Guideline: Chemo- and targeted therapy for women with human epidermal growth factor 2 (HER2)-negative (or unknown) advanced breast cancer.
	Methodik **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. An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature. **Literature search**:

Society of Clinical Oncology Clinical Practice Guideline This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation.	• 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) The primary outcome measures of interest included overall survival, progression-free survival, overall response, Clinical Benefit Rate, quality of life, and/or adverse events. **Study Quality Assessment** • Study quality was formally assessed for the studies identified. • design aspects related to the individual study quality were assessed by one reviewer and included factors such as 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. **LoE/GoR:** Definitions for Types of recommendation, Strengths of evidence Strengths of recommendation→ Anhang Author’s disclosure of potential conflict of interest available At annual intervals, the Update Committee Co-Chairs and two Committee members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. *Hinweis zur LL* • 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.
	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) [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.

[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.

[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

[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.

[6] 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

[7] 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.

[8] 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]

[9] 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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phase III trials in early and advanced disease. Cancer Res 71, 2012 (suppl 3; abstr P5-18-06)
[30] Xu HB, Xu Q, Li L: A literature-based meta-analysis taxane-based doublet versus single-agent taxane chemotherapy in patients with advanced breast cancer. J Cancer Res Clin Oncol 137:1005-1013, 2011</td></tr>
<tr><td rowspan="3">NICE, 2009 [25].

Advanced breast cancer (update) Diagnosis and treatment

Issued: February 2009
last modified: August 2017.
NICE (CG81)

<u>Hinweis</u>: Die Empfehlungen der LL-Version aus 2009 wurden 2015 auf ihre Aktualität überprüft und als weiterhin gültig angesehen. Die nächste Überprüfung ist für 2017 geplant.</td><td>Fragestellung

What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer?</td></tr>
<tr><td>Methodik/Grundlage der Leitlinie

• systematische Evidenzaufbereitung (Formulierung von PICO-Fragen; Systematische Literaturrecherche in mehreren Datenbanken; Datenextraktion, Qualitätsbewertung der gefundenen Literatur auf Basis der SIGN Kriterien für systematische Reviews/Meta-analysen und RCTs)
• Formulierung der Empfehlung basierend auf klinischer und ökonomischer Evidenz in Konsensusprozessen; bei schwacher Evidenz basierend auf informellen Konsens
• Anwendung von GRADE - GoR finden sich in den Formulierungen wieder: "To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations."
• Literaturrecherche der LL-Version 2009: bis 30.06.2008

Regelmäßige Überprüfung der Aktualität der Empfehlungen: letzter Surveillance Report vom November 2015: Es wurden in Bezug auf die Therapieempfehlungen keine neue Evidenz identifiziert, die zu einer Änderung dieser Empfehlungen führen würde

Aktualisierungen:

• Update 2014: review of the evidence on exercise for people with or at risk of lymphoedema and addition of 2 recommendations to section 1.5
• Update 2017: Review of the evidence and update of recommendations in section 1.1 on assessing oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status on disease recurrence.</td></tr>
<tr><td>Empfehlungen

Systemic disease-modifying therapy

Recommendations

<table><tr><td>1.3.1</td><td>Offer endocrine therapy as first-line treatment for the majority of</td></tr></table></td></tr>
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	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

Recommendations

1.3.4	Offer an aromatase inhibitor (either non-steroidal or steroidal) to: • postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy • postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. [2009]
Qualifying statement: These recommendations are based on high quality evidence of clinical and cost effectiveness. There is no evidence directly comparing these agents so it is not possible to recommend any particular aromatase inhibitor. All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival).	
1.3.5	Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. [2009]
1.3.6	Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression. [2009]
Qualifying statement: These recommendations are based on one moderate quality RCT report showing a survival benefit for combination therapy over single agents in pre-menopausal patients. There is also evidence of clinical effectiveness from one high-quality systematic review of randomised trials in pre-menopausal women. There was GDG consensus that perimenopausal women should be treated in the same manner. The GDG has made no recommendation on the optimal endocrine management	

of patients with ER-positive disease who relapse whilst on adjuvant tamoxifen as there is no data in this area. Current UK practice varies, with the use of either ovarian suppression or ovarian suppression in combination with aromatase inhibitors being used.

Clinical Evidence:

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

- Mauri D, et al. (2006) Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 98(18): 1285–1291.
- Chia S, et al. (2008) Double-blind, Randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptorpositive, advanced breast cancer: Results from EFECT. J Clin Oncol 26: 1664–1670.
- Mouridsen HT (2007) Letrozole in advanced breast cancer: the PO25 trial. Breast Cancer Res Treat 105(1): 19–29.
- Catania C, et al. (2007a) Fulvestrant in heavily pre-treated patients with advanced breast cancer: results from a single compassionate use programme centre. Breast Cancer Res Treat 106: 97–103.

