Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

sowie

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

Vorgang: 2016-B-141-z Palbociclib

Stand: November 2016

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

Palbociclib
[zur Behandlung des HR-positiven/HER2-negativen fortgeschrittenen/metastasierten Mammakarzinoms]

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 Hormonrezeptor-negative Mammakarzinome - für das HER2/neu-positive Mammakarzinom - bei Chemotherapien: nach vorausgegangener Chemotherapie (Zweitlinientherapie)
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.	- Beschluss vom 22. Januar 2015 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Eribulin - Beschluss des G-BA über eine Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V (DMP-Richtlinie/DMP-RL) in der Fassung vom 16. Februar 2012 - Beschluss vom 17. März 2011 über Empfehlungen zur Aktualisierung des DMP Brustkrebs - 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:	
Palbociclib L01XE33 Ibrance®	*Anwendungsgebiet laut Positive Opinion:* Ibrance is indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer: - in combination with an aromatase inhibitor; - in combination with fulvestrant in women who have received prior endocrine therapy (see section 5.1). In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.
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 postmenopausalen Frauen mit Östrogenrezeptor-positivem lokal fortgeschrittenem oder metastasiertem Mammakarzinom bei Rezidiv während oder nach adjuvanter Antiöstrogen-Therapie oder bei Progression der Erkrankung unter der Behandlung mit einem Antiöstrogen.
Aromatase-Inhibitoren (nicht-steroidal):	
Anastrozol L02BG03 Arimidex®	Arimidex® ist angezeigt für die: - Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen. - Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen. - Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen, die bereits 2 bis 3 Jahre adjuvant Tamoxifen erhalten haben.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Letrozol L02BG04 Femara®	- Adjuvante Therapie postmenopausaler Frauen mit hormonrezeptor-positivem primärem Mammakarzinom. - Erweiterte adjuvante Therapie des hormonabhängigen primären Mammakarzinoms bei postmenopausalen Frauen nach 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:	
Leuprorelin L02AE02 Enantone-Gyn®	Mammakarzinom prä- und perimenopausaler Frauen, sofern eine endokrine Behandlung angezeigt ist.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Goserelin L02AE03 Zoladex®	Behandlung von Patientinnen mit Mammakarzinom (prä- und perimenopausale Frauen), bei denen eine endokrine Behandlung angezeigt ist.
Proteinkinase-Inhibitoren:	
Everolimus L01XE10 Afinitor®	Hormonrezeptor-positives, fortgeschrittenes Mammakarzinom: Afinitor wird in Kombination mit Exemestan zur Therapie des Hormonrezeptor-positiven, HER2/neu-negativen, fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen ohne symptomatische viszerale Metastasierung angewendet, nachdem es zu einem Rezidiv oder einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.
Monoklonale Antikörper:	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Paclitaxel zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet. Bevacizumab wird in Kombination mit Capecitabin zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet, bei denen eine Behandlung mit anderen Chemotherapie-Optionen, einschließlich Taxanen oder Anthracyclinen, als nicht geeignet angesehen wird. Patienten, die innerhalb der letzten 12 Monate Taxan- und Anthracyclin-haltige Therapieregime im Rahmen der adjuvanten Behandlung erhalten haben, sollten nicht mit Avastin in Kombination mit Capecitabin therapiert werden.
Zytostatika:	
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: […] - Adjuvante Therapie des Mammakarzinoms nach Resektion des Tumors beziehungsweise Mastektomie - Palliative Therapie des fortgeschrittenen Mammakarzinoms.
Ifosfamid L01AA06 Holoxan®	Zur Palliativtherapie bei fortgeschrittenen, therapierefraktären bzw. rezidivierenden Mammakarzinomen.
Methotrexat L01BA01 Methotrexat-GRY®	Mammakarzinome: In Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
5-Fluorouracil L01BC02 Fluorouracil-GRY®	– fortgeschrittenes und/oder metastasiertes Mammakarzinom
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.
Paclitaxel L01CD01 Bendatax ®	Im Rahmen einer adjuvanten Therapie ist, BENDATAX indiziert zur Behandlung von Patientinnen mit nodal-positivem Mammakarzinom im Anschluss an eine Anthrazyklin/Cyclophosphamid-Therapie (AC). Die adjuvante Therapie mit BENDATAX sollte als Alternative zu einer verlängerten AC-Therapie angesehen werden. 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.
Docetaxel L01CD02 Taxotere®	Taxotere® ist in Kombination mit Doxorubicin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs ohne vorausgegangene Chemotherapie angezeigt. [Weitere Indikationen: Adjuvante Therapie; HER2-überexprimierendes Mammakarzinom; nach Versagen einer Chemotherapie].
Doxorubicin L01DB01 Adrimedac®; Liposomal: Caelyx®, Myocet®	– Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: […] – Mammakarzinom. (FI Adrimedac®) – 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
Mitoxantron L01DB07 Onkotrone®	– fortgeschrittenes und/oder metastasiertes Mammakarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet

Mitomycin L01DC03 Urocin®	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Bei intravenöser Gabe ist es in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei folgenden metastasierenden Tumoren wirksam: […] – Mammakarzinom

Quellen: AMIS-Datenbank, Fachinformationen

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

Inhalt

Indikation für die Recherche:

‘’indicated for the treatment of hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer:
• in combination with an aromatase inhibitor;
• in combination with fulvestrant in women who have received prior endocrine therapy
In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinizing hormone releasing hormone (LHRH) agonist.”

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „Mammakarzinom“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.10.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP.
Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen

Leitlinien (z.B. NICE, SIGN). Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 2424 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 24 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ABC	Advanced breast cancer
AE	Adverse event
AGREE	Appraisal of Guidelines for Research & Evaluation
AI	Aromataseinhibitoren
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BC	Breast Cancer
centA	Central Assessment
CI	Konfidenzintervall
CrI	credible confidence intervall
DAHTA	Deutsche Agentur für Health Technology Assessment
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
DKG	Deutsche Krebsgesellschaft e. V.
DOR	Duration of Response
EMA	European Medicines Agency
ER	Östrogenrezeptor
EVE	Everolimus
EXE	Exemestan
FDA	Food and Drug Administration
f/up	Follow-up
G-BA	Gemeinsamer Bundesausschuss
GCP	Good clinical practice
GDG	Guideline development group
GIN	Guidelines International Network
GnRH	Gonadotropin-Releasing-Hormon
GoR	Grade of Recommendation
HER2	human epidermal growth factor receptor 2
HR	Hormonrezeptor
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITT	Intention to treat
k. A	keine Angaben
KCE	Belgian Health Care Knowledge Centre
LL	Leitlinie
locA	Local assessment
LoE	Level of Evidence
MA	Megastrolacetat
MBC	Metastasierender Brustkrebs
mo	months
MPA	Medroxyprogesteronacetat

NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PD	Pathomorphologische Diagnostik
PFS	Progresion free survival
PgR	Progesteronrezeptor
QoL	Quality of Life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomisierte kontrollierte Studie
RFI	Rezidivfreies Intervall
RR	Relatives Risiko
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious adverse event
SR	Systematischer Review
TAM	Tamoxifen
TOR	Toremifen
TRIP	Turn Research into Practice Database
TTF	Time to Failure
TTP	Time to Progression
VEGF	Vascular-endothelial-growth-factor
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2015 [6]. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Eribulin (neues Anwendungsgebiet)	**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.
G-BA, 2014 [8]. Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von	1.6.1.1 Therapie des Lokalrezidivs 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

Anforderungen an die Ausgestaltung von Strukturierten Behandlungsprogrammen nach §137f Abs. 2 SGB V (DMP-Richtlinie/DMP-RL) 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 20. November 2014 veröffentlicht im Bundesanzeiger (BAnz AT 6. Januar 2015 B1) in Kraft getreten am 7. Januar 2015	Notwendigkeit und Möglichkeit zusätzlicher Behandlungen (systemische endokrine und/oder chemotherapeutische Behandlungsverfahren) geprüft werden. 1.6.1.2 Therapie bei metastasierten Erkrankungen Eine endokrine Therapie ist bei positivem Hormonrezeptorstatus zu empfehlen. Eine Chemotherapie sollte unter Berücksichtigung der individuellen Risikosituation und des Therapieziels in Erwägung gezogen werden, insbesondere 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 [9]. Zusammenfassende Dokumentation über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use Gemcitabin in der Monotherapie beim Mammakarzinom der Frau	**Fazit:** Die Expertengruppe kommt in ihrem Fazit zu der Empfehlung, dass der „Off-Label-Einsatz“ von Gemcitabin als Monotherapie beim metastasierten Mammakarzinom wegen des nicht gesicherten klinischen Nutzens nicht gerechtfertigt ist.
G-BA, 2015 [7]. Beschluss des Gemeinsamen Bundesausschusses über eine Einstellung der Methodenbewertung gemäß § 137c des Fünften Buches Sozialgesetzbuch zu acht Methoden der Stammzelltransplantation vom 19. März 2015	Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 19. März 2015 folgenden Beschluss gefasst: I. Die Beratungen zur Methodenbewertung gemäß § 137c des Fünften Buches Sozialgesetzbuch (SGB V) für folgenden Methoden werden eingestellt: ... • Autologe Stammzelltransplantation beim Mammakarzinom bei Erwachsenen ...
G-BA, 2009 [5]. Beschluss vom 28. Mai 2009: Protonentherapie beim Mammakarzinom	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	1. Fragestellung To compare the efficacy and safety of toremifene (TOR) with tamoxifen (TAM)

[13]. Toremifene versus tamoxifen for advanced breast cancer.	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 Suchzeitraum (Aktualität der Recherche): until 1 July 2011, reference lists of relevant trials or reviews screened Anzahl eingeschlossene Studien/Patienten (Gesamt): 7 RCTs/2061 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. Ergebnisdarstellung • median or mean age of patients: 60 to 65 years • five studies performed in post-menopausal women • one 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

	six studies • in one 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 <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. Hinweise der FB Med:* • *HER-2 Status nicht thematisiert* • *meist Erstlinie* • *Toremifen nur first-line*
Wagner AD et al., 2012 [23]. Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer (Review)	Die Ergebnisse dieses Cochrane Reviews sind in die Conclusions und Empfehlung zur Therapie mit Biologika der KCE Leitlinie eingeflossen und werden somit hier nicht nochmal aufgeführt (siehe Wildiers H et al., 2013).

Systematische Reviews

Bachelot T et al., 2014 [2]. Comparative efficacy	1. Fragestellung This network analysis was conducted to compare the efficacy of everolimus plus exemestane versus fulvestrant in patients with advanced breast cancer who are

of everolimus plus exemestane versus fulvestrant for hormone-receptor-positive advanced breast cancer following progression/ recurrence after endocrine therapy: a network meta-analysis	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 Suchzeitraum (Aktualität der Recherche): in 2012 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 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)
	3. Ergebnisdarstellung • 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

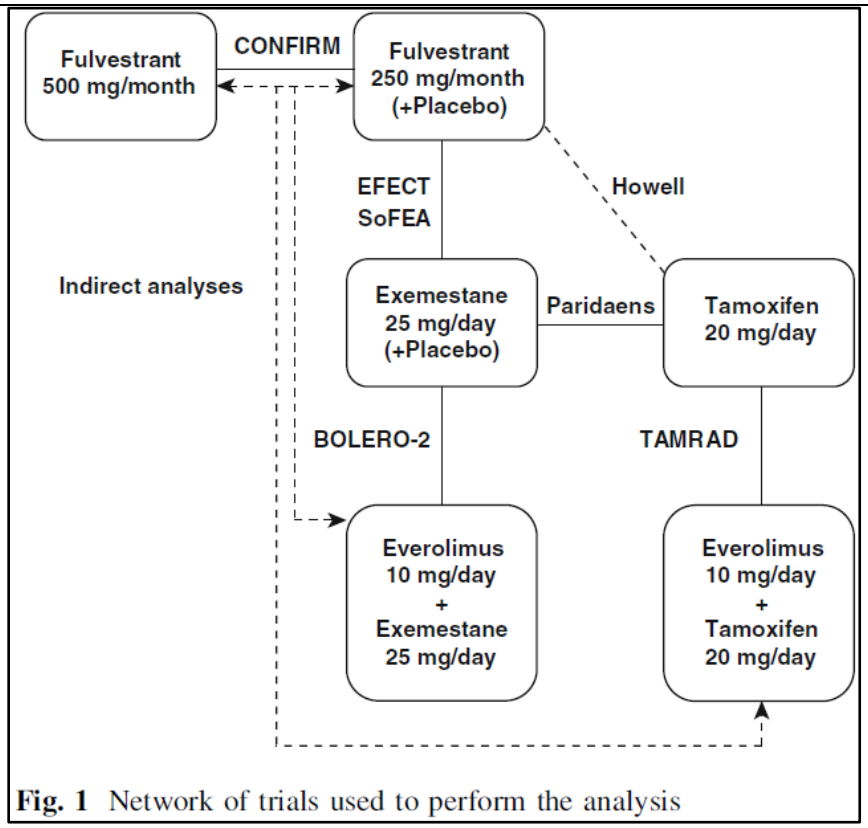


Fig. 1 Network of trials used to perform the analysis

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. Anmerkungen FBMed

- *Research was funded by Novartis Pharmaceuticals Corporation (pU für Everolimus).*
- *Conflict of interests TB: Advisor for Novartis Pharmaceuticals Corporation, received research support and speaker honoraria from Novartis. RMcC: Received research support from Novartis Pharmaceuticals Corporation. SD: Received research support from Novartis Pharmaceuticals Corporation. JG: Received research support from Novartis Pharmaceuticals Corporation. DV:*

