Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2018-B-255 Talazoparib

Stand: Mai 2019

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

Talazoparib
[zur Behandlung des HER2-negativen lokal fortgeschrittenen oder metastasierten Brustkrebses]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht "II. Zugelassene Arzneimittel im Anwendungsgebiet"*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** - Eribulin: Beschluss vom 22. Januar 2015 **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Wirkstoffe, die in zulassungs-überschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind:** - Gemcitabin in der Monotherapie beim Mammakarzinom der Frau **Richtlinie Methoden Krankenhausbehandlung § 4 Ausgeschlossene Methoden:** - Protonentherapie bei Hirnmetastasen - 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:	
Talazoparib N.N. N.N.	Zugelassenes Anwendungsgebiet: „Talazoparib wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom aufweisen. Die Patienten sollten zuvor mit einem Anthrazyklin und/ oder einem Taxan im (neo)adjuvanten, lokal fortgeschrittenen oder metastasierten Setting behandelt worden sein, es sei denn, sie waren für diese Behandlungen nicht geeignet. Patienten mit Hormonrezeptor (HR)-positivem Brustkrebs sollten außerdem bereits eine endokrin-basierte Therapie erhalten haben oder für diese als nicht geeignet eingestuft sein.“
Monoklonale Antikörper	
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Paclitaxel zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet. Zu weiteren Informationen wie auch zum humanen epidermalen Wachstumsfaktor-Rezeptor 2 (HER2)- Status siehe Abschnitt 5.1. Bevacizumab wird in Kombination mit Capecitabin zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet, bei denen eine Behandlung mit anderen Chemotherapie-Optionen, einschließlich Taxanen oder Anthracyclinen, als nicht geeignet angesehen wird. Patienten, die innerhalb der letzten 12 Monate Taxan- und Anthracyclin-haltige Therapieregime im Rahmen der adjuvanten Behandlung erhalten haben, sollten nicht mit Avastin in Kombination mit Capecitabin therapiert werden. Zu weiteren Informationen wie auch zum HER2-Status siehe Abschnitt 5.1.
Zytostatika	
5-Fluorouracil L01BC02 5-FU medac	- Fortgeschrittenes und/oder metastasiertes Mammakarzinom
Capecitabin L01BC06 Xeloda®	Xeloda wird angewendet: - in Kombination mit Docetaxel (siehe Abschnitt 5.1) zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom nach Versagen einer zytotoxischen Chemotherapie. Eine frühere Behandlung sollte ein Anthracyclin enthalten haben. - als Monotherapie zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom, bei denen eine Therapie mit Taxanen und Anthracyclinen versagt hat oder eine weitere Anthracyclinbehandlung nicht angezeigt ist.

Cyclophos-phamid L01AA01 Endoxan	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: Endoxan Pulver zur Herstellung einer Injektionslösung: - Palliative Therapie des fortgeschrittenen Mammakarzinoms Endoxan überzogene Tabletten: - Palliative Therapie des metastasierten Mammakarzinoms
Docetaxel L01CD02 TAXOTERE®	<u>Brustkrebs</u> TAXOTERE ist in Kombination mit Doxorubicin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs ohne vorausgegangene Chemotherapie angezeigt. Die TAXOTERE-Monotherapie ist zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die vorausgegangene Chemotherapie sollte ein Anthracyclin oder Alkylanzien enthalten haben. TAXOTERE ist in Kombination mit Capecitabin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die frühere Behandlung sollte ein Anthracyclin enthalten haben.
Doxorubicin L01DB01 Doxorubicin-hydrochlorid Teva®	- Mammakarzinom
Doxorubicin (liposomal) L01DB01 Caelyx®	Caelyx ist indiziert: - Als Monotherapie bei Patientinnen mit metastasierendem Mammakarzinom mit erhöhtem kardialen Risiko.
Doxorubicin (liposomal) L01DB01 Myocet®	Myocet in Kombination mit Cyclophosphamid wird angewendet bei der First-line -Behandlung von metastasiertem Brustkrebs bei erwachsenen Frauen.
Epirubicin L01DB03 Riboepi®	- Mammakarzinom

Eribulin L01XX41 HALAVEN®	HALAVEN ist indiziert für die Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Brustkrebs, bei denen nach mindestens einer Chemotherapie zur Behandlung einer fortgeschrittenen Brustkrebserkrankung eine weitere Progression eingetreten ist (siehe Abschnitt 5.1). Die Vortherapien sollen ein Anthrazyklin und ein Taxan entweder als adjuvante Therapie oder im Rahmen der metastasierten Situation enthalten haben, es sei denn, diese Behandlungen waren ungeeignet für den Patienten.
Gemcitabin L01BC05 Gemzar®	Gemcitabin ist angezeigt in Kombination mit Paclitaxel für die Behandlung von Patientinnen mit nicht operablem, lokal rezidiviertem oder metastasiertem Brustkrebs, bei denen es nach einer adjuvanten/neoadjuvanten Chemotherapie zu einem Rezidiv kam. Die vorausgegangene Chemotherapie sollte ein Anthracyclin enthalten haben, sofern dieses nicht klinisch kontraindiziert war.
Ifosfamid L01AA06 Holoxan®	Mammakarzinom Zur Palliativtherapie bei fortgeschrittenen, therapierefraktären bzw. rezidivierenden Mammakarzinomen.
Methotrexat L01BA01 Methotrexat-GRY®	Methotrexat in niedriger (Einzeldosis < 100 mg/m² Körperoberfläche [KOF]) und mittelhoher Dosierung (Einzeldosis 100-1.000 mg/m2 KOF) ist angezeigt bei folgenden onkologischen Erkrankungen: <u>Mammakarzinome</u> - in Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.
Mitomycin L01DC03 Mitomycin medac	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: - fortgeschrittenes und/oder metastasierendes Mammakarzinom
Mitoxantron L01DB07 Onkotrone	- Onkotrone ist indiziert zur Behandlung des metastasierten Mammakarzinoms.
Nab-Paclitaxel L01CD01 Abraxane®	Abraxane-Monotherapie ist indiziert für die Behandlung des metastasierten Mammakarzinoms bei erwachsenen Patienten, bei denen die Erstlinientherapie der metastasierten Erkrankung fehlgeschlagen ist und für die eine standardmäßige Anthracyclin-enthaltende Therapie nicht angezeigt ist (siehe Abschnitt 4.4).
Paclitaxel L01CD01 Paclitaxel-GRY®	Mammakarzinom Paclitaxel-GRY® ist zur Anfangsbehandlung von lokal fortgeschrittenem oder metastasierendem Mammakarzinom angezeigt, entweder in Kombination mit einem Anthracyclin bei Patientinnen, bei denen eine Anthracyclintherapie in Betracht kommt oder in Kombination mit Trastuzumab bei Patientinnen, die den humanen epidermalen Wachstumsfaktor-Rezeptor 2 (HER-2) – ermittelt durch immunhistochemische Methoden – mit Grad 3+ überexprimieren und für die eine Therapie mit Anthracyclinen nicht geeignet ist (siehe Abschnitte 4.4 und 5.1). Als Monotherapie ist Paclitaxel-GRY® indiziert zur Behandlung des metastasierenden Mammakarzinoms bei Patientinnen, bei denen eine anthracyclinhaltige Standardtherapie erfolglos war oder nicht geeignet ist.

Vinblastin L01CA01 Vinblastinsulfat Teva®	Vinblastinsulfat wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: - rezidivierendes oder metastasierendes Mammakarzinom (wenn eine Behandlung mit Anthracyclinen nicht erfolgreich war)
Vincristin L01CA02 Vincristinsulfat -TEVA®	Vincristinsulfat-TEVA® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom, […]
Vinorelbin L01CA04 Navelbine®	Behandlung - als Monotherapie bei Patientinnen mit metastasierendem Brustkrebs (Stadium 4), bei denen eine Behandlung mit einer anthrazyklin- und taxanhaltigen Chemotherapie versagt hat oder nicht angezeigt ist.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-255 (Talazoparib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	17. Januar 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

5´-FU	5'-fluorouracil
ABC	Advanced Breast Cancer
ADR	Adverse drug reactions
ADs	adverse events
AI	aromatase inhibitors
AWG	Anwendungsgebiet
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BEV	Bevacizumab
CAP	capecitabine
CBR	Clinical benefit rate
CDK	cyclin-dependent kinase
CR	complete response CR
CR	Complete response
CT	Chemotherapy
DAHTA	DAHTA Datenbank
DCR	Disease Control Rate
DOC	docetaxel
DTX	Docetaxel
ECOG	Eastern Cooperative Oncology Group
ER	Estrogene rezeptor
G-BA	Gemeinsamer Bundesausschuss
GEM	gemcitabine
GIN	Guidelines International Network
GoR	Grade of Recommendations
HDAC	Histone deacetylase
HER2	Human epidermal growth factor receptor 2
HR	Hormonrezeptor
HR	Hazard Ratio

IHC	Immunhistochemie
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ISH	In-situ-Hybridisierung
KI	Konfidenzintervall
LHRH	Luteinizing Hormone-Releasing Hormone
LoE	Level of Evidence
MBC	Metastatic breast cancer
MBC	Metastatic breast cancer
mTOR	mechanistic Target of Rapamycin
n.s.	Not significant
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
OR	Odds Ratio
ORR	Objective response rate
ORR	Overall response rate
OS	Overall survival
PAC	paclitaxel
PAL	Palbociclib
PLD	pegylated liposomal doxorubicin
PFS	Progression free survival
PgR	progesterone receptor
PR	Partial response
RR	Relatives Risiko
SD	Stable disease
SERD	Selective estrogen receptor degrader
SERM	Selective estrogen receptor modulators
SIGN	Scottish Intercollegiate Guidelines Network
TKI	Tyrosine kinase inhibitors

TRIP	Turn Research into Practice Database
TRZ	trastuzumab
TT	targeted therapies
TTF	Time to treatment failure
TTP	Time to progression
VEGF	Vascular Endothelial Growth Factor
VIN	vinorelbine
WHO	World Health Organization

1 Indikation

zur Behandlung von erwachsenen Patienten mit humanem epidermalen Wachstums-faktor-Rezeptor-2 (HER2)-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs, für die eine Chemotherapie angezeigt ist.

[Hinweis: Für das vorliegende Anwendungsgebiet wird davon ausgegangen, dass für die Patienten eine alleinige endokrin-basierte Therapie nicht mehr angezeigt ist und eine Indikation für eine Chemotherapie besteht.]

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Mammakarzinom* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 18.07.2017 durchgeführt, die Folgerecherchen am 20.04.2018 und am 30.11.2018. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherchen übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 3683 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 20 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

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3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2015 [6].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 22. Januar 2015 – Eribulin.

Anwendungsgebiet

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.]