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

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

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

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

A moderate quality systematic review (Klijn et al. 2001) and meta-analysis of data from four RCTs (one unpublished) concluded that combination therapy with LHRH agonists, buserelin or goserelin, combined with tamoxifen produced significant improvements in tumour response,

reduction in the risk of death (~22%) and disease progression (~30%) than LHRH agonist monotherapy. Lack of methodological detail suggests caution in the interpretation of these results.

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

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

Chemotherapy

Recommendations

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.

Hinweise FB: 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.
Wildiers H et al., 2013 [36]. **Belgian Health Care Knowledge Centre (KCE)** Breast cancer in women: diagnosis, treatment and follow-up (KCE Reports 143 – 3rd	This guideline was the result of collaboration between the College of Oncology and the KCE and covered a broad range of topics: diagnosis, staging, treatment, reconstructive surgery, supportive therapy and follow up. It primarily concerned women with invasive early or advanced breast cancer. The KCE is a federal institution which is financed for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, food chain safety and environment, and Federal Public Service of social security. The development of clinical practice guidelines is part of the legal mission of the KCE. A clinical practice guideline (CPG) on the management of breast cancer was firstly published in 2007 [1], and completely updated in 2010 [2]. [1] Christiaens et al. Support scientifique du Collège d'Oncologie: un guideline pour la prise en charge du cancer du sein. Brussels: Centre fédéral d'expertise des soins de santé; 2007. Good Clinical Practices (GCP) 63B

EDITION)

[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

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

Formulation of recommendations:

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.
	Recommendations -Treatment of metastatic breast cancer: **Systemic treatment** <u>Endocrine therapy and ER antagonists</u> Recommendation • In premenopausal women with hormone receptor-positive or hormone receptor-unknown metastatic breast cancer, suppression of ovarian function in combination with tamoxifen is the first-line hormonal therapy of choice (**1A evidence**). • In postmenopausal women with hormone receptor-positive or hormone receptor-unknown metastatic breast cancer, first-line treatment consists of third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) or Tamoxifen. In the choice of the agent, the adjuvant endocrine therapy received should be taken into consideration. As second-line treatment, a third generation aromatase inhibitor or Fulvestrant is recommended (**1A evidence**). • Fulvestrant may be considered as an alternative to third generation aromatase inhibitors for metastatic breast cancer in postmenopausal women with hormone receptor-positive (ER+ and/or PgR+) breast cancer that has recurred after prior adjuvant tamoxifen therapy or progressed during prior tamoxifen therapy for advanced disease (**1B evidence**). Clinical evidence: A meta-analysis of 4 RCTs found a significant survival benefit (HR 0.78, p=0.02) and progression-free survival benefit (HR 0.70, p=0.0003) in favour of the combined treatment [214]. In a recent systematic review including 6 RCTs, aromatase inhibitors were found to have a clear advantage in overall response rate, clinical benefit, and time to progression over tamoxifen as first-line hormonal treatment in postmenopausal patients with metastatic breast cancer [215]. Overall survival did not differ significantly. These results confirm the recommendations of CBO [66], the German Cancer Society [17], Cancer Care Ontario [216] and the Central European Cooperative Oncology Group [204] . However, tamoxifen remains an acceptable alternative as first-line treatment. Based on data from RCTs, following tamoxifen failure, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) or fulvestrant are recommended for second-line treatment for post-menopausal patients with HR-positive metastatic breast cancer based upon the more favourable side-effect profile [204, 216]. Flemming et al. [217, 218] reported results from two phase III, multicentre RCTs comparing fulvestrant versus anastrozole in patients with prior metastatic or adjuvant endocrine therapy. No significant differences were observed between fulvestrant and anastrozole therapy arms for time-to-progression (primary endpoint), objective response rate, time-to-treatment failure, clinical benefit, and overall survival (median follow-up ranging from 15.1 to 27.0 months). No significant differences in tolerability measures were identified between therapy arms with the exception of a higher incidence of joint disorders (including arthralgia, arthrosis, and arthritis) for patients treated with anastrozole (12.8% vs. 8.3%, p = 0.0234). Flemming et al. [217, 218] also reported the results of the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) (n = 693) [219] comparing fulvestrant with exemestane in women with HR-positive breast cancer recurring after prior adjuvant non-steroidal aromatase inhibitor (NSAI) therapy (during or within 6

months of discontinuation) or progressing during prior NSAI therapy for advanced disease. At a median follow-up of 13 months, there were no significant differences for median time-to-progression (primary endpoint), objective response rate, clinical benefit rate, or duration of response. Fulvestrant and exemestane were both well tolerated, with no significant differences noted across any adverse events.