	Received research support from Novartis Pharmaceuticals Corporation. KF: Received research support from Novartis Pharmaceuticals Corporation. JZ: Employee of Novartis Pharmaceuticals Corporation. GJ: Advisor for Novartis Pharmaceuticals Corporation, received research support and speaker honoraria from Novartis. • *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*
Gong DD et al., 2014 [10]. Fulvestrant 250mg versus Anastrozole 1 mg in the Treatment of Advanced Breast Cancer: a Meta-Analysis of Randomized Controlled Trials.	1. Fragestellung This meta-analysis was designed to compare the efficacy and tolerability of fulvestrant 250mg with anastrozole 1mg in postmenopausal women with advanced breast cancer
	2. Methodik Population: postmenopausal women with advanced breast cancer Intervention: Fulvestrant 250mg Komparator: Anastrozole 1mg Endpunkte: TTF, TTP, DOR Suchzeitraum (Aktualität der Recherche): Electronic literature databases (Cochrane Library, Medline, and Embase) were searched for randomized controlled trials (RCTs) published prior to August 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): Four RCTs covering 1,226 patients (fulvestrant, n=621; anastrozole, n=605) were included in the meta-analysis. Qualitätsbewertung der Studien: The methodological quality of each study was assessed in accordance with the guidelines in the Cochrane reviewers' handbook. All studies ranked LoE: B Heterogeneity of effect sizes across studies was assessed by using the Cochrane Q statistic and the I^2 statistic.
	3. Ergebnisdarstellung • Fulvestrant increased the DOR compared to anastrozole (HR =1.31, 95% confidence interval [CI] 1.13–1.51). • There was no statistically significant difference between fulvestrant and anastrozole in terms of TTF, complete response, and partial response. • As for safety, there was no statistical significance between the two groups for common adverse events.
	4. Fazit der Autoren: Fulvestrant 250mg is as effective and well-tolerated as anastrozole 1mg treatment for advanced breast cancer in postmenopausal

	women whose disease progressed after prior endocrine treatment. Thus, fulvestrant may serve as a reasonable alternative to anastrozole when resistance is experienced in breast cancer cases. 5. Hinweise durch Autoren • Heterogeneity in the design and modes of treatment used in each study→ more patients in the fulvestrant group (32%) than in the anastrozole group (24%) had undergone two previous rounds of chemotherapy, potentially giving those patients in the fulvestrant 250 mg group a worse prognosis. Limited number of eligible trials is not enough to perform further subgroup analysis, such as based on ER and/or PgR analysis. • All of the included trials were classified as having low or moderate risk of bias according to the methodological quality assessment • Potential publication bias was assessed by both Begg's rank correlation test (Begg and Mazumdar, 1994) and Egger's linear regression test (Egger et al., 1997) with $p<0.10$ indicating statistical significance 6. Anmerkung FBMed • k. A. zu Funding oder CoI • Folgende zwei Studien sind auch im systematischen Review von Al-Mubarak M et al., 2013 enthalten: o Howell et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20(16):3396–403. o Osborne et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20(16):3386–95.
Al-Mubarak M et al., 2013 [1]. Fulvestrant for advanced breast cancer: A meta-analysis.	1. Fragestellung The objectives were to assess the relative efficacy and toxicity of fulvestrant compared to other endocrine therapy options.
	2. Methodik Population: postmenopausal women with inoperable locally advanced or metastatic breast cancer Intervention: fulvestrant-based therapy Komparator: Non-fulvestrant-based endocrine therapy regimen Endpunkte: TTP, PFS, SAEs Suchzeitraum (Aktualität der Recherche): Systematic literature search 2005–2011; databases: MEDLINE (host: OVID); EMBASE (host: OVID); American Society of Clinical Oncology Annual Meetings, 2005–2011; and San Antonio Breast Cancer Symposium Annual Meetings, 2005–2011; Reference lists of eligible studies Anzahl eingeschlossene Studien/Patienten (Gesamt): Therefore, 9 reports comprising 8 randomized trials were eligible for analysis

Table 1
Study characteristics.

Study	Treatment group	Control group	Dosing regimen of fulvestrant[a]	Number of patients	Age range (years)	Percentage who received adjuvant endocrine therapy	Line of treatment	Percentage in 1st line	Efficacy endpoint	Median TTP/PFSin treatment and control groups (months)
Howell et al.[4]	Fulvestrant	Anastrozole	Low dose	451	33–89	53.2%	1st/2nd[c]	43.5%	TTP	5.5 vs 5.1
Osborne et al.[5]	Fulvestrant	Anastrozole	Low dose	400	33–94	59.5%	1st/2nd[c]	48.3%	TTP	5.4 vs 3.4
Howell et al.[6]	Fulvestrant	Tamoxifen	Low dose	587	43–93	23.3%	1st	100%	TTP	6.8 vs 8.3
Chia et al.[8]	Fulvestrant	Exemestane	Loading dose	693	32–91	60.0%	1st/2nd/3rd[d]	12.3%	TTP	3.7 vs 3.7
Robertson et al.[23]	Fulvestrant	Anastrozole	High dose	205	40–89	25.4%	1st	100%	TTP[b]	23.4 vs 13.1
Johnston et al.[9]	Fulvestrant	Exemestane	Loading dose	480	57–75	70.0%	1st/2nd[e]	19.2%	PFS	4.8 vs 3.4
Bergh et al.[10]	Fulvestrant + anastrozole	Anastrozole	Loading dose	514	33–90	67.7%	1st	100%	TTP	10.8 vs 10.2
Mehta et al.[11]	Fulvestrant + anastrozole	Anastrozole	Loading dose	707	27–92	40.3%	1st	100%	PFS	15 vs 13.5

TTP, time to progression; PFS, progression free survival.
[a] Low dose is 250 mg IM monthly. Loading dose is 500 mg on day 0, 250 mg on days 14, 28 and 250 mg every 28 days. High dose is 500 mg on day 0, 14, 28 and then every 28 days.
[b] TTP was a secondary endpoint. The primary end point was clinical benefit rate.
[c] Relapsed/progressed during adjuvant endocrine therapy or first line endocrine therapy for advanced disease (predominantly tamoxifen).
[d] Relapsed/progressed during (or within 6 months of) adjuvant non-steroidal aromatase inhibitor or during nonsteroidal aromatase inhibitor treatment for advanced disease.
[e] Relapsed/progressed on non-steroidal aromatase inhibitor treatment given as either adjuvant therapy for at least 12 months or first line therapy for advance disease for at least 6 months.

Qualitätsbewertung der Studien: k. A.

3. Ergebnisdarstellung

Wirksamkeit:

When all studies were pooled, there was no significant difference between the fulvestrant and control groups.

This estimate was not significantly different when assessed separately for studies of fulvestrant monotherapy and those where fulvestrant was given in addition to AI.

There appeared to be a difference in the effect of fulvestrant monotherapy on TTP depending on whether it was compared to AI or tamoxifen. Comparison to AI (5 studies) showed a modest improvement in TTP (HR: 0.93, 95% CI 0.84–1.02), while comparison to tamoxifen (1 study) showed a detrimental effect (HR: 1.18, 95% CI 0.97–1.44, subgroup difference p = 0.03).

Meta-regression showed that when compared to AI, fulvestrant monotherapy was associated with lower hazards for TTP if used in patients with limited exposure to adjuvant endocrine therapy (p for trend <0.001), in those receiving treatment in the first line setting for advanced breast cancer (p for trend <0.001) and when higher doses of fulvestrant were used (p for trend <0.001).

Sicherheit:

Data on the SAEs were available from 6 studies. For studies of fulvestrant monotherapy, there was no difference in SAEs between the fulvestrant and controls groups.

For studies of fulvestrant and AI versus AI alone, there was a non-significant association for higher SAEs with the fulvestrant group.

Subgroup analyses showed that rates of SAEs were no different based on line of therapy, the control group or the dose of fulvestrant.

Same non-significant results for treatment discontinuation (also in subgroups) between the groups.

Fulvestrant monotherapy was associated with significantly less arthralgia (OR: 0.73, 95%CI 0.57-0.95, p = 0.02).

The addition of fulvestrant to AI was not associated with improved TTP, but led to increased toxicity.

	4. Fazit der Autoren: In unselected patients, fulvestrant monotherapy is associated with similar efficacy, but reduced arthralgia compared with other endocrine therapy options. Use of high dose fulvestrant monotherapy in first line or in patients with limited prior exposure to adjuvant endocrine therapy may delay progression compared with AI. 5. Anmerkung FBMed • CoI: E. Amir has served as a consultant for and has received honoraria from AstraZeneca. All remaining authors have declared no conflicts of interest. • Folgende zwei Studien sind auch im systematischen Review von Gong DD et al., 2014 enthalten: o Howell et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol 2002;20(16):3396–403. o Osborne et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 2002;20(16):3386–95.
Cope S et al., 2013 [4]. 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 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) Endpunkte: PFS, TTP Suchzeitraum (Aktualität der Recherche): in January 2010 Anzahl eingeschlossene Studien/Patienten (Gesamt): 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) Qualitätsbewertung der Studien: im Methodenteil nicht beschrieben
	3. Ergebnisdarstellung • 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

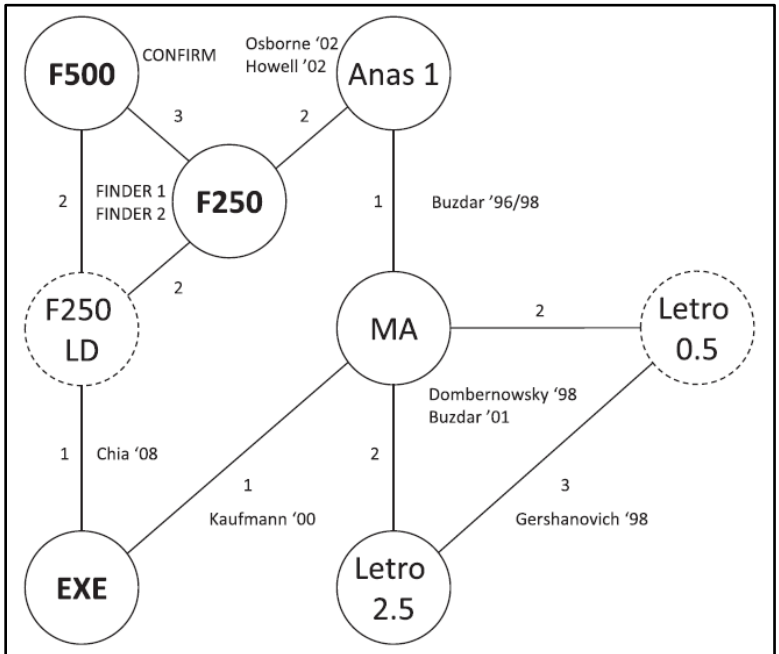


Fig. 2 – Network of randomized controlled trials. ANAS1, anastrozole 1 mg; EXE, exemestane 1 mg; F250, fulvestrant 250 mg; F250LD, fulvestrant 250 mg loading dose; F500, fulvestrant 500 mg; LETRO 0.5, letrozole 0.5 mg; LETRO2.5, letrozole 2.5 mg; MA, megestrol acetate 160 mg OD or 40 mg QID; OD, once 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. Anmerkung FBMed

- *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) • *In addition, study documents for fulvestrant were made available by AstraZeneca* • *Empfohlene Dosis von Fulvestrant beträgt 500 mg* • *Megestrolacetat in der pallitiven Therapiesituation zugelassen* • *Allen eingeschlossenen Studien untersuchten Therapiearme mit Dosierungen und/oder Wirkstoffen außerhalb der Zulassung.* • *Endpunkte PFS/TTP nicht per se patientenrelevant*
Belfiglio M et al., 2012 [3]. Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer.	1. Fragestellung The aim of this work is to compare OS, TTP, and ORR in patients with MBC receiving docetaxel alone or docetaxel in combination with other chemotherapeutic agents using a formal meta-analysis
	2. Methodik Population: participants with metastatic breast cancer. Intervention: docetaxel alone Komparator: docetaxel in combination with other chemotherapeutic agent Endpunkte: OS, TTP, ORR, and toxicity Suchzeitraum (Aktualität der Recherche): from January 2000, to December 2010 in Medline, Cochrane Central, EmBase, and Cancer Lit, and conference proceedings Anzahl eingeschlossene Studien/Patienten (Gesamt): three trials enrolled 1,313 patients: 654 of them received docetaxel combinations and 659 docetaxel as a single agent. . … All the selected studies enrolled patients pretreated with anthracyclines in different settings (i.e., adjuvant, neoadjuvant, or metastatic). *Hinweis:* In einer Studie →Prior hormonal treatment and/ or one regimen of chemotherapy for metastatic disease were acceptable In den beiden anderen Studien→ Anthracycline-pretreated metastatic breast cancer bzw. Anthracycline pretreated in the neoadjuvant/adjuvant setting/No previous chemotherapy for metastatic breast cancer Heterogeneity between studies was assessed with the Cochran's Q and the I^2 statistics Qualitätsbewertung der Studien: Based on current standards, the quality of the included studies was suboptimal. Allocation concealment was adequately described in two of the three studies and unclear in the remainder. All the studies adequately described blinding of outcome assessors and the others domains. One of these was interrupted earlier.
	3. Ergebnisdarstellung • No significant benefit in OS was found with a chemotherapy agent plus docetaxel compared with docetaxel alone. Heterogeneity among the studies

	in this analysis was moderate (I^2= 57%). • A significant reduction in risk ratio was found in TTP with chemotherapy agent plus docetaxel compared with docetaxel alone (RR: 0.66, 0.58–0.74; P < 0.0001). Heterogeneity was not significant among studies in this analysis. • Regarding ORR, polychemotherapy did not increase the probability of response as compared with docetaxel alone. Heterogeneity in this analysis was moderate (I^2= 61%). • Toxizität: docetaxel alone is associated with a lower incidence of grade 3 neutropenic fever, nausea, neutropenia, diarrhea, and stomatitis, although only for diarrhea and stomatitis, the results have statistical significance (diarrhea, RR: 2.51, 1.45–4.34; P = 0.011; stomatitis, RR: 5.62, 2.16–14.63; P = 0.0004). Heterogeneity among the studies in this analysis was not significant regarding diarrhea and moderate relative to stomatitis I^2 = 45%).
	4. Fazit der Autoren: In conclusion, combination chemotherapy regimens with docetaxel versus single-agent docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in women with MBC, but they also produce more toxicity in terms of diarrhea and stomatitis. The results and limitations of this review confirm that it seems unlikely that any single agent or combination regimen will emerge as superior in all patients with MBC, most probably due to the highly heterogeneous nature of this disease. 6. Anmerkung FBMed: • CoI: None of the authors has any potential financial conflict of interest related to this manuscript.
Graham J et al., 2016 [11]. Clinical predictors of benefit from fulvestrant in advanced breast cancer: A Meta-analysis of randomized controlled trials	1. Fragestellung Beyond the ER, a common marker predictive of benefit from all endocrine therapies, additional biological or clinical markers have not been identified to predict for a higher benefit from fulvestrant. In an attempt to further investigate this question, we conduct a meta-analysis of different sub-groups of patients from RCTs comparing fulvestrant or its combination with an aromatase inhibitor to either aromatase inhibitor or tamoxifen alone.
	2. Methodik Population: women with inoperable locally advanced or metastatic breast cancer Intervention: Fulvestrant oder Kombination Fulvestrant mit Anastrozol Komparator: Anastrozol oder Exemestan Endpunkte: TTP und PFS Suchzeitraum (Aktualität der Recherche): A comprehensive search of MEDLINE, EMBASE, and COCHRANE databases from the inception to May 2015

	Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 RCTs / N=2.382 patients (Experimental: n=1.190; Control: n=1.192). Only the studies reporting HRs for predefined sub-groups were included. Studiencharakteristika siehe Anhang Bergh J et al. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J Clin Oncol 2012;30:1919–25. Chia S et al. Doubleblind, 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 2008;26:1664–70. Johnston SR et al. 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 2013;14:989–98. Mehta RS et al. Combination anastrozole and fulvestrant in metastatic breast cancer. New Engl J Med 2012;367:435–44. Qualitätsbewertung der Studien: Risk of bias mittels Cochrane collaboration's tool. Chi² statistics was used to measure the difference between subgroups and evidence of heterogeneity among studies was assessed using I² statistics. Subgruppenanalysen • Age: >65 versus ≤ 65 • Visceral Metastasis: yes / no • Time to recurrence: >5 years versus ≤ 5 years • HER2: Overexpressed versus normal Ein CoI liegt laut Autoren nicht vor.
	3. Ergebnisdarstellung Qualität der Studien: None of the included studies had major flaws in assessment of their risk of bias. A common caveat however was the expected absence of blinded intervention. Studiencharakteristika: siehe Anhang Ergebnisse Subgruppenanalyse: siehe Anhang The fulvestrant containing arm was found to be significantly better in terms of TTP/PFS in 3 sub-groups: • Age >65 years (HR 0.86, 95% CI 0.75–0.99), • visceral metastasis present (HR 0.85, 95% CI 0.77–0.95), and • time to recurrence >5 years (HR 0.80, 95% CI 0.66–0.96), whereas TTP/PFS didn't favor either arms in the sub- groups of age <65 years, non-visceral metastases, and time to recurrence <5 years. Similarly, both HER2 overexpressed and HER2 normal tumors did not show significant difference between the arms.

	Fulvestrant was associated with statistically significant (?) greater benefit in patients with visceral metastasis (HR 0.85 vs 1.02 for no visceral disease, p for difference = 0.05) and in those patients with a time to recurrence >5 years (HR 0.80 vs 1.09 for recurrence ≤5 years, p for difference = 0.02). There was no apparent difference in benefit based on age >65 years or HER2/neu status.

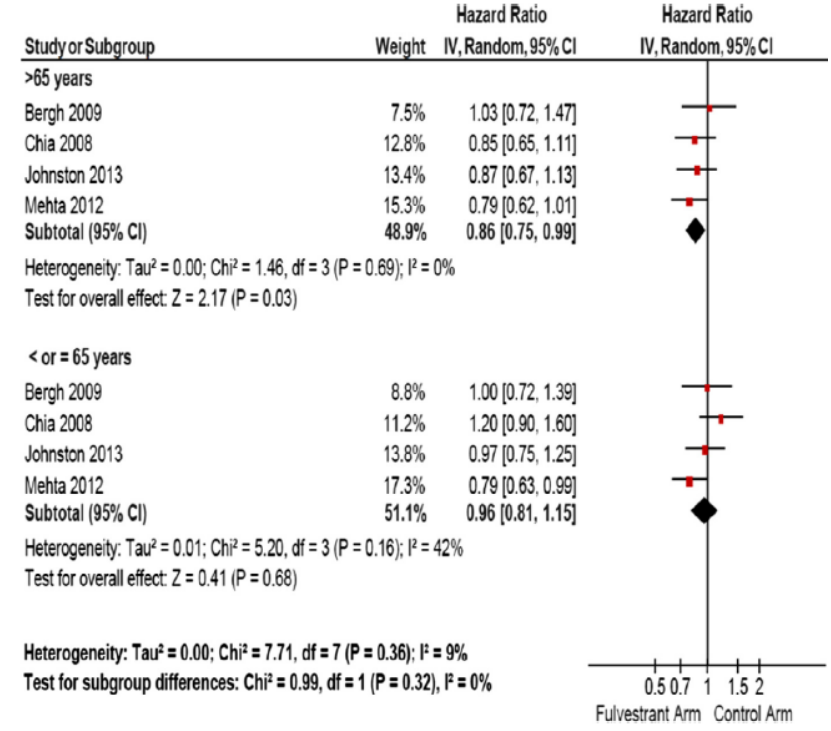


Fig. 2A. Pooled subgroup analysis for TTP/PFS based on age.

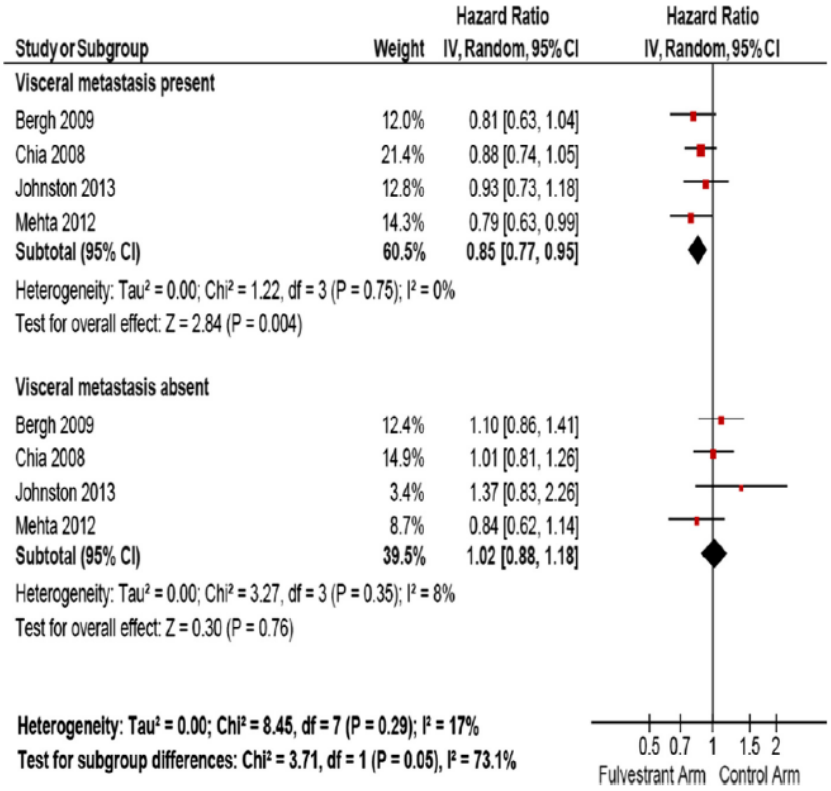


Fig. 2B. Pooled subgroup analysis for TTP/PFS based on visceral metastases.

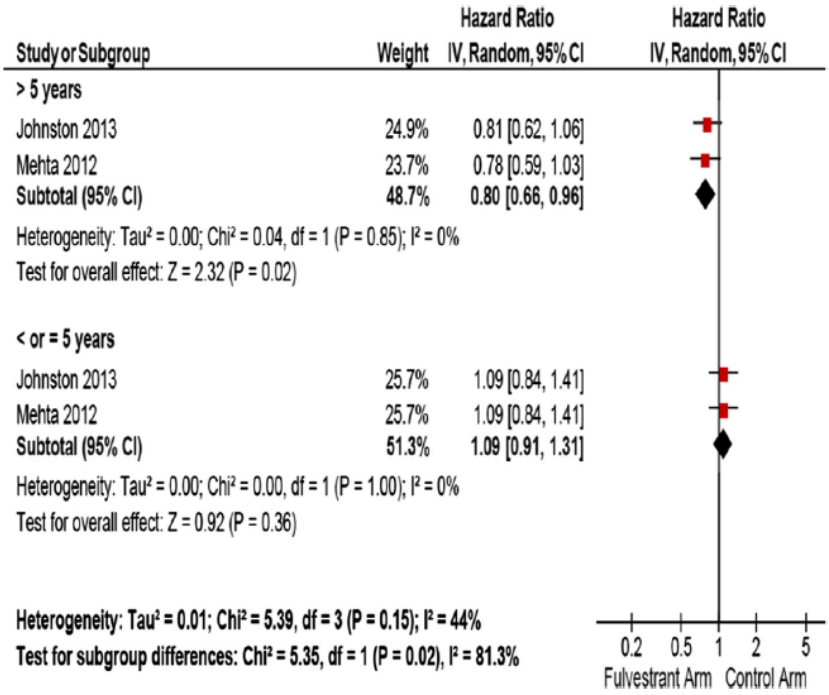


Fig. 2C. Pooled subgroup analysis for TTP/PFS based on time to recurrence.

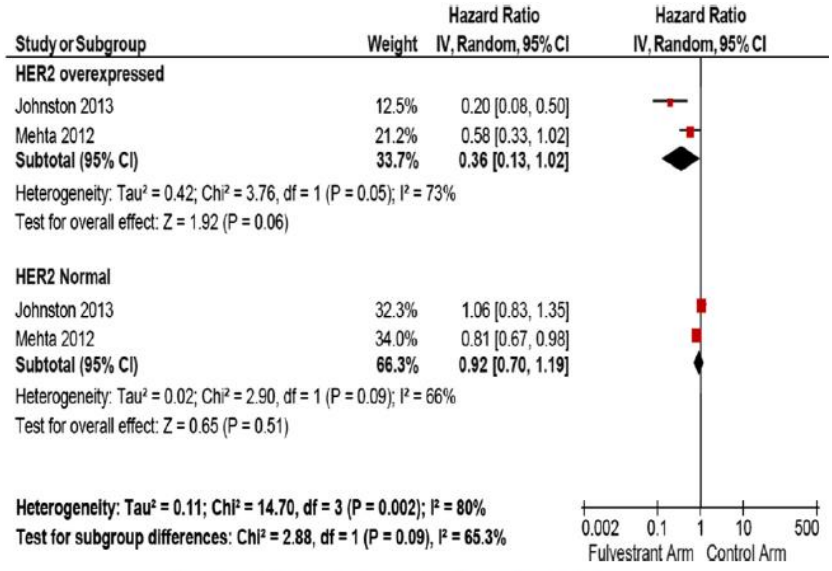


Fig. 2D. Pooled subgroup analysis for TTP/PFS based on HER2 status.

4. Fazit der Autoren:

[…] among patients with advanced ER positive breast cancer, treatment with fulvestrant is associated with improved outcomes for women with visceral metastases and longer time to cancer recurrence compared to non-visceral metastasis and shorter time (<5 years) to cancer recurrence, respectively.

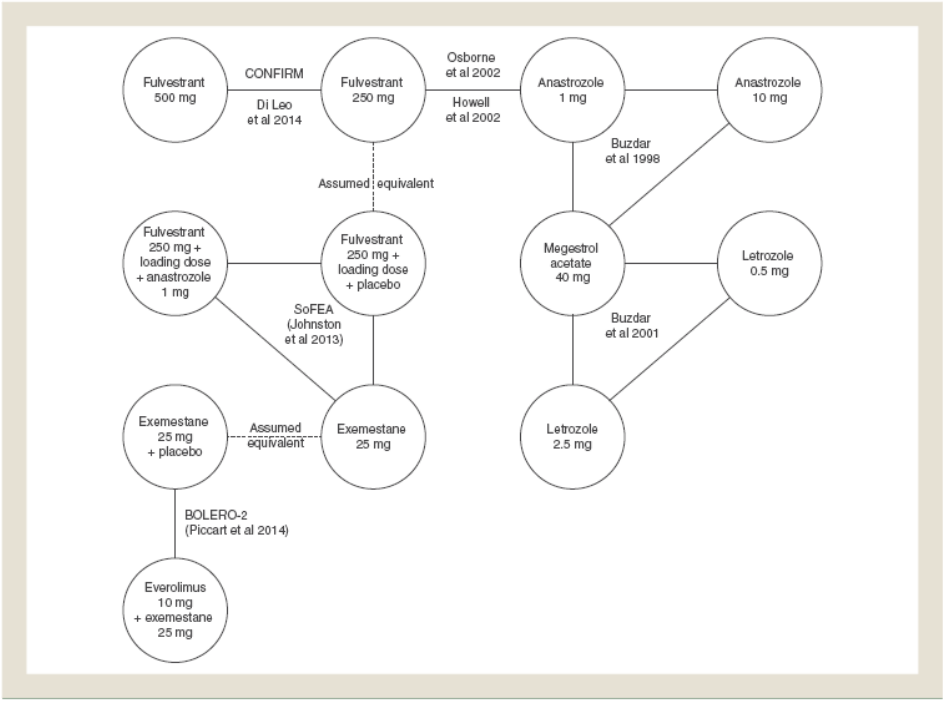
5. Anmerkung FBMed:

- Hohe Heterogenität in den Subgruppen HER2 overexpressed bzw. HER2 normal (siehe Fig. 2D)
- Therapielinien sind für Chia et al. 2008 und Johnston et al. 2013 nicht separat voneinander dargestellt.

