Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2015-09-01-D-177 Pertuzumab

Stand: September 2014

Gemeinsamer Bundesausschuss

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pertuzumab [zur neoadjuvanten Behandlung von HER2-positivem, lokal fortgeschrittenem, entzündlichem Brustkrebs]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe 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 des G-BA über eine Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V (DMP-Richtlinie/DMP-RL) in der Fassung vom 16. Februar 2013. • Beschluss vom 17. März 2011 über Empfehlungen zur Aktualisierung des DMP Brustkrebs. • Beschluss vom 15. Juli 2010 über eine Beauftragung des IQWiG: Nutzenbewertung von Aromatasehemmern zur Behandlung des Mammakarzinoms der Frau. • Beschluss vom 20. Mai 2010 über eine Änderung der AM-RL: Anlage VI – Off-Label-Use; Gemcitabin in der Monotherapie beim Mammakarzinom der Frau (nicht verordnungsfähig) • Beschluss vom 28. Mai 2009: Protonentherapie beim Mammakarzinom • Beschluss vom 19. April 2012 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Eribulin • Beschluss vom 1.Oktober 2013 über eine Änderung der AM-RL: Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pertuzumab

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
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Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

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II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code ggf. Handelsname	Anwendungsgebiet (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pertuzumab L01XC13	Perjeta ist zur Anwendung in Kombination mit Trastuzumab und Docetaxel bei erwachsenen Patienten mit HER2-positivem metastasiertem oder lokal rezidivierendem, inoperablem Brustkrebs indiziert, die zuvor noch keine anti-HER2-Therapie oder Chemotherapie zur Behandlung ihrer metastasierten Erkrankung erhalten haben. neu laut Beratungsanforderung: Perjeta ist in Kombination mit Trastuzumab und Docetaxel, bei erwachsenen Patienten zur neoadjuvanten Behandlung von HER2-positivem, lokal fortgeschrittenem, entzündlichem Brustkrebs oder frühem Brustkrebs (Durchmesser > 2 cm) als Teil der Therapie des frühen Brustkrebses indiziert (siehe Abschnitt 5.1)."
Docetaxel L01CD02	Docetaxel ist in Kombination mit Doxorubicin und Cyclophosphamid für die adjuvante Therapie von Patientinnen mit operablem, nodal positivem Brustkrebs angezeigt. Docetaxel ist in Kombination mit Doxorubicin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs ohne vorausgegangene Chemotherapie angezeigt. Die Docetaxel-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. Docetaxel ist in Kombination mit Trastuzumab angezeigt zur Behandlung von Patientinnen mit metastasiertem Mammakarzinom, deren Tumore HER2 überexprimieren und die vorher noch keine Chemotherapie gegen ihre metastasierte Erkrankung erhalten haben. Docetaxel 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	Mammakarzinom Doxorubicin wird häufig in der KombinationsChemotherapie zusammen mit anderen zytotoxischen Arzneimitteln angewendet.
Epirubicin L01DB03	Epirubicin wird zur Behandlung verschiedener Neoplasien eingesetzt, einschließlich Mammakarzinom.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Fluorouracil L01BC02	fortgeschrittenes und/oder metastasiertes Mammakarzinom
Goserelin L02AE03	Behandlung von Patientinnen mit Mammakarzinom (prä- und perimenopausale Frauen), bei denen eine endokrine Behandlung angezeigt ist.
Leuprorelin L02AE02	Mammakarzinom prä und perimenopausaler Frauen, sofern eine endokrine Behandlung angezeigt ist.
Mitoxantron L01DB07	Fortgeschrittenes und/oder metastasiertes Mammakarzinom
Paclitaxel L01CD01	Mammakarzinom: - zur adjuvanten Therapie von Patientinnen mit nodalpositivem Mammakarzinom im Anschluss an eine Anthracyclin-/Cyclophosphamid- Therapie (AC). Die adjuvante Therapie mit Paclitaxel HEXAL sollte als Alternative zu einer ver-längerten AC-Therapie angesehen werden. - zur Erstbehandlung bei Patientinnen mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom entweder in Kombination mit einem Anthracyclin bei Patientinnen, für die eine Anthracyclin-Therapie angezeigt ist, oder in Kombination mit Trastuzumab, wenn HER2 gemäß immunhistochemischer Bestimmung als 3+ eingestuft und wenn eine Anthracyclin-haltige Therapie nicht angezeigt ist. - als Monotherapie für die Behandlung des meta- stasierten Mammakarzinoms bei Patientinnen, bei denen eine Standardtherapie mit Anthracyc- linen erfolglos war oder für die eine Therapie mit einem Anthracyclin nicht angezeigt ist.
Trastuzumab L01XC03	Metastasierter Brustkrebs Herceptin ist zur Behandlung von erwachsenen Patienten mit HER2-positivem metastasiertem Brustkrebs (metastatic breast cancer – MBC) indiziert: – als Monotherapie zur Behandlung von Patienten, die mindestens zwei Chemotherapieregime gegen ihre metastasierte Erkrankung erhalten haben. Die vorangegangene Chemotherapie muss mindestens ein Anthrazyklin und ein Taxan enthalten haben, es sei denn, diese Behandlung ist für die Patienten nicht geeignet. Bei Patienten mit positivem Hormonrezeptor-Status muss eine Hormonbehandlung erfolglos gewesen sein, es sei denn, diese Behandlung ist für die Patienten nicht geeignet. – in Kombination mit Paclitaxel zur Behandlung von Patienten, die noch keine Chemotherapie gegen ihre metastasierte Erkrankung erhalten haben und für die ein Anthrazyklin ungeeignet ist. – in Kombination mit Docetaxel zur Behandlung von Patienten, die noch keine Chemotherapie gegen ihre metastasierte Erkrankung erhalten haben. – in Kombination mit einem Aromatasehemmer zur Behandlung von postmenopausalen Patienten mit hormonrezeptorpositivem MBC, die noch nicht mit Trastuzumab behandelt wurden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Brustkrebs im Frühstadium Herceptin ist zur Behandlung von erwachsenen Patienten mit HER2-positivem Brustkrebs im Frühstadium (early breast cancer – EBC) indiziert: – nach einer Operation, Chemotherapie (neoadjuvant oder adjuvant) und Strahlentherapie (soweit zutreffend). – nach adjuvanter Chemotherapie mit Doxorubicin und Cyclophosphamid, in Kombination mit Paclitaxel oder Docetaxel. – in Kombination mit adjuvanter Chemotherapie mit Docetaxel und Carboplatin. – in Kombination mit neoadjuvanter Chemotherapie gefolgt von adjuvanter Therapie mit Herceptin, bei lokal fortgeschrittenem (einschließlich entzündlichem) Brustkrebs oder Tumoren > 2 cm im Durchmesser. Herceptin ist nur bei Patienten mit metastasiertem Brustkrebs oder Brustkrebs im Frühstadium anzuwenden, deren Tumore entweder eine HER2- Überexpression oder eine HER2-Genamplifikation aufweisen, die durch eine genaue und validierte Untersuchung ermittelt wurde.
Vincristin L01CA02	Wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

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

Inhalt

Indikation für die Recherche bei Wirkstoff (evtl. Markenname):

Pertuzumab ist in Kombination mit Trastuzumab und Docetaxel, bei erwachsenen Patienten zur neoadjuvanten Behandlung von HER2-positivem, lokal fortgeschrittenem, entzündlichem Brustkrebs oder frühen Brustkrebs (Durchmesser >2cm) als Teil der Therapie des frühen Brustkrebses indiziert.

Berücksichtigte Wirkstoffe/Therapien:

Für das Anwendungsgebiet zugelassenen Arzneimittel, s. Unterlage zur Beratung in AG: „Übersicht zVT, Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet“

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation „früh oder lokal fortgeschrittenem Mammakarzinom“ durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 26.08.2014 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), Leitlinien.de (ÄZQ), AWMF, DAHTA, G-BA, GIN, IQWiG, NGC, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien (z.B. NICE, SIGN). Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **816** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **87** Quellen eingeschlossen. Insgesamt ergab dies **20** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

AC	doxorubicin [adriamycin], cyclophosphamide
AD	Absolute Difference
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
BC	breast cancer
CAF	6 cycles of C100×14 A30×2 F500×2, given 4-weekly
CCO	Cancer Care Ontario
CEF	cyclophosphamide, epirubicin, fluorouracil
CHF	congestive heart failure
CMF	cyclophosphamide, methotrexate, and fluorouracil
DAHTA	Deutsche Agentur für Health Technology Assessment
DD regime	Dose-dense regime
DFS	Disease-free survival
DGGG	Deutsche Gesellschaft für Gynäkologie und Geburtshilfe
DKG	Deutsche Krebsgesellschaft
EBC	Early breat cancer
EBC	early breast cancer
EBCTCG	Early Breast Cancer Trialists’ Collaborative Group
ECFi	epirubicin, cyclophosphamide, filgrastim
EFS	event-free survival
ER	estrogen receptor
ESMO	European Society for Medical Oncology
ET	endocrine therapy
EVMTV	epirubicin, vincristine, mitomycin C, thiotepa, vindesine
FAC	fluorouracil, doxorubicin [adriamycin], cyclophosphamide

FEC-100	epirubicin 100 mg/m2 with 5-fluorouracil 500 mg/m2 and cyclophosphamide 500 mg/m2
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITT	Intention-to-treat
KI	Konfidenzintervall
LK	Lymphknoten
LVEF	linksventrikuläre Ejektionsfraktion
LVEF	Linksventrikuläre Ejektionsfraktion.
MM	mitoxantrone [mitozantrone], methotrexate
NACT	neoadjuvante Chemotherapie
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NSABP	National Surgical Adjuvant Breast and Bowel Project
NYHA	New York Heart Association
OS	Overall survival
Pcr	pathological complete response
pCR	pathological complete response
QoL	Quality of Life
RCT	randomized-controlled trial
RR	relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TNM	TNM Classification of Malignant Tumours
TRIP	Turn Research into Practice Database
UICC	Union internationale contre le cancer
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