References:

[204]. Beslija S et al. Second consensus on medical treatment of metastatic breast cancer. Annals of Oncology. 2007;18(2):215-25.
[214.] Klijn JG et al. Combined tamoxifen and luteinizing hormonereleasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol. 2001;19(2):343-53.
[215]. Ferretti G et al. Second- and third-generation aromatase inhibitors as first-line endocrine therapy in postmenopausal metastatic breast cancer patients: a pooled analysis of the randomised trials. Br J Cancer. 2006;94(12):1789-96.
[216.] Eisen A, Prichard K, Johnston M, Oliver T, Breast Cancer Disease Site Group. Role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Toronto: Cancer Care Ontario; 2003.
[217.] Flemming J, Madarnas Y, Franek JA. Fulvestrant for Systemic Therapy of Locally Advanced or Metastatic Breast Cancer in Postmenopausal Women: Guideline Recommendations. Toronto: Cancer Care Ontario; 2008. Evidence-based Series #1-13: Section 1
[218.] Flemming J, Madarnas Y, Franek JA. Fulvestrant for systemic therapy of locally advanced or metastatic breast cancer in postmenopausal women: a systematic review. Breast Cancer Research & Treatment. 2009;115(2):255-68.
[219]. Chia S, Gradishar W. Fulvestrant vs exemestane following nonsteroidal aromatase inhibitor failure: first overall survival data from the EFECT trial. Breast Cancer Res Treat. 2007;106(Suppl 1):S115, A2091.

<u>Chemotherapy</u>

Recommendation

- 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: [175] Farquhar et al. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Cochrane Database Syst Rev. 2005(3):CD003142. [220] Carrick et al. Single agent versus combination chemotherapy for metastatic breast cancer (Review). 2009. Cochrane Database of Systematic Reviews Issue 2. Art. No.: CD003372. DOI: 10.1002/14651858.CD003372.pub3. [221] Carrick et al. Platinum containing regimens for metastatic breast cancer. Cochrane Database Syst Rev. 2004(3):CD003374. [222] Carrick et al. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database of Systematic Reviews. 2005(2):CD003372. [223] Sledge GW ND, Bernardo P 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;21:588-92. [224] Cardoso F, Bedard PL, Winer EP, Pagani O, Senkus-Konefka E, Fallowfield LJ, et al. International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst. 2009;101(17):1174-81. [225] Bonneterre J, Dieras V, Tubiana-Hulin M, et al. Phase II multicentre randomised study of docetaxel plus epirubicin vs 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. Br J Cancer. 2004;91:1466-71. [226] Jassem J, Pienkowski T, Pluzanska A, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. J Clin Oncol. 2001;19:1707-15. [227] O'Shaughnessy J, Miles D, Vukelja S, et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol. 2002;20:2812-23. [228] Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, Pluzanska A, et al. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol. 2008;26(24):3950-7. [229] Chan S, Romieu G, Huober J, et al. Phase III study of gemcitabine plus docetaxel compared with capecitabine plus docetaxel for anthracycline-pretreated patients with metastatic breast cancer. J Clin Oncol. 2009;27(11):1753-60.

Biological therapy

Bevacizumab:

Recommendation
- 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 overall survival, progression- free survival 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 Recommendations: • 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.

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

<table>
<tr>
<td>NICE, 2013 [28].

Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy

Technology appraisal guidance TA 295</td>
<td>
1 Guidance

1.1 Everolimus, in combination with exemestane, is not recommended within its marketing authorisation for treating postmenopausal women with advanced human epidermal growth factor receptor 2 (HER2) negative hormone-receptor-positive breast cancer that has recurred or progressed following treatment with a non-steroidal aromatase inhibitor.
<table>
<tr><td colspan="2">Evidence for clinical effectiveness</td></tr>
<tr><td rowspan="3">Availability, nature and quality of evidence</td><td>The Committee concluded that the indirect treatment comparison that estimated the clinical effectiveness of everolimus plus exemestane compared with fulvestrant should be regarded with caution.</td></tr>
<tr><td>The Committee noted that the TAMRAD trial did not compare everolimus within its licensed indication (that i in combination with exemestane) with tamoxifen. The Committee noted that no conclusions on the effectiven of everolimus plus exemestane compared with tamoxif were possible.</td></tr>
<tr><td>The Committee concluded that the 'naive chained indir analysis', which estimated the clinical effectiveness of everolimus plus exemestane compared with chemotherapy relied on untested assumptions and on a systematic review that included studies that no longer reflect clinical practice</td></tr>
<tr><td>Relevance to general clinical practice in the NHS</td><td>The Committee heard from the clinical specialists that t BOLERO-2 trial population represented patients who would be offered everolimus plus exemestane in the UI</td></tr>
<tr><td rowspan="3">Uncertainties generated by the evidence</td><td>The Committee agreed that the immaturity of the overa survival data from the BOLERO-2 trial generated considerable uncertainty associated with the longer-ter benefits of everolimus plus exemestane.</td></tr>
<tr><td>The Committee concluded that there was considerable uncertainty about the validity of the comparison of everolimus plus exemestane with tamoxifen, but noted previous conclusions that, of the endocrine therapies, t comparison of everolimus plus exemestane with exemestane alone was the most relevant to the apprais</td></tr>
<tr><td>The Committee concluded that it was not possible to make robust comparisons between everolimus plus exemestane and chemotherapies based on the availab evidence.</td></tr>
<tr><td>Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?</td><td>The Committee noted that, although the manufacturer included no plans to test for interaction in its statistical analysis plan, it had stated that it had not identified any statistically significant differences in progression-free survival between subgroups.</td></tr>
<tr><td rowspan="2">Estimate of the size of the clinical effectiveness including strength of supporting evidence</td><td>The Committee concluded that everolimus plus exemestane is effective in prolonging progression-free survival compared with exemestane alone.</td></tr>
<tr><td>The Committee agreed that the immaturity of the overa survival data resulted in considerable uncertainty associated with the longer-term benefits of everolimus plus exemestane.</td></tr>
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</table>

CADTH, 2013 [4]. 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.
NICE, 2012 [26]. 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.
NICE, 2012 [27]. Eribulin for the treatment of locally advanced or metastatic breast cancer Technology appraisal guidance TA 250	**Key conclusion** **1.1** Eribulin is not recommended, within its licensed indication, for the treatment of locally advanced or metastatic breast cancer that has progressed after at least two chemotherapy regimens for advanced disease. **Evidence for clinical effectiveness** **4.2, 4.3** The EMBRACE trial formed most of the clinical-effectiveness evidence in the manufacturer's submission. The Committee noted that no health-related quality of life data were collected during the EMBRACE trial and that data were presented from two phase II trials in which there was no comparator arm. The Committee considered quality of life to be an important outcome measure in advanced cancer and that this was an important omission from the phase III trial. The Committee concluded that the effects of eribulin on health-related quality of life had not been adequately captured.

CADTH, 2012 [3] Pan-Canadian Oncology Drug Review Final Clinical Guidance Report: Eribulin (Halaven) for Metastatic Breast Cancer.	**Conclusion:** The pCODR Breast Clinical Guidance Panel concluded that there is a net overall clinical benefit to eribulin in the 3rd line or greater treatment of women with incurable locally advanced/ metastatic breast cancer previously exposed to anthracyclines and taxanes, based on a single high-quality randomized controlled trial (EMBRACE)1 that demonstrated a clinically and statistically significant benefit in overall survival for women treated with eribulin compared with those treated with physician's choice.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 18.07.2017

#	Suchfrage
1	MeSH descriptor Breast Neoplasms explode all trees
2	(breast or mamma*):ti,ab,kw
3	(cancer*):ti,ab,kw or (tumor*):ti,ab,kw or (tumour*):ti,ab,kw or (carcinoma*):ti,ab,kw or (adenocarcinoma*):ti,ab,kw or neoplas*:ti,ab,kw or lesions*:ti,ab,kw or mass*:ti,ab,kw
4	(advanced):ti,ab,kw or (metastat*):ti,ab,kw or (metastas*):ti,ab,kw or (recurren*):ti,ab,kw or (relaps*):ti,ab,kw or progression*:ti,ab,kw
5	#2 and #3
6	#1 or #5
7	#4 and #6
8	#7 Publication Year from 2012 to 2017

SR, HTAs in Medline (PubMed) am 02.08.2017

#	Suchfrage
1	"breast neoplasms/drug therapy" OR "breast neoplasms/radiotherapy" OR "breast neoplasms/therapy" OR "breast neoplasms/treatment"
2	(breast[Title]) OR mamma*[Title]) 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[Title]) OR mamma*[Title]
5	((((((cancer[Title/Abstract]) OR tumour*[Title/Abstract]) OR tumor[Title/Abstract]) OR tumors[Title/Abstract]OR carcinom*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR malignan*[Title/Abstract]) OR adenocarcinom*[Title/Abstract]
6	(((((((advanced[Title/Abstract]) OR metastas*[Title/Abstract]) OR metastat*[Title/Abstract]) OR recurren*[Title/Abstract]) OR relaps*[Title/Abstract]) OR progression*[Title/Abstract]) OR progressive*[Title/Abstract]) OR disseminat*[Title/Abstract]
7	#4 AND #5 AND #6
8	((((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]) OR chemotherap*[Title/Abstract]) OR neoadjuvant*[Title/Abstract]) OR (Aromatase[Title/Abstract] AND Inhibitors*[Title/Abstract])
9	(#7) AND #8
10	(#3) OR #9