Telford et al., 2016 [22]. Network Meta-Analysis Comparing Overall Survival for Fulvestrant 500 mg Versus Alternative Therapies for Treatment of Postmenopausal, Estrogen Receptor-Positive Advanced Breast Cancer Following Failure on Prior Endocrine Therapy.	1. Fragestellung to compare the overall survival (OS) with fulvestrant 500 mg versus alternative treatment for estrogen receptor-positive advanced breast cancer following endocrine therapy failure.
	2. Methodik Fixed-effect NMA of HRs and a Bayesian approach that involved formal combination of a prior probability distribution that reflects a vague/uninformative previous belief of the possible values of the pooled relative effects, with a likelihood distribution of the pooled effect based on the observed data in the different studies to obtain a posterior distribution of the pooled relative effect. The model parameters were estimated using Markov chain Monte Carlo techniques with WinBUGS, version 1.4.1.16 Population: postmenopausal women with locally advanced or metastatic breast cancer and documented ER-positive status with progression or relapse after first-line hormonal therapy. Intervention/Komparator: fulvestrant 500 mg vs. alternative hormonal therapies Subgruppen: Three patient population scenarios were included in the analysis based on the prior treatment of patients entering each study. The overall (basecase) population included patients previously treated with AO or AI therapy. The comparators of interest were anastrozole 1 mg, letrozole 2.5 mg, fulvestrant 250 mg, exemestane 25 mg, megestrol acetate 40 mg, and everolimus 10 mg plus exemestane 25 mg. Because second-line hormonal treatment varies depending on the first-line treatment, 2 subgroups were also investigated. A post-AO (following an AO) subgroup network compared fulvestrant 500 mg with anastrozole 1 mg, letrozole 2.5 mg, fulvestrant 250 mg, and megestrol acetate 40 mg. A post-AI (following an AI) subgroup network compared fulvestrant 500 mg with fulvestrant 250 mg, exemestane 25 mg, and everolimus 10 mg plus exemestane 25 mg. Endpunkt: OS Suchzeitraum (Aktualität der Recherche): November 2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): From the systematic literature review, 7 relevant phase III studies that had reported OS data were identified and included in the analysis. Qualität der Studien: each potential study identified was independently evaluated by 2 reviewers to ensure its relevance against the pre-determined criteria. → keine weiteren Angaben.
	3. Ergebnisdarstellung (*siehe auch figure 1*)

- In the overall analysis, the HRs suggested improved OS for fulvestrant 500 mg versus fulvestrant 250 mg and megestrol acetate 40 mg, and numerically favorable differences with fulvestrant 500 mg versus other comparators.
- In the anti-estrogen subgroup, the HRs suggested improved OS for fulvestrant 500 mg versus fulvestrant 250 mg and megestrol acetate 40 mg; numerical differences in the HRs were seen versus anastrozole 1 mg and letrozole 2.5 mg.
- In the aromatase inhibitor subgroup, the HRs for OS numerically favored fulvestrant 500 mg versus fulvestrant 250 mg and exemestane 25 mg.

Figure 1 The Network of Trials Included in the OS NMA



Abbreviations: BOLERO = Breast cancer trials of OraL EveROlimus; CONFIRM = Comparison of Faslodex in Recurrent Metastatic Breast Cancer; NMA = network meta-analysis; OS = overall survival; SoFEA = Study of Faslodex with or without concomitant Arimidex vs. Exemestane following progression on nonsteroidal Aromatase Inhibitors.
Data Sources: Di Leo et al,[7] Osborne et al,[19] Howell et al,[20] Buzdar et al,[17,18] Johnston et al,[21] and Piccart et al[22]

4. Anmerkungen/Fazit der Autoren: *The findings from our NMA of randomized clinical trial data suggest that fulvestrant 500 mg might provide improved OS compared with fulvestrant 250 mg and megestrol acetate 40 mg for the treatment of postmenopausal, ER-positive ABC following failure on prior endocrine therapy. Although the OS efficacy versus other comparators (everolimus 10 mg plus exemestane 25 mg [for overall evidence network], anastrozole 1 mg, exemestane 25 mg, and letrozole 2.5 mg) is numerically favorable or similar (in the case of everolimus 10 mg plus exemestane 25 mg within the post-AI network), additional studies are required to draw formal conclusions. However, these results add to the evidence base that can guide treatment decisions in this patient population.*

5. Hinweise durch FB Med

- A key limitation → indirect nature of the evidence governed by the degrees of separation in the evidence network, such that the comparative estimates of fulvestrant 500 mg with other treatments were connected through the

	fulvestrant 250 mg comparator. • assumptions have been made regarding the equivalence of treatment arms to bridge trials

Leitlinien

NCCN, 2016 [14]. Breast Cancer Version 2.2016	Fragestellung • nicht spezifiziert Update of the NCCN Guidelines for Breast Cancer from Version 1.2016
	Methodik*:* Grundlage der Leitlinie: Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - Diskussion der Literatur und Empfehlungen im Expertenpanel - eigenes Graduierungssystem (siehe unten) - industriefinanziert - Angaben zu CoI in zugehörigen Publikationen des JNCCN zu finden Literatursuche (Update): in PubMed zwischen 06/2014 und 06/2015 GoR, LoE: 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.**
	<u>Endocrine Therapy</u> *Endocrine Therapy*: Neoadjuvant endocrine therapy alone may be offered to those with strongly hormone receptor-positive tumors.[304-311] According to the NCCN Panel, the endocrine therapy options include an aromatase inhibitor (with ovarian suppression for premenopausal women) or tamoxifen. The preferred endocrine therapy option for postmenopausal women is an aromatase inhibitor. <u>Endocrine Therapy for recurrent or stage IV disease</u> Postmenopausal Patients • Non-steroidal aromatase inhibitor (anastrozole, letrozole) • Steroidal aromatase inactivator (exemestane) • Exemestane + everolismus[1]

	• Palbociclib + letrozole[2] • Palbociclib + fulvestrant (category 1)[3] • Fulestrant[4] • 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, or any time on tamoxifen). [2] Palbociclib 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. [3] 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 endocrine therapy. [4] 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. Algorithmus: systemic treatment of recurrent or stage IV disease [BINV-20] siehe Anhang
NICE, 2014 [15]. Advanced breast cancer (update) Diagnosis and treatment Issued: February 2009 last modified: July 2014. NICE (CG81) ***Hinweis***: Die Empfehlungen der LL (vorherige Version aus 2009) wurden auf ihre Aktualität überprüft und als weiterhin gültig angesehen. Die nächste Überarbeitung ist für 2015 geplant. Daher werden die	Fragestellung What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer? Methodik Grundlage der Leitlinie: Methodenreport beschreibt systematische Evidenzaufbereitung und Konsensusprozesse (je nach Bedarf fomal oder informal) - eigene Checklisten - 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.“ Suchzeitraum der Literaturrecherche: Aktualisierung ab 30.06.2008 Freitext/Empfehlungen/Hinweise **Systemic disease-modifying therapy** *Recommendations* 1.3.1 Offer endocrine therapy as first-line treatment for the majority of patients with ER positive advanced breast cancer. [2009]

Empfehlungen aus der LL 2009 hier mit aufgeführt.	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

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]

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]

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]* 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] **Supportive care** 1.4.1 Healthcare professionals involved in the care of patients with advanced breast cancer should ensure that the organisation and provision of supportive care services comply with the recommendations made in Improving outcomes in breast cancer: manual update (NICE cancer service guidance [2002]) and Improving supportive and palliative care for adults with cancer (NICE cancer service guidance [2004]), in particular the following two recommendations: • 'Assessment and discussion of patients' needs for physical, psychological, social, spiritual and financial support should be undertaken at key points (such as diagnosis; at commencement, during, and at the end of treatment; at relapse; and when death is approaching).' • 'Mechanisms should be developed to promote continuity of care, which might include the nomination of a person to take on the role of "key worker" for individual patients.' [2009]
Partridge AH et al., 2014 [20]. Chemo- and Targeted Therapy for Women With Human Epidermal Growth Factor Receptor 2-Negative (or unknown) Advanced Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline	This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. 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. To identify optimal 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: MEDLINE (Ovid):2009 through to May 2013 for first-line trials; 1993 through to May 2013 for second-line trials. The 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.

Guide 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.

Guide for Strength of Recommendations

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.

Guide for Rating Strength 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.

Study Quality Assessment
Study quality was formally assessed for the studies identified. For the ASCO quality assessment, 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. The risk of bias is assessed as “low,” “intermediate,” or “high” for the identified evidence.

Author’s disclosure of potential conflict of interest available

Recommendations

[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*

[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.** [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* [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** [5] Chemotherapy should be continued until progression of disease as tolerated because it modestly improves overall survival and substantially improves progression-free survival, but this has to be balanced against toxicity and quality of life. Short breaks, flexibility in scheduling, or a switch to endocrine therapy (in patients with hormone receptor–positive disease) may be offered to selected patients. A. The benefits are more time before disease-progression and modestly improved survival (**potential benefit: high**). The harm is more prolonged toxicity (**potential harm: moderate**). B. The evidence quality is high, and is based on a systematic review with

	meta-analysis. **C. The strength of the recommendation is strong, and is supported by evidence and expert consensus.** ● *Qualifying statement: It is recognized that the balance between continuing treatment to maintain disease control and coping with progressive AEs and/or toxicity is a difficult one. It will be influenced by many factors, including drug used (eg, long-term use of capecitabine is relatively easy, whereas docetaxel is severely limited by cumulative toxicity) and requires a continuing dialogue between doctor and patient.* [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**. **9** Smith et al: American Society of Clinical Oncology provisional clinical opinion: The integration of palliative care into standard oncology care. J Clin Oncol 30:880-887, 2012 **10** Banerji et al: Factors determining outcome after third line chemotherapy for metastatic breast cancer. Breast 16: 359-366, 2007
Wildiers H et al., 2013 [24]. Breast cancer in women: diagnosis, treatment and follow-up; Vers. 3 (KCE 143 report)	This guideline was the result of collaboration between the College of Oncology and the KCE and covered a broad range of topics: diagnosis, staging, treatment, reconstructive surgery, supportive therapy and follow up. It primarily concerned women with invasive early or advanced breast cancer. The KCE is a federal institution which is financed for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, food chain safety and environment, and Federal Public Service of social security. The development of clinical practice guidelines is part of the legal mission of the KCE. A clinical practice guideline (CPG) on the management of breast cancer was firstly published in 2007 [1], and completely updated in 2010 [2]. **1** Christiaens et al. Support scientifique du Collège d'Oncologie: un guideline pour la prise en charge du cancer du sein. Brussels: Centre fédéral d'expertise des soins de santé; 2007. Good Clinical Practices (GCP) 63B **2** Cardoso et al. Soutien scientifique au Collège d'Oncologie: mise à jour des recommandations de bonne pratique pour la prise en charge du cancer du sein. Brussels: Centre Fédéral d'expertise des Soins de santé; 2010. Good Clinical Practices (GCP) KCE report 143

Methodik

- A broad search of electronic databases (Medline, PreMedline, EMBASE), specific guideline websites and websites of organisations in oncology … was conducted.
- quality appraisal: AGREE for clinical practice guidelines, QUADAS 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)**. 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 <u>first-line</u> hormonal treatment in <u>postmenopausal patients</u> 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] (Table 50, Appendix 5.6.1). However, tamoxifen remains an acceptable alternative as first-line treatment. (siehe Anhang) [17] Kreienberg et al. Interdisciplinary S3 Guidelines for the Diagnosis and Treatment of Breast Cancer in Women. Frankfurt: German Cancer Society; 2003. [66] Kwaliteitsinstituut voor de Gezondheidszorg (CBO) en Vereniging van Integrale Kankercentra (VIKC), V. Zuiden (Eds). Richtlijn Behandeling van het mammacarcinoom 2005. Alphen aan den Rijn: 2005. [204] Beslija et al. Second consensus on medical treatment of metastatic breast cancer. Annals of Oncology. 2007;18(2):215-25. *[215] Ferretti 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 et al. Role of aromatase inhibitors in the treatment of postmenopausal women with metastatic breast cancer. Toronto: Cancer Care Ontario; 2003. • 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)**.

Chemotherapy

Chemotherapy is indicated for women with hormone refractory or HR negative metastatic breast cancer, rapidly progressive disease or symptomatic disease, or with life-threatening disease (e.g. diffuse lung or liver metastases, massive bone marrow metastases with pancytopenia) [66]. Multiple systematic reviews exist evaluating different chemotherapy regimens for women with metastatic breast cancer [175, 220-222]

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
- 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)**.

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.
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.

Biological therapy

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

<table>
<tr><td></td><td>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)

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).

Wagner et al. Vascularendothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database Syst Rev. 2012;7:CD008941.</td></tr>
<tr><td>AWMF, 2012 [12].