Vergleichstherapie

Patientinnen, die nicht mehr mit Taxanen oder Anthrazyklinen behandelt werden können:

- patientenindividuell bestimmte Chemotherapie unter Verwendung der Wirkstoffe als Monotherapie mit Capecitabin, Vinorelbin

Patientinnen, die für eine erneute Anthrazyklin- oder Taxan-haltige Behandlung infrage kommen:

- patientenindividuell bestimmte Chemotherapie mit einer erneuten Anthrazyklin- oder Taxan-haltigen Therapie

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:

- Lapatinib in Kombination mit Capecitabin oder Lapatinib in Kombination mit Trastuzumab

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Patientinnen, die nicht mehr mit Taxanen oder Anthrazyklinen behandelt werden können

- gegenüber einer Monotherapie mit Capecitabin, Vinorelbin: Anhaltspunkt für einen beträchtlichen Zusatznutzen.

Patientinnen, die für eine erneute Anthrazyklin- oder Taxan-haltige Behandlung infrage kommen

- gegenüber einer erneuten Anthrazyklin- oder Taxan-haltigen Therapie: Ein Zusatznutzen ist nicht belegt.

Patientinnen mit HER2-positivem Brustkrebs, für die eine Anti-HER2-Therapie angezeigt ist:

- gegenüber Lapatinib in Kombination mit Capecitabin oder Lapatinib in Kombination mit Trastuzumab: Ein Zusatznutzen gilt als nicht belegt.

G-BA, 2017 [5].

Richtlinie des Gemeinsamen Bundesausschusses zur Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung): in der Fassung vom 21. März 2006; veröffentlicht im Bundesanzeiger 2006 (S. 4 466); in Kraft getreten am 01. April 2006; zuletzt geändert am 15. Juni 2017; veröffentlicht im Bundesanzeiger (BAnz AT 28.08.2017 B2); in Kraft getreten am 29. August 2017.

§ 4 Ausgeschlossene Methoden

(1) Im Rahmen der Krankenhausbehandlung sind folgende Methoden von der Erbringung zu Lasten der gesetzlichen Krankenkassen ausgeschlossen, wobei die Durchführung klinischer Studien hiervon unberührt bleibt:

- **3 Protonentherapie**
  - 3.1 Protonentherapie bei Hirnmetastasen
  - 3.5 Protonentherapie beim Mammakarzinom

G-BA, 2017 [4].

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

Fazit

1.4.6.2 Lokal fortgeschrittener Brustkrebs

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

1.6.1.1 Therapie des Lokalrezidivs

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

Bei lokoregionärem Rezidiv nach Mastektomie sollte eine postoperative Bestrahlung durchgeführt werden, sofern es auf Grund der bisherigen Strahlenbelastung vertretbar ist. Darüber hinaus soll ergänzend die Notwendigkeit und Möglichkeit zusätzlicher Behandlungen

(systemische endokrine und/oder chemotherapeutische Behandlungsverfahren) geprüft werden.

1.6.1.2 Therapie bei metastasierten Erkrankungen

Bei nachgewiesenen Fernmetastasen steht die Lebensqualität der betroffenen Patientin im Vordergrund der therapeutischen Maßnahmen. Diese haben sich darauf auszurichten, eine Lebensverlängerung unter möglichst langem Erhalt der körperlichen Leistungsfähigkeit, einer akzeptablen Lebensqualität und Linderung tumorbedingter Beschwerden zu erreichen. Die individualisierte Therapiestrategie hat die krankheitsspezifischen Risikofaktoren (viszerale Metastasierung, Knochenmetastasierung, Hirnmetastasierung) sowie die persönliche Situation der Patientin zu beachten. Zur Therapie einer Fernmetastasierung kommen in Abhängigkeit von der individuellen Befundkonstellation medikamentöse, strahlentherapeutische und operative Maßnahmen allein oder in Kombination zum Einsatz.

Eine endokrine Therapie ist bei positivem Hormonrezeptorstatus zu empfehlen.

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

Eine Therapie mit Bisphosphonaten ist bei Patientinnen mit Knochenmetastasen indiziert. Bei Schmerzen, Frakturgefahr oder drohenden bzw. bereits bestehenden neurologischen Ausfällen in Folge von Knochenmetastasen kann zusätzlich eine lokale Therapie (Strahlentherapie, Operation) indiziert sein.

Bei standardisierter immunhistologisch oder molekularbiologisch geprüfter Positivität für HER2/neu besteht die Indikation einer zielgerichteten Therapie gegen HER2/neu.

Bei der Feststellung von Hirnmetastasen ist eine Strahlentherapie indiziert. Eine stereotaktisch geführte Strahlentherapie wird bei einer limitierten Hirnmetastasierung in Ergänzung zur Ganzhirnbestrahlung empfohlen. Bei solitärer Hirnmetastase soll eine Metastasektomie erwogen werden.

Das Ansprechen der therapeutischen Verfahren muss in angemessenen Abständen kontrolliert und die geeigneten therapeutischen Konsequenzen müssen ergriffen werden, um im Hinblick auf die oben genannten Therapieziele das Optimum erreichen zu können.

G-BA, 2010 [3].

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

Fazit / Ausmaß des Zusatznutzens / Ergebnis

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

3.2 Cochrane Reviews

Es wurden eine relevanten Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Puglisi F et al., 2016 [15]

Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review

Fragestellung

to identify and appraise overall survival (OS), progression-free survival (PFS), time to progression (TTP) and Grade ≥ 3 adverse event evidence for single-agent chemotherapy in this setting.

Methodik

Population:

- Patients to receive single-agent chemotherapy as a second-line treatment for HER2-negative advanced or metastatic breast cancer ('secondline' was defined as patients who had received one prior line of chemotherapy treatment in the advanced or metastatic setting)

Intervention/Komparator:

- The single-agent comparators for the treatment of MBC included in the SR were: taxanes (paclitaxel, nab-paclitaxel, docetaxel), vinca alkaloids (vinorelbine, vinblastine, vincristine), platinum-based treatments (cisplatin, carboplatin), anthracyclines (doxorubicin, pegylated liposomal doxorubicin [PLD], epirubicin) and other monotherapy (capecitabine, gemcitabine, eribulin, melphelan or cyclophosphamide) vs. any comparator

Endpunkte:

- Overall survival (OS), progression free survival (PFS), and time to progression (TTP). Data for QoL and other patient-reported outcomes were also sought.
- The following toxicity outcomes were included: withdrawal from treatment due to toxicity, haematological adverse events (AEs), non-haematological AEs, Grade three and four AEs, and mortality.

Recherche/Suchzeitraum:

- The original SR searches were run in the electronic databases of MEDLINE, EMBASE and The Cochrane Library on 17th September 2012. A subsequent update search in these databases was conducted on 30th October 2013. A further update was performed in PubMed for the period 30th October 2013 to 14th November 2014.

Qualitätsbewertung der Studien:

- Quality appraisal of the elements of selection, attrition, detection, and performance bias was performed in accordance with the NICE Guidelines Manual 2009.

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 53 RCTs were included, of which 14 reported data specifically for second- and/or later-line treatment within the metastatic setting.

Charakteristika der Population:

- Of the 14 second- and/or later-line papers, five reported data for a purely second-line patient population, three reported data from mixed-line treatment but provided results for the second-line subgroup separately; three had unclear second-line status (i.e. it was unclear whether the previous therapy had been given in the adjuvant or metastatic setting), two reported data from second- or later-line patients, and one reported data from a second- or later line subgroup separately.
- Only three trials enrolled confirmed HER2-negative patients specifically. Papadimitriou et al. enrolled unselected patients reporting that 21–24% were HER2+, 29–34% HER2-negative, and 34–42% of unknown HER2 status. Palmieri et al. also enrolled unselected patients but did not report their HER2 status. The other nine trials did not report HER2 status.

Qualität der Studien:

- Of the 14 RCTs, 13 were full papers and so could be assessed for quality. Seven reported efficacy data on an intention-to-treat basis, randomisation was carried out appropriately in five, but concealment of treatment allocation was unclear in most trials. Only one trial was double-blinded and almost all trials did not have blinded outcome assessors. In terms of the distribution of patient characteristics between treatment groups, slight imbalances in potential prognostic factors were noted in six trials. Few trials reported confidence intervals around point estimates and only three confirmed HER2-negative status at enrolment. No trial assessed or commented on discordant HER2 status between the primary tumour and metastases.

Studienergebnisse:

- Overall survival in second- and later-line setting
  - Only one trial demonstrated a statistically significant difference in OS in the second- and later-line setting: nab-paclitaxel demonstrated significantly longer median OS compared with standard paclitaxel 175 mg/m2 every 3 weeks (q3w) (13.0 vs. 10.7 months, respectively; hazard ratio [HR] 0.73, p = 0.024) in a large (n = 268) phase III multinational trial performed in USA/Canada, UK and Russia/Ukraine.
- Progression-free survival in second- and later-line setting
  - Median PFS was reported in four trials. Three trials demonstrated significantly longer PFS: capecitabine + sorafenib (6.4 months) vs. capecitabine (4.1 months), HR 0.58 (95% CI: 0.41, 0.81), p = 0.001; capecitabine + low dose DTX (10.5 months) vs. DTX monotherapy before having sequential capecitabine (9.8 months), HR 0.62 (95% CI: 0.40, 0.97), p = 0.0342; bevacizumab + chemotherapy (6.3 months, 95% CI: 5.4, 7.2) vs. single-agent treatment of physician's choice (TPC) (approx. 60% capecitabine) (4.2 months, 95% CI: 3.9, 4.7), HR 0.75 (95% CI: 0.61, 0.93), p = 0.0068.

  - In Keller et al. pegylated liposomal doxorubicin showed no benefit over control therapy of either vinorelbine or mitomycin C + vinblastine (PFS 2.9 and 2.5 months, respectively; HR 1.26 (95% CI: 0.98, 1.62); p = 0.11.