11	(#10) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
12	(((#11) AND ("2012/07/01"[PDAT] : "2017/07/31"[PDAT])) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 18.07.2017

#	Suchfrage
1	"breast neoplasms"[MeSH Major Topic]
2	(breast[Title]) OR mamma*[Title]
3	(((((cancer*[Title]) OR tumour*[Title]) OR tumors[Title/Abstract] OR tumor[Title]) OR carcinom*[Title]) OR adenocarcinom*[Title]) OR neoplas*[Title]
4	(#2) AND #3
5	(#1) OR #4
6	(#5) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
7	((#6) AND ("2012/07/01"[PDAT] : "2017/07/30"[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

Zu Systematischen Reviews

Beith et al. 2016 [2]

Table 2 Efficacy results by study

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

Table 2 Continued

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

Image 2012 (LUX-Lung 3) did not report any data for the above table

Cope 2013 [5]

Table 1 – Key study characteristics for all randomized controlled trials.

Study	Treatment	N	Centers	Follow-up
Di Leo et al. [14]: CONFIRM (phase III)	Fasludex 500 mg Fasludex 250 mg	362 374	128 centers in 17 countries	Maximum FU 48 mo
Ohno et al. [15]: FINDER1 (phase II)	Fasludex 250 mg* Fasludex 250 mg loading dose† Fasludex 500 mg‡	45 51 47	Japan	Data cutoff for this study was to be when all patients (except withdrawals) had been followed up for at least 24 wk
Pritchard et al. [16]: FINDER2 (phase II)	Fasludex 250 mg* Fasludex 250 mg loading dose† Fasludex 500 mg‡	47 51 46	35 centers in six countries	FU every 12 wk regardless of treatment discontinuation. Data cutoff when all patients (except withdrawals) had been followed up for at least 24 wk
Howell et al. [17]: Trial 0020 (phase III)	Fulvestrant 250 mg§ Anastrozole 1 mg OD	222 229	Europe, Australia, and South Africa	Median FU of 14.4 mo
Osborne et al. [18]: Trial 0021 (phase III)	Fulvestrant 250 mg§ Anastrozole 1 mg OD	206 194	North America	16.8 mo
Buzdar et al. [23,24]: Phase III	Anastrozole 1 mg OD Megestrol acetate 40 mg QID Anastrozole 10 mg OD‖	263 253 248	Two trials, one in North America (49 centers), the other in Europe, Australia, and South Africa (73 centers)	Median FU about 6 mo for 1996; 31 mo for 1998
Buzdar et al. [25]: Phase III	Letrozole 0.5 mg Letrozole 2.5 mg Megestrol acetate (40 mg QID)	202 199 201	120 centers in the United States, Canada, and Europe (seven countries)	18 mo of FU from the first visit of the last patient enrolled
Chia and Gradishar [26]: EFECT (phase III)	Fasludex 250 mg loading dose† Exemestane 25 mg OD	351 342	Argentina, Belgium, Brazil, Canada, Denmark, France, Germany, Hungary, Israel, Russia, South Africa, Spain, Sweden, the United Kingdom, and the United States	Median FU for 13 mo for those alive. Withdrawals preprogression followed for response until progression and death. Mean duration 159 ± 131 d
Kaufmann et al. [29]: Phase III	Exemestane 25 mg OD Megestrol acetate 40 mg QID	366 403	144 centers in 19 countries (Europe, South Africa, Mexico, Brazil, and Argentina)	Median FU 48.9 wk (≈11.25 mo)
Dombernowsky et al. [27]	Megestrol acetate 160 mg OD Letrozole 0.5 mg OD Letrozole 2.5 mg OD	189 188 174	91 centers in 10 countries	Patients monitored for response and safety for up to 33 mo (median ≈5.5 mo) and up to 45 mo for survival (median 18–20 mo)
Gershanovich et al. [28]‖	Letrozole 0.5 mg Letrozole 2.5 mg Aminoglutethimide 250 mg BID¶	192 185 178	86 centers across 11 countries	TTP involved 9-mo FU; OS involved 39 mo after study initiation. Six monthly updates of OS were planned until 90% of the patients died. Survival analyzed 15 mo after last enrollment. Median overall FU was 15 mo.