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

Langversion 3.0, Aktualisierung 2012

AWMF-Register-Nummer: 032-045OL</td><td>Leitlinie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); federführende Fachgesellschaften Deutsche Krebsgesellschaft e.V. (DKG) und Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

Methodik

Grundlage der Leitlinie:

Systematische Recherche nach Studien, Leitlinien und Cochrane-Reviews; anschließender Konsensus Prozess zur Formulierung der Empfehlungen (detaillierte Darstellung der Methodik im Leitlinienreport siehe http://leitlinienprogramm-onkologie.de/uploads/tx_sbdownloader/S3-Brustkrebs-v2012-OL-LL-Report.pdf, Abruf: 19.11.2015)

Suchzeitraum der Literaturrecherche von 2006 bis August 2011 (teils Aktualisierung der Version aus 2008)

Empfehlungsgraduierung
<table><tr><th>Empfehlungs-grad</th><th>Beschreibung</th><th>Syntax</th></tr><tr><td>A</td><td>Starke Empfehlung</td><td>soll</td></tr><tr><td>B</td><td>Empfehlung</td><td>sollte</td></tr><tr><td>0</td><td>Empfehlung offen</td><td>kann</td></tr><tr><td>GCP</td><td colspan="2">Statements/Empfehlungen, für die eine Überarbeitung auf der Grundlage von Expertenkonsens der Leitliniengruppe beschlossen wurde, sind als solche ausgewiesen mit der Graduierung „GCP“.</td></tr></table>
<table><tr><th colspan="2">LoE</th><th>Studien zu Therapie, Prävention, Ätiologie</th></tr><tr><td>1</td><td>1a</td><td>Qualitativ hochwertiger Systematischer Review (SR) von randomisiert-kontrollierten Studien (RCT) mit geringem Risiko für Verzerrungen</td></tr><tr><td></td><td>1b</td><td>Einzelne RCT mit geringem Risiko für Verzerrungen</td></tr><tr><td></td><td>1c</td><td>„Alle oder Keiner“-Prinzip*</td></tr></table></td></tr>
</table>

2	**2a**	SR von Kohortenstudien mit geringem Risiko für Verzerrungen
	2b	Einzelne Kohortenstudie mit geringem Risiko für Verzerrungen
	2c	Ergebnisforschung; ökologische Studien
3	**3a**	SR von Fallkontrollstudien
	3b	Einzelne Fallkontrollstudie
4		Fallserie
5		Expertenmeinung oder basierend auf pathophysiologischen Modellen oder experimenteller Grundlagenforschung oder „Grundprinzipien“

Diese Leitlinie wurde von der Deutschen Krebshilfe im Rahmen des Onkologischen Leitlinienprogramms gefördert.

Empfehlungen

Primär lokal/lokoregional fortgeschrittene Tumore

Neoadjuvante systemische Therapie

Eine neoadjuvante (primäre, präoperative) systemische Therapie wird als Standardbehandlung bei Patientinnen mit lokal fortgeschrittenen, primär inoperablen oder inflammatorischen Mammakarzinomen im Rahmen eines multimodalen Therapiekonzeptes angesehen. (**GCP**)

(Brito 2001; Fisher 1997; Kaufmann 2006; von Minckwitz 2011)

Radiotherapie bei lokal weit fortgeschrittenem Tumor und bei primärer Inoperabilität

a. Für Patientinnen mit primär inoperablen bzw. inflammatorischen Karzinomen wird eine primäre Systemtherapie, gefolgt von Operation und postoperativer Strahlentherapie empfohlen. *(Empfehlungsgrad **A**, Evidenzlevel: **1b**)*

(Kaufmann. 2003; Kaufmann 2010; NCCN 2011; NICE 2009a)

b. Wird durch die Systemtherapie keine Operabilität erreicht, ist eine Strahlentherapie – eventuell auch in Kombination mit simultaner Systemtherapie – indiziert.

(Kaufmann 2003; Kaufmann 2010; NCCN 2007; NCCN 2011; Shenkier 2004; Truong 2004)

Primäre Hormontherapie bei postmenopausalen Patientinnen

Eine primäre antiöstrogene systemische Therapie stellt eine Option für postmenopausale Patientinnen mit rezeptorpositivem und HER2-negativem Tumor dar, bei denen eine Operation kontraindiziert ist oder eine Operation abgelehnt wird. (**GCP**)

Systemische Therapie des metastasierten Mammakarzinoms

Systemische endokrine Therapie

Die endokrine Therapie ist die Therapie der Wahl bei positivem Hormonrezeptorstatus. (Empfehlungsgrad **A**, Evidenzlevel: **1b**)

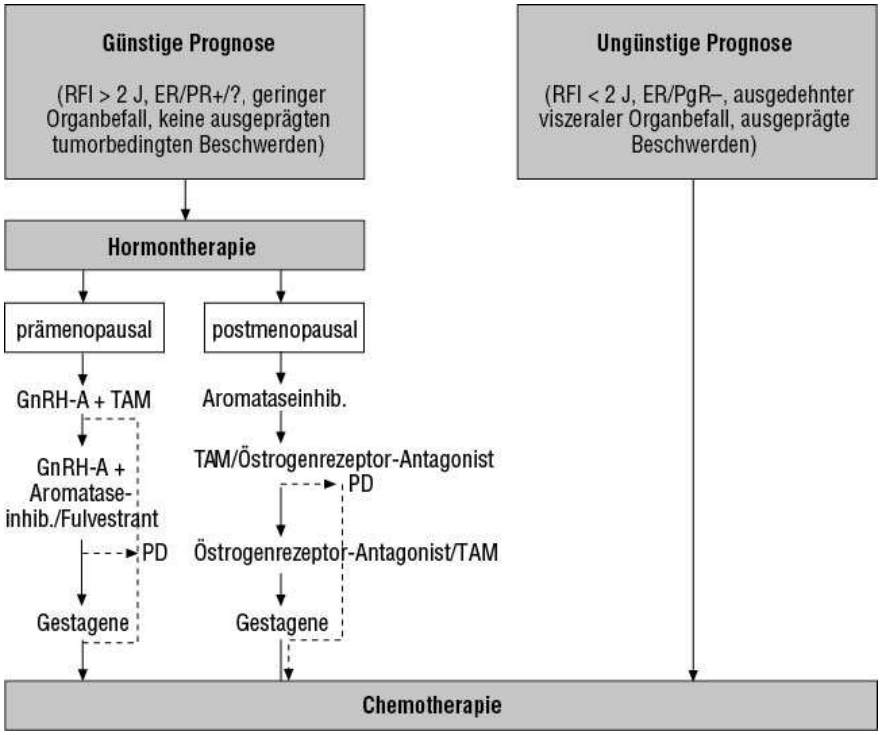
(Fossati 1998; NICE 2009b; Stockler 1997; Stockler 2000)

Kombinierte chemo-endokrine Therapie

Eine kombinierte chemo-endokrine Therapie wird nicht empfohlen. Sie kann

	zwar die Remissionsraten erhöhen, führt aber auch zu gesteigerter Toxizität ohne Verlängerung des progressionsfreien Intervalls oder des Gesamtüberlebens. (Empfehlungsgrad **A**, Evidenzlevel: **1a**) *(Cochrane: Carrick 2005; Sledge 2000)* <u>Endokrine Therapie der prämenopausalen Patientin</u> • Bei prämenopausalen Patientinnen ist die Ausschaltung der Ovarialfunktion (GnRHAnaloga, Ovarektomie, Radiomenolyse) in Kombination mit Tamoxifen die Therapie der ersten Wahl. (Empfehlungsgrad **A**, Evidenzlevel: **1*b***) *(Klijn 2001; NBOCC 2010; NICE 2009b)* • In der Folge kann in der Prämenopause eine Ovarialsuppression in Kombination mit einem Aromatasehemmer zum Einsatz kommen. Einen weiteren Schritt stellt die Behandlung mit hoch dosierten Gestagenen (MA/MPA) dar. (Empfehlungsgrad **0**, Evidenzlevel: **2c**) Weitere Erläuterung zur Empfehlung: Der initiale Therapieschritt ist die Ausschaltung der Ovarialfunktion (GnRH-Analoga, Ovarektomie oder Radiomenolyse) in Kombination mit Tamoxifen. Bei Progression des Tumorgeschehens oder Kontraindikation von Tamoxifen sollte ein Aromataseinhibitor der dritten Generation eingesetzt werden. Bei weiterer Progression ist dann der Einsatz von Gestagenen gerechtfertigt. *(NICE 2009b [LL]; Taylor et al. 1998 [RCT]; von Minckwitz et al. 1991 [Beobachtungsstudie])* <u>Endokrine Therapie der postmenopausalen Patientin</u> • Bei der sicher postmenopausalen Frau sind Aromatasehemmer der 3. Generation dem Tamoxifen hinsichtlich des krankheitsfreien Überlebens überlegen. *(*Evidenzlevel: **1b***)* *(Burstein et al. 2010 [SR von RCTs]; NZGG 2009 [LL])* • Aromatasehemmer bei postmenopausalen Patientinnen: Als erster endokriner Behandlungsschritt bei Metastasierung soll bei postmenopausalen Patientinnen ein Aromatasehemmer eingesetzt werden, wenn adjuvant ausschließlich Tamoxifen oder keine adjuvante endokrine Therapie erfolgt ist. (Empfehlungsgrad **A**, Evidenzlevel: **1a***)* *(Cochrane: Gibson 2009; Ellis 2000; Fossati 1998; Hayes 1995; Mouridsen 2001a; Mouridsen 2001b; NICE 2009b)* • Behandlungskaskade bei postmenopausalen Patientinnen: Weitere Schritte in der endokrinen Behandlungskaskade bei postmenopausalen Patientinnen stellen je nach Vorbehandlung der Einsatz von Antiöstrogenen, Östrogenrezeptor-Antagonisten, der Wechsel des Aromataseinhibitors von einem steroidalen auf einen nicht steroidalen Aromataseinhibitor oder vice versa oder der Einsatz von hoch dosierten Gestagenen dar. (**GCP**) *(Fossati 1998; Robertson 2003)* <u>Antiangiogenese: VEGF-Inhibitoren (Bevacizumab)</u> Bei Einsatz von Paclitaxel oder Capecitabine als zytostatische Erstlinientherapie bei metastasiertem Mammakarzinom kann zur Verbesserung des Therapieerfolges zusätzlich Bevacizumab eingesetzt werden. (**GCP**) *(NBOCC 2010; Robert 2011)*

	Literatur zur Evidenzbasis: o Brito et al. Long-term results of combined modality therapy for locally advanced breast cancer with ipsilateral supraclavicular metastases: The University of Texas M.D. Anderson Cancer Center experience. J Clin Oncol 2001; 19(3):628-633. o Burstein et al. American Society of Clinical Oncology clinical practice guideline: update on adjuvant endocrine therapy for women with hormone receptor-positive breast cancer. J Clin Oncol 2010; 28(23):3784-3796. o Cochrane: Carrick et al. Single agent versus combination chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev 2005;(2):CD003372. o Cochrane: Gibson et al. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. Cochrane Database Syst Rev 2009;(4):CD003370. o Ellis et al. Treatment of metastatic breast cancer. Cancer 2000;749-797. o Fisher et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol 1997; 15(7):2483-2493. o Fossati et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J Clin Oncol 1998; 16(10):3439-3460. o Hayes et al. Treatment of metastatic breast cancer: present and future prospects. Semin Oncol 1995; 22(2 Suppl 5):5-19. o Kaufmann et al. International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. J Clin Oncol 2003; 21(13):2600-2608. o Kaufmann at al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol 2006; 24(12):1940-1949. o Kaufmann et al. Locoregional treatment of primary breast cancer: consensus recommendations from an International Expert Panel. Cancer 2010; 116(5):1184-1191. o Klijn et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. J Clin Oncol 2001; 19(2):343-353. o Mouridsen et al. First-line therapy with letrozole (Femara) for advanced breast cancer prolongs time to worsening of Karnofsky Performance Status com-pared with tamoxifen [abstract]. Breast Canc Res Treat 2001a; 69. [CANADA] o Mouridsen et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 2001b; 19(10):2596-2606. o NBOCC. National Breast and Ovarian Cancer Center: Recommendations for use of Chemotherapy for the treatment of advanced breast cancer, NBOCC, Surry Hills. 2010. o NCCN. Clinical Practice Guidelines in Oncology: Breast Cancer - Version V.1. 2007. o NCCN. National Comprehensive Cancer Network. Breast cancer. V. 2.2011. 2011. o NICE. National Institute for Clinical Excellence (NICE): Early and locally advanced breast cancer: diagnosis and treatment. 2009a. o NICE. National Institute for Clinical Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009b. o NZGG. New Zealand Guidelines Group: Management of early breast cancer. Wellington: 2009. o Robert et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011; 29(10):1252-1260. o Robertson et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. Cancer 2003; 98(2):229-238. o Shenkier et al. Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. CMAJ 2004; 170(6):983-994.

	○ Sledge et al. Comparison of chemotherapy with chemohormonal therapy as first-line therapy for metastatic, hormone-sensitive breast cancer: An Eastern Cooperative Oncology Group study. J Clin Oncol 2000; 18(2):262-266. ○ Stockler et al. The management of advanced breast cancer: systemic reviews of randomised controlled trials regarding the use of cytotoxic chemotherapy and endocrine therapy. Woolloomooloo 1997; NHMRC National Breast Cancer Centre. [NHMRC] ○ Stockler et al. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. Cancer Treat Rev 2000; 26(3):151-168 ○ Taylor et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. J Clin Oncol 1998; 16(3):994-999. ○ Truong et al. Clinical practice guidelines for the care and treatment of breast cancer: 16. Locoregional post-mastectomy radiotherapy. CMAJ 2004; 170(8):1263-1273. ○ von Minckwitz et al. Hormonelle Folgetherapien nach Goserelin (ZoladexR) beim metastasierten Mammakarzinom prämenopausaler Patientinnen. Arch Gynecol Obst 1991; 250:258-260. [AGO] Algorithmus zur systemischen Therapie beim metastasierten Mammakarzinom. 
Rugo H et al. 2016 [21]. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline.	Leitlinie der American Society of Clinical Oncology (ASCO)
	Fragestellung To develop recommendations about endocrine therapy for women with hormone receptor (HR) –positive metastatic breast cancer (MBC). **Clinical Question 1**: Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for HR-positive metastatic breast cancer? 1.1: For postmenopausal women: What are the optimal sequence and duration? 1.2. Should hormone therapy be administered in combination with other

	hormonal agents or chemotherapy? 1.3 For premenopausal women:What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting? 1.4 Are there demonstrated differences between pre- and postmenopausal patients? Clinical Question 2: Is there an optimal second- or later-line endocrine therapy for HR-positive MBC? 2.1 Should other treatment or disease-free interval play a role in treatment selection? 2.2 Which hormone therapy should be offered? 2.3 What are the optimal timing, dose, and schedule of treatment? **Clinical Question 3**: How or should endocrine therapies be used in combination or sequence with: 3.1 mTOR inhibitors (everolimus)? 3.2 CDK 4/6 inhibitors (palbociclib)? **Clinical Question 4:** Does estrogen or progesterone expression (high v low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women? **Clinical Question 5**: How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting? **Clinical Question 6:** In which patients or settings is hormone therapy recommended over chemotherapy? 6.1 Is there a role for combined cytotoxic and endocrine therapies? 6.2 What is the optimal duration of treatment with hormone therapy? **Clinical Question 7:** Is there a role for additional biomarkers in the selection of treatment for patients for HR-positive disease?
	Methodik 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. The MEDLINE (OVID: 2008 through week 4 of April 2014) and Cochrane Library databases (http://www.cochranelibrary.com; to Issue 3 of March 2013) were searched for evidence reporting on outcomes of interest. Additionally, the San Antonio Breast Cancer Symposium (2011 to 2014) and ASCO abstracts (2012 to 2014) were searched for reports on systematic reviews (with or without meta-analyses) and randomized controlled trials (phase II or III) … (see Data Supplement) The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. As seen in the Study Quality Assessment Table in the Methodology Supplement

(online only), study quality was formally assessed for the 29 trials identified. Design aspects related to individual study quality were assessed by one reviewer and independently audited by another, with factors such as blinding, allocation concealment (blinding to treatment arm), placebo control, intention to treat, funding sources, and so on considered. The overall risk of bias was assessed as either low to intermediate or intermediate for the included trials.