- Time to progression
  - Of seven trials reporting TTP, three showed a significantly longer TTP: 3-weekly paclitaxel showed benefit over mitomycin (median TTP 3.5 vs. 1.6 months, respectively; p = 0.026); capecitabine + sorafenib was superior to capecitabine alone (median TTP 6.8 vs. 4.1 months, respectively; HR 0.56 [95% CI: 0.39, 0.8]; p = 0.001); and nab-paclitaxel was associated with significantly greater TTP vs. standard paclitaxel q3w (median TTP 4.8 vs. 3.7 months, respectively; HR 0.73; p = 0.02).
  - No benefit in terms of TTP was demonstrated for doxorubicin + vinorelbine vs. doxorubicin monotherapy (TTP 4.3 vs. 5.3 months, respectively), for pegylated liposomal doxorubicin vs. vinorelbine or mitomycin C + vinblastine (p > 0.05), for 3-weekly docetaxel vs. vinorelbine (2.4 vs. 1.7 months, respectively; p = 0.82), or for epirubicin vs. epirubicin + vindesine (TTP 6 months in both treatment arms).
- Grade ≥ 3 adverse events, discontinuation and safety summary
  - Of the treatments or treatment combinations showing significant efficacy benefit, the only treatment with a demonstrated better overall safety profile was nab-paclitaxel vs. 3-weekly standard paclitaxel. Although grade III sensory neuropathy occurred more frequently with nab-paclitaxel (10% vs. 2%, respectively), treatment-related grade IV neutropenia was significantly lower on nab-paclitaxel (9% vs. 22%, p < 0.001), there were no grade III/IV hypersensitivity reactions with nab-paclitaxel (despite being no premedication in this arm) whereas there were such reactions with standard paclitaxel (with premedication given), and AE-related discontinuations and dose reductions or delays were low in both arms (3% with nab-paclitaxel and 7% on standard paclitaxel), as was febrile neutropenia (<2% in both arms).
  - Low-dose (60 mg/m2) docetaxel + capecitabine concomitantly, which had shown a PFS benefit vs. docetaxel 70 mg/m2 (prior to sequential capecitabine) showed non-significantly reduced haematological AEs, higher frequency of hand-foot syndrome (7.4% vs. 0%, respectively) and lower frequencies of fatigue and peripheral oedema. Paclitaxel 3qw had shown increased TTP vs. mitomycin, but the safety profile was difficult to interpret because although taxane therapy was associated with more frequent grade III/IV neutropenia & peripheral neuropathy, patients received substantially more courses of PTX than mitomycin. Thrombocytopenia was more common with mitomycin. Sorafenib added to capecitabine had shown increased TTP and PFS, but was associated with a significantly higher frequency of grade III/IV hand-foot syndrome (44% vs. 14% with monotherapy capecitabine) and discontinuation due to AEs (mainly hand-foot syndrome and diarrhoea) were higher also (20% vs. 9%, respectively). The addition of bevacizumab to (mainly) capecitabine was beneficial to PFS, yet grade III/IV AEs were more common with the combination treatment, mainly due to higher incidences of grade III hypertension and proteinuria. Discontinuation was also higher with the combination.

Anmerkung/Fazit der Autoren

There are few RCTs conducted specifically in the second-line HER2-negative MBC setting. Nab-paclitaxel was the only single agent that demonstrated a survival advantage at the

second-line and beyond. Few treatment options provide clinical benefit without adversely influencing tolerability. Given that MBC is an incurable disease and that an equally important aim of treatment at this stage is to enhance QoL and enable patients to be at home with their families, it is vital that trial investigators and clinicians set standards for the design and conduct of clinical trials with this aim in mind, with patients enrolled according to the treatment line received within the metastatic setting, with sufficient sample size to enable outcomes to be estimated with greater precision, with HER2-negative status and any discordant status established, a non-invasive method that has recently been tested in phase I, and with PROs recorded.

Beith J et al., 2016 [1].

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

Fragestellung

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

Methodik

Population:

- women with hormone receptor positive, HER2 negative metastatic breast cancer

Intervention/ Komperator (exclusion of adjuvant therapy):

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

Endpunkt:

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

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

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

Ergebnisse

Anzahl eingeschlossener Studien:

- 32 Studien (n= 10.405 Patienten)

Charakteristika der Population:

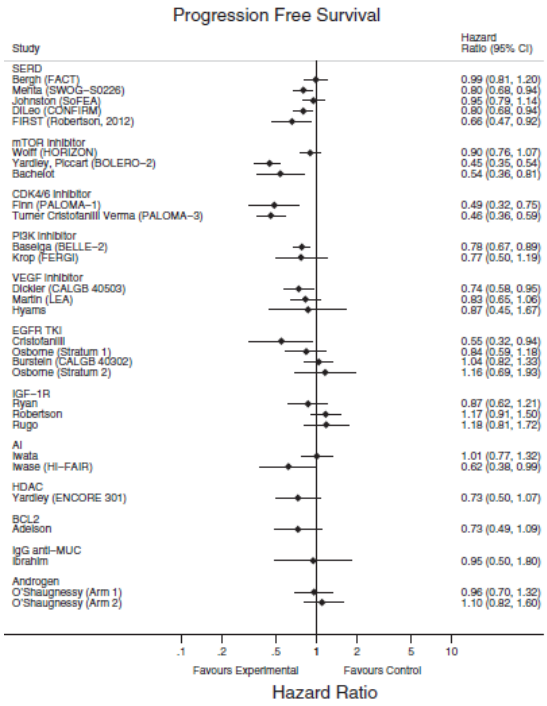
- 555 (5%) had HER2 positive metastatic breast cancer.
- Interventions: addition of a trial agent to standard treatment (n=24), optimization strategies (n=8)
- 12 Studien=First-line; 5 Studien= First- oder Second-line; 9 Studien= Second-line und später; 6 Studien ohne nähere Informationen
- The majority (n = 21) of the studies were in endocrine resistant settings, with a further 10 studies with a mixed population of women with endocrine resistant or sensitive tumors

Qualität der Studien:

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

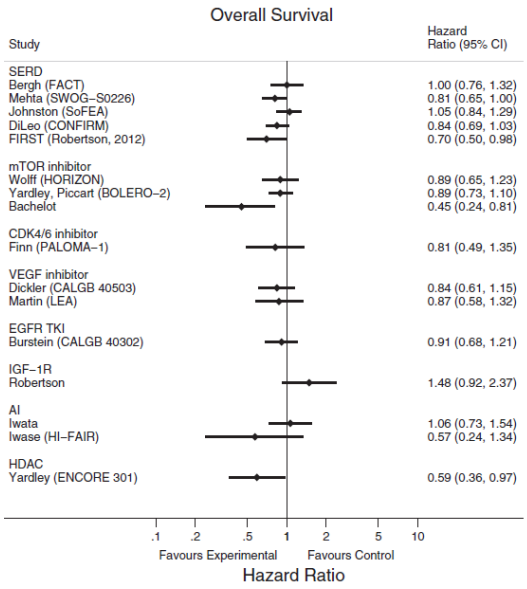
Studienergebnisse

- PFS



- greatest difference in PFS between arms was seen with the addition of a CDK4/6 inhibitor to either an AI or a SERD (HR between 0.36 and 0.75).
- Addition of treatment with an mTOR inhibitor (HR between 0.35 and 1.07), Pi3K inhibitor (HR between 0.50 and 1.19), SERD (HR between 0.47 and 1.20) and VEGF inhibitors (HR between 0.45 and 1.67) showed significant benefit in PFS in some studies.
- With the exception of one study, no significant PFS improvement was seen with EGFR TKIs and all IGFR inhibitor studies failed to show a benefit.
- Phase 2 data from a study with an HDAC inhibitor and another with a BCL2 inhibitor showed a trend toward benefit (HR 0.73 [95% CI 0.50, 1.07]; HR 0.73 [95% CI 0.49, 1.09], respectively), but this needs to be confirmed in larger ongoing phase III studies.

- Overall survival



- None of the studies included in this review were powered for OS; results were reported for 16 of the 32 studies.
- No significant improvements in OS were reported with SERDs (HR between 0.24 and 1.34) and VEGF inhibitors (HR between 0.58 and 1.32)
- Of the 3 mTOR inhibitor studies with OS results, 1 showed a significant OS advantage (HR 0.45; 95% CI 0.24–0.81) for the combination of an mTOR inhibitor with tamoxifen.
- The results of the phase 2 HDAC study look promising, but need to be confirmed in larger studies.

- Clinical benefit rate
  - relative risk of clinical benefit was not improved in any studies regardless of the class of experimental agent
- Safety
  - Of the 32 studies included in the review, 28 reported toxicity data.
  - Where more than 1 study reported discontinuation rates, they were generally highest with VEGF inhibitors (between 20.5% and 39%), with the LEA study reporting an unexpectedly high rate of toxicity-related deaths (4.2%; n = 8) with the combination of a VEGF inhibitor with endocrine therapy compared to no deaths with endocrine therapy alone, prompting the authors to suggest a possible toxicity interaction between these agents EGFR TKIs (12–20%), mTOR inhibitors (7.5–29%) and SERDs (2–27%) also reported higher discontinuation rates than those seen with AIs (0–6%) and IGF-1R inhibitors (1–12.8%).
  - Stomatitis and hyperglycemia were commonly reported with mTOR inhibitors; pain and fatigue with SERDs; hypertension, diarrhea, proteinuria and dyspnea with VEGF inhibitors; stomatitis and neutropenia with IGFR inhibitors; neutropenia, leukopenia and anemia with CDK4/6 inhibitors; and hyperglycemia, rash and abnormal blood chemistry levels with Pi3K inhibitors.
  - In addition, a study of an IGFR inhibitor in combination with an mTOR inhibitor and an AI was stopped early due to high rates of stomatitis with an overall rate of 68% (22/33 patients) and grade 3 stomatitis in 11 (35%) patients. Dose reduction of the mTOR

inhibitor improved rates of grade 3 stomatitis but rates remained high for grade 1 and 2 stomatitis.

Anmerkung/Fazit der Autoren

PFS benefit has been shown with the addition of a SERD or novel agents targeting CDK4/6,mTOR and Pi3K pathways. If early results can be confirmed by phase 3 studies, the benefits of new combination therapy may lead to significant changes to the way we treat these patients. Phase 3 studies with CDK4/6 inhibitors, Pi3K inhibitors and HDAC inhibitors are currently ongoing.

Kommentare zum Review

- Heterogenes Patientenkollektiv, insbesondere hinsichtlich Therapielinie, keine separate Auswertung nach Therapielinie.
- Funding and Conflict of Interests reported
- Risk of bias –Bewertung nur als Zusammenfassung dargestellt, Verknüpfung der Ergebnisse der Einzelstudien mit dem individuellen Verzerrungsrisiko nicht möglich.

Zheng R et al., 2015 [20].

Role of Taxane and Anthracycline Combination Regimens in the Management of Advanced Breast Cancer.

Fragestellung

This meta-analysis compares the benefits of using a combination of anthracyclines along with taxanes versus using single-agent-based chemotherapeutic regimens in the treatment of MBC.

Methodik

Population:

- patients with advanced breast cancer or metastatic disease

Intervention:

- Combination of taxanes and anthracyclines

Komparator:

- Either an anthracycline or taxane-based treatment regimen.

  Hinweis: Taxanes or anthracyclines were used either alone or in combination as first-line therapy in cases of advanced-stage breast cancer.

Endpunkte:

- The primary endpoint was OS, and secondary endpoints were PFS, TTF, TTP, ORR, DCR, and safety.

Recherche/Suchzeitraum:

- PubMed, Embase, and the Central Registry of Controlled Trials of the Cochrane Library were searched for meeting (ASCO and ESMO) abstracts, and results of selected studies

presented between January 1990 (the time when taxane treatment was first introduced for patients) and January 2014.

Qualitätsbewertung der Studien:

- Selected studies were evaluated for their quality based on the following 4 factors described in the Cochrane Reviewers' Handbook: method of randomization, allocation concealment, blindness, and adequacy of follow-up.