G-BA, 2007: Tragende Gründe zum Beschluss über eine Änderung der Arzneimittel-Richtlinie in Anlage 9 Teil A (Off-Lable-Use) der Arzneimittel-Richtlinie.[5] *siehe auch:* **G-BA, 2010:** Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über die Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage VI – Off-Label-Use 5-Fluorouracil-haltige Arzneimittel zur adjuvanten Chemotherapie des primären invasiven Mammakarzinoms [6]	**Fazit:** Mit Schreiben vom 22.11.2006 hat die Firma Pfizer den Gemeinsamen Bundesausschuss über die Zulassung des Arzneimittels Aromasin® mit dem Wirkstoff Exemestan für die adjuvante Therapie des Östrogen-Rezeptor positiven, invasiven frühen Mammakarzinoms bei postmenopausalen Frauen nach 2- 3 Jahren Initialtherapie mit Tamoxifen informiert. Dementsprechend wird in der Anlage 9 der Arzneimittel-Richtlinie im Teil A unter I. 5-Fluorouracil-haltige Arzneimittel 1. Hinweise zur Anwendung von 5-Fluorouracil gemäß Nr. 24 c) Folgende Wirkstoffe sind für die Indikation Mammakarzinom zugelassen: nach der Wirkstoffbezeichnung „Anastrozol“ die Wirkstoffbezeichnung „Exemestan“ hinzugefügt.
G-BA, 2011: Beschluss des Gemeinsamen Bundesausschusses über Empfehlungen zur Aktualisierung der Anforderungen an strukturierte Behandlungsprogramme für Patientinnen mit Brustkrebs und zur Aktualisierung der Anforderungen an die Dokumentation an strukturierte Behandlungsprogramme für Patientinnen mit Brustkrebs. [7] *siehe auch:* **G-BA, 2012:** Beschluss des Gemeinsamen Bundesausschusses über eine Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V (DMP-Richtlinie/DMP-RL) Erstfassung. [8]	**Maßnahmen im Rahmen der Primärtherapie:** Neben der histologischen Sicherung einschließlich der speziellen pathologischen Diagnostik müssen vor Einleitung der Primärtherapie folgende Untersuchungen abgeschlossen sein: − die klinische Untersuchung, − Mammographie in zwei Ebenen, − Ultraschalldiagnostik Eine perioperative Suche nach Fernmetastasen muss durchgeführt werden, sofern dies für die weitere Therapieplanung von Bedeutung ist. Es sind grundsätzlich alle erhobenen diagnostischen Vorbefunde zu nutzen. Zur definitiven Therapieplanung gehört eine eingehende Überprüfung der vorhandenen und der noch zu erhebenden pathomorphologischen Befunde. Insbesondere folgende Inhalte der Befundung sind zu fordern: − Tumortyp, − metrische Messung der Tumorgröße, − Lymphangiosis carcinomatosa, Gefäßeinbrüche, − Multifokalität / Multizentrizität, − Lymphknotenstatus, − Beurteilung der Schnittränder (Tumorinfiltration, Breite des gesunden Gewebesaumes), − Ausdehnung des intraduktalen Tumoranteils, − Differenzierungsgrad (Grading), − Hormonrezeptor-Status, − HER2/neu-Status für invasive Karzinome. **Systemische adjuvante Therapie (endokrine Therapie, Chemotherapie und Antikörpertherapie):** Für alle Patientinnen muss nach individueller Nutzen-Risikoabwägung die Einleitung einer adjuvanten systemischen Therapie geprüft werden. Ob und welche adjuvante systemische Therapie begonnen wird, ist nach Aufklärung und Be-ratung der Patientin insbesondere im Hinblick auf Nutzen und mögliche Nebenwirkungen zu entscheiden. Diese sollte durch eine

	angemessene supportive Therapie (z. B. Antiemese, Versorgung mit Perücken etc.) flankiert werden. Die Entscheidung über die Notwendigkeit und Art einer adjuvanten Therapie berücksichtigt die Tumorgröße, den Lymphknotenstatus, das Grading, den Hormonrezeptorstatus, den HER2/neu-Status, den Menopausenstatus, weitere Erkrankungen und das Alter als wichtigste Faktoren zur Risikoeinstufung. Die betroffenen Patientinnen müssen unterschiedlichen Risikogruppen zugeordnet werden. Zu der Gruppe mit niedrigem Risiko gehören Patientinnen, unabhängig vom Menopausenstatus, die alle der folgenden Bedingungen erfüllen müssen: - Patientinnen mit 35 Jahren oder älter, - Tumordurchmesser ≤ 2 cm, - Grading I, - positiver Östrogen- und/oder Progesteronrezeptor, - negativer HER2/neu-Status, - negativer Lymphknotenstatus Bei Patientinnen mit HER2/neu positiven Tumoren (ab Stadium pT1c und/oder LK Befall) soll eine Behandlung mit Trastuzumab erfolgen. Wirksame Begleitmaßnahmen, insbesondere eine ausreichende Antiemese, sind Bestandteil der systemischen Therapie. **Primär systemische/neoadjuvante Therapie:** Die primäre systemische Therapie, weitgehend synonym werden die Begriffe neoadjuvante Therapie oder präoperative Therapie gebraucht, beschreibt die Therapieformen, die nach der gesicherten Diagnose eines Mammakarzinoms vor einer operativen Therapie zur Anwendung kommen. Die primäre systemische Therapie ist die Therapie der Wahl bei inflammatorischem Mammakarzinom und weit fortgeschrittenen primär inoperablen Mammakarzinomen, um durch eine Tumorverkleinerung eine Operation mit tumorfreien Resektionsgrenzen erreichen zu können. Bei primär resektablen Tumoren, die wegen der Tumorgröße eine Mammaablatio indizieren, kann eine primäre systemische Therapie zur Reduktion des Tumorvolumens eingesetzt werden, um eine brusterhaltende Operation zu ermöglichen. In Sondersituationen, z.B. bei Kontraindikationen gegen eine operative Therapie, kann die primäre systemische Therapie mit dem Ziel der Tumorkontrolle zum Einsatz kommen. Zur Therapieauswahl der primär systemischen Therapie sind die gleichen klinischen und pathomorphologischen Befunde zu erheben (klinische Tumorgröße und Lymphknotenstatus, Grading, Hormonrezeptorstatus, HER2/neu-Status, Menopausenstatus, weitere Erkrankungen und das Alter) wie bei der adjuvanten Therapie. Der Effekt der primär systemischen Therapie ist regelmäßig zu überwachen.
G-BA, 2014: Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V –Trastuzumab	**Fazit:** Auf Basis der Kriterien gemäß 5. Kapitel § 6 Abs. 3 der VerfO und nach Würdigung der vom pharmazeutischen Unternehmer und den maßgeblichen medizinischen Fachgesellschaften vorgebrachten Argumente, erachtet der G-BA es als gerechtfertigt, die ursprünglich für die Nutzenbewertung von Trastuzumab Emtansin bestimmte zweckmäßige Vergleichstherapie für die Behandlung von Patienten mit HER2-positivem, inoperablem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die eine vorangegangene Therapie mit Trastuzumab und einem Taxan erhalten haben wie folgt zu fassen:

Emtansin. [9] *siehe auch:* **IQWiG, 2014:** Dossierbewertung: Trastuzumab Emtansin – Nutzenbewertung gemäß § 35a SGB V. Auftrag: A14-01 [10]	<u>Teilpopulation a):</u> Patientinnen mit HER2-postivem, inoperablem lokal fortgeschrittenem Brustkrebs: - Strahlentherapie (für Patientinnen, die für eine Strahlentherapie in Frage kommen) *<u>oder</u>* - Eine patientenindividuelle, optimierte Therapie nach Maßgabe des Arztes, grundsätzlich unter Beachtung des jeweiligen Zulassungsstatus der eingesetzten Wirkstoffe (für Patientinnen, die nicht für eine Strahlentherapie in Frage kommen) *<u>Ausführungen: Teilpopulation a</u>* Für Patientinnen mit HER2-postivem, inoperablem lokal fortgeschrittenem Brustkrebs ist auf Grundlage vorhandener Evidenz die Strahlentherapie einer medikamentösen Behandlung vorzuziehen, wenn die maximal tolerierte Gesamtdosis durch eine vorherige Strahlentherapie noch nicht ausgeschöpft ist. Die Therapie von Patientinnen mit HER2-postivem, inoperablem lokal fortgeschrittenem Brustkrebs, die nicht für eine Strahlentherapie in Frage kommen ist geprägt von patienten-individuellen Entscheidungen des behandelnden Arztes. Grundsätzlich kommen in diesem Zusammenhang viele im Anwendungsgebiet zugelassene Wirkstoffe als zweckmäßige Behandlungsoptionen in Frage. Eine patientenindividuelle, optimierte Therapie nach Maßgabe des Arztes, wird deshalb als zweckmäßige Vergleichstherapie für das beschriebene Patientenkollektiv festgelegt. Davon umfasst ist auch eine Therapie aus Lapatinib in Kombination mit Capecitabin, wenn Patientinnen zulassungskonform mit Taxanen und Anthrazyklinen vorbehandelt wurden. **<u>Zusammenfassend wird der Zusatznutzen von Trastuzumab Emtansin wie folgt bewertet:</u>** *Teilpopulation a): Patientinnen mit HER2-postivem, inoperablem lokal fortgeschrittenem Brustkrebs:* Für Patientinnen der Teilpopulation a gilt ein Zusatznutzen gegenüber der zweckmäßigen Vergleichstherapie als nicht belegt. *<u>Begründung:</u>* Die erforderlichen Nachweise wurden nicht erbracht (§ 35a Absatz 1 Satz 5 SGB V).

Cochrane Reviews

Moja, 2012: Trastuzumab containing regimens for early breast cancer [14]	1. Fragestellung To assess the evidence on the efficacy and safety of therapy with trastuzumab, overall and in relation to its duration, concurrent or sequential administration with the standard chemotherapy regimen in patients with HER2-positive early breast cancer.
	2. Methodik Population: Women with HER2-positive breast cancer (early or locally advanced) of any age, menopausal status, nodal or hormone-receptor status. Intervention: Trastuzumab given following or in combination with standard chemotherapy regimen Komparator: The same chemotherapy regimen used in the intervention group without trastuzumab Endpunkt: • Primäre Endpunkte: Overall survival (OS) using intention-to-treat (ITT) analysis; Disease-free survival (DFS) • Sekundäre Endpunkte: Cardiac toxicity using per protocol analysis (all patients who received the experimental treatment regardless of compliance); Tumour recurrences (only if data about OS and DFS were unavailable); Other toxicities (defined and graded according to the World Health Organization and National Cancer Institute criteria) evaluated according to per protocol analyses; Brain metastases as first site of relapse; Treatment-related deaths; Quality of life (QoL). Suchzeitraum (Aktualität der Recherche): We searched the Cochrane Breast Cancer Group's (CBCGs) Specialised Trials Register, and used the search strategy developed by the CBCG to search for randomised controlled trials (RCTs) in CENTRAL, MEDLINE, EMBASE, BIOSIS, TOXNET, and the WHO ICTRP search portal (up to February 2010). Anzahl eingeschlossene Studien/Patienten (Gesamt): Eight studies involving 11,991 patients were included. Qualitätsbewertung der Studien: Since the trials were large and conducted at multiple sites, it is likely that these trials had unbiased central randomisation procedures, protocol integrity and rigorous and reliable data registration, in order to satisfy regulatory authorities and human investigation committees. The direct assessment of the methodological quality could not be performed, because details of the methods used (such as the mechanism of allocation concealment) were not always provided in the published reports or congress presentations. None of the studies used blinding to treatment allocation, a common practice in phase III oncological trials, because of the difficulty in concealing different infusion times, schedules and toxicities. This was unlikely to bias the results of the studies where OS was measured, as this outcome was not subject to observer or patient bias in interpretation.
	3. Ergebnisdarstellung Allgemein: Six trials evaluated trastuzumab as an adjuvant therapy (surgery

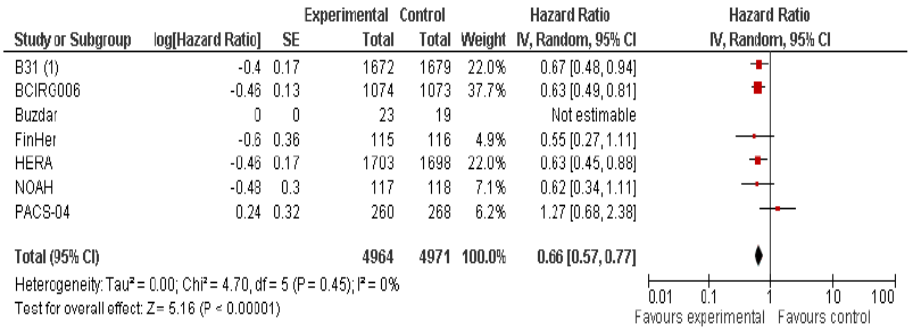
followed by chemotherapy plus or minus trastuzumab) while the **Buzdar and NOAH trials** enrolled patients before surgery and gave trastuzumab on a neoadjuvant basis, together or without chemotherapy. The two neoadjuvant trials included patients with T3N1, T4, any T plus N2 or N3, or any T plus involvement of ipsilateral supraclavicular nodes (NOAH), or patients with clinical stage II-IIIA (Buzdar).