BID, twice daily; FU, follow-up; OD, once daily; QID, four times daily; TTP, time to progression.

* One injection on days 0 and 28 and every 28 days.

† Five hundred milligrams intramuscularly on day 0, 250 mg on days 14 and 28, and 250 mg every 28 days thereafter.

‡ Two injections on days 0, 14, and 28 and every 28 days.

§ Once monthly intramuscular injection.

¶ Data from Buzdar et al. [23,24] for anastrozole 10 mg were not included because this was not considered a treatment of interest.

‖ Data from Gershanovich et al. [28] for aminoglutethimide were excluded.

Puglisi et al. 2016 [30]-Safety results

Table 5
Grade 3 + toxicities, withdrawal & safety summary in second- and/or later-line setting.

Line of therapy within metastatic setting	First author, year	Treatment arms	N	Key grade III/IV toxicities (%)	Withdrawals due to AEs	Summary of safety
2nd line	Gasparini, 1991	Epirubicin	22	Leukopenia 0% Thrombocytopenia 0%	NR	Considering all grade AEs leukopenia and thrombocytopenia significantly more frequent on doxorubicin. Significantly greater frequency of dose delays due to haematological AEs with doxorubicin
		Doxorubicin	21	Leukopenia 5% (1 patient, grade III) Thrombocytopenia 0%	NR	
	Dieras, 1995	Paclitaxel 175 mg/m^2 q3w	41	Neutropenia 61% Peripheral neuropathy 11% Thrombocytopenia 3%	4 patients due to peripheral neuropathy	Neutropenia & peripheral neuropathy more frequent on PTX but patients received more courses of PTX than mitomycin. Thrombocytopenia more common with mitomycin. Febrile neutropenia occurred in 1 patient (3%) on PTX
		Mitomycin	40	Neutropenia 3% Neuropathy 0% Thrombocytopenia 20%	1 patient due to persistent neutropenia	
	Venturino, 2000	Vinorelbine	33	Anaemia 3% Leukopenia 18% Thrombocytopenia 0% Diarrhoea 0% Paralitic ileus 3% Any grade III AE 27%	NR	Lower incidence of grade III/IV toxicities in mitoxantrone combination arm. Authors consider that it is not always the single agent therapy that is best tolerated and that analysis of QoL, pain and symptom control (nausea, fatigue, improvement in performance status) is needed in trials in patients with incurable cancers, and comparison with best supportive care
		Leucovorin then 5-fluorouracil	33	Anaemia 0% Leukopenia 3% Thrombocytopenia 0% Diarrhoea 12% Paralitic ileus 0% Any grade III AE 15%	NR	
		Mitoxantrone + leucovorin then 5-fluorouracil	33	Anaemia 0% Leukopenia 3% Thrombocytopenia 3% Diarrhoea 0% Paralitic ileus 0% Any grade III AE 18%	NR	
	Papadimitriou, 2009	Docetaxel 40 mg/m^2 weekly	30	Anaemia 0% Neutropenia 3% Thrombocytopenia 3% Leukopenia 10% Stomatitis 10% Diarrhoea 3% Alopecia 13% Any grade III/IV AE 3%	NR	Higher frequency of grade III/IV neutropenia with DTX + GEM (23%) vs. DTX (3%) ($p = 0.035$). Such patients received G-CSF. Grade I or II febrile neutropenia occurred in 41% with DTX + GEM vs. 23% with DTX
		Docetaxel 35 mg/m^2 + gemcitabine	39	Anaemia 5% Neutropenia 23% Thrombocytopenia 6% Leukopenia 18% Stomatitis 3% Diarrhoea 0% Alopecia 23% Any grade III/IV AE 23%	NR	
	Von Minckwitz, 2014/TANIA	Bevacizumab + chemotherapy	245	Any grade III/IV AE 59% Grade III hypertension 13% Proteinuria 7%	18% discontinued BEV, mostly for proteinuria, venous embolism and pulmonary embolism 16% discontinued chemotherapy	Grade III/IV AEs more common with combination treatment, mainly due to higher frequency of grade III hypertension and proteinuria AE leading to chemotherapy discontinuation in >2% of patients was hand-foot syndrome in BEV + chemotherapy group, all of whom were receiving capecitabine
		Single-agent chemotherapy (investigator's choice)	238	Any grade III/IV AE 46% Grade III hypertension 7% Proteinuria <1%	8% discontinued chemotherapy	