Guide 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.

Guide for Strength of Recommendations

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.

Guide for Rating Strength 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.

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.

Recommendation 1.1

Postmenopausal women with HR-positive MBC should be offered AIs as first-line endocrine therapy (Fig 1) (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong.)

Recommendation 1.2

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 (Fig 1) *(Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).*

Recommendation 1.3

Premenopausal women with HR-positive MBC should be offered ovarian suppression or ablation in combination with hormone therapy. Ovarian suppression with either GnRH agonists or ablation with oophorectomy seems to achieve similar results in MBC. For most patients, clinicians should use guidelines for postmenopausal women to guide the choice of hormone treatment, although sequential therapy can also be considered. Patients without exposure to prior hormone therapy can also be treated with tamoxifen or ovarian suppression or ablation alone, although combination therapy is preferred. Treatment should be on the basis of the biology of the tumor and the menopausal status of the patient, with careful attention paid to production of ovarian estrogen (Fig 1) *(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).*

Recommendation 1.4

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 (Fig 1) *(Type: evidence and consensus based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).*

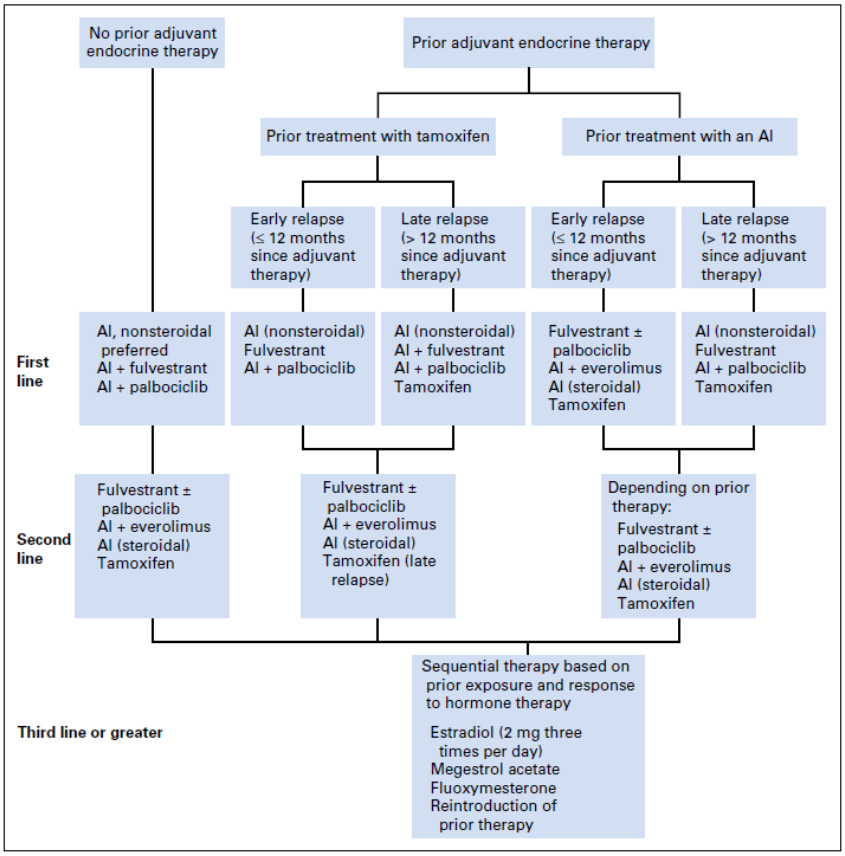


Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered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

Recommendation 2.1

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).*

Recommendation 2.2

Sequential hormone therapy should be offered to patients with endocrine-responsive disease. Options are shown in Fig 1 *(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).*

Recommendation 2.3

Fulvestrant should be administered using the 500-mg dose and with a loading schedule *(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).*

Recommendation 3.1

Exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC who experience progression during treatment with nonsteroidal AIs, either before or after treatment with fulvestrant, because PFS but not OS was improved compared with exemestane alone. Other options are

	shown in Figures 1 and 2. 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 na¨ıve to hormone therapy *(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).* **Recommendation 3.2** A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-na¨ıve HR-positive MBC; PFS but not OS was improved compared with the nonsteroidal AI letrozole alone. Other options are shown in Figures 1. The accelerated approval of palbociclib is dependent on results of an ongoing phase III trial in the same setting (Data Supplement 8; PALOMA-2 trial). Results from the PALOMA-2 trial will be presented at the ASCO 2016 Annual Meeting. A press release74a confirms that the trial met its primary end point. Letrozole plus palbociclib improved PFS compared with letrozole alone as firstline therapy for HR-positive metastatic breast cancer in postmenopausal women. Survival data are not yet available. 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).* **Recommendation 4** Hormone therapy should be offered to patients whose tumors express any level of ER and/or progesterone receptor (PR) *(Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).* **Recommendation 5** 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 (Figs 1). 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).* **Recommendation 6** 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 who experience rapid visceral recurrence during adjuvant endocrine therapy *(Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).* **Recommendation 6.1** The use of combined endocrine therapy and chemotherapy is not recommended *(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).* **Recommendation 6.2** Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. Tumor markers or circulating tumor cells should not be used as the sole criteria for determining progression *(Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).* **Recommendation 7** Use of additional biomarkers is experimental and should be reserved for selection of treatment in clinical trials. There is no routine clinical role for genomic or expression profiling in the selection of treatment for HR-positive MBC *(Type: consensus based, benefits outweigh harms; Evidence quality: low;*

	Strength of recommendation: moderate).

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

NICE, 2013 [18].

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

Technology appraisal guidance TA 295

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.

Evidence for clinical effectiveness	
Availability, nature and quality of evidence	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.
	The Committee noted that the TAMRAD trial did not compare everolimus within its licensed indication (that is, in combination with exemestane) with tamoxifen. The Committee noted that no conclusions on the effectiveness of everolimus plus exemestane compared with tamoxifen were possible.
	The Committee concluded that the 'naive chained indirect 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
Relevance to general clinical practice in the NHS	The Committee heard from the clinical specialists that the BOLERO-2 trial population represented patients who would be offered everolimus plus exemestane in the UK.
Uncertainties generated by the evidence	The Committee agreed that the immaturity of the overall survival data from the BOLERO-2 trial generated considerable uncertainty associated with the longer-term benefits of everolimus plus exemestane.
	The Committee concluded that there was considerable uncertainty about the validity of the comparison of everolimus plus exemestane with tamoxifen, but noted its previous conclusions that, of the endocrine therapies, the comparison of everolimus plus exemestane with exemestane alone was the most relevant to the appraisal.
	The Committee concluded that it was not possible to make robust comparisons between everolimus plus exemestane and chemotherapies based on the available evidence.
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	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.

	Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that everolimus plus exemestane is effective in prolonging progression-free survival compared with exemestane alone.
		The Committee agreed that the immaturity of the overall survival data resulted in considerable uncertainty associated with the longer-term benefits of everolimus plus exemestane.

Jeitler K et al., 2012 {#714}.

Everolimus (Afinitor® or Votubia®) in combination with exemestane in postmenopausal women with oestrogen receptor positive, HER2- negative locally advanced or metastatic breast cancer who are refractory to letrozole or anastrozole. (DSD-HSO Nr.32)

Current regulatory status
… the European Medicines Agency (EMA) granted market authorization of Afinitor®

for the treatment of hormone receptor (HR)-positive, HER2-negative advanced BC, in combination with exemestane, in postmenopausal women without symptomatic visceral disease after recurrence or progression following a non-steroidal aromatase inhibitor[2]. […]

In July 2012, the U.S. Food and Drug Administration (FDA) approved everolimus (Afinitor®) based on the results of a randomized, double-blind, multicenter trial:

- for the treatment of postmenopausal women with advanced HR-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole[7]. […]

6 Evidence
A systematic literature search for primary literature in medical databases (Medline/Pubmed, Embase, Cochrane Central Register of Controlled Trials) was conducted on 3rd August 2012 and yielded 130 records after removal of duplicates. Of those, 7 records reporting on one phase III trial were included [31-37]. In addition a hand search was performed which included reference lists of topic related reviews (retrieved from the Cochrane databases and CRD) and the websites of the EMA and the FDA. This search resulted in 3 further publications belonging to the already identified RCT [38-40]. On request the manufacturer sent 5 additional conference posters relevant to the topic [41-45]. In summary 15 publications (2 full text publications, 1 letter and 12 conference abstracts) reporting on one relevant phase III trial (BOLERO- 2) were identified [31-45]

6.1 Efficacy and safety – Phase III studies

Auszug aus Table 1: summary of efficacy

Effect estimate per comparison	**PFS**	**HR***	**95% CI**	**P value**
Interim analysis 7,5 mo f/up	locA[+]	0.43	0.35-0-54	<0.001
	centA[#]	0.36	0.27-0.47	<0.001
Updated analysis 12,5 mo f/up	locA[+]	0.44	0.36-0-53	<0.001
	centA[#]	0.36	0.28-0.45	<0.001
Updated analysis 18 mo f/up	locA[+]	0.45	0.38-0-54	<0.0001
	centA[#]	0.38	0.31-0.48	<0.0001
Intervention group	n=485	Everolimus + Exemestan		
Control group	n=239	Placebo + Exemestan		

***** HR Intervention versus control
[+] locA: local assessment
[#] centA: central assessment (by an independent radiology committee)

9 Commentary
In addition, BOLERO-2 does not address the question on safety and efficacy of everolimus alone in comparison to everolimus in combination with aromatase inhibitors or in comparison to chemo-therapy, the preferred regimen for women with more aggressive tumours (i.e. with symptomatic visceral disease). The

	EMA has therefore, and in contrast to the FDA, restricted the indication to patients without visceral involvement. … In summary, the interim results of the BOLERO-2 study indicate that everolimus in combination with exemestane can extend PFS when compared to exemestane alone. Overall, fewer women died in the everolimus group although there was a higher rate of adverse events, serious adverse events and on-treatment deaths. Final data on QoL and the OS can be expected in 2015. These as well as the results of the upcoming BOLERO-6 trial will be helpful in deciding on the use of everolimus for the therapy in postmeno-pausal women with ER-positive, HER2-negative locally advanced or metastatic BC. [2] European Medicines Agency (EMA). Afinitor: EPAR - Product Information 2012 07.August 2012 10.August]; Available from: http://www.ema.europa.eu/docs/ en_GB/document_library/EPAR_-_Product_Information/human/001038/ WC500022814.pdf. [7] U.S. Food and Drug Administration (FDA). Drugs@FDA - Afinitor; Supplemental Approval. 2012 20.July 2012 10.August]; Available from: http://www.accessdata. fda.gov/drugsatfda_docs/appletter/2012/022334Orig1s016ltrRepl.pdf. [31] Gnant, M., Late Breaking Abstracts EBCC8 - European Breast Cancer Conference 2012. European Journal of Cancer, 2012. 48. [32] Baselga et al., Everolimus in combination with exemestane for postmenopausal women with advanced breast cancer who are refractory to letrozole or anastrozole: Results of the BOLERO-2 phase III trial. European Journal of Cancer, 2011. 47: p. 6-7. [33] Campone et al., Bolero-2: Everolimus in combination with exemestane in the treatment of postmenopausal women with estrogen receptor-positive advanced breast cancer refractory to letrozole or anastrozole. Breast, 2011. 20: p. S30. [34] Kasprowicz et al., Evaluation of RAD001 (everolimus) in the setting of resistance to letrozole or anastrozole in postmenopausal ER-positive breast cancer patients: BOLERO-2 trial. Archives of Gynecology and Obstetrics, 2010. 282: p. S126. [35] Baselga et al., Everolimus in postmenopausal hormone-receptorpositive ad-vanced breast cancer. New England Journal of Medicine, 2012. 366(6): p. 520-9. [36] Beaver and Park, The BOLERO-2 trial: the addition of everolimus to exemestane in the treatment of postmenopausal hormone receptor-positive advanced breast cancer. Future Oncology, 2012. 8(6): p. 651-7. [37] Rugo et al., Everolimus (EVE) for postmenopausal women with advanced breast cancer (ABC) refractory to letrozole or anastrozole: Long-term efficacy and safety results of the bolero-2 trial. European Journal of Cancer, 2012. 48: p. S116. [38] Rugo et al., Updated results of the BOLERO-2 phase III trial evaluating Everolimus (EVE) for postmenopausal women with advanced breast cancer (ABC). Annals of Oncology, 2012. 23(Supplement 2): p. 46. [39] Hortobagyi et al., Everolimus for Postmenopausal Women with Advanced Breast Cancer: Updated Results of the BOLERO-2 Phase III Trial. Cancer Research, 2011. 71(24 Supplement): p. 105. [40] Massarweh, S., J. Croley, and H. Weiss, Everolimus in HR-Positive Advanced Breast Cancer. New England Journal of Medicine, 2012. 366(18): p. 1738. [41] Beck et al., BOLERO-2: Health-Related Quality-of-Life in Metastatic Breast Cancer Patients Treated With Everolimus and Exemestane Versus Exemestane. ASCO Annual Meeting, 2012. abstract # 539. [42] Piccart et al., Everolimus for Postmenopausal Women With Advanced Breast Cancer: Updated Results of the BOLERO-2 Phase III Trial. ASCO Annual Meeting, 2012. abstract # 559. [43] Gnant et al., Effects of Everolimus on Disease Progression in Bone and Bone Markers in Patients With Bone Metastases. ASCO Annual Meeting, 2012. abstract # 512. [44] Noguchi et al., BOLERO-2: Everolimus With Exemestane Versus Exemestane Alone in Asian Patients With HER2- Negative, Hormone-Receptor–Positive Breast Cancer. ASCO Annual Meeting, 2012. abstract # 540. [45] Pritchard et al., Safety of Everolimus for Women Over 65 Years of Age With Advanced Breast Cancer (BC): 18-Month Follow-up of BOLERO-2. ASCO Annual Meeting, 2012. abstract # 551.
NICE, 2012 [16]. Bevacizumab in combination with	**Key conclusion** **1.1** Bevacizumab in combination with capecitabine is not recommended within its marketing authorisation for the first-line treatment of metastatic breast