➔ ***Hinweis*: Hinsichtlich Studien die eine neoadjuvante bzw. adjuvante Therapiesituation untersucht hatten, wurde keine getrennte Analyse durchgeführt.**

Wirksamkeit:

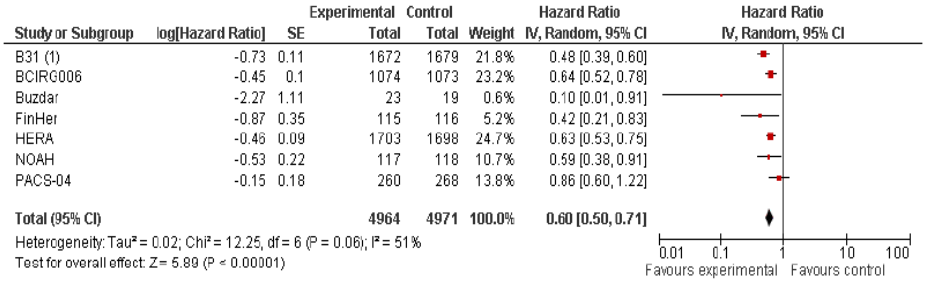
- **OS**: Insgesamt zeigte sich ein statistisch signifikanter Effekt unter einer Trastuzumab-haltigen Therapie im Vergleich zum Kontrollarm (HR: 0.66; 95% KI 0.57 - 0.77, P < 0.00001). Bei Betrachtung der beiden Studien in denen ausschließlich eine neoadjuvante Behandlung untersucht wurde, zeigte sich dieser Effekt nicht (siehe Abbildung unten).
  Hinweis: In the Buzdar trial, no events were reported during a median follow-up of 36.1 months.

Figure 4. Overall survival: all studies.



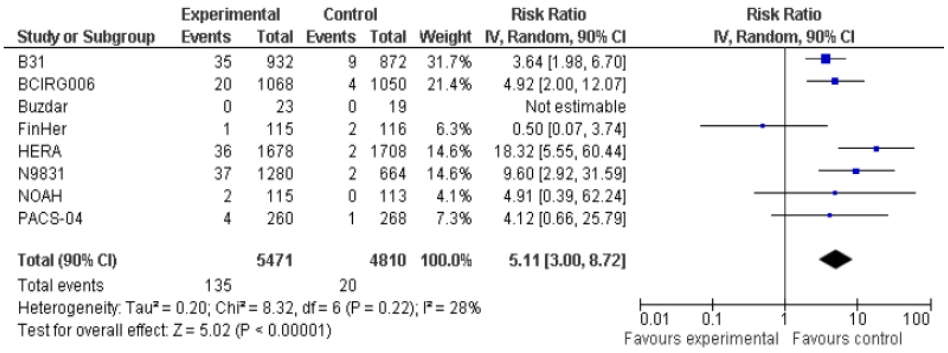
- **DFS:** The overall HR for DFS significantly favoured the trastuzumab-containing regimens (HR 0.60; 95% CI 0.50 to 0.71, P < 0.00001). Heterogeneity across trials was moderate (I^2 = 51%). Dieser Effekt zeigte sich auch Betrachtung der beiden relevanten Studien zur neoadjuvanten Behandlung.
  Hinweis: Hier ist jedoch auf das sehr breite KI bei der Studie von Buzdar (kleine Studie) zu verweisen (siehe Abbildung unten).

Figure 7. Disease-free survival: all studies.



Sicherheit:

- **CHF**: The overall result indicated a higher risk of CHF with trastuzumab (RR 5.11; 90% CI 3.00 to 8.72, P < 0.00001). Heterogeneity was minimal (I^2 = 28%). Bei Betrachtung der beiden Studien in denen ausschließlich eine

	neoadjuvante Behandlung untersucht wurde, zeigte sich dieser signifikante Effekt nicht (siehe Abbildung unten). *Hinweis*: Die Ergebnisse zu diesem Endpunkt für die Studie von Budzar konnten nicht eingeschätzt werden (siehe Abbildung unten). **Figure 8. Congestive heart failure (CHF): all studies.**  • Auch bei den weiteren Sicherheitsendpunkten wie: LVEF (LVEF: RR 1.83; 90% CI 1.36 to 2.47, P = 0.0008) und das Auftreten von Neutropenien (RR: 1.10 [95%KI: 1.00, 1.22; P = 0.096; I²= 51%)], zeigte sich insgesamt ein statistisch signifikant erhöhtes Risiko unter der Therapie mit Trastuzumab, bei Betrachtung der relevanten Studien zu einer neoadjuvanten Therapie zeigte sich kein signifikanter Unterschied zwischen den beiden Armen. • Bei dem Endpunkt neutropenisches Fieber zeigte sich kein statistisch signifikanter Nachteil hinsichtlich einer Kombinationstherapie mit Trastuzumab. Dies war auch der Fall bei Betrachtung der beiden Studien zur neoadjuvanten Therapiesituation. • Ergebnisse zu weiteren Endpunkten wurden für die beiden relevanten Studien (Buzdar und NOAH) nicht berichtet.
	4. Fazit der Autoren: *Trastuzumab significantly improves OS and DFS in HER2-positive women with early and locally advanced breast cancer, although it also significantly increases the risk of CHF and LVEF decline. The available subgroup analyses are limited by the small number of studies. Studies that administered trastuzumab concurrently or sequentially did not differ significantly in efficacy. Shorter duration of therapy may reduce cardiotoxicity and maintain efficacy, however there is insufficient evidence at present to conclude this due to small numbers of patients in these trials.*

Systematische Reviews

Stebbing, 2011: Breast cancer (non-metastatic) [20]	1. Fragestellung siehe Ergebnisdarstellung
	2. Methodik Population: Locally advanced breast cancer (defined according to the TNM staging system of the UICC as stage 3B (includes T4 a–d; N2 disease, but absence of metastases. It is a disease presentation with clinical or histopathological evidence of skin and/or chest-wall involvement, and/or axillary nodes matted together by tumour extension)

	Intervention/Komparator: Siehe Ergebnisteil Endpunkt: OS; rates of local and regional recurrence, rates of mastectomy after breast-conserving treatment, rates of development of metastases, cosmetic outcomes, quality of life; Adverse effects of treatment, including upper-limb lymphoedema Suchzeitraum (Aktualität der Recherche): Clinical Evidence search and appraisal April 2009 Anzahl eingeschlossene Studien/Patienten (Gesamt): Siehe Ergebnisteil Qualitätsbewertung der Studien: Siehe Ergebnisteil zu den einzelnen Studien
	3. Ergebnisdarstellung **Chemotherapy plus monoclonal antibody (Trastuzumab) in women with overexpressed HER2/neu Oncogene:** **Treatment success** *Compared with observation (during or after chemotherapy):* Trastuzumab started after or during chemotherapy, is more effective at 1 year at increasing disease-free survival in HER2-positive women compared with 2 years of observation (moderate-quality evidence). **Mortality** *Compared with observation (during or after chemotherapy):* Trastuzumab, started after chemotherapy but not during chemotherapy, is more effective at 1 year at increasing overall survival in HER2-positive women compared with 2 years of observation (moderate-quality evidence). **Adverse effects** Trastuzumab has been associated with cardiac dysfunction. **Benefits:** *Trastuzumab versus placebo:* We found no systematic review or RCTs. *Trastuzumab versus observation, after chemotherapy:* We found one RCT comparing three treatments: trastuzumab every 3 weeks for 1 year; trastuzumab every 3 weeks for 2 years; or observation. Women completed locoregional therapy and at least 4 cycles of primary or adjuvant chemotherapy before randomisation. The RCT found that 1 year of trastuzumab increased disease-free survival (absence of recurrence, contralateral breast cancer, second non-breast malignant disease, or death without prior recurrence) compared with observation at 2 years (5081 women with HER2-positive and either node-positive or nodenegative breast cancer; AR of recurrence, secondary primary event, or death without prior recurrence: 127/1694 [7%] with 1 year of trastuzumab *v* 220/1693 [13%] with observation; HR 0.54, 95% CI 0.43 to 0.67). It found no significant difference in overall survival between 1 year of trastuzumab and observation at 2 years. Outcomes with 2 years of trastuzumab were not reported. A later subgroup analysis of these data defined populations by nodal status (4 groups: nodal status not assessed, node negative, 1–3 positive nodes, or 4 or more positive nodes) and by steroid hormone receptor status (4 groups: oestrogen-receptor negative plus progesteronereceptor negative, oestrogen-receptor negative plus progesterone-receptor positive, oestrogenreceptor positive plus progesterone-receptor negative, or oestrogen-receptor positive plus progesterone-receptor positive). The analyses found that trastuzumab improved disease-free survival across subgroups compared with observation, with estimated difference in 3-year disease-free survival ranging from +11.3% in women with both hormone receptor-positive, node-negative disease to +0.6% for

	women with hormone receptor-negative, node-negative disease. *Trastuzumab versus observation, starting during chemotherapy:* We found a pooled analysis of two RCTs, which compared doxorubicin plus cyclophosphamide followed by paclitaxel versus doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab (for 1 year). One of the RCTs also included a group with doxorubicin plus cyclophosphamide followed by paclitaxel followed by trastuzumab, which was excluded from joint analysis. The RCTs found that 1 year of trastuzumab significantly increased disease-free survival and overall survival compared with observation at a median follow-up of 2 years (3351 women with HER2-positive and either node-positive or node-negative breast cancer; AR for disease-free survival events: 133/1672 [8%] with trastuzumab *v* 261/1679 [16%] with observation; HR 0.48, 95% CI 0.39 to 0.59; AR for death: 62/1672 [4%] with trastuzumab *v* 92/1679 [6%] with observation; HR 0.67 95% CI 0.48 to 0.93). **Harms:** In women with previous exposure to anthracycline, there is concern about cardiac toxicity associated with trastuzumab therapy. Therefore, the RCTs only included women with normal left ventricular ejection fraction. *Trastuzumab versus observation, after chemotherapy:* The RCT found that 1 year of trastuzumab significantly increased grade 3 or 4 toxicity and severe congestive heart failure compared with observation (at least one grade 3 or 4 event: 132/1677 [8%] with 1 year of trastuzumab *v* 75/1710 [4%] with observation; P <0.001; severe congestive heart failure: 9/1677 [0.5%] with 1 year of trastuzumab *v* 0/1710 [0%] with observation; P = 0.002). It found that left ventricular ejection fraction decreased in a significantly higher proportion of women with trastuzumab than with observation (113/1677 [7%] with trastuzumab *v* 34/1710 [2%] with observation; P <0.001). *Trastuzumab versus observation, starting during chemotherapy:* The RCT found that 1 year of trastuzumab increased cardiac toxicity compared with observation (New York Heart Association class III or IV congestive heart failure or death from cardiac causes; in the first RCT: 4% with trastuzumab *v* 1% with observation; second RCT: 3% with trastuzumab *v* 0% with observation; significance not reported). The RCT found no differences in any other common toxicity criteria (data not reported). ➔ **Clinical guide:** There is no consensus in HER2-positive (either 3+ or FISH-positive) women about whether to start trastuzumab during or after chemotherapy, and current expert opinion seems to favour continuing trastuzumab for 1 year with 3-monthly echocardiograms to assess cardiac function. Patients with HER2+ tumours by immunohistochemistry should have the appropriate HER2 status assessment by FISH. **Primary Chemotherapy:** **Treatment success:** Compared with adjuvant chemotherapy Primary chemotherapy seems to more effective at reducing mastectomy rates but not at reducing locoregional recurrences at 4 years (moderate-quality evidence). **Mortality:** Compared with adjuvant chemotherapy Primary chemotherapy and adjuvant chemotherapy seem to be equally effective at improving overall survival (moderate-quality evidence). **Adverse effects:** Adverse effects of chemotherapy include fatigue, nausea and vomiting, hair loss, bone marrow suppression, neuropathy, and gastrointestinal disturbance. Chemotherapy may impair fertility and ovarian function. **Benefits:**