2nd line (subgroup)	Nielsen, 1990	Epirubicin Epirubicin + vindesine	42 33	NR for subgroup	NR for subgroup	NR for subgroup but overall: thrombocytopenia significantly less frequent on epirubicin plus vindesine vs. epirubicin monotherapy ($p < 0.01$); mild-moderate peripheral neuropathy occurred in 40% of patients on combination therapy; 9 patients on epirubicin & 6 on combination had febrile neutropenia. CHF occurred in on epatient with cumulative dose of epirubicin <1000 mg/m^2 and 7/15 patients with >1000 mg/m^2; 4 patients died from CHF
	Joensuu, 1998	Epirubicin (1st line) then mitomycin (2nd line)	74	NR for 2nd line subgroup	8 patients discontinued M (12%)	Significantly greater frequency of toxicity with mitomycin + vinblastine vs. mitomycin single-agent therapy, due to more leukopenia ($p = 0.005$), nausea or vomiting ($p = 0.01$), alopecia ($p = 0.003$) and tendency for more anaemia ($p = 0.07$).
		CEF (1st line) then mitomycin + vinblastine (2nd line)	88	NR for 2nd line subgroup	17 patients discontinued MV (20%)	No difference in frequency of thrombocytopenia ($p = 0.28$)
	Norris, 2000	Doxorubicin + vinorelbine	NR	NR for subgroup	NR for subgroup	NR for subgroup. However, in the overall population greater incidences of grade 3/4 neurotoxicity, mild venous toxicity and febrile neutropenia were observed in the doxorubicin + vinorelbine arm. 11% of patients in combination arm discontinued vs. 4% in monotherapy arm
		Doxorubicin	NR	NR for subgroup	NR for subgroup	
Unclear if 2nd line	Baselga, 2012	Capecitabine + sorafenib	65	HFSR/HFS 44% (grade III)	20% discontinued, mainly due to HFSR/HFS (9 patients) and diarrhoea (1 patient)	Grade III/IV HFSR/HFS occurred significantly more frequently with sorafenib than with placebo. With all grade HFSR/HFS it also occurred earlier with sorafenib (median 14 days to first occurrence vs. 64 days) HFSR/HFS potentially impacts QoL and treatment changes Other grade III/IV events occurred with similar frequency in treatment arms All grade AEs were numerically higher with sorafenib for diarrhoea, mucosal inflammation, rash, neutropenia, hypertension and HFSR/HFS
		Capecitabine + placebo	51	HFSR/HFS 14% (grade III)	9% discontinued, mainly due to HFSR/HFS (4 patients) and diarrhoea (3 patients)	Dose delays and reductions to manage toxicities more frequent with sorafenib
	Sato, 2012	DTX 60 3-weekly + CAPE	82	Decreased neutrophil count 57.3% Neutropenia 8.5% Febrile neutropenia 6.1%	NR	ADRs with at least 5% difference in frequency were HFS (7.3% vs. 0%), fatigue (2.4% vs. 8.8%) and peripheral edema (1.2% vs. 6.3%) in the concurrent vs. sequential groups
		Sequential DTX 70 3-weekly until progression, then CAPE	81	Decreased neutrophil count 60.0% Neutropenia 12.5% Febrile neutropenia 10.0%	NR	
2nd line or later	Keller, 2004	Pegylated liposomal doxorubicin 50 mg/m^2 q4w	150	Leukopenia 20% Neutropenia 2% Febrile neutropenia 0 patients PPE 18% grade III, 1 patient grade IV LVEF changes consistent with cardiac toxicity in 22 patients	4 discontinued due to LVEF changes	Myelosuppression was lower with PLD: grade III/IV leukopenia less frequent with PLD than with control group, and grade III/IV neutropenia less frequent with PLD than with vinorelbine Most common ADR with PLD was palmar-plantar erythrodysesthesia (37% any grade). Infusion reactions and any grade stomatitis were more common with PLD
		Control: vinorelbine	151	Leukopenia 54% Neutropenia 8% Febrile neutropenia 2 patients	Unclear	
		Control: mitomycin C + vinblastine		Leukopenia 30% Febrile neutropenia 0 patients	Unclear	
	Palmieri, 2012	Docetaxel 100 mg/m^2 q3w	18	Grade III/IV AEs 27 events Grade III/IV haematological AEs and infections 20 events	High rate of discontinuation or interruption of treatment (% unspecified)	Grade III/IV toxicity (in particular haematological AEs and infections) more frequent with DTX than with vinorelbine
		Vinorelbine 25 mg/m^2 q2w	18	Grade III/IV AEs 4 events Grade III/IV haematological AEs and infections 2 events		

(continued on next page)