Ergebnisse

Anzahl eingeschlossener Studien:

- Fifteen trials including a total of 3623 patients. Taxane-based combination regimens were evaluated in 6 RCTs involving 949 patients (taxanes combined with capecitabine in 4 RCTs involving 807 patients and taxanes combined with platinum in 2 RCTs involving 415 patients). Anthracycline-based combination regimens were evaluated in 12 RCTs involving 2401 patients (anthracyclines combined with cyclophosphamide in 6 RCTs involving 1776 patients and anthracyclines along with 5-fluorouracil and cyclophosphamide in 3 RCTs involving 625 patients).

Qualität der Studien:

- Six trials received a score of A (low risk of bias), 5 received a score of B (intermediate risk of bias), and 4 were scored as C (high risk of bias).

Studienergebnisse:

- OS:
  - Unfavorable evidence from combined taxane along with anthracycline regimens compared with anthracycline or taxane-based combination regimens originated from the HR analysis in terms of OS (n.s.).
  - A subgroup analysis identified a non statistically significant advantage regarding OS for both taxane along with capecitabine therapy, and taxane along with platinum therapy, whereas the combination of anthracyclines and cyclophosphamide failed to show a significant advantage.
  - However, the subgroup combination of anthracyclines, 5-fluorouracil, and cyclophosphamide revealed a survival trend favoring combination therapy with taxanes and anthracyclines (HR: 0.696; 95% CI: 0.576–0.841).
- PFS/TTF and TTP: Four of the 15 RCTs included in this meta-analysis reported results of a PFS analysis. The TTF analysis in 2 eligible RCTs and TTP analysis in 6 HR analyses showed that:
  - use of combined taxanes and anthracyclines did not yield significantly higher efficacy when compared with combined taxane along with capecitabine therapy in terms of PFS and TTP.
  - Furthermore, combined taxanes and anthracyclines showed lower efficacy when compared to a combination regimen of taxanes along with platinum in terms of TTF.
  - However, the combined regimen of taxanes and anthracyclines showed higher efficacy when compared with a triple combination therapy consisting of anthracyclines, 5-fluorouracil, and cyclophosphamide in terms of TTP (HR for TTP: 0.703; 95% CI: 0.587–0.843).

  - Additionally, the taxanes along with anthracyclines regimen was superior to a combined anthracyclines and cyclophosphamide regimen in terms of TTP (HR for TTP: 0.792; 95% CI: 0.665–0.942), but not PFS and TTF.

- ORR and Toxicity: Results of ORR and toxicity analyses were included in 15 RCTs, and results of DCR analyses were reported in 14 of the 15 eligible RCTs.
  - Analysis revealed that combined taxanes and anthracyclines failed to show higher efficacy when compared with taxane-based therapies in terms of ORR and DCR (OR for DCR: 1.530; 95% CI: 1.300–1.800).
  - However, in a 2-armed study, combined taxanes and anthracyclines showed greater efficacy than an anthracycline-based combination therapy in terms of ORR (OR for ORR: 1.530, 95% CI: 1.300–1.800), but not DCR.
  - When compared with a combined taxanes and anthracyclines group, a taxane-based combination group had significantly fewer adverse events of neutropenia (I–IV), infection/ febrile neutropenia (III–IV), nausea (I–IV), and vomiting (I–IV). An anthracycline-based combination group showed lower incidences of neutropenia (III–IV), infection/febrile neutropenia (III–IV), anorexia (III–IV), stomatitis/mucosal inflammation (I–IV; III–IV), diarrhea (I–IV; III–IV), and sensory neuropathy (I–IV; III–IV). In contrast, a taxane-based combination group showed significantly higher incidences of hand–foot syndrome (I–IV) and diarrhea (III–IV).
  - A subgroup analysis revealed lower incidences of diarrhea (I–IV; III–IV), hand–foot syndrome (I–IV; III–IV), and sensory neuropathy (I–IV) in the taxanes along with capecitabine combination group, but higher incidences of leucopenia (III–IV), neutropenia (I–IV), anemia (I–IV), infection/febrile neutropenia (I–IV), nausea (I–IV), and vomiting (I–IV) in that group. The incidence of neutropenia (I–IV) in the taxanes along with platinum combination group was also higher.
  - The combined anthracyclines along with cyclophosphamide group had significantly higher incidences of nausea (I–IV) and vomiting (I–IV; III–IV), but lower incidences of neutropenia (III–IV), infection/febrile neutropenia (III–IV), anorexia (III–IV), stomatitis/mucosal inflammation (I–IV), diarrhea (I–IV; III–IV), and sensory neuropathy (I–IV; III–IV). The triple combination therapy group (anthracyclines, 5-fluorouracil, and cyclophosphamide) had a significantly lower incidence of infection/febrile neutropenia (III–IV).

Anmerkung/Fazit der Autoren

This meta-analysis was not conducted to modify current clinical practice, but rather to reevaluate current treatment options and make suggestions for future prospective trials. Our statistical results suggest that patients with MBC should be treated with taxane-based combination regimens, and especially with a combination of taxanes and capecitabine. Compared with the patients treated with combined anthracycline with taxane regimens, patients treated with taxanes along with capecitabine realized the same benefits in terms of TTP, OS, ORR, and DCR, but experienced fewer hematological and gastrointestinal toxicities. In the era of nontaxane and nonanthracycline-based combination therapies, novel approaches based on verified preclinical findings, a more rational use of currently available drugs, and an improved method for selecting patients may be needed to address this topic.

Kommentare zum Review

- Keine Angabe zur Vortherapie (z.B. endokriner Therapie) und HR/HER2 Status.

Xu et al., 2016 [18].

Siehe auch Zhang et al. 2016 [19]

A meta-analysis of combination therapy versus single-agent therapy in anthracycline- and taxane-pretreated metastatic breast cancer: results from nine randomized Phase III trials.

Fragestellung

A meta-analysis of Phase III randomized clinical trials (RCTs) comparing the efficacy and toxicity of combination therapy with single-agent therapy in those MBC patients who had been heavily pretreated with anthracyclines and taxanes.

Methodik

Population:

- adults with MBC pretreated with an anthracycline and/or a taxane as adjuvant or palliative treatment

Intervention:

- combination therapy

Komparator:

- single therapy

Endpunkte:

- efficacy and toxicity

Recherche/Suchzeitraum:

- in PubMed, EMBASE, and Cochrane library until 01/08/2015; search for onging trials (ClinicalTrials.gov); screening of references lists, conference proceedings)

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 trials (n= 4641)
- 7 trials with combination chemotherapy vs. single-agent therapy;
- 2 trials with chemotherapy plus targeted therapy (sunitinib or bevacizumab) vs. single-agent therapy.

Qualität der Studien:

- All studies had a Jadad scale of 3.

Studienergebnisse:

- OS

  - Overall: Superiority of combination therapy (HR 0.90 [95% CI 0.84; 0.96])
  - two chemotherapy agents combination vs single-agent therapy: HR 0.87 [94% CI 0.81; 0.94]
  - targeted drug plus chemotherapy vs single drug not significant
- PFS
  - two chemotherapy agents combination v single-agent therapy: HR 0.77 [94% CI 0.70; 084]
  - targeted drug plus chemotherapy vs single drug: HR =0.85 [95% CI 0.74–0.97]
- Safety
  - Concerning the grade 3 or 4 hematological toxicities, leukopenia, anemia, neutropenia, thrombocytopenia, and febrile leukopenia were more frequent in the doublet agents group
  - doublet agents produced significantly increased gastrointestinal toxicities including nausea, stomatitis, and pharyngitis than did single agent, whereas the incidence of diarrhea and anorexia in the doublet agents did not differ from the single agent

Anmerkung/Fazit der Autoren

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

Shin et al., 2018 [16].

Increased risk of adverse drug events secondary to bevacizumab treatment in patients with advanced or metastatic breast cancer: a meta-analysis of randomized controlled trials.

Fragestellung

to assess the overall incidence and risk of common toxicities associated with bevacizumab in patients with advanced or metastatic breast cancer and, secondarily, to descriptively review study results concerning a potential correlation between bevacizumab-induced hypertension and its efficacy for breast cancer treatment.

Methodik

Population:

- patients with advanced or metastatic breast cancer

Intervention/Komparator:

- bevacizumab or placebo/control treatment in addition to concurrent anticancer therapy

Endpunkte:

- incidence of safety endpoints, such as hypertension, proteinuria, and other toxicities commonly associated with bevacizumab

Recherche/Suchzeitraum:

- The Cochrane Library and PubMed were searched, without geographical and language restrictions, for articles published between October 2014 and July 2017.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 RCTs with 6,260 patients
- Of the total patient population included in this assessment, 3,621 were enrolled in the bevacizumab arm and 2,639 were in the alternative therapy arm.
- There were nine Phase III and three Phase II trials.
- Five RCTs were placebo-controlled and double-blinded two other RCTs had placebo as controls and the remainder of the RCTs had active controls.
- Nine RCTs intended to evaluate the therapeutic benefit of the addition of bevacizumab to standard therapy along with treatment-associated adverse events, and three RCTs aimed to investigate the treatment effect of new anticancer agents relative to bevacizumab or placebo when administered in combination with standard chemotherapy

Charakteristika der Population:

- Most patients had baseline Eastern Cooperative Oncology Group (ECOG) performance status of between 0 and 1.
- In 10 trials, participants were predominantly classified as HER2-negative breast cancer (85%–100%) whereas in two trials the percentage of patients with HER2-negative cancer was as low as 8% or unknown.
- The majority of patients in 10 RCTs had hormone receptor-positive breast cancer.
- One trial enrolled only patients with triple-negative breast cancer.

Qualität der Studien:

- Overall, the risk of bias in the included RCTs was considered to be acceptable.

Studienergebnisse:

- Five types of high-grade (Grade 3 or 4) adverse drug events were identified as being correlated with bevacizumab treatment versus alternative treatment with statistical significance:

  hypertension (OR 5.67, 95% CI 3.02–10.65) → For the subgroup analysis, we only included those trials that predominantly enrolled patients with HER2-negative breast cancer (two studies involving HER2-positive cases were excluded) and found that the overall OR and its statistical significance persisted (OR 4.52, 95% CI 2.47–8.29; P,0.00001).

  - Proteinuria (OR 10.09, 95% CI 4.79–21.27) → keine Angaben zu Subgruppe HER2-negative Patienten!
  - Bleeding (OR 3.45, 95% CI 2.25–5.30) → keine Angaben zu Subgruppe HER2-negative Patienten!
  - Cardiac toxicity (OR 2.15, 95% CI 1.29–3.59), and neutropenic fever (OR 1.51, 95% CI 1.15–2.00). → keine Angaben zu Subgruppe HER2-negative Patienten!

- The prognostic value of bevacizumab-induced hypertension for its antitumor efficacy among patients with breast cancer remains controversial, with mixed results presented in the five retrospective studies that were identified from our additional literature search.

→ keine Angaben zu Subgruppe HER2-negative Patienten!