	Survival: We found no systematic review but found 5 RCTs, which compared primary chemotherapy versus adjuvant chemotherapy. *The first RCT* (272 women with tumours 3 cm or more in whom mastectomy was indicated) compared primary EVMTV (epirubicin, vincristine, mitomycin C, thiotepa, vindesine) chemotherapy versus mastectomy followed by the EVMTV regimen. At an initial median follow-up of 34 months, a significant survival difference was reported in favour of primary chemotherapy (results presented graphically; log rank P = 0.04). However, the final analysis at 124 months showed that the survival improvement was no longer significant, with survival of about 55% in both groups. *The second RCT* (414 women) compared 4 cycles of FAC (fluorouracil, doxorubicin [adriamycin], cyclophosphamide) as primary or adjuvant chemotherapy. At 54 months' follow-up, the primary chemotherapy group had a better overall survival (86% with primary *v* 68% with adjuvant; P = 0.039); however, a subsequent analysis at 105 months did not show a long-term survival benefit. *The third RCT* (309 women) compared 4 cycles of primary MM (mitoxantrone [mitozantrone], methotrexate) chemotherapy followed by surgery and 4 further cycles of MM versus surgery followed by 8 cycles of adjuvant MM. At 48 months' follow-up, there was no difference in survival between the primary and adjuvant groups (84% with primary *v* 82% with adjuvant; reported as not significant). *The fourth, and largest, RCT* (National Surgical Adjuvant Breast and Bowel Project [NSABP]), in which 1523 women were randomised to 4 cycles of AC (doxorubicin [adriamycin], cyclophosphamide) as primary or adjuvant chemotherapy, found identical survival rates (67%) in the two groups at 60 months. *The fifth RCT* (698 women) compared 4 cycles of fluorouracil, epirubicin, and cyclophosphamide, as primary or adjuvant chemotherapy. It found no significant difference between primary and adjuvant chemotherapy in overall survival, progression-free survival, or locoregional recurrence at 4 years (overall survival: 82% with primary *v* 84% with adjuvant; HR 1.16, 95% CI 0.83 to 1.63; progression-free survival: 65% with primary *v* 70% with adjuvant; HR 1.15, 95% CI 0.89 to 1.48; locoregional recurrence at 4 years: 21.5% with primary *v* 17.8% with adjuvant; HR 1.13, 95% CI 0.70 to 1.81). *Mastectomy rates:* We found no systematic review but found three RCTs, which compared mastectomy rates with primary chemotherapy versus adjuvant chemotherapy. *The first RCT* (309 women receiving MM chemotherapy) found that primary chemotherapy significantly reduced the mastectomy rate compared with adjuvant chemotherapy (13% with primary *v* 28% with adjuvant; P <0.005). *The second RCT* (1523 women receiving AC chemotherapy) found that breast conservation rates were lower in the adjuvant arm (60% with adjuvant *v* 67% with primary), although this was not significant. *The third RCT* assessed 272 women at diagnosis in terms of the recommended surgical procedure, and two of three women who were initially advised to have mastectomy were able to have breast-conserving surgery after primary chemotherapy with FAC. **Harms:** We found no evidence that primary chemotherapy has a negative impact on survival. None of the RCTs examining effects on mastectomy rates reported a significantly higher local recurrence rate with primary chemotherapy compared with adjuvant chemotherapy.

	Different primary chemotherapy regimes versus each other **Treatment success:** *Standard compared with dose-intensified anthracycline-based regimens*: A standard-based regimen (cyclophosphamide, epirubicin, fluorouracil) and a dose-intensified regimen (epirubicin, cyclophosphamide, filgrastim) seem to be equally effective at increasing time to progression in women with locally advanced breast cancer (moderate-quality evidence). ➔ *Evidenz Benefits*: We found no systematic review but found one RCT. The RCT (448 women with locally advanced breast cancer) compared a CEF (cyclophosphamide, epirubicin, fluorouracil) regimen versus a dose-intensified ECFi (epirubicin, cyclophosphamide, filgrastim) regimen. It found no significant difference between the regimens in time to progression (recurrence or death) or 5-year survival (median time to progression: 34 months with CEF v 33.7 months with ECFi; P = 0.68; 5-year survival: 53% with CEF v 51% with ECFi; P = 0.94). Complete clinical response rates were similar with both regimens (31% with CEF v 27% with ECFi; P value and RR not reported). ➔ *Evidenz Harms:* In the RCT comparing a CEF versus a dose-intensified ECFi regimen, there were similar numbers of serious adverse events requiring admission to hospital in the groups (60 events with CEF v 68 events with ECFi; absolute numbers of women affected in each group and P value not reported). The dose-intensified ECFi regimen increased nausea and vomiting, and induced more grade 3 and 4 anaemia, but there were fewer febrile neutropenic episodes with ECFi compared with CEF (AR for nausea: 12% with CEF v 22% with ECFi; vomiting: 11% with CEF v 19% with ECFi; anaemia: 16% with CEF v 51% with ECFi; febrile neutropenia: 14% with CEF v 8% with ECFi; P values not reported for any outcome). *FAC regimen (fluorouracil, doxorubicin [adriamycin], and cyclophosphamide) compared with single-agent paclitaxel:* We don't know whether FAC regimens are more effective at improving response rates (low-quality evidence). ➔ *Evidenz Benefits*: We found no systematic review but found one RCT. The RCT (174 women in the USA) compared conventional FAC (fluorouracil, doxorubicin [adriamycin], cyclophosphamide) versus singleagent paclitaxel, and found similar response rates in both groups (79% with FAC v 80% with paclitaxel), with no significant difference in survival rates. ➔ *Evidenz Harms:* In the RCT comparing FAC versus paclitaxel, rates of septic neutropenia and use of granulocyte colony-stimulating factor were higher in women taking paclitaxel (neutropenia: 53% with paclitaxel v 21% with FAC; use of granulocyte colony-stimulating factor: 56% with paclitaxel v 25% with FAC). **Mortality**: *Standard compared with dose-intensified anthracycline-based regimens:* A standard-based (cyclophosphamide, epirubicin, fluorouracil) and a dose-intensified anthracycline regimen (epirubicin, cyclophosphamide, filgrastim) seem to be equally effective at increasing time to death, or 5-year survival rates in women with locally advanced breast cancer (moderate-quality evidence). *FAC regimen (fluorouracil, doxorubicin [adriamycin], cyclophosphamide) compared with single-agent paclitaxel:* We don't know whether FAC regimens are more effective at improving survival (low-quality evidence). **Comment**: More research is needed to determine the optimal regimen for primary treatment.We found little evidence in the literature comparing different combinations, but anthracycline-based combinations probably remain the treatment of choice, with dose intensification not proved to confer additional clinical benefit. Ongoing RCTs are investigating the role of taxane sequencing after anthracycline-based treatment (National Surgical Adjuvant Breast and Bowel Project [NSABP]) and anthracycline in combination with fluorouracil infusion.

	Fazit der Autoren: *Siehe ,,comments“ bei den jeweiligen Ergebnissen.*
Peto, 2012: Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100 000 women in 123 randomised trials. [16]	1. Fragestellung The present report reviews the preliminary taxane trial results and updates the other chemotherapy trial results, assessing the relevance of scheduled drug dosage and investigating whether any of the available patient or tumour characteristics (eg, age, nodal status, tumour diff erentiation, oestrogen receptor [ER] status, use of tamoxifen) aff ect the proportional reductions with modern chemotherapy in breast cancer recurrence and death.
	2. Methodik Population: Early breast cancer patients Intervention / Komparator: Any taxane-plusanthracycline-based regimen versus the same, or more, non-taxane chemotherapy (n=44 000); one anthracyclinebased regimen versus another (n=7000) or versus cyclophosphamide, methotrexate, and fluorouracil (CMF; n=18 000); and polychemotherapy versus no chemotherapy (n=32 000). Endpunkt: breast cancer mortality rate ratios (RRs) Suchzeitraum (Aktualität der Recherche): Methods of trial identification, data checking, analysis, and involvement of trialists in the interpretation of results are as in previous EBCTCG reports (Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer, vol 1: worldwide evidence 1985-1990. Oxford: Oxford University Press, 1990). Information about each individual patient was sought during 2005–10 from all randomised trials begun during 1973–2003. Anzahl eingeschlossene Studien/Patienten (Gesamt): 33 Studien mit n= 45 000 Frauen
	3. Ergebnisdarstellung • In trials adding four separate cycles of a taxane to a fixed anthracycline-based control regimen, extending treatment duration, breast cancer mortality was reduced (RR: 0·86, p=0·0005). • In trials with four such extra cycles of a taxane counterbalanced in controls by extra cycles of other cytotoxic drugs, roughly doubling non-taxane dosage, there was no significant difference. • Trials with CMF-treated controls showed that standard 4AC and standard CMF were equivalent, but that anthracycline-based regimens with substantially higher cumulative dosage than standard 4AC (e.g. CAF or CEF) were superior to standard CMF (RR: 0·78, p=0·0004). • Trials versus no chemotherapy also suggested greater mortality reductions with CAF (RR 0·64, p<0·0001) than with standard 4AC (RR: 0·78, p=0·01) or standard CMF (RR: 0·76, p<0·0001). • In all meta-analyses involving taxane-based or anthracycline-based regimens, proportional risk reductions were little affected by age, nodal status, tumour diameter or diff erentiation (moderate or poor; few were well diff erentiated), oestrogen receptor status, or tamoxifen use. Hence, largely independently of age (up to at least 70 years) or the tumour characteristics currently available to us for the patients selected to be in these trials, some

	taxane-plus-anthracycline-based or higher-cumulative-dosage nthracycline-based regimens (not requiring stem cells) reduced breast cancer mortality by, on average, about one-third. • 10-year overall mortality differences paralleled breast cancer mortality differences, despite taxane, anthracycline, and other toxicities. ➔ Results are also given for subsets of ERpositive disease by HER2 status, age, and differentiation (with a trend towards greater taxane benefit in well differentiated [RR: 0·68, SE 0·16, 2=0·04, n=3000] or moderately differentiated [RR: 0·77, SE 0·07, p=0·001, n= 11 000] ER-positive tumours than in poorly differentiated ER-positive tumours). Most of the women with ER-positive disease had endocrine therapy after their chemotherapy. **Scheduled number of cycles and cytotoxic treatment per cycle** Standard CMF: 6 cycles of C100×14 M40×2 F500×2, given 4-weekly; widely studied Near-standard CMF[5]: 6–12 cycles with same doses as standard CMF and/or C600×2 replacing C100×14 Standard 4AC: 4 cycles of A60 C600, given iv 3-weekly; widely studied Standard 4EC: 4 cycles of E90 C600, given iv 3-weekly CAF: 6 cycles of C100×14 A30×2 F500×2, given 4-weekly CEF: 6 cycles of C75×14 E60×2 F500×2, given 4-weekly Data are drug dose, mg/m²×frequency per cycle (×14=days 1–14 oral; ×2=days 1 and 8 iv). Tabulated treatment schedules do not include any supportive care or cytotoxic dose reduction for acute toxicity. C=cyclophosphamide. M=methotrexate. F=fluorouracil. A=doxorubicin (Adriamycin). E=epirubicin. iv=intravenous. ***Table:*** **Terminology—standard regimens and higher-cumulative-dose regimens**
	4. Fazit der Autoren: *10-year gains from a one-third breast cancer mortality reduction depend on absolute risks without chemotherapy (which, for oestrogen-receptor-positive disease, are the risks remaining with appropriate endocrine therapy). Low absolute risk implies low absolute benefi t, but information was lacking about tumour gene expression markers or quantitative immunohistochemistry that might help to predict risk, chemosensitivity, or both.*
Petrelli, 2011: Neoadjuvant chemotherapy and concomitant trastuzumab in breast cancer: a pooled analysis of two randomized trials. [17]	1. Fragestellung The aim of this meta analysis was to evaluate the benefit of adding concomitant trastuzumab to neoadjuvant (anthracycline and taxane-based) chemotherapy, which was assessed based on two published randomized controlled trials.
	2. Methodik Population: Patients with pathologically confirmed BC and untreated earlier Intervention: Chemotherapy (anthracycline-based) combined with concomitant trastuzumab Komparator: Chemotherapy alone Endpunkt: percentage of patients acquiring pCR in breast and nodes [(bn)pCR],