2nd line or later (subgroup)	Gradishar, 2005	ABI-007 (nab-paclitaxel)	131	NR for subgroup	NR for subgroup	Subgroup analyses reported showed that safety profiles of 1st line patients similar to those of 1st and 2nd/later line overall population Treatment-related grade IV neutropenia significantly lower on nab-paclitaxel (9%) than on standard paclitaxel (22%), $p < 0.001$, enabling the dose to be increased by 50%. Febrile neutropenia <2% in both arms Grade III sensory neuropathy 10% with nab-paclitaxel vs. 2% with standard paclitaxel, but easily managed with dose interruption or reduction No grade III/IV hypersensitivity reactions to nab-paclitaxel (in spite of no premedication) whereas they did occur with standard paclitaxel despite premedication
		Paclitaxel 175 mg/m^2 q3w	136	NR for subgroup	NR for subgroup	AE-related discontinuations, dose reductions and dose delays were low frequency in both arms (3% with nab-paclitaxel and 7% on standard paclitaxel)

ADR, adverse drug reaction (treatment-related adverse event); CEF, cyclophosphamide, epirubicin and fluorouracil; CR, complete response; ER, estrogen receptor; M, mitomycin; MV, mitomycin + vinblastine; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, progesterone receptor; PRe, partial response; QoL, quality of life; SD, stable disease; TTP, time to progression.

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ASCO Guidelines [34]

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.

Rugo et al. 2016 [34]: 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.

Table 3. Efficacy Outcomes

Source	Intervention or Comparison	Treatment Line	No. of Patients Evaluated	Survival (months)		CBR (%)*	Time to Initiation of Chemotherapy
				OS	PFS or TTP		
Single-agent *v* single-agent hormone therapies							
Phase II							
Llombart-Cussac[23]; SBCG 2001/03	Exemestane	First	47	Median, 19.9	Median TTP, 6.1	59.6	NR
	Anastrozole		50	48.3	12.1	68	NR
P				NS	NS		
Robertson[14,15]; FIRST	Fulvestrant	First	102	Median, 54.1 (n = 86)	Median TTP, 23.4	72.5	NR
	Anastrozole		103	48.4 (n = 84)	13.1	67.0	NR
P				**.041**	**.01**	.386 (primary end point)	
Ohno[24]; FINDER-1	Fulvestrant (250 mg/month)	Second	45	NR	Median TTP, 6.0	42.2	NR
	Fulvestrant (250 mg + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		51	NR	7.5	54.9	NR
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		47	NR	6.0	46.8	NR
Pritchard[25]; FINDER-2	Fulvestrant (250 mg per month)	Second	47	NR	Median TTP, 3.1	31.9	NR
	Fulvestrant (250 mg + 500 mg on day 0, 250 mg on days 14 and 28, and monthly thereafter)		50	NR	6.1	47.1	NR
	Fulvestrant (500 mg per month + 500 mg on day 14 of month 1)		46	NR	6.0	47.8	NR
Phase III							
Di Leo[21,26]; CONFIRM	Fulvestrant 250 mg	Second	374	**Median, 22.03**	**Median PFS, 5.5**	39.6	NR
	Fulvestrant 500 mg		362	**26.4**	**6.5**	45.6	NR
P				**< .05**	**< .05**	NS	
Iwata[22]	Exemestane	First	147	Median, not reached	Median, 13.8 (range, 10.8-16.5)	75 (range, 66.7-82.1)	NR
	Anastrozole		145	60.1	11.1 (range, 10.8-16.6)	77.3 (range, 69.1-84.3)	NR
P				NS	NS		
Xu[26]	Fulvestrant	Second	121	NR	Median TTP, 3.6	48.2	NR
	Anastrozole		113	NR	5.2	36.1	NR
P					NS		
Chia[20]; EFECT	Fulvestrant	Second	351	NR	Median PFS, 3.7	32.2	NR
	Exemestane		342	NR	3.7	31.5	NR
P					NS	NS	
Paridaens[37]	Exemestane	First	182	1 year, 86%; Median, 37.2	1-year PFS, 41.7%; Median, 9.9	NR	NR
	Tamoxifen		189	82%; 43.3	31.2%; 5.8	NR	NR
P				NS	NS		
Single-agent *v* combination endocrine therapies							
Phase II							
Johnston[30]; SoFEA	Fulvestrant + placebo	Second	231	19.4 (A *v* B)	4.8 (A *v* B)	NR	NR
	Fulvestrant + anastrozole		243	Median, 20.2	Median PFS, 4.4	NR	NR
P				NS	NS		
	Exemestane		249	21.6 (B *v* C)	3.4 (B *v* C)	NR	NR
P				NS	NS		

(continued on following page)

Table 3. Efficacy Outcomes (continued)

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

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Table 3. Efficacy Outcomes (continued)

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

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

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