Anmerkung/Fazit der Autoren

The addition of bevacizumab to anticancer therapy was associated with a significant surge in the risk of high-grade adverse events, including hypertension, proteinuria, bleeding, cardiac toxicity, and neutropenic fever, among patients with advanced or metastatic breast cancer. Close monitoring and effective management of treatment-induced toxicities – most importantly, hypertension – is crucial for those patients receiving bevacizumab in order to prevent significant anti-VEGF-induced adverse consequences. Although several retrospective analyses suggested a prognostic importance of elevated blood pressure secondary to bevacizumab therapy, the role of hypertension as a predictive biomarker for its antitumor efficacy remains controversial, and further prospective clinical trials are urgently needed to confirm such a correlation.

Li C et al., 2017 [8].

Optimizing the treatment of bevacizumab as first-line therapy for human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer: an updated meta-analysis of published randomized trials

Fragestellung

to assess the benefits of bevacizumab with chemotherapy and to identify the ideal chemotherapy partner of bevacizumab in the first-line setting for HER2-negative advanced breast cancer patients.

Methodik

Population:

- HER2-negative advanced breast cancer patients

Intervention:

- Bevacizumab with chemotherapy

Komparator:

- chemotherapy alone or combining bevacizumab with different chemotherapy regimens as first-line therapy

Endpunkte:

- PFS, OS, ORR

Recherche/Suchzeitraum:

- PubMed, Web of Science, EMBASE and EBSCO databases from January 2000 to March 2017

Qualitätsbewertung der Studien:

- Publication bias was evaluated using funnel plots and Begg's test. Sensitivity analyses were performed to quantify the impact of individual trials on the overall effect. A two-sided P-value of 0.05 was considered significant. Keine weiteren Angaben zur Qualitätsbewertung der eingeschlossenen Studien.

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 eligible trials with a total of 3,984 patients. Three of these studies were used to evaluate the efficacy of adding bevacizumab to chemotherapy, including 1,558 women who received bevacizumab combined with chemotherapy and 896 women who were administered chemotherapy alone. The other 4 trials were obtained to assess the optimal chemotherapy partner of bevacizumab.

Qualität der Studien:

- Einzige Angabe: ''Considering the quality of the data, we included all the potentially eligible phase III randomized clinical trials with available information for the target population.''
- 3 trials were double blinded and 4 studies were open label.

Studienergebnisse:

- Efficacy of adding bevacizumab to chemotherapy
  - Improvement in PFS with the addition of bevacizumab to chemotherapy (RR, 0.869; 95% CI, 0.772–0.977; P=0.019). There was significant between-study heterogeneity in the RR for PFS (heterogeneity χ2, 27.15; I2, 85.3%; P,0.001)
  - No significant between-study heterogeneity was observed in both RR for OS (heterogeneity χ2, 3.12; I2, 0.0%; P=0.538; Figure S2) and OR for ORR. □Bevacizumab elicited great benefit in ORR (OR, 0.560; 95% CI, 0.475–0.661; P,0.001) rather than in OS (n.s.).
- Efficacy of bevacizumab plus capecitabine-based chemotherapy compared with bevacizumab plus taxane-based chemotherapy
  - No significant between-study heterogeneity in the RRs for PFS and OS as well as in the OR for ORR data.
  - A deleterious effect of bevacizumab plus capecitabine-based chemotherapy on PFS (RR, 1.190; 95% CI, 1.103–1.283; P,0.001) and ORR (OR, 1.897; 95% CI, 1.535–2.344; P,0.001) compared with bevacizumab plus taxane-based regimen was found.
- Efficacy of bevacizumab-based doublet therapy compared with bevacizumab-based triplet therapy
  - Significant between-study heterogeneity in both RR for PFS (heterogeneity χ2, 8.43; I2, 76.3%; P=0.015) and OR for ORR (heterogeneity χ2, 6.80; I2, 70.6%; P=0.033) rather than in the RR for OS.
  - Bevacizumab-based triplet therapy did not significantly improve the PFS or ORR when compared with bevacizumab-based doublet therapy.
  - No statistical significance was observed for OS.

Anmerkung/Fazit der Autoren

This meta-analysis indicated that the combination of bevacizumab and chemotherapy as first-line treatment significantly improved the PFS and ORR in locally recurrent or metastatic breast cancer patients. Greater benefits in PFS and ORR were observed in bevacizumab plus taxane-based regimens compared with bevacizumab plus capecitabine-based ones. In view of the non-inferiority for OS, however, increasing evidence supports the use of bevacizumab plus capecitabine as a preferable first-line option in the USA. Nevertheless, it is far from the end of the story. Additional studies are necessary to further optimize the first-line treatment of bevacizumab.

Kommentare zum Review

- Keine Angaben zur Vortherapie (z.B. endokrine Therapie) und Hormonstatus

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Liu X et al., 2016 [9].

Efficacy and safety of adding an agent to bevacizumab/taxane regimens for the first-line treatment of Her2-negative patients with locally recurrent or metastatic breast cancer: results from seven randomized controlled trials.

Fragestellung

to evaluate the efficacy and safety of adding an agent to the BEV/taxane regimens for the treatment of Her2-negative patients with LR/MBC in a first-line setting.

Methodik

Population:

- histologically confirmed Her2-negative LR/MBC

Intervention:

- BEV/taxane-based triplet regimens

Komparator:

- BEV/taxane-based doublet regimens (as the first-line treatment)

Endpunkte:

- ORR, PFS, OS, and toxic effects

Recherche/Suchzeitraum:

- PubMed, Web of Science, EMBASE, EBSCO, and the Cochrane Library databases were searched. from January 2000 to October 2015.

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs with 1,124 patients. Of the 7 articles, 3 were designed to receive the BEV/taxane regimens with the addition of a cytotoxic agent and four with the addition of a biologic agent versus the BEV/taxane doublet regimens.

Qualität der Studien:

- No obvious evidence of publication bias. Most of the studies were well performed and high in quality (3 Studies had a Jadad score of 5; 3 Studies had a Jadad score of 3, and 1 study had a Jadad score of 2).

Studienergebnisse:

- Objective response rate: Among the seven included trials, six trials reported the outcome measure of ORR and 1,078 patients were included in the analysis.
  - The pooled analysis of ORR showed that BEV/taxane-based triplet regimens were associated with significantly high ORR when compared with BEV/taxane-based doublet regimens in the first-line treatment of Her2-negative LR/MBC (OR =1.31, 95% CI: 1.03–1.67, *P*=0.03).
  - Similarly, a subset analysis showed that adding a cytotoxic agent to BEV/taxane therapy was associated with significantly improved ORR when compared with BEV/taxane-based doublet therapy (OR =1.46, 95% CI: 1.09–1.95, *P*=0.01).
  - No statistical significance was achieved when a biologic agent was added.
- Progression-free survival: PFS was selected as the outcome measure in the six trials
  - The pooled HR for PFS demonstrated that there was no statistically significant difference between the two regimens as the first-line treatment for Her2-negative patients with LR/MBC.
  - A subset analysis showed that adding a cytotoxic agent to BEV/taxane therapy did not significantly improve the PFS when compared with the BEV/taxane-based doublet therapy
- Overall survival: Data for OS were available from five trials.
  - The BEV/taxane-based triplet therapy did not show a significant advantage over the BEV/taxane-based doublet therapy for Her2-negative LR/MBC in the first-line setting.
  - The pooled HR for OS indicated that there was no significant difference between the groups of the BEV/taxane-based triplet therapy and the BEV/taxane-based doublet therapy.
  - Similarly, a subset analysis showed that adding neither a cytotoxic agent nor a biologic agent to BEV/taxane therapy was associated with a significant improvement in the OS when compared with the BEV/taxane-based doublet therapy.
- Safety: Common drug-related adverse events were reported in all included trials, and the majority were mild (grade 1) or moderate (grade 2) in severity.
  - The focus of our analysis is grade 3 or 4 adverse events:

  Incidences of neutropenia and neutropenic fever were not significantly different between the groups.

Incidences of thrombosis were higher with the BEV/taxane-based triplet therapy compared with the BEV/taxane-based doublet therapy (OR =3.8, 95% CI: 1.86–7.79, *P*=0.0003).

When non-haematological adverse events were compared, significantly more grade 3–4 fatigue and diarrhoea occurred in the BEV/taxane-based triplet therapy group (OR =1.55, 95% CI: 1.05–2.27, *P*=0.03; OR =2.1, 95% CI: 1.29–3.41, *P*=0.003, respectively).

- There were no statistically significant differences in nausea, hypertension, and peripheral neuropathy between the two arms.

Anmerkung/Fazit der Autoren

Our results showed that adding an agent to BEV/taxane treatment regimens did not significantly improve PFS and prolong OS, except for conferring a significant advantage toward improved ORR in the first-line therapy for Her2-negative patients with LR/MBC. However, its side effects are predictable and manageable.

Kommentare zum Review

- Keine Subgruppenanalysen hinsichtlich der Art der Vortherapie. Teilweise gemischte Population bzw. Patientenanteile in den Studien enthalten, die bereits eine CT erhalten haben.

Fang Y et al., 2015 [2]

The efficacy and safety of bevacizumab combined with chemotherapy in treatment of HER2-negative metastatic breast cancer: a meta-analysis based on published phase III trials

Fragestellung

to evaluate the efficacy and safety of Bev + standard chemotherapy for HER2-negative MBC

Methodik

Population:

- predominantly patients with HER2-negative MBC

Intervention:

- Bevacizumab + chemotherapy

Komparator:

- Chemotherapy alone

Endpunkte:

- PFS (primary endpoint), OS, toxicity

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials, the Cochrane databases, EMBASE, MEDLINE, and ClinicalTrials.gov from the first available year until May 2014.

Qualitätsbewertung der Studien:

- seven-point Jadad ranking system

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 randomized controlled trials consisting of 3082 patients. The E2100, AVADO, and RIBBON-1 trials investigated Bev + chemotherapy as a first-line treatment for HER2-negative MBC, and the RIBBON-2 trial evaluated it as a second-line treatment for HER2-negative MBC patients that had received one previous cytotoxic treatment. The docetaxel + Bev (7.5 mg/kg) arm of AVADO trial was excluded from the combined analysis because its dosage was not approved for MBC treatment. A total of 3082 patients were included in the meta-analysis, and of these patients, 1877 received Bev + standard chemotherapy and 1205 received either standard chemotherapy alone or standard chemotherapy + a placebo.