	median OS, DFS or event-free survival (EFS), specific grade III/IV cardiotoxicity data Suchzeitraum (Aktualität der Recherche): The deadline for the trial publication of this analysis was May 30, 2010. Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 45 trials were retrieved from the primary search after electronic searching on May 30, 2010, and two trials were selected for full review. The other trials have been excluded because they were not randomized, including the patients with metastatic disease, and did not include any arm with concomitant trastuzumab and anthracyclines. Forty-two patients have been analyzed in Buzdar's trial and 235 in Gianni's trial (NOAH Studie) (n= 279 total). In particular, 138 patients received chemotherapy plus trastuzumab and 132 patients received chemotherapy alone in their allocated arms.
	3. Ergebnisdarstellung *Hinweis: Bei den beiden Studien handelt es sich um die beiden betrachteten Studien in dem Cochrane Review von Moja aus dem Jahr 2012!* • The RR of obtaining a pathologically complete response in breast and nodes was 2.07 in the experimental arms (1.41–3.03; P = 0.0002; P for heterogeneity 0.63; fixed effect model). • The RR of being disease-free was 0.67 in favor of the experimental arms (0.48–0.94; P = 0.02; P for heterogeneity 0.22; fixed affect model). • The RR 0.67 of being alive was, not statistically signifikant in favor of the experimental arms (0.39–1.15; P= 0.15). • The RR of a cardiac event was 1.09 in the arms treated with chemotherapy and concomitant trastuzumab, but that is not significant (0.6–1.98; P =0.77).
	4. Fazit der Autoren: *The addition of concomitant trastuzumab to neoadjuvant chemotherapy doubles the risk of obtaining a pathologically complete response in both breast and nodes compared with controls. Trastuzumab significantly reduces the risk of relapse and does not increase the risk of cardiotoxicity, despite being associated with anthracyclines. The largest benefit was observed in a locally advanced patient study.*
Bonilla, 2010: Dose-Dense Chemotherapy in Nonmetastatic Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials [1]	1. Fragestellung We performed a systematic review and meta-analysis of the existing data from randomized controlled trials regarding the efficacy and toxicity of the dose-dense chemotherapy approach in nonmetastatic breast cancer.
	2. Methodik Population: Adult women older than 18 years with early-stage breast cancer (neoadjuvant or adjuvant setting) Intervention: Dose-dense chemotherapy Komparator: Standard chemotherapy schedule Endpunkt: Death, recurrence, adverse events

	Suchzeitraum (Aktualität der Recherche): The Cochrane Cancer Network register of trials, The Cochrane Library, and LILACS and MEDLINE databases (from January 1966 to January 2010) were searched. Anzahl eingeschlossene Studien/Patienten (Gesamt): 10 Studien mit N= 11989 Patientinnen
	3. Ergebnisdarstellung Allgemein: Ten trials met the inclusion criteria and were classified into two categories based on trial methodology. Three trials enrolling 3337 patients compared dose-dense chemotherapy with a conventional chemotherapy schedule (similar agents). Seven trials enrolling 8652 patients compared dose-dense chemotherapy with regimens that use standard intervals but with different agents and/or dosages in the treatment arms. • Patients who received dose-dense chemotherapy had better overall survival (HR of death = 0.84, 95% C] = 0.72 to 0.98, P = .03) and better disease-free survival (HR of recurrence or death = 0.83, 95% CI = 0.73 to 0.94, P = .005) than those on the conventional schedule. • Seven trials enrolling 8652 patients compared dose-dense chemotherapy with regimens that use standard intervals but with different agents and/or dosages in the treatment arms. Similar results were obtained for these trials with respect to overall survival (HR of death = 0.85, 95% CI = 0.75 to 0.96, P = .01) and disease-free survival (HR of recurrence or death = 0.81, 95% CI = 0.73 to 0.88, P < .001). • The rate of nonhematological adverse events was higher in the dose-dense chemotherapy arms than in the conventional chemotherapy arms.
	4. Fazit der Autoren: *Dose-dense chemotherapy results in better overall and disease-free survival, particularly in women with hormone receptor–negative breast cancer. However, additional data from randomized controlled trials are needed before dose-dense chemotherapy can be considered as the standard of care.* 5. Anmerkungen der Autoren: • There was substantial statistical heterogeneity among the trials. • The small number of included trials makes the outcomes more likely to have been influenced by a potential publication bias.
Dent, 2013: HER2-targeted therapy in breast cancer: A systematic review of neoadjuvant [4]	1. Fragestellung In this paper we systematically review neoadjuvant clinical trial data in HER2-positive breast cancer and discuss key unanswered clinical questions.
	2. Methodik Population: Metastatic and early HER2-overexpressing breast cancer Intervention: Trastuzumab plus Chemotherapie Komparator: Trastuzumab allein Endpunkt: pathological complete response (pCR)

	Suchzeitraum (Aktualität der Recherche): All trials of HER2-targeted neoadjuvant therapy were identified through non-date-limited searches of PubMED and Biosis and congress abstract book searches from 2000–2011. Anzahl eingeschlossene Studien/Patienten (Gesamt): A total of 50 trials fulfilled the eligibility criteria; 41 single-arm phase II studies were identified, 37 with trastuzumab and 4 with lapatinib with significant variability in baseline tumour characteristics and pCR rates (range 12–66.7%). Of 9 randomised phase II/III trials, 4 assessed the addition of trastuzumab to chemotherapy and a further 5 randomised trials assessed different HER2-targeting approaches. Four of these studies assessed dual HER2-targeting approaches.
	3. Ergebnisdarstellung • Four randomised trials evaluated the role of single-agent trastuzumab added to a chemotherapy backbone versus the same chemotherapy alone. Overall, these trials reported an increase in pCR rates with the addition of trastuzumab to chemotherapy (pCR 26–65%), compared to chemotherapy alone (pCR 19–27%). This appears to be relatively independent of the type of chemotherapy employed. These results have led to the adoption of combination chemotherapy and trastuzumab as the standard of care in the neoadjuvant setting for women with HER2-overexpressing nonmetastatic breast cancer. • A further five randomised trials evaluated the benefit of other HER2 blockade approaches, including four studies on dual-HER2 blockade. The targeted therapies in each study were combined with conventional chemotherapy backbones comprising taxanes and/or anthracyclines. HER2-targeting approaches universally increased pCR at the expense of increased non-cardiac toxicity when lapatinib, but not pertuzumab, was added to trastuzumab.
	4. Fazit der Autoren: *Overall, the future is looking brighter for patients diagnosed with HER2-positive breast cancer with combinations of HER2-targeted agents showing great promise in improving outcomes. The neoadjuvant setting provides an ideal testing ground for novel agents, where relatively small trials, with carefully conducted sequential biopsy and correlative biomarker studies, are taking us closer to the goal of personalised medicine.*
Chen, 2011: Risk of cardiac dysfunction with trastuzumab in breast cancer patients: A meta-analysis [3]	1. Fragestellung We did a systematic review and meta-analysis of published randomized controlled trials (RCTs) to assess the overall risk of cardiac dysfunction associated with trastuzumab treatment.
	2. Methodik Population: patients with breast cancer; Tumors had to be HER-2 positive Intervention: cancer treatment with trastuzumab Komparator: cancer treatment without trastuzumab Endpunkt: Incidences of congestive heart failure, asymptomatic LVEF decrease

	and cardiac death were extracted from the safety profile in each trial Suchzeitraum (Aktualität der Recherche): We searched PubMed and Web of Science (January 1966–July 2009) and American Society of Clinical Oncology conferences held (January 2000–July 2009) for relevant articles and abstracts. Anzahl eingeschlossene Studien/Patienten (Gesamt): 11,882 patients with breast cancer from 10 RCTs were included for analysis.
	3. Ergebnisdarstellung • The incidences of LVEF decrease and congestive heart failure (CHF) were 7.5% (95% CI 4.2–13.1) and 1.9% (95% CI 1.0–3.8) among patients receiving trastuzumab. Trastuzumab significantly increased the risk of LVEF decrease (RR = 2.13, 95% CI, 1.31–3.49; p = 0.003). • In addition, it significantly increased the risk of CHF (RR = 4.19, 95% CI 2.73–6.42; p < 0.00001). The increased risk of CHF was observed in patients with early stage (RR = 4.05, 95% CI 2.49–6.58; p < 0.00001) as well as metastatic disease (RR = 4.75, 95% CI 1.93–11.71; p = 0.0007). • Furthermore, trastuzumab significantly increased the risk of CHF (RR = 4.27, 95% CI 2.75–6.61, p < 0.00001) in patients receiving anthracycline-based chemotherapy, but not in patients receiving non-anthracycline chemotherapy (RR = 2.42, 95% CI 0.36–16.19, p= 0.36).
	4. Fazit der Autoren: *In conclusion, our study showed that the widely used anti-HER2 antibody trastuzumab is associated with a significantly increased risk of CHF and LVEF decrease in patients with breast cancer. The increased risk was observed in patients with metastatic and early state disease. Risk factors include the use of anthracycline chemotherapy.* 5. Anmerkungen der Autoren: • The New York Heart Association (NYHA) classification used for CHF evaluation in these trials is subjective, with a consequence of potential bias and variation. • The criteria for LVEF decrease varied among these studies. This may contribute to heterogeneity of incidence analysis. Third, although we used the latest follow-up data, it was still inadequate to assess the long-term cardiac toxicity. Long time follow-up may be needed in order to find late sequelae of trastuzumab therapy. Fourth, the meta-analysis was performed at study level; confounding factors for risk factor analysis at patient level cannot be assessed. 6. Anmerkungen FBMed: • Die Heterogenität der Studien war bei dem Vergleich in Bezug auf LVEF sehr hoch (zwischen 78% und 85%, je nach Subgruppe).
Kümler, 2014: A systematic review of dual targeting in HER2-positive breast cancer [11]	1. Fragestellung The present review addresses efficacy and toxicity of dual targeting in HER2-positive breast cancer.
	2. Methodik Population: HER2-positive BC population and phase II or III clinical trials.