capecitabine for the first-line treatment of metastatic breast cancer Technology appraisal guidance TA 263	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 [17]. 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.
NICE, 2011 [19]. Fulvestrant for the treatment of locally advanced or metastatic breast cancer Technology appraisal guidance TA 239	**1 Guidance** **1.1** Fulvestrant is not recommended, within its licensed indication, as an alternative to aromatase inhibitors for the treatment of oestrogen-receptor-positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer has relapsed on or after adjuvant anti-oestrogen therapy, or who have disease progression on anti-oestrogen therapy. **Reasons for recommendation:** • Fulvestrant has a marketing authorisation for patients who have been treated previously with an anti-oestrogen (that is; second line as an alternative to aromatase inhibitors). • The CONFIRM trial population consisted of a mixture of patients who had last received either an anti-oestrogen or an aromatase inhibitor. The only comparator included in the CONFIRM trial was fulvestrant 250 mg. • There was high uncertainty about the validity of the manufacturer's network meta-analysis because of heterogeneity between the studies included, the selection of studies included and the parametric survival models used to project TTP and overall survival. • The most plausible ICER presented for fulvestrant 500 mg compared with

anastrozole was £35,000 per QALY gained (based on the ERG's exploratory analysis). However, there remained considerable uncertainty about this estimate because it was based on the same trials in the network meta-analysis as those used in the manufacturer's network meta-analysis.

- The Committee concluded that fulvestrant did not fulfil the end-of-life criteria as it is indicated for patients with a life expectancy of more than 24 months.

Evidence for clinical effectiveness	
Availability, nature and quality of evidence	The Committee was aware that the only treatment comparator in the CONFIRM trial was low-dose (250 mg) fulvestrant.
	The Committee noted that although the marketing authorisation for fulvestrant 500 mg is for patients who have received previous antiestrogen treatment, the CONFIRM trial population consisted of a mixture of patients who had last received either an anti-oestrogen or an aromatase inhibitor. The Committee noted heterogeneity between these two subgroups in terms of previous treatment and patient characteristics. The Committee therefore agreed that only data from the subgroup in the CONFIRM trial who had received an anti-oestrogen as their last treatment should be included in the network meta-analyses.
	The Committee noted that fulvestrant 500 mg was linked to other treatments in the network only through fulvestrant 250 mg, which was used as the baseline comparator in the manufacturer's network meta-analysis. The Committee noted that the manufacturer had sought advice from key opinion leaders about setting firm criteria for the selection of trials for inclusion in the meta-analysis (for example, including only recent trials, or agreeing a certain percentage of patients with cancer of unknown oestrogen receptor status), but that no such criteria could be agreed. The main inclusion criterion was relaxed by the manufacturer to include trials for comparators with at least 70% of patients with documented oestrogen-receptor-positive status. The Committee was aware that, based on this criterion, exemestane was excluded as a comparator in the base-case costeffectiveness analysis. The Committee also highlighted sources of heterogeneity between the trials included in the network metaanalysis. The Committee concluded that the results of the manufacturer's network meta-analysis were subject to bias from the selection of studies included in the network.
Relevance to general clinical practice in the NHS	The Committee was aware of the restriction to the marketing authorisation to patients who had been treated previously with an anti-oestrogen, which places fulvestrant as an alternative to aromatase inhibitors after anti-oestrogen treatment.
	The Committee considered that third-line or fourth-line use was not within the remit of this technology appraisal.

	Uncertainties generated by the evidence	The Committee concluded that there was high uncertainty about the validity of the results of the manufacturer's network meta-analysis because of heterogeneity between the studies selected and the parametric survival models used to project TTP and overall survival.
	Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee noted that the CONFIRM trial population consisted of a mixture of patients who had last received either an antiestrogen or an aromatase inhibitor. The Committee noted heterogeneity between these two subgroups in terms of previous treatment and patient characteristics. The Committee therefore agreed that only data from the subgroup in the CONFIRM trial who had received an anti-oestrogen as their last treatment should be included in the network meta-analyses, in line with the marketing authorisation for fulvestrant.
	Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee noted that the results of the network meta-analyses by the manufacturer showed no significant differences in overall survival between fulvestrant, anastrozole and letrozole, although fulvestrant resulted in significantly longer TTP compared with anastrozole (but not letrozole). However, the Committee concluded that, because of the issues identified by the ERG concerning the fit of the parametric survival models used by the manufacturer, there was high uncertainty about these results.
NICE, 2011 [16]. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer Technology appraisal guidance TA 214	**Key conclusion** **1.1** Bevacizumab in combination with a taxane is not recommended for the first-line treatment of metastatic breast cancer. **Evidence for clinical effectiveness** **4.3, 4.4, 4.7, 4.8** The Committee noted that the original submission was based on one trial (E2100) which compared bevacizumab plus paclitaxel with weekly paclitaxel. The Committee heard from the ERG that the E2100 trial had several limitations, such as the lack of blinding. The Committee heard from the clinical specialist that the response in E2100 to paclitaxel alone was lower than demonstrated in previous studies. The Committee noted that evidence from the AVADO study for the clinical effectiveness of bevacizumab plus docetaxel had been provided by the manufacturer after consultation on the appraisal consultation document. The Committee noted the ERG's comments related to the reliability of the indirect treatment comparison included in the manufacturer's submission and concluded that the indirect treatment comparison was not robust and that the results were not considered reliable.	

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews) **am 05.08.2016**

#	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 progression*:ti,ab,kw
5	#2 and #3
6	#1 or #5
7	#7 Publication Year from 2011 to 2016

SR, HTAs in Medline (PubMed) am 13.10.2016

#	Suchfrage
1	"breast neoplasms/drug therapy" OR "breast neoplasms/radiotherapy" OR "breast neoplasms/therapy" OR "breast neoplasms/treatment"
2	("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 carcinom*[Title/Abstract]) OR neoplas*[Title/Abstract]) OR maligant*[Title/Abstract]) OR adenocarcinom*[Title/Abstract]
6	(((((((advanced[Title/Abstract]) OR metastas*[Title/Abstract]) OR metastat*[Title/Abstract]) OR recurren*[Title/Abstract]) OR progression*[Title/Abstract]) OR progressive*[Title/Abstract]) OR disseminat*[Title/Abstract]
7	#4 AND #5 AND #6
8	(#3) AND (Chemotherapy, Adjuvant[MesH] OR Neoadjuvant Therapy[MESH] OR Antineoplastic Combined Chemotherapy Protocols[MESH] OR Estrogen Antagonists[MESH] OR Aromatase Inhibitors[MesH])
9	((((((((((((((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])
10	#7 AND #9
11	(#8) OR #10
12	(#11) 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]))))

13	(((#12) AND ("2011/10/13"[PDAT] : "2016/10/13"[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 08.08.2016

#	Suchfrage
1	"breast neoplasms"[MeSH Major Topic]
2	(breast[Title]) OR mamma*[Title]
3	(((((cancer*[Title]) OR tumour*[Title]) OR tumor*[Title]) OR carcinom*[Title]) OR adenocarcinom*[Title]) OR neoplas*[Title]
4	(#2) AND #3
5	(#1) OR #4
6	(((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]
7	(#5) AND #6
8	(#7) AND ("2011/08/01"[PDAT] : "2016/08/08"[PDAT])

Literatur:

1. **Al-Mubarak M, Sacher AG, Ocana A, Vera-Badillo F, Seruga B, Amir E.** Fulvestrant for advanced breast cancer: a meta-analysis. Cancer Treat Rev 2013;39(7):753-758.

2. **Bachelot T, McCool R, Duffy S, Glanville J, Varley D, Fleetwood K, et al.** Comparative efficacy of everolimus plus exemestane versus fulvestrant for hormone-receptor-positive advanced breast cancer following progression/recurrence after endocrine therapy: a network meta-analysis. Breast Cancer Res Treat 2014;143(1):125-133.

3. **Belfiglio M, Fanizza C, Tinari N, Ficorella C, Iacobelli S, Natoli C.** Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer. J Cancer Res Clin Oncol 2012;138(2):221-229.

4. **Cope S, Ouwens MJ, Jansen JP, Schmid P.** Progression-free survival with fulvestrant 500 mg and alternative endocrine therapies as second-line treatment for advanced breast cancer: a network meta-analysis with parametric survival models. Value Health 2013;16(2):403-417.

5. **Gemeinsamer Bundesausschuss (G-BA).** Abschlussbericht des Gemeinsamen Bundesausschusses nach § 91 Abs. 7 SGB V „Krankenhausbehandlung“ Methode: Protonentherapie, Indikation: Mammakarzinom, vom 28.05.2009 [online]. Berlin (GER): G-BA; 2009. [Zugriff: 13.10.2016]. URL: https://www.g-ba.de/downloads/40-268-1800/2009-05-28-RL-Kh-Protonen-Mamma_ZD.pdf.

6. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Eribulin (neues Anwendungsgebiet), vom 22. Januar 2015 [online]. Berlin (GER): G-BA; 2015. [Zugriff: 13.10.2016]. URL: https://www.g-ba.de/downloads/39-261-2148/2015-01-22_AM-RL-XII_Eribulin_2014-08-01-D-125_BAnz.pdf.

7. **Gemeinsamer Bundesausschuss (G-BA).** Beschluss des Gemeinsamen Bundesausschusses über eine Einstellung der Methodenbewertung gemäß § 137c des Fünften Buches Sozialgesetzbuch zu acht Methoden der Stammzelltransplantation vom 19. März 2015 [online]. Berlin (GER): G-BA; 2015. [Zugriff: 13.10.2016]. URL: https://www.g-ba.de/downloads/39-261-2221/2015-03-19_Einstellung-8-Methoden-SZT.pdf.

8. **Gemeinsamer Bundesausschuss (G-BA).** Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von Strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V, vom 16. Februar 2012, zuletzt geändert am 20. November 2014 [online]. Berlin (GER): G-BA; 2014. [Zugriff: 13.10.2016]. URL: https://www.g-ba.de/downloads/62-492-963/DMP-RL_2014-11-20_iK-2015-01-07.pdf.

9. **Gemeinsamer Bundesausschuss (G-BA).** Zusammenfassende Dokumentation über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use: Gemcitabin in der Monotherapie beim Mammakarzinom der Frau, vom 20. Mai 2010 [online]. Berlin (GER): G-BA; 2010. [Zugriff: 13.10.2016]. URL: https://www.g-ba.de/downloads/40-268-1232/2010-05-20-AMR-VI-Gemcitabin_ZD.pdf.

10. **Gong DD, Man CF, Xu J, Fan Y.** Fulvestrant 250 mg versus anastrozole 1 mg in the treatment of advanced breast cancer: a meta-analysis of randomized controlled trials. Asian Pac J Cancer Prev 2014;15(5):2095-2100.

11. **Graham J, Pitz M, Gordon V, Grenier D, Amir E, Niraula S.** Clinical predictors of benefit from fulvestrant in advanced breast cancer: A Meta-analysis of randomized controlled trials. Cancer Treat Rev 2016;45:1-6.

12. **Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften).** Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 3.0 [online]. AWMF-Register-Nr. 032-045OL. Berlin (GER): Deutsche Krebsgesellschaft; 2012. [Zugriff: 13.10.2016]. URL: http://leitlinienprogramm-onkologie.de/uploads/tx_sbdownloader/S3-Brustkrebs-v2012-OL-Langversion.pdf.

13. **Mao C, Yang ZY, He BF, Liu S, Zhou JH, Luo RC, et al.** Toremifene versus tamoxifen for advanced breast cancer. Cochrane Database of Systematic Reviews [online]. 2012; (7):Cd008926. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008926.pub2/abstract.

14. **National Comprehensive Cancer Network (NCCN).** NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 2.2016 [online]. Fort Washington (USA): NCCN; 2016. [Zugriff: 13.10.2016]. URL: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

15. **National Institute for Health and Care Excellence (NICE).** Advanced breast cancer: diagnosis and treatment (updated and addendum 2014) [online]. London (GBR): 2014. [Zugriff: 13.10.2016]. (NICE Clinical guideline; Band 81). URL: http://www.nice.org.uk/guidance/cg81/resources/advanced-breast-cancer-diagnosis-and-treatment-975683850181.

16. **National Institute for Health and Care Excellence (NICE).** Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer [online]. London (GBR): NICE; 2011. [Zugriff: 13.10.2016]. (NICE Technology appraisal guidance; Band 214). URL: http://www.nice.org.uk/guidance/ta214/resources/bevacizumab-in-combination-with-a-taxane-for-the-firstline-treatment-of-metastatic-breast-cancer-82600249661125.