Qualität der Studien:

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

Studienergebnisse:

- Bev + standard chemotherapy improved PFS (HR 0.70, CI 0.64–0.77, P=0.000) but had no effect on OS (HR 0.92, CI 0.82–1.02, P=0.119).
- Bev + chemotherapy increased the incidence of febrile neutropenia (RR 1.45, CI 1.00 to 2.09, P=0.048), proteinuria (RR 11.68, CI 3.72–36.70, P=0.000), sensory neuropathy (RR 1.33, CI 1.05–1.70, P=0.020), and grade ≥3 hypertension (RR 13.94, CI 7.06–27.55, P=0.000).
- No differences in efficacy were observed between Bev + paclitaxel and Bev + capecitabine (Cape), but Bev + Cape increased the incidence of neutropenia.
- Bev + standard chemotherapy improved PFS in HER2-negative MBC patients. No benefit in OS was observed.
- Bev + Cape and Bev + paclitaxel had similar treatment efficacy, but Bev + Cape had a higher incidence of neutropenia.
    - Subgroup analysis: Whether the clinical benefits of Bev + standard chemotherapy for HER2-negative MBC were affected by different prognostic factors such as hormone receptor status, patient age, number of metastatic sites, tumor grade, prior taxane therapy, or visceral disease was investigated.

  The AVADO trial was excluded from the subgroup analysis because the stratified 95 % CIs (or P values) were not provided and could not be acquired by another method.

  The estimated effect of Bev (vs control) on PFS in HER2-negative MBC patients was stratified according to prognostic factors (hormone receptor status, patient age, number of metastatic sites, tumor grade, prior taxane therapy, or visceral disease).

  The addition of Bev to standard chemotherapy was consistently beneficial in terms of PFS in all of the subgroups analysed.
- Influence of the chemotherapy regimen: the efficacy of Bev stratified by the type of chemotherapy, including paclitaxel and Cape was investigated. The taxane/ anthracycline chemotherapy arm of the RIBBON-1 trial was removed from the analysis because it yielded mixed results.

- Crude data was extracted from the E2100 and RIBBON-1 trials for analysis. The different chemotherapies had similar efficacies: Bev + Cape reduced progression risk by 32 %, and Bev + paclitaxel reduced progression risk by 40 %.
- The occurrence of adverse events was similar in the control and experimental arms of the RIBBON-1 and E2100 trials.
- A difference was only observed in sensory neuropathy in both the control and experimental arms of the RIBBON-1 and E2100 trials (control arms: $\chi 2=37.866$, $P=0.000$; experimental arms: $\chi 2=73.118$, $P=0.000$).
- No differences were observed in neutropenia in patients in the control arms of the E2100 and RIBBON-1 trials ($\chi 2=1.162$, $P=0.281$).
- However, the rate of neutropenia in patients receiving Bev + Cape was significantly higher than that of Bev + paclitaxel ($\chi 2=4.547$, $P=0.033$).
- Differences were observed in ATE events in patients in the control arms of the two trials ($\chi 2=5.193$, $P=0.023$), but there were minimal differences in the experimental arms ($\chi 2=0.216$, $P=0.642$).

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis indicates that Bev + standard chemotherapy improves PFS significantly in HER2-negative MBC patients. However, the addition of Bev was associated with more toxicities including febrile neutropenia, proteinuria, sensory neuropathy, and grade ≥3 hypertension. We also found that Bev + paclitaxel and Bev + Cape had similar therapeutic efficacy. Based on the data, we conclude Bev + Cape had a higher incidence of neutropenia than Bev + paclitaxel.

3.4 Leitlinien

AWMF, 2017 [7].

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften)

Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 4.1 (September 2018).

Leitlinienorganisation/Fragestellung

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

Methodik

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

Systematische Recherche Auswahl und Bewertung von Leitlinien

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

Primärliteraturrecherche

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

Formulierung der Empfehlungen und formale Konsensusfindung

- Arbeitsgruppen erarbeiteten zunächst themenbezogen entsprechende Statements und Empfehlungen. In Telefonkonferenzen, in welchen immer mindestens ein Methodiker der AWMF oder des OL anwesend war, wurden diese nach den Regeln des nominalen Gruppenprozesses diskutiert, falls nötig angepasst und schließlich innerhalb der AG als Vorlage für die Konsensuskonferenz verabschiedet.

- **Empfehlungen** Empfehlungen sind thematisch bezogene handlungsleitende Kernsätze der Leitlinie. Die Abstimmung des Empfehlungstextes und des dazugehörenden Empfehlungsgrades durch die Leitlinien-Gruppe erfolgte im Rahmen eines moderierten, formalen Konsensusverfahrens (Nominaler Gruppenprozess).
- **Expertenkonsens (EK)** Als EK werden Empfehlungen bezeichnet, zu denen keine ausreichende Evidenz aus Studien, Leitlinien oder anderer aggregierter Literatur gefunden werden konnte. In der Regel adressieren diese Empfehlungen Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können.
- In der LL wird zu allen Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in der LL drei Empfehlungsgrade unterschieden (siehe Tabelle 9), die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.
- Empfehlungen, welche nicht durch Leitlinienadaptation oder durch Primärrecherche generiert wurden, sind als Expertenkonsens (EK) ausgewiesen. Der Empfehlungsgrad ergibt sich lediglich anhand der Ausdrucksweise (soll/sollte/kann) und wird nicht explizit mit A/B/0 gekennzeichnet.

Tabelle 10: Festlegungen hinsichtlich der Konsensstärke

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

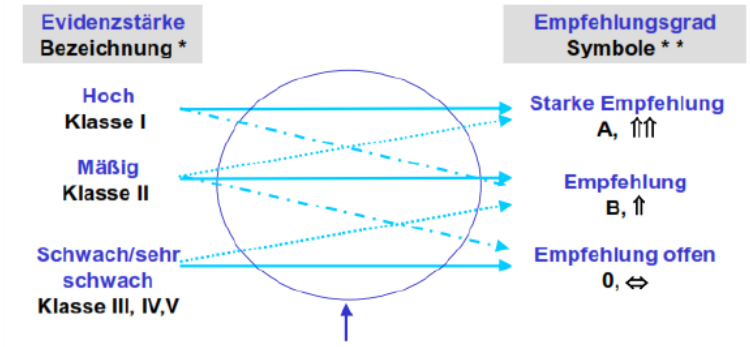
LoE

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

GoR

Tabelle 9: verwendete Empfehlungsgrade

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



Kriterien für die Graduierung (Konsensusaspekte):

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

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

Quelle: modifiziert AWMF-Regelwerk [29]

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

Sonstige methodische Hinweise

- neu seit 02.12.2017; 06.09.2018: Lang- und Kurzfassung nach redaktionellen Änderungen ausgetauscht

Empfehlungen

Systemische adjuvante Therapie (endokrine, Chemo-, Antikörpertherapie)

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

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

4.61.	Konsensbasierte Empfehlungen/Statements
	Neoadjuvante Chemotherapiekombination
EK	a.) Wenn eine neoadjuvante Chemotherapiekombination zum Einsatz kommt, sollte diese ein Anthrazyklin und ein Taxan enthalten. Die Dauer der präoperativen Therapie sollte 18–24 Wochen betragen. Bei HER2-positiven Tumoren und Indikation zur neoadjuvanten Chemotherapie sollte eine Therapie mit Trastuzumab erfolgen. Bei HER2-Positivität und High-risk Situation (klinisch/sonographisch oder stanzbioptisch N+, Tumorgröße > 2cm) sollte die Therapie durch Pertuzumab ergänzt werden.
	Starker Konsens
EK	b.) Platinsalze erhöhen beim triple-negativen Mammakarzinom (TNBC) unabhängig vom BRCA-Status die Komplettremissions-Rate (pCR-Rate). Der Vorteil auf das progressionsfreie Überleben (PFS) und das Gesamtüberleben ist nicht abschließend geklärt. Die Toxizität ist höher.
	Starker Konsens

4.62.	Konsensbasierte Empfehlung
	Postneoadjuvante Behandlung
EK	Bei adäquater Anthrazyklin-Taxan-haltiger neoadjuvanter Chemotherapie ist bei Tumorresiduen in der Brust und/oder in den Lymphknoten keine zusätzliche adjuvante Chemotherapie zu empfehlen. Eine postneoadjuvante Chemotherapiebehandlung sollte nur im Rahmen von Studien durchgeführt werden.
	Starker Konsens

<u>Therapie des lokalen/lokoregionalen Rezidivs</u>

- Medikamentöse Therapie

5.11.	Konsensbasierte Empfehlung
	Postoperative Systemtherapie
EK	Eine Systemtherapie nach R0-Resektion eines lokoregionären Rezidivs soll für ein verlängertes krankheitsfreies Intervall als auch ein verlängertes Gesamtüberleben erwogen werden.
	Starker Konsens

- Strahlentherapie

5.12.	Konsensbasierte Empfehlungen
	Bestrahlung nach Rezidivoperation
EK	a.) Eine Bestrahlung nach Rezidivoperation sollte interdisziplinär diskutiert und entschieden werden. Eine postoperative Radiotherapie sollte durchgeführt werden, wenn keine vorangegangene Radiotherapie erfolgt war oder das Lokalrezidiv nicht radikal operiert wurde (R1–2).
	Starker Konsens
EK	b.) Bei inoperablem Lokalrezidiv kann eine palliative Radiotherapie, ggf. in Kombination mit einer Chemotherapie, zur Symptomkontrolle sinnvoll sein.
	Starker Konsens
EK	c.) Bei Vorliegen eines intramammären Rezidivs beziehungsweise Thoraxwandrezidivs ohne Vorbestrahlung nach brusterhaltender Operation (R0) beziehungsweise nach Mastektomie (R0) sollte die Indikation zur adjuvanten Strahlentherapie analog zu den Empfehlungen in der Primärsituation erfolgen.
	Starker Konsens
EK	d.) Bei Vorliegen eines intramammären Rezidivs nach Vorbestrahlung nach brusterhaltender Operation (R0) soll die Indikation zur adjuvanten Strahlentherapie interdisziplinär diskutiert werden und kann insbesondere bei Patientinnen ohne gravierende Spätfolgen von der 1. Strahlentherapie gestellt werden.
	Starker Konsens
EK	e.) Bei Vorliegen eines Thoraxwandrezidivs nach Vorbestrahlung nach Mastektomie (R0) sollte eine erneute Bestrahlungsindikation zur lokalen Kontrolle interdisziplinär diskutiert werden.
	Starker Konsens

5.12.	Konsensbasierte Empfehlungen
EK	f.) Bei einem Brustwandrezidiv nach primärer Mastektomie ohne nachfolgende Strahlentherapie nach Resektion des Rezidivs (R0) sollte bei Vorliegen von Risikofaktoren (knappe Resektion, rpN+, G3, Lymphgefäßinvasion) die Indikation zu einer adjuvanten Strahlentherapie gestellt werden.
	Starker Konsens
EK	g.) Bei einem Brustwandrezidiv nach primärer Mastektomie mit nachfolgender Strahlentherapie nach Resektion des Rezidivs (R0) sollte bei Vorliegen von Risikofaktoren (knappe Resektion, rpN+, G3, Lymphgefäßinvasion) die Indikation zu einer erneuten adjuvanten Strahlentherapie interdisziplinär diskutiert werden. Diese kann bei Patientinnen ohne gravierende Spätfolgen von der 1. Strahlentherapie gestellt werden.
	Starker Konsens
EK	h.) Für Rezidive, die nicht in einem zuvor bestrahlten Bereich liegen und R1/R2-reseziert wurden - ohne Möglichkeit mit vertretbarem Risiko chirurgisch eine R0-Situation zu erzeugen -, soll eine zusätzliche Strahlentherapie in dieser Situation empfohlen werden.
	Starker Konsens
EK	i.) Bei Vorliegen von Rezidiven nach R1/R2-Resektion und erfolgter Vorbestrahlung ohne Möglichkeit, mit vertretbarem Risiko operativ eine R0-Situation zu erzeugen, sollte die Indikation zu einer erneuten Strahlentherapie interdisziplinär diskutiert werden. Diese kann bei Patientinnen ohne gravierende Spätfolgen von der 1. Strahlentherapie gestellt werden.
	Starker Konsens