	However, if no phase II or III trial were identified for a given combination, we also retrived phase Istudies. Intervention: This paper describes efficacy and safety of lapatinib, pertuzumab or trastuzumab-DM1 in combination with trastuzumab in the (neo)adjuvant and metastatic settings. Furthermore, combinations of trastuzumab and drugs targeting the downstream pathway are described. Komparator: siehe Ergebnisdarstellung Endpunkt: pCR, disease-free survival Suchzeitraum (Aktualität der Recherche): Studies were identified using the PubMed database (all years). In addition, abstracts from annualmeetings of the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium 2007–2013 were retrieved using the same search criteria. Finally, we searched clinicaltrials.gov for ongoing studies. Thereference list was updated in August 2013. Anzahl eingeschlossene Studien/Patienten (Gesamt): In total five studies were phase I/II, 12 were phase II and 5 phase III studies. Very few studies were identified with mTOR inhibitors and drugs targeting the PI3K pathway.
	3. Ergebnisdarstellung • The neoadjuvant trials NeoALTTO and NeoSphere investigating the combination of trastuzumab plus lapatinib and trastuzumab plus pertuzumab, respectively, offered the first evidence of dual targeting being superior to single agent therapy with trastuzumab, in terms of pCR, although data of impact on disease-free survival are still needed. The adjuvant trials ALTTO and APHINITY will provide the proof-of-concept for this strategy. • Although pCR is widely accepted as a surrogate marker of survival, a study by von Minckwitz investigating pCR impact on long term survival demonstrated that pCR is only reliable in some subpopulations. Most of the trials conducted so far in the neoadjuvant setting have not reported on subgroups and even the endpoint of pCR is interpreted different in different studies. Thus, results should be interpreted with caution. • Nevertheless dual targeting seems to be more efficient than single blockade in some patients and if so, the question remains to what extent this is due to reversal of trastuzumab resistance or to independent additive mechanisms; probably more than one mechanism may be involved. In this context not all patients might need dual blockade. On the other hand, from some neoadjuvant trials it also seems clear that selected patients obtain pCR on dual biologic treatment alone and thus can be spared the adverse effects of chemotherapy.
	4. Fazit der Autoren: *Dual blockade is likely to represent a substantial advance for patients with HER2-positive breast cancer. However, the relevant subpopulation remains to be defined and side effects including cardiotoxicity might be a limiting factor to the use. There is an urgent need for prospective biomarker-driven trials to identify patients for whom dual targeting is cost-*

	effective. *In our opinion, dual targeting is here to stay and will evolve during the years to come. However, the absence of response to dual blockade in a sizeable proportion of patients highlight the need for predictive biomarkers of response in view of pursuing this chemotherapy- free option. Furthermore results from ongoing phase III trials are eagerly awaited in order to consolidate the evidence of effect of dual targeting.*
Lemos, 2012: Dose-dense chemotherapy versus conventional chemotherapy for early breast cancer: A systematic review with meta-analysis. [13]	1. Fragestellung This systematic review evaluates the impact of dose-dense (DD) regimens as adjuvant chemotherapy for early breast cancer (EBC).
	2. Methodik Population: patients with breast cancer; Tumors had to be HER-2 positive Intervention: conventional adjuvant chemotherapy Komparator: DD regimen (Dose-dense regimens included the same drugs and total amount as conventional chemotherapy, but applied in shorter intervals) Endpunkt: overall survival (OS), disease-free survival (DFS), and toxicities Suchzeitraum (Aktualität der Recherche): A wide search of computerized databases was conducted, including PubMed/MEDLINE, EMBASE, LILACS, ClinicalTrials.gov and CENTRAL. The ASCO, ESMO and SABCS Meeting websites were also scrutinized. All references of relevant articles were scanned and additional studies of potential interest were retrieved for further analysis. No language restrictions were applied. The last systematic search was dated 03 December 2011. Anzahl eingeschlossene Studien/Patienten (Gesamt): Four studies (N=3418 patients) were included.
	3. Ergebnisdarstellung • The meta-analysis demonstrated that DD therapy can improve DFS (N=3356 patients; HR = 0.83; 95% CI 0.73-0.95; p= 0.005), independent of hormone receptor expression status. There was no OS benefit with DD therapy (N=3356 patients; HR = 0.86; 95% CI 0.73-1.01; p= 0.06) irrespective of tumor hormone receptor status (OS in hormone-positive stratum HR = 0.94; 95% CI 0.74-1.21; OS in hormone-negative stratum HR = 0.78; 95% CI 0.62-0.99; interaction test p= 0.28). • DD regimens caused a small increase in anemia and mucositis, but had no impact on cardiac events, leukemia or myelodysplasia.
	4. Fazit der Autoren: *DD adjuvant chemotherapy can improve DFS of EBC patients with little impact on safety. However there is no clear benefit in OS. Further research may indicate if there is any impact on OS not presently seen due to small sample size, and which patients may derive greater benefit.*

Leitlinien

AWMF, 2012: Interdisziplinäre S3-Leitlinie: Mammakarzinom der Frau: Diagnostik, Therapie und Nachsorge.[12]

Leitlinie der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); federführende Fachgesellschaften Deutsche Krebsgesellschaft e.V. (DKG) und Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

Methodik

Grundlage der Leitlinie: Systematische Recherche nach Studien, Leitlinien und Cochrane-Reviews; anschließender Konsensusprozess zur Formulierung der Empfehlungen (detaillierte Darstellung der Methodik im Leitlinienreport)

Suchzeitraum der Literaturrecherche bis August 2011 (teilweise Aktualisierung der Version aus 2008)

Empfehlungsgrad	**Beschreibung**	**Syntax**
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann
GCP	Statements/Empfehlungen, für die eine Überarbeitung auf der Grundlage von Expertenkonsens der Leitliniengruppe beschlossen wurde, sind als solche ausgewiesen mit der Graduierung „GCP“.	

Level of Evidence (LOE)		**Studien zu Therapie, Prävention, Ätiologie**
1	1a	Qualitativ hochwertiger Systematischer Review (SR) von randomisiert-kontrollierten Studien (RCT) mit geringem Risiko für Verzerrungen
	1b	Einzelne RCT mit geringem Risiko für Verzerrungen
	1c	„Alle oder Keiner“-Prinzip*
2	2a	SR von Kohortenstudien mit geringem Risiko für Verzerrungen
	2b	Einzelne Kohortenstudie mit geringem Risiko für Verzerrungen
	2c	Ergebnisforschung; ökologische Studien
3	3a	SR von Fallkontrollstudien
	3b	Einzelne Fallkontrollstudie
4		Fallserie
5		Expertenmeinung oder basierend auf pathophysiologischen Modellen oder experimenteller Grundlagenforschung oder „Grundprinzipien“

Neoadjuvante (primär systemische) Therapie (NACT oder PST):

- 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.
  Empfehlungsgrad: GCP (Evidenzquellen: Brito, RA et al. 2001; Fisher, B et al. 1997; Kaufmann, M et al. 2006; von Minckwitz, G et al. 2011)

Neoadjuvante oder adjuvante Chemotherapie

- 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. *Empfehlungsgrad: 0 / LoE: 1a (Evidenzquellen: Kaufmann, M et al. 2006; von Minckwitz, G et al. 2011)* • Der Effekt ist bei hormonrezeptornegativen Karzinomen am größten. *LoE: 1a (Evidenzquellen: Bear, HD et al. 2006; von Minckwitz, G et al. 2005; von Minckwitz, G et al. 2011)* • Eine Resektion in den neuen Tumorgrenzen ist möglich, wenn eine R0-Resektion mit ausreichendem Sicherheitsabstand erreicht werden kann. *LoE: 1a (Evidenzquellen: Kaufmann, M et al. 2003; von Minckwitz, G et al. 2011)* **Primäre Hormontherapie bei postmenopausalen Patientinnen** • Eine primäre antiöstrogene systemische Therapie stellt eine Option für postmenopausale Patientinnen mit rezeptorpositivem und HER2-negativem Tumor dar, bei denen eine Operation kontraindiziert ist oder eine Operation abgelehnt wird. *Empfehlungsgrad: GCP* **Neoadjuvante Chemotherapiekombination** • Wenn neoadjuvant eine Chemotherapiekombination zum Einsatz kommt, sollte diese ein Anthrazyklin und ein Taxan (bei HER2-Positivität Trastuzumab) enthalten. Die Dauer der präoperativen Therapie sollte 6–8 Zyklen (entspr. 18–24 Wochen) betragen. *Empfehlungsgrad: GCP (Evidenzquelle: von Minckwitz, G et al. 2011)* *<u>Erläuterungen</u>:* *Zahlreiche Studien haben gezeigt, dass bezüglich des Langzeitüberlebens keinerlei Unterschiede zwischen neoadjuvantem und adjuvantem Einsatz einer Chemotherapie bestehen. In einigen Studien scheint das Lokalrezidivrisiko bei neoadjuvanter Therapie erhöht, wobei hier zum Teil unterlegene bzw. heute nicht mehr dem Standard entsprechende Chemotherapieregime Anwendung fanden (Cochrane: Mieog, JS et al. 2007; Mauri, D et al. 2005).* *Gründe für den Einsatz der neoadjuvanten Chemotherapie (NACT) sind, neben der Verbesserung der Operabilität bzw. der Erhöhung der Rate brusterhaltender Operationen, der Erkenntnisgewinn über die Wirksamkeit der Therapie und die Möglichkeit, im Rahmen der neoadjuvanten Studien schneller individuelle Therapieansätze zu entwickeln (Kaufmann, M et al. 2006). Bei Patientinnen mit HER2-positiver/hormonrezeptornegativer oder triple-negativer Erkrankung kann im Falle einer pathologischen Komplettremission (pCR) von einer sehr günstigen Langzeitprognose ausgegangen werden (von Minckwitz, G et al. 2011).* *Die NACT sollte ein Anthrazyklin und ein Taxan enthalten und über mindestens 6 Zyklen, sämtlich vor der Operation, durchgeführt werden. Bei Patientinnen mit HER2-überexprimierendem Tumor kann die präoperative*

	Gabe von Trastuzumab simultan zur Chemotherapie die pCR signifikant erhöhen (Buzdar, AU et al. 2005; Gianni, L et al. 2010; Untch, M et al. 2011). Die Trastuzumab-Therapie sollte postoperativ für die Dauer von einem Jahr fortgesetzt werden. *Bei postmenopausalen Patientinnen mit hoch hormonrezeptorpositiven Mammakarzinomen kann, wenn eine Operation und eine Chemotherapie nicht möglich sind, eine neoadjuvante endokrine Therapie durchgeführt werden. In dieser Indikation werden Aromatasehemmer der dritten Generation empfohlen (Ellis, MJ et al. 2001; Smith, IE et al. 2005).* **Management von primär lokal/lokoregional fortgeschrittenen Tumoren:** Unter einem lokal fortgeschrittenen Karzinom werden üblicherweise T3- und T4-Tumoren mit oder ohne Axillabefall verstanden, welche noch nicht metastasiert sind. Für manche der Patientinnen mit einem solchen Befund ist eine initiale operative Therapie möglich und sollte entsprechend den vorangegangenen Statements durchgeführt werden (NCCN 2007; Shenkier, T et al. 2004; keine Angabe zur Stärke der Empfehlungen). *Primäre systemische Therapie* Für die meisten dieser Patientinnen ist eine systemische Chemotherapie die Therapie der Wahl. Es ist mit einem Ansprechen von über 60 % zu rechnen. Ziel der Chemotherapie ist das Erreichen der Operabilität. Eine primäre Radiotherapie allein wird nicht empfohlen, kann jedoch in Kombination mit einer systemischen Chemotherapie eingesetzt werden (De Lena, M et al. 1981; Hortobagyi GN et al. 1987; keine Angabe zur Stärke der Empfehlungen). *Inflammatorisches Mammakarzinom* Eine primäre (präoperative, neoadjuvante) systemische Therapie ist beim inflammatorischen Mammakarzinom im Rahmen eines multimodalen Therapiekonzeptes erforderlich (Lucas, FV et al. 1978; NCCN 2007; Thomas, F et al. 1995; Thoms, WW, Jr. et al. 1989; Ueno, NT et al. 1997; keine Angabe zur Stärke der Empfehlungen). Das inflammatorische Mammakarzinom erreicht nur bei optimaler Chemotherapie eine 5-Jahres-Überlebensrate von höchstens 50 % und stellt damit eine prognostisch besonders ungünstige Untergruppe des Mammakarzinoms dar (Genet, D et al. 2007; keine Angabe zur Stärke der Empfehlungen). Die beste lokale Kontrolle sowie die besten Ergebnisse bezüglich des Überlebens werden durch eine Kombination von Chemotherapie, Mastektomie und Strahlentherapie erreicht (keine Evidenzangaben). *Inoperable Patientinnen* Die meisten inoperablen Patientinnen sind ältere Frauen mit beträchtlicher Komorbidität oder schlechtem funktionalem Zustand. Das Ziel der Behandlung dieser Patientinnen ist die Erhaltung der bestmöglichen

<table>
<tr><td></td><td>Lebensqualität bei lokaler Tumorkontrolle.