17. **National Institute for Health and Care Excellence (NICE).** Eribulin for the treatment of locally advanced or metastatic breast cancer [online]. London (GBR): NICE; 2012. [Zugriff: 13.10.2016]. (NICE Technology appraisal guidance; Band 250). URL: http://www.nice.org.uk/guidance/ta250/resources/eribulin-for-the-treatment-of-locally-advanced-or-metastatic-breast-cancer-82600484807365.

18. **National Institute for Health and Care Excellence (NICE).** Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy [online]. London (GBR): NICE; 2013. [Zugriff: 13.10.2016]. (NICE Technology appraisal guidance; Band 295). URL: http://www.nice.org.uk/guidance/ta295/resources/everolimus-in-combination-with-exemestane-for-treating-advanced-her2negative-hormonereceptorpositive-breast-cancer-after-endocrine-therapy-82600735070149.

19. **National Institute for Health and Care Excellence (NICE).** Fulvestrant for the treatment of locally advanced or metastatic breast cancer [online]. London (GBR): NICE;

2011. [Zugriff: 13.10.2016]. (NICE Technology appraisal guidance; Band 239). URL: http://www.nice.org.uk/guidance/ta239/resources/fulvestrant-for-the-treatment-of-locally-advanced-or-metastatic-breast-cancer-82600378991557.

20. **Partridge AH, Rumble RB, Carey LA, Come SE, Davidson NE, Di Leo A, et al.** Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2014;32(29):3307-3329.

21. **Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, et al.** Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline. J Clin Oncol 2016.

22. **Telford C, Jones N, Livings C, Batson S.** Network Meta-Analysis Comparing Overall Survival for Fulvestrant 500 mg Versus Alternative Therapies for Treatment of Postmenopausal, Estrogen Receptor-Positive Advanced Breast Cancer Following Failure on Prior Endocrine Therapy. Clin Breast Cancer 2016;16(3):188-195.

23. **Wagner AD, Thomssen C, Haerting J, Unverzagt S.** Vascular-endothelial-growth-factor (VEGF) targeting therapies for endocrine refractory or resistant metastatic breast cancer. Cochrane Database of Systematic Reviews [online]. 2012; (7):Cd008941. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008941.pub2/abstract.

24. **Wildiers H, Stordeur S, Vlayen J, Scholten R, Wetering F, Bourgain C, et al.** Breast cancer in women: diagnosis, treatment and follow-up [online]. Belgian Health Care Knowledge Centre (KCE); 2013. [Zugriff: 13.10.2016]. (KCE Report; Band 143). URL: http://kce.fgov.be/sites/default/files/page_documents/KCE_143_Breast_cancer_0.pdf.

Anhang

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

Study	Treatment	N	Centers	Follow-up
Di Leo et al. [14]: CONFIRM (phase III)	Faslodex 500 mg Faslodex 250 mg	362 374	128 centers in 17 countries	Maximum FU 48 mo
Ohno et al. [15]: FINDER1 (phase II)	Faslodex 250 mg* Faslodex 250 mg loading dose† Faslodex 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)	Faslodex 250 mg* Faslodex 250 mg loading dose† Faslodex 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)	Faslodex 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.

Abbildung 1: aus Cope S, et al. 2013

Gemeinsamer Bundesausschuss

Studiencharakteristika aus Graham J et al., 2016

Table 1
Study characteristics.

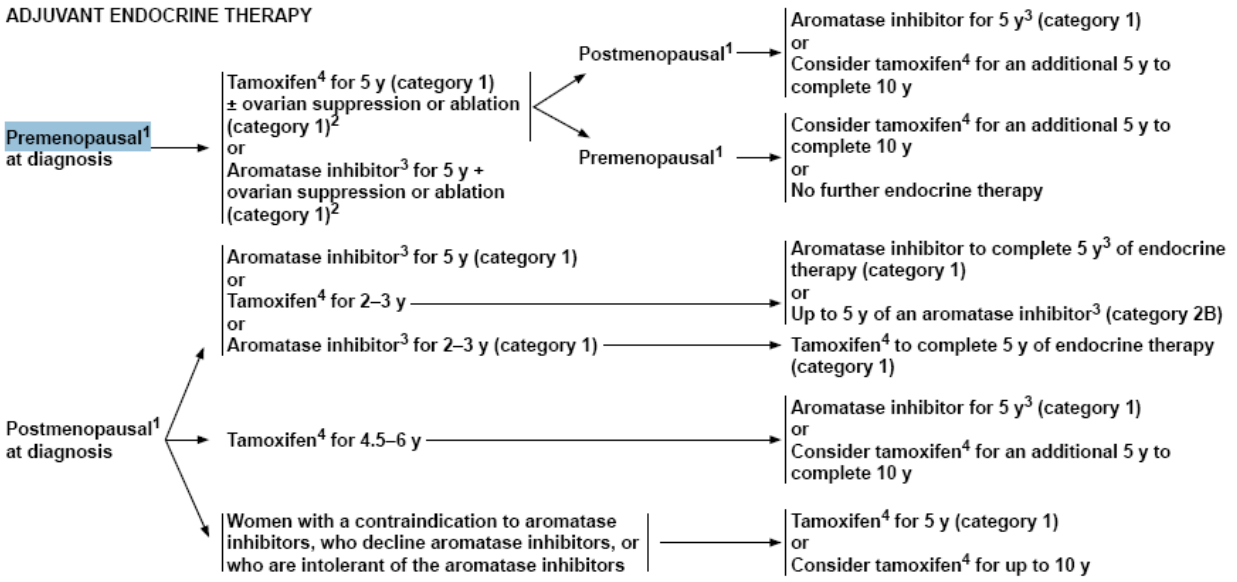
Study	Treatment group	Control group	*N* (Experimental)	*N* (Control)	Efficacy endpoint	Line of therapy	Age range (years)
Chia et al. 2008 [5]	Fulvestrant	Exemestane	351	342	TTP	1st/2nd/3rd	32–91
Johnston et al. 2013 [6]	Fulvestrant	Exemestane	231	249	PFS	1st/2nd	57–75
Bergh et al. 2012 [4]	Fulvestrant + anastrozole	Anastrozole	258	256	TTP	1st	33–90
Mehta et al. 2012 [10]	Fulvestrant + anastrozole	Anastrozole	350	345	PFS	1st	27–92

Subgruppenanalyse aus Graham J et al., 2016

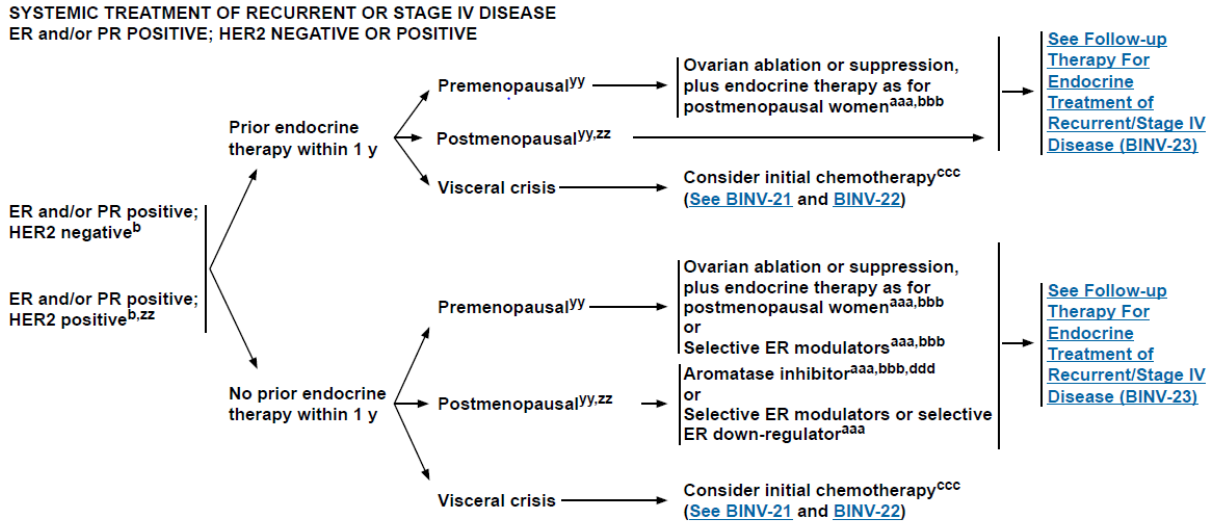
Table 3
Pooled analysis of subgroups reporting PFS/TTP from RCTs comparing fulvestrant containing regimen to an aromatase inhibitor or tamoxifen.

Sub-groups		Studies	Sample size	HR [95% CI]	*p* (subgroup difference)
Age	>65	4	2382	0.86 [0.75,0.99]	0.32
	<65			0.96 [0.81,1.15]	
Visceral Metastasis	Yes	4	2382	0.85 [0.77,0.95]	0.05
	No			1.02 [0.88,1.18]	
Time to Recurrence	>5 years	2	1174	0.80 [0.66,0.96]	0.02
	<5 years			1.09 [0.91,1.31]	
HER2	Overexpressed	2	1174	0.36 [0.13,1.02]	0.09
	Normal			0.92 [0.70,1.19]	

Algorithmus aus: NCCN Guidelines Version 2.2016 [14]



[1] See Definition of Menopause (BINV-M).
[2] Aromatase inhibitor or tamoxifen for 5 y plus ovarian suppression should be considered, based on SOFT and TEXT clinical trial outcomes, for premenopausal women at higher risk of recurrence (ie, young age, high-grade tumor, lymph node involvement, Pagani, NEJM 2014, Prudence, NEJM 2014).Survival data still pending.
[3] The panel believes the three selective aromatase inhibitors (ie, anastrozole, letrozole, exemestane) have shown similar anti-tumor efficacy and toxicity profiles in randomized studies in the adjuvant and preoperative settings. The optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.
[4] Some SSRIs like fluoxetine and paroxetine decrease the formation of endoxifen, 4-OH tamoxifen, and active metabolites of tamoxifen, and may impact its efficacy. Caution is advised about coadministration of these drugs with tamoxifen. However, citalopram and venlafaxine appear to have minimal impact on tamoxifen metabolism. At this time, based on current data the panel recommends against CYP2D6 gene testing for women being considered for tamoxifen therapy. Coadministration of strong inhibitors of CYP2D6 should be used with caution.



[b] See Principles of HER2 Testing (BINV-A).
[yy] See Definition of Menopause (BINV-M).
[zz] Limited studies document a progression-free survival advantage of adding trastuzumab or lapatinib to aromatase inhibition in postmenopausal patients with ER-positive, HER2-positive disease. However, no overall survival advantage has been demonstrated.
[aaa] See Endocrine Therapy for Recurrent or Stage IV Disease (BINV-N).
[bbb] It is unclear that women presenting at time of initial diagnosis with metastatic disease will benefit from the performance of palliative local breast surgery and/or radiation therapy. Generally this palliative local therapy should be considered only after response to initial systemic therapy.
[ccc] See Chemotherapy Regimens for Recurrent or Metastatic Breast Cancer (BINV-O).
[ddd] 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.

[BINV-20]

Ergänzung: aus dem **Supplement** zu **Wildiers H et al., 2013**

5.6.1. *Endocrine therapy*

Table 49 – Use of aromatase inhibitors in pre-menopausal women

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[221]	July 2008	Premenopausal women with ER-positive advanced breast cancer	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. Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression.	A moderate quality systematic review (Klijn et al. 2001) and one RCT (Klijn et al. 2000) reported a survival benefit for combination therapy over single agents in pre-menopausal patients with metastatic breast cancer. GDG consensus for peri-menopausal women.		Moderate
NICE 2009[221]	July 2008	Men with ER-positive advanced breast cancer.	Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer.	Two small retrospective case series (Ribeiro 1983 and Patterson et al. 1980) and GDG consensus		Low
CECOG 2007[271]	May 2005	Premenopausal women	Tamoxifen, ovarian function suppression, or a combination of both are suitable options for endocrine treatment of premenopausal patients.	Three small randomized studies have compared the combination of tamoxifen and LHRH agonist versus LHRH agonist alone (Boccardo et al. 1994; Jonat et al. 1995; Klijn et al. 2000). A small meta-analysis combined these data and suggested that combination of LH-RH agonist and tamoxifen may be superior to LH-RH agonist alone in all analyzed efficacy parameters (OS, PFS, RR) (Klijn et al. 2001).		Moderate

				At present, there are insufficient data on the use of aromatase inhibitors or fulvestrant in premenopausal patients. If aromatase inhibitors are considered, they definitely should be given in conjunction with some form of ovarian function suppression.		

Table 50 – Use of aromatase inhibitors in post-menopausal women

CPG ID	Search date	Population	Recommendation	Supporting evidence	Comments	Level of evidence
NICE 2009[221]		Post-menopausal women with MBC	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.	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).		High
CECOG 2007[271]	May 2005	postmenopausal patients with hormone receptor-positive MBC	Based upon the more favorable toxicity profile, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) is recommended as first-line treatment for postmenopausal patients with hormone receptor-positive MBC, but tamoxifen remains a valuable option.	First-line endocrine therapy anastrozole versus tamoxifen Two randomized phase III trials compared anastrozole with tamoxifen (Bonneterre et al. 2000, 2001; Nabholtz 2000, 2003). →TTP : no difference between anastrozole and tamoxifen letrozole versus tamoxifen A randomized phase III trial compared letrozole to tamoxifen (Mouridsen et al. 2001, 2003). →TTP and ORR : better results with letrozole →OS : no difference between letrozole and tamoxifen exemestane versus tamoxifen A randomized phase III trial compared exemestane and tamoxifen (Paridaens et al. 2003) →TTP and ORR: better results with exemestane Fulvestrant versus tamoxifen A randomized phase III study compared fulvestrant and tamoxifen (Howell et al. 2004) → ORR and TTP : no difference between fulvestrant and tamoxifen → OS: better results with tamoxifen		High