Systemische Therapie des metastasierten Mammakarzinoms

- Chemotherapie des metastasierten Mammakarzinoms

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

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

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

5.24.	Evidenzbasierte Empfehlungen
	Polychemotherapie/Kombinationstherapie
Empfehlungsgrad **B**	a.) Bei Indikation zu einer Chemotherapie sollten Patientinnen ohne hohen Remissionsdruck eine sequentielle Chemotherapie erhalten.
Level of Evidence **1a**	De-novo-Recherche: [1032, 1033]
	Starker Konsens
Empfehlungsgrad **0**	b.) Die Kombinationstherapie aus Chemotherapie und Bevacizumab kann in der Erstlinientherapie das progressionsfreie Überleben verbessern, allerdings mit erhöhter Nebenwirkungsrate und ohne Einfluss auf das Gesamtüberleben.
Level of Evidence **1a**	Quellen: [1034, 1035] [1036-1039]
	Starker Konsens
Empfehlungsgrad **0**	c.) Bei stärkeren Beschwerden und raschem Wachstum bzw. aggressivem Tumorverhalten, d.h. bei hohem Remissionsdruck, kann eine Polychemotherapie oder eine Chemotherapie + Bevacizumab durchgeführt werden.
Level of Evidence **1a**	Quellen: [1003], [1032]
	Starker Konsens

Hintergrund: (…) Aufgrund der Heterogenität der Metastasen und der individuellen Krankheitsverläufe kann keine einheitliche Therapiestrategie vorgegeben werden. Dies gilt insbesondere für die zytostatische Behandlung des metastasierten Mammakarzinoms. Die Monotherapie weist zwar niedrigere Remissionsraten als Polychemotherapien auf, die Überlebenszeit wird hiervon jedoch nicht signifikant negativ beeinflusst. Monotherapien sind besser verträglich, sodass – wann immer möglich – eine Monotherapie durchgeführt werden sollte. Bei geringen Beschwerden und langsamem Tumorwachstum bzw. Ineffektivität einer endokrinen Therapie sollte eine Monotherapie eingesetzt werden. Lediglich bei starken Beschwerden, raschem Tumorwachstum und aggressivem Tumor-verhalten ist eine Polychemotherapie indiziert. (…)

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

Wildiers et al., 2013 [17].

Belgian Health Care Knowledge Centre (KCE)

Breast cancer in women: diagnosis, treatment and follow-up (3rd Ed.)

Leitlinienorganisation/Fragestellung

A clinical practice guideline (CPG) on the management of breast cancer

Methodik

Grundlage der Leitlinie

- A broad search of electronic databases (Medline, PreMedline, EMBASE), specific guideline websites and websites of organisations in oncology … was conducted. (until 2010, update einiger Fragestellungen in 2013)
- quality appraisal: AGREE for clinical practice guidelines, checklists of the Dutch Cochrane Centre for original studies
- 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.

LoE/GoR

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

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

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

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

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

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

Recommendations: Systemic treatment

Chemotherapy

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

account quality of life, toxicity, characteristics of the disease and the ease of administration (1A evidence).

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

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

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

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

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

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Biological therapy

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

  Clinical Evidence: Wagner et al: evaluated overall survival, progression- free survival and harms of VEGF-targeting therapies in patients with hormone-refractory or hormone-receptor negative metastatic breast cancer search of the electronic databases until September 8, 2011.
  - overall risk of bias of this review was considered as low
  - total number of seven RCTs, data from one register, and five ongoing trials examining the effect of bevacizumab in combination with chemotherapy
  - Five of the included RCTs addressed (predominantly) HER-2 negative patients (with a maximum of 4% HER-2 positive patients)
  - Overall survival did not differ significantly between the groups with and without bevacizumab, neither in first-line chemotherapy (HR=0.93; 95%CI 0.84-1.04), nor in second-line chemotherapy (HR=0.90; 95%CI 0.71-1.14) in HER-2 negative patients.
  - Progression-free-survival was significantly better after treatment with bevacizumab in both first-line (HR=0.67; 95%CI 0.61-0.73) and second-line chemotherapy (HR=0.78; 95%CI 0.64-0.93).

- Significantly higher rates of grade 3/4 adverse events (OR=1.77; 95%CI 1.44-2.18) and serious adverse events (OR=1.41; 95%CI 1.13-1.75) were observed in patients treated with bevacizumab.

Conclusions: Among women with HER-2 negative metastatic breast cancer, treated with bevacizumab in combination with chemotherapy versus chemotherapy alone:

- A difference in overall survival between bevacizumab in combination with first-line chemotherapy and first-line chemotherapy alone could neither be demonstrated nor refuted (Wagner 2012; low level of evidence).
- A difference in overall survival between bevacizumab in combination with second-line chemotherapy and second-line chemotherapy alone could neither be demonstrated nor refuted (Wagner 2012; moderate level of evidence).

- It is plausible that bevacizumab in combination with first-line chemotherapy has a positive effect on progression free survival as compared to first-line chemotherapy alone (Wagner 2012; moderate level of evidence).
- It is demonstrated that bevacizumab in combination with second-line chemotherapy has a positive effect on progression free survival in women with HER-2 negative metastatic breast cancer as compared to second-line chemotherapy alone (Wagner 2012; high level of evidence)
- It is plausible that bevacizumab in combination with first-line chemotherapy leads to more grade 3 or higher adverse events as compared to first-line chemotherapy alone (Wagner 2012; moderate level of evidence)
- There are indications that bevacizumab in combination with first or second-line chemotherapy leads to more serious adverse events as compared to first or second-line chemotherapy alone (Wagner 2012; low level of evidence)

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Treatment of locoregional relapse

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

Clinical Evidence: Few trials exist on the use of systemic treatment for a locoregional recurrence that has been completely excised [66].

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National Institute for Health and Care Excellence (NICE)

Advanced breast cancer: diagnosis and treatment.

Leitlinienorganisation/Fragestellung

Behandlung von metastasierenden Brustkrebs (Tumorstadium 4) mit Focus auf die systemische Behandlung, Lymphödeme und Behandlung von Metastasen (z. B. Knochen, Gehirn)

Methodik

Grundlage der Leitlinie

- Formulierung von PICO-Fragen
- Systematische Literaturrecherche in mehreren Datenbanken (bis Juni 2008), Datenextraktion, Qualitätsbewertung der gefundenen Literatur auf Basis der SIGN Kriterien für systematische Reviews/Meta-analysen und RCTs
- Ein regelmäßiger Abgleich der Empfehlung mit neuer Evidenz findet statt (letztmalig November 2015). Im Bezug zur Indikation wurde keine neue Evidenz identifiziert die zu einer Änderung der bisherigen Empfehlungen führen würde.
- Bewertung der Evidence und Stärke der Empfehlung
- Einbezug von gesundheitsökonomischer Evidenz
- Formulierung der Empfehlung basierend auf klinischer und ökonomischer Evidenz
- Bei schwacher Evidenz: Empfehlung basierend auf informellen Konsens.
- To avoid giving the impression that higher-grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations. Stärke der Empfehlung durch Formulierung ausgedrückt;

Recommendations

Chemotherapy:

- On disease progression, offer systemic sequential therapy to the majority of patients with advanced breast cancer who have decided to be treated with chemotherapy.
    - Qualifying statement: These recommendations are based on limited randomised trial evidence and GDG consensus.
- 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.
    - Qualifying statement: This recommendation is based on randomised trial evidence confirming increased response rate and toxicity from combination chemotherapy and uncertainty over overall survival benefit compared with sequential single agent chemotherapy.

  Clinical Evidence: Evidence for comparing single chemotherapy with sequential chemotherapy comprised five RCTs (Creech et al. 1979; Chlebowski et al. 1979; Sledge et al. 2003; Smalley et al. 1976 and Baker et al. 1974) and one observational study (Chlebowski et al. 1989). The older studies were not always very stringently reported.

  Two small, poor quality trials (Baker et al . 1974 and Creech et al . 1979) found no significant difference in tumour response, response duration, time to progression or overall survival when chemotherapy agents were given together or sequentially (on disease progression). Two other studies (Chlebowski et al. 1979 and Smalley et al. 1976)

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

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

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

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

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

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

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

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

- 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 second-line treatment).

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

While it was acknowledged that there is no direct evidence comparing alternative chemotherapy sequences, the GDG considered it important to explore the cost effectiveness of plausible sequences using the best available data. An indirect treatment comparison methodology was an important component of this, but it was restricted to an assessment of the relative effectiveness of alternative first-line treatments based on the available RCT data.

Clinical Evidence:

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

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

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

Taxanes: There was good quality evidence on the use of taxanes as first- or second-line monotherapy or in combination, comprising a high quality Cancer Care Ontario guideline (Verma et al. 2003), two good systematic reviews (Ghersi et al. 2005 and Bria et al. 2005) and four RCTs (Lin et al. 2007; Cassier et al.2008; Bontenbal et al.2005 and Jones et al. 2005). The total patient number exceeded 15,000. Anthracycline naïve women did not derive any benefit from paclitaxel (PAC) as first line monotherapy compared with controls. A large systematic review (Verma et al. 2003) found that for anthracycline naïve patients, when taxanes were added to anthracycline based regimes, there were no significant differences in time to progression (TTP) or overall survival (OS) but tumour response was significantly improved. However, PAC and doxorubicin (DOX) combined therapy resulted in superior

median OS and TTP compared with 5´-FU, DOX and cyclophosphamide (FAC) combined. There was no evidence to suggest a significant difference in quality of life between DOC and PAC when either was combined with anthracycline as first-line therapy. One moderate RCT (Bontenbal et al.2005) demonstrated that DOX and DOC combined therapy in first line treatment of advanced disease resulted in superior tumour response and clinical benefit, when compared with FAC. Time to event analyses also showed significant reductions in the risk of death and time to progression with AT therapy compared to FAC but there were more reports of febrile neutropenia with FAC. Meta-analysis demonstrated significant improvements in TTP, tumour response and time to treatment failure in favour of taxane containing regimes compared with non-taxane containing regimes and a borderline advantage in OS. However, statistical significance for OS and TTP was lost when only first-line therapy with taxanes was considered. Taxanes and taxane-containing regimes were reported to have a higher incidence of neurotoxicity and leukopenia but fewer cases of nausea and vomiting than controls.