Bei solchen Patientinnen sollte eine systemische endokrine Therapie versucht werden. Ein Ansprechen auf eine Therapie mit Antiöstrogenen oder Aromatasehemmern kann in den meisten Fällen erwartet werden. Eine (ausschließliche) Radiotherapie stellt eine zusätzliche oder alternative Behandlungsoption dar, insbesondere bei (drohender) Exulzeration des Tumors (De Lena, M et al. 1978; De Lena, M et al. 1981; NCCN 2007; NHS 1994; keine Angabe zur Stärke der Empfehlungen).</td></tr>
<tr><td rowspan="2">NICE, 2009: Early and locally advanced breast cancer. Diagnosis and treatment [15]

Note: This guideline updates and replaces NICE technology appraisal guidance 109 (docetaxel), 108 (paclitaxel) and 107 (trastuzumab)</td><td>The NICE guideline on advanced breast cancer has been updated. It includes recommendations on exercise for people with or at risk of breast-cancer-related lymphoedema, and these are also relevant for people with early or locally advanced breast cancer.</td></tr>
<tr><td>Methodik

Grundlage der Leitlinie: Systematische Literaturrecherche

Suchzeitraum bis 2008

LoE und GoR:

<table>
<tr><td colspan="2">LoE</td></tr>
<tr><td>1++</td><td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td></tr>
<tr><td>1+</td><td>well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td></tr>
<tr><td>1 -</td><td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td></tr>
<tr><td>2++</td><td>High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td></tr>
<tr><td>2+</td><td>Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td></tr>
<tr><td>2 -</td><td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td></tr>
<tr><td>3</td><td>Non-analytic studies, eg case reports, case series</td></tr>
<tr><td>4</td><td>Expert opinion</td></tr>
</table>
Early Breast Cancer:

Recommendations

• Treat patients with early invasive breast cancer, irrespective of age, with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless significant comorbidity precludes surgery.
Qualifying statement: This recommendation is based on a Cochrane review of RCTs with small patient numbers.
• Preoperative systemic therapy can be offered to patients with early invasive breast cancer who are considering breast conserving surgery that is not advisable at presentation. However, the increased risk of local recurrence with breast conserving surgery and radiotherapy rather than mastectomy after systemic therapy should be discussed with the patient.
Qualifying statement: This recommendation is based on the results of a</td></tr>
</table>

	Cochrane review of RCTs of good quality. **<u>Erläuterung zur Evidenz:</u>** *The evidence that describes the role of primary systemic treatment in patients with early invasive breast cancer has been drawn from three systematic reviews (Hind et al., 2006; Mieog et al., 2007 and Trudeau et al,. 2005) and a review providing updated results of two RCTs (Rastogi et al., 2008).* *<u>Primary endocrine therapy</u>: A systematic review of RCTs provides the most applicable data for the use of endocrine therapy as initial treatment in patients > 70 years and reported no significant difference in overall survival between surgery and primary endocrine treatment (Hind et al., 2006). There was evidence of a non-significant trend in favour of surgery plus endocrine therapy over primary endocrine therapy (Hind et al., 2006). There is a statistically significant effect in favour of surgery plus endocrine therapy over endocrine therapy for breast cancer specific survival (Hind et al., 2006).* *<u>Primary chemotherapy</u>: A systematic review (Mieog et al., 2007) and a subsequently published review (Rastogi et al., 2008) reported no significant difference in overall survival or disease-free survival between preoperative and postoperative chemotherapy. A statistically significant difference in rate of mastectomy in favour of preoperative chemotherapy was observed based on pooled estimates from good quality RCTs (Mieog et al., 2007).* **Locally Advanced or Inflammatory Breast Cancer:** **Recommendations** • Offer local treatment by mastectomy (or in exceptional cases, breast conserving surgery) followed by radiotherapy to patients with locally advanced or inflammatory breast cancer who have been treated with chemotherapy. *Qualifying statement: This recommendation is based on evidence from a RCT and retrospective studies and GDG consensus.* **<u>Erläuterung zur Evidenz:</u>** *There is a considerable body of high-quality evidence on the role of primary chemotherapy in patients with locally advanced breast cancer, inflammatory breast cancer, or operable breast cancer. Patients also received loco-regional treatment, the effect of which was not the main focus of the study resulting in little direct evidence on the individual effects of surgery or radiotherapy following primary chemotherapy.*
SIGN, 2013: Treatment of primary breast cancer. [18]	Fragestellung: This guideline provides recommendations based on current evidence for best practice in the treatment of patients with operable early breast cancer. It includes recommendations on surgery, chemotherapy, radiotherapy, endocrine therapy and other therapies, for example biological therapy. It excludes diagnosis, staging, follow up, and management of patients with metastatic disease.
	Methodik

Methodenreport beschreibt systematische Evidenzaufbereitung ohne Konsensusprozesse - eigene Checklisten - Anwendung von GRADE - eigenes Graduierungssystem (siehe Tabellenblatt "SIGN LoE GoR") - keine formalen Konsensusprozesse

LoE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 -	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies, high quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 -	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
GoR	
A	At least one meta-analysis, systematic review, or RCT rated as 1++,and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and

	demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Presenting recommendations:

In this guideline SIGN is piloting new methodology, based on the principles of Grading of Recommendations Assessment, Development and Evaluation (GRADE).

The most apparent difference to other SIGN guidelines is the absence of grades of recommendation. The wording of the recommendation reflects how strongly the guideline development group believes following the recommendation will achieve the expected benefits.

Recommendations are denoted by an **R**. Good practice points on the clinical experience of the guideline development group are denoted by a ✔.

Empfehlungen:

Neoadjuvant systemic therapy

- Neoadjuvant chemotherapy should be considered for all patients with breast cancer whose disease is either:
  - inoperable (locally advanced or inflammatory) but localised to the breast/locoregional lymph node groups, or
  - the only surgical option is mastectomy and downstaging might offer the patient the opportunity for breast conservation.

  (Empfehlungsgrad: R).

Evidenzbasis:

- *Neoadjuvant chemotherapy is widely recommended as part of a multimodal treatment approach for patients with inoperable (locally advanced or inflammatory) breast cancer.(LoE: 1++)*
- *Neoadjuvant chemotherapy is associated with higher rates of breast conservation than adjuvant chemotherapy, with equivalent rates of overall survival and locoregional recurrence, providing surgery is part of the treatment pathway. A Cochrane review concluded that overall survival is equivalent for preoperative chemotherapy compared to adjuvant chemotherapy (HR 0.98, 95% CI 0.87 to 1.09, p=0.67).90 Increased breast conservation rates were observed in patients who received neoadjuvant chemotherapy (RR 0.82 (95% CI,0.76 to 0.89; p<0.00001). No significant increase in locoregional recurrence rates was observed (HR 1.12, 95% CI 0.92 to 1.37, p=0.25) with neoadjuvant chemotherapy compared to adjuvant chemotherapy. Patients who achieve pathological complete response (pCR) show improved survival, compared with patients with residual disease (HR 0.48, 95% CI 0.33 to 0.69, p=0.0001 (LoE: 1++)*
- *There are no significant differences between adjuvant and neoadjuvant*

	chemotherapy for postoperative complications, nausea/vomiting or alopecia. Events of leucopenia and infections (RR 0.69, 95% CI 0.56 to 0.84, p=0.0003) were significantly lower with neoadjuvant chemotherapy.(LoE: 1++) ***Neoadjuvant endocrine therapy*** • Aromatase inhibitor is recommended for ER positive postmenopausal women receiving neoadjuvant endocrine therapy *(Empfehlungsgrad: R).* *<u>Evidenzbasis:</u> A meta-analysis of trials conducted in postmenopausal women concluded that an aromatase inhibitor is associated with higher clinical response rate, RR 1.29 (95% CI 1.14 to 1.47) and radiological (ultrasound) response rate, (RR 1.29, 95% CI 1.10 to 1.51) when compared with tamoxifen. Aromatase inhibitor is also associated with a higher rate of breast conservation surgery than tamoxifen, (RR 1.36, 95% CI 1.16 to 1.59). Although no data on long term outcome (DFS, OS) were reported, adjuvant studies demonstrate that treatment with an AI is likely to be superior.* *In postmenopausal women, there was no significant difference in the rates of hot flushes, nausea, or fatigue in the aromatase inhibitor group compared with tamoxifen groups. Headache was more common in the women treated with AI (RR 2.02, 95% CI 1.18 to 3.45).* *One Japanese RCT showed AI and concomitant ovarian suppression to be superior to tamoxifen in pre-menopausal women. There are insufficient data to guide the optimum endocrine therapy in premenopausal women. There is insufficient evidence to recommend one AI over another, or for duration of therapy.* *(LoE: 1+)* **Anthracycline-taxane combinations** • <u>Empfehlung</u>: Anthracycline-taxane-based chemotherapy combinations should be considered for all patients receiving neoadjuvant chemotherapy (Empfehlungsgrad: R). *<u>Evidenz</u>: Breast conservation rates and rates of pCR are higher in patients treated with a combination of anthracycline and taxane-based neoadjuvant chemotherapy, compared with non-taxane based chemotherapy.94,95 Breast conservation surgery rates were higher with a taxane (absolute difference (AD) 3.4%, p=0.12). There was a trend to higher pCR in patients treated with taxanes, which reached statistical significance in patients receiving sequential anthracyclines/taxanes (AD 2.4%, p=0.013).96 Pooled analysis of seven trials indicated higher pCR in patients receiving a taxane (29% v 15% in ER negative patients, p<0.001 and 8.8% v 2.0% in ER+ patients, p<0.001) compared to no taxane.* *(LoE:* 1+; 1++; 2-) **Trastuzumab** <u>Empfehlungen:</u>

	• Patients with HER-2 positive breast cancer, receiving neoadjuvant chemotherapy, should receive trastuzumab, either as adjuvant treatment or with non-anthracycline-based neoadjuvant chemotherapy. • Cardiac function should be monitored in patients being treated with anthracyclines and/or trastuzumab. • Trastuzumab should be used with caution in patients with significant cardiac comorbidity. The benefits of adjuvant chemotherapy with or without trastuzumab may be outweighed by the potential harms in these patients, and treatment should only be recommended after careful consideration. *(Empfehlungsgrad: R).* *Evidenz: In patients with HER-2 positive disease, adjuvant or neoadjuvant trastuzumab leads to improved DFS (HR 0.60, 95% CI 0.50 to 0.71, p<0.00001) and OS (HR 0.66, 95% CI 0.57 to 0.77, p<0.00001) with no heterogeneity of effect between adjuvant and neoadjuvant administration of trastuzumab. A meta-analysis has shown that use of neoadjuvant trastuzumab also improves pCR rates (RR 1.85, 95% CI 1.39 to 2.46, p<0.001), although no difference was seen in the rate of breast conservation surgery (OR 0.98, 95% CI 0.80 to1.19, p=0.82). A higher rate of breast conservation surgery has been reported in one trial of patients with locally advanced breast cancer receiving neoadjuvant trastuzumab in addition to chemotherapy (23% v 13%).A combined analysis of neoadjuvant and adjuvant trials reported a significantly increased risk of congestive heart failure (RR 5.11, 90% CI 3.00 to 8.72, p<0.00001) and LVEF decline (RR 1.83, 90% CI 1.36 to 2.47, p=0.0008) when trastuzumab is added to chemotherapy. There was no difference in haematological toxicities.* *(LoE:* 1+ - 1++)
CCO, 2011: The Role of Taxanes in Neoadjuvant Chemotherapy for Women with Non-metastatic Breast Cancer.[2] ***Hinweis:*** *Evidence-based Series 1-20 Version 2 was reviewed in January 2014 and the Breast Disease Site Group (DSG) made the decision that EBS 1-20 Version 2 will not be updated as it will be replaced by a*	Fragestellungen: 1. Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes (clinical response, pathologic response, breast conservation, disease-free survival, or overall survival) relative to other neoadjuvant regimens? 2. Do neoadjuvant taxane-containing regimens improve clinically meaningful outcomes relative to adjuvant taxane-containing regimens? 3. What is the preferred dose and schedule for neoadjuvant taxane administration? 4. What are the harms associated with neoadjuvant taxane-containing regimens?
	Methodik Evidenz- und konsensbasierte LL This guidance document was originally released by the Program in Evidence-based Care, Cancer Care Ontario, in 2004. In July 2011 the PEBC guideline update strategy was applied and the new updated document released in

comprehensive practice guideline on Optimal Systematic Therapy for Early Female Breast Cancer that include the more recent literature.	September 2011. The Summary and the Full Report in this version are the same as in the December 2004 version.