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

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

Surveillance decision

The section on chemotherapy should list a cross -referral to NICE technology appraisal TA423 Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens (2016) [12].

- Eribulin is recommended as an option for treating locally advanced or metastatic breast cancer in adults, only when:
  - o it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine)
  - o the company provides eribulin with the discount agreed in the patient access scheme.

TA515 Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen (2018) [11].

- Eribulin is not recommended for treating locally advanced or metastatic breast cancer in adults who have had only 1 chemotherapy regimen.

Biological therapy

TA421 Everolimus with exemestane for treating advanced breast cancer after endocrine therapy (2016) [13].

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

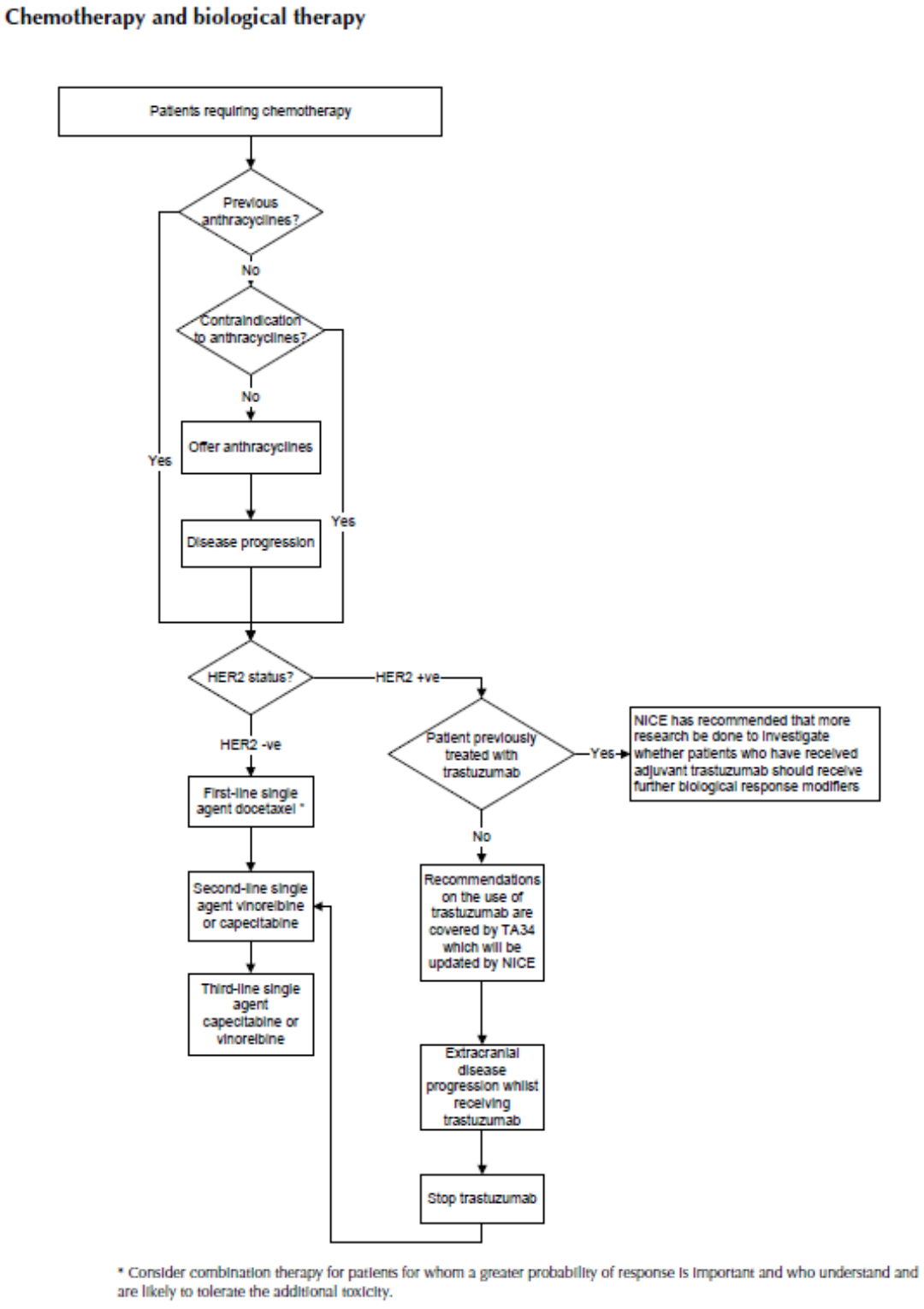

Figure 1: Therapiealgorhythmus

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American Society of Clinical Oncology Clinical (ASCO)

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

Leitlinienorganisation/Fragestellung

To identify optimal chemo- and targeted therapy for women with human epidermal growth factor 2 (HER2)-negative (or unknown) advanced breast cancer.

Methodik

Grundlage der Leitlinie

- Target Population: Women with advanced breast cancer (locally advanced/ non-resectable or metastatic disease treated with non-curative 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.

Recherche/Suchzeitraum:

- 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. Grey Literature: annual meeting proceedings of ASCO (2012, 2013), San Antonio Breast Cancer Symposium (SABCS) (2011, 2012)

LoE/GoR

- 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.

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.

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.

Author's disclosure of potential conflict of interest available

Recommendations

- Endocrine therapy, rather than chemotherapy, should be offered as the standard first-line treatment for patients with hormone receptor–positive advanced/metastatic breast cancer, except for immediately life threatening disease or if there is concern regarding endocrine resistance.
  - A. The main benefit is less toxicity and better quality of life for the patient associated with endocrine therapy compared with chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly and prove fatal if there is no response, but the risk of this is low (potential harm: low).
  - B. The quality of the evidence is intermediate, and is based on the NCCC systematic review.
  - C. The strength of this recommendation is strong and is supported by the evidence and expert consensus.

  Qualifying statement: It should be noted that the basis for this recommendation is the relative likelihood of response to chemotherapy versus endocrine therapy and not the rapidity of response, for which there are no good data.

  Clinical Evidence: The prior systematic review[3] addressed the role of endocrine therapy compared with CT as first-line treatment for advanced hormone receptor–positive breast cancer. One high-quality systematic review[4] was used to form recommendations, which entailed an analysis of 10 randomized controlled trials (RCTs) comparing CT with endocrine treatments. In that review, no difference was found in OS, and no data were available on QoL or AEs, but the authors report that CT was associated with higher levels of toxicity, especially nausea, vomiting, and alopecia. They recommended endocrine therapy first unless disease was rapidly progressing, in which case CT was appropriate, as a fast response was medically necessary.
- Sequential single-agent chemotherapy rather than combination therapy should be offered, although combination regimens may be considered for immediately life-threatening disease for which time may allow only one potential chance for therapy.
  - A. The benefit is less toxicity and better quality of life (potential benefit: high). The potential harm is for rapidly progressing, life-threatening disease to escape control if response to a single agent isn't achieved (potential harm: high). The main benefit is

there is less toxicity and better quality of life for the patient associated with sequential single agent chemotherapy compared with combination chemotherapy (potential benefit: high). The harm is that metastatic disease could progress rapidly if there is no response, but the risk of this is low (potential harm: low).

- B. The evidence quality is high, and includes a large RCT.
- C. The strength of this recommendation is strong.

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

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

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

- With regard to targeted agents, the role of bevacizumab is controversial, and this therapy should be considered (where available) with single-agent chemotherapy only when there is immediately life-threatening disease or severe symptoms, in view of improved response rates (similar to Recommendation 2 regarding the use of combination chemotherapy). It is recognized that there is not currently an approved indication for bevacizumab in the United States because the weight of evidence shows no significant survival benefit. Other targeted agents should not be used either in addition to, or as a replacement for, chemotherapy in this setting outside of a trial
  - A. The benefit is improved disease control (potential benefit: moderate). The potential harms are unique toxicity, increased costs, and barriers to access (potential harm: high)
  - B. The quality of the evidence is high and is supported by multiple trials.
  - C. The strength of the recommendation is moderate and is based on both evidence and expert consensus.

  Qualifying statement: Bevacizumab added to single-agent chemotherapy improves response and progression-free survival but not overall survival

  Clinical Evidence from SR: The addition of bevacizumab to CT has demonstrated improvements in objective response rate (ORR) and PFS[17,26,28] but not in duration of response[17,26,28] or OS. One study reported no differences in AEs associated with the addition of bevacizumab,[26] whereas another reported increased rates of hypertension.[17]
- No single agent has demonstrated superiority in the treatment of patients with advanced breast cancer, and there are several active agents appropriate for first-line chemotherapy.

The evidence for efficacy is strongest for taxanes and anthracyclines. Other options include capecitabine, gemcitabine, platinum-based compounds, vinorelbine, and ixabepilone. Treatment selection should be based on previous therapy, differential toxicity, comorbid conditions, and patient preferences. Specifically, drugs for which clinical resistance has already been shown should not be reused

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

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

- 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

- 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]

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Hinweis FBMed:

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

Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 30.11.2018

#	Suchfrage
1	[mh “Breast Neoplasms”]
2	(breast or mamma*):ti,ab,kw
3	(cancer* or tum*r* or carcinoma* or neoplas* or adenocarcinoma* or sarcoma* or lesions*):ti,ab,kw
4	(advanced or metastat* or metastas* or recurren* or relaps* or progression*):ti,ab,kw
5	#1 or (#2 and #3)
6	#4 and #5
7	#6 with Cochrane Library publication date from Nov 2013 to Nov 2018

Systematic Reviews in Medline (PubMed) am 30.11.2018

#	Suchfrage
1	breast neoplasms/TH
2	((breast[ti]) OR mamma*[ti]) AND (neoplasm metastasis/TH OR neoplasm recurrence, local/TH)
3	(#1) OR #2
4	(breast[ti]) OR mamma*[ti]
5	(#4) AND (((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplasm*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR malignan*[tiab])
6	(#5) AND (((((((advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab]) OR relaps*[tiab]) OR progression*[tiab]) OR progressive*[tiab]) OR disseminat*[tiab])
7	(#6) AND ((((((((((((treatment*[tiab]) OR therapy[tiab]) OR therapies[tiab]) OR therapeutic[tiab]) OR monotherap*[tiab]) OR polytherap*[tiab]) OR pharmacotherap*[tiab]) OR effect*[tiab]) OR efficacy[tiab]) OR treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]) OR chemotherap*[tiab])
8	#3 OR #7
9	(#8) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
10	((#9) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 30.11.2018

#	Suchfrage
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	cancer*[ti] OR tumour*[ti] OR tumor[ti] OR tumors[ti] OR carcinom*[ti] OR neoplas*[ti] OR malignan*[ti]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
7	(((#6) AND ("2013/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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