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version Dec 2004	1980 - 2004	Full Report	Peer review publication[1] Web publication	Not Applicable
Version 2 Sep 2011	2004-2011	New data found in Document Assessment and Review Tool	Updated Web publication	Original recommendations ENDORSED

Note: The 2004 guideline recommendations are ENDORSED: This means that the recommendations are still current and relevant for decision making.

New search (September 2004–April 2011)

Recommendations

- When neoadjuvant 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or doxorubicin and cyclophosphamide (AC) chemotherapy regimen is planned for a woman with non-metastatic breast cancer, a neoadjuvant taxane (paclitaxel or docetaxel) should also be offered. Based on evidence from clinical trials, the following regimens are recommended:
- Paclitaxel (80mg/m2), administered weekly for 12 weeks prior to the anthracycline-based regimen.
- Docetaxel (100mg/m2), administered every three weeks for four cycles following the anthracycline-based regimen.
- There is no evidence at this time to suggest that one taxane is superior to the other in the neoadjuvant setting.

Qualifying Statements

- Neoadjuvant therapy is not the standard of care for operable breast cancer but is usually given to improve the likelihood of breast conservation for large operable breast cancer or to increase the possibility of operability for locally advanced or inflammatory breast cancer.
- There is no evidence in the neoadjuvant setting for the use of taxanes after optimally dosed anthracycline-based regimens, such as 5-fluorouracil, epirubicin, and cyclophosphamide (FEC-100 or CEF).
- The recommended schedule for paclitaxel therapy (i.e., weekly) is based on two trials of weekly versus three-weekly regimens. There were no direct comparisons available for docetaxel; therefore, the recommended schedule (i.e., three-weekly) is based on that which showed improved efficacy in trials comparing a docetaxel-containing regimen with a non-docetaxel regimen. The suggested doses for paclitaxel and docetaxel are those associated with the recommended schedule.
- While neoadjuvant paclitaxel and docetaxel are recommended in sequence with a standard anthracycline-based regimen, it may be appropriate to switch to an anthracycline-based regimen from paclitaxel or to docetaxel from an anthracycline-based regimen earlier if the

	patient's disease progresses while on the initial regimen. • The data supporting neoadjuvant taxane therapy are maturing. While results to date do not support an increase in adverse events relative to other settings, physicians should monitor patients carefully for toxicity, especially hematologic toxicity, neurologic toxicity (with paclitaxel), and hand-foot syndrome (with docetaxel). **Key Evidence** • Nine randomized paclitaxel trials (five phase III and four phase II) were identified. Three trials compared neoadjuvant paclitaxel-containing regimens to other neoadjuvant regimens, one compared a neoadjuvant paclitaxel-containing regimen to a paclitaxel-containing adjuvant regimen, and five evaluated a neoadjuvant paclitaxel dose and/or schedule. • One of three trials with comparative data showed significantly improved complete pathologic response with neoadjuvant paclitaxel and epirubicin therapy compared with neoadjuvant 5-fluorouracil, epirubicin, and cyclophosphamide therapy (n=30). • Improved rates of breast conservation and nodal involvement at surgery were reported with neoadjuvant therapy in the only trial comparing neoadjuvant with adjuvant paclitaxel (n=923). • Of the five paclitaxel trials evaluating neoadjuvant dose and/or schedule, three reported statistically significant differences. The first detected improved pathologic and clinical complete response rates with weekly cisplatin, epirubicin, and paclitaxel therapy versus three-weekly epirubicin and paclitaxel therapy (n=130). The second reported superior pathologic complete response with weekly paclitaxel therapy followed by 5-fluorouracil, doxorubicin, and cyclophosphamide compared with three-weekly paclitaxel followed by 5-fluorouracil, doxorubicin, and cyclophosphamide (n=236). The third (n=475) reported superior pathologic complete response and breast conservation rates with sequential paclitaxel and epirubicin therapy compared with combination therapy. • Nine randomized docetaxel trials (six phase III and three phase II) were identified. Seven trials compared neoadjuvant docetaxel-containing regimens to other neoadjuvant regimens, and two trials evaluated neoadjuvant docetaxel dose and/or schedule. • Of six docetaxel trials comparing a neoadjuvant docetaxel-containing regimen to other neoadjuvant regimens, two reported significant differences. The first reported improved clinical response, breast conservation, disease-free survival, and overall survival rates with neoadjuvant docetaxel therapy compared with neoadjuvant cyclophosphamide, vincristine, doxorubicin, and prednisolone in patients who received and responded to initial cyclophosphamide, vincristine, doxorubicin, and prednisolone (n=145). There was a trend towards improved complete pathologic response. A second trial demonstrated improved complete breast response, overall clinical response, and pathologic node status in women receiving neoadjuvant doxorubicin and cyclophosphamide followed by docetaxel compared with those receiving

	neoadjuvant doxorubicin and cyclophosphamide alone (n=2,255). Disease-free and overall survival was not reported. • Of two trials evaluating docetaxel dose and/or schedule, one (n=288) detected improved pathologic complete response and breast conservation with longer combination epirubicin and docetaxel therapy (six versus three cycles). • One practice guideline was identified. The Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer report 15, Treatment for Women with Stage III or Locally Advanced Breast Cancer, endorsed the use of neoadjuvant anthracycline-based chemotherapy. As of September 2004, the Committee felt that there were insufficient data to make definitive recommendations concerning the use of taxane-containing regimens in locally advanced breast cancer; however, this was subsequently questioned.
EMSO, 2013: Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. [19]	Allgemeine Empfehlungen zum frühen Brustkrebs
	Methodik Keine allgemeinen Angaben zur Methodik - ist jedem einzelnen Treffer zu entnehmen.
	Primary (neoadjuvant) systemic therapy: • In locally advanced and large 'operable' cancers, in particular when mastectomy is required due to tumour size, primary systemic therapy (used before local treatment) may allow for achieving operability or decreasing the extent of surgery *[I, A]*. • In operable cases, the timing of treatment (pre- versus postoperative) has no effect on long-term outcomes *[II, C].* • All modalities (chemotherapy, ET and targeted therapy) used in adjuvant treatment may also be used preoperatively. If chemotherapy is used, it is recommended to deliver all planned treatment without unnecessary breaks, i.e. without dividing it into preoperative and postoperative periods, irrespective of the magnitude of tumour response *[V, B].* • This will increase the probability of achieving a pCR, which is a proven factor for good prognosis. For the same reason, in HER2-positive breast cancer, trastuzumab therapy should be started in the neoadjuvant setting in association with the taxane part of the chemotherapy regimen, thus increasing the probability of achieving a pCR. The chemotherapy regimens to be used in the neoadjuvant setting are the same ones used in the adjuvant setting. Unfortunately, there are no validated predictive markers to allow the tailoring of the regimen to the individual patient. It is therefore recommended that a sequential regimen of anthracyclines and taxanes is used *[I, B].* • ER-positive, HER2-negative carcinomas, especially of the lobular subtype, are generally less responsive to primary chemotherapy than ER-negative and HER2-positive tumours and may benefit more from primary ET. ET is usually given for 4–6 months before surgery and

	continued postoperatively; for post-menopausal patients, AIs are more effective than tamoxifen in decreasing the tumour size and facilitating less extensive surgery *[I, A].*

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 26.08.2014

#	Suchfrage
#1	cancer* or tumour* or tumor* or adenocarcinoma* or carcinoma* or neoplasm* or malignancy:ti (Word variations have been searched)
#2	breast:ti (Word variations have been searched)
#3	#1 and #2
#4	MeSH descriptor: [Breast Neoplasms] explode all trees
#5	#3 or #4
#6	early or locally next advanced or LABC or IBC or inflammatory or neoadjuvant or neo next adjuvant or non next metastatic:ti,ab,kw (Word variations have been searched)
#7	operable or pre next operative or preoperative or pre next surgery or presurgery or pre next surgical or presurgical:ti,ab,kw (Word variations have been searched)
#8	(stage next (I* or II* or III* or T2*)):ti,ab,kw (Word variations have been searched)
#9	#6 or #7 or #8
#10	#5 and #9
#11	primary next breast next cancer:ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#12 Publication Year from 2009 to 2014

MEDLINE (PubMed) SR/ HTA am 26.08.2014

#	Suchfrage
#1	Search ((((((cancer*[Title]) OR tumour*[Title]) OR tumor*[Title]) OR adenocarcinoma*[Title]) OR carcinoma*[Title]) OR neoplasm*[Title]) OR malignancy[Title]
#2	Search breast[Title]
#3	Search (#1 AND #2)
#4	Search "breast neoplasms/drug therapy"[MeSH Terms]
#5	Search ((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR treat*[Title/Abstract]
#6	Search (#3 AND #5)
#7	Search (#4 OR #6)
#8	Search early[Title/Abstract]
#9	Search locally advanced[Title/Abstract]
#10	Search LABC[Title/Abstract]
#11	Search IBC[Title/Abstract]
#12	Search inflammatory[Title/Abstract]
#13	Search operable[Title/Abstract]
#14	Search pre operative[Title/Abstract]
#15	Search preoperative[Title/Abstract]
#16	Search pre surgery[Title/Abstract]
#17	Search presurgery[Title/Abstract]
#18	Search pre surgical[Title/Abstract]
#19	Search presurgical[Title/Abstract]
#20	Search (neoadjuvant[Title/Abstract]) OR neo adjuvant[Title/Abstract]

#21	Search stage I*[Title/Abstract]
#22	Search stages I*[Title/Abstract]
#23	Search stage II*[Title/Abstract]
#24	Search stages II*[Title/Abstract]
#25	Search stage III*[Title/Abstract]
#26	Search stages III*[Title/Abstract]
#27	Search stage T2*[Title/Abstract]
#28	Search stages T2*[Title/Abstract]
#30	Search non-metastatic[Title/Abstract]
#31	Search (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #30)
#32	Search primary breast cancer[Title/Abstract]
#33	Search (#5 AND #32)
#34	Search (#7 AND #31)
#35	Search (#33 OR #34)
#36	Search ((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#37	Search (#35 AND #36)
#38	Search (#33 OR #34) Filters: Systematic Reviews
#39	Search (#33 OR #34) Filters: Systematic Reviews; Meta-Analysis
#40	Search (#33 OR #34) Filters: Systematic Reviews; Meta-Analysis; Technical Report
#41	Search (#37 OR #40)
#42	Search (#37 OR #40) Filters: published in the last 5 years

MEDLINE (PubMed) nach Leitlinien am 18.08.2014

#	Suchfrage
#3	Search "Breast Neoplasms"[Majr]
#4	Search breast[Title]
#5	Search ((((((cancer*[Title]) OR tumour*[Title]) OR tumor*[Title]) OR adenocarcinoma*[Title]) OR carcinoma*[Title]) OR neoplasm*[Title]) OR malignancy[Title]
#6	Search (#4 AND #5)
#7	Search (#3 OR #6)
#8	Search ((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR ((guideline*[Title]) NOT medline[sb])
#9	Search (#7 AND #8)
#10	Search (#7 AND #8) Filters: published in the last 5 years

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