Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-B-232 Trastuzumab Emtansin

Stand: Dezember 2019

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

Trastuzumab Emtansin
zur adjuvanten Behandlung von Patienten mit HER2-positivem Brustkrebs nach einer neoadjuvanten Taxan-basierten und HER2-gerichteten Therapie

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“* • Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für das metastasierte Mammakarzinom
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Strahlentherapie • Radiomenolyse • Ovarektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Pertuzumab: Beschluss vom 20.12.2018 Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (Off-Label-Use), Stand 13. Juli 2018: • Gemcitabin in der Monotherapie beim Mammakarzinom der Frau (nicht verordnungsfähig) Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL), Stand 19. April 2018 • Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen für Patientinnen mit Brustkrebs Beschlussdes Gemeinsamen Bundesausschusses vom 15. Juli 2010 über eine Beauftragung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG): Nutzenbewertung von Aromatasehemmern zur Behandlung des Mammakarzinoms der Frau Richtlinie des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung), Stand 17. Mai 2018 • Protonentherapie beim Mammakarzinom

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

Trastuzumab Emtansin
zur adjuvanten Behandlung von Patienten mit HER2-positivem Brustkrebs nach einer neoadjuvanten Taxan-basierten und HER2-gerichteten Therapie

Kriterien gemäß 5. Kapitel § 6 VerfO	
	Beschluss des Gemeinsamen Bundesausschusses vom 19. Dezember 2013 über die Einleitung des Beratungsverfahrens: Antrag auf Bewertung biomarkerbasierter Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mamma-Karzinom gemäß §135 Abs. 1 und §137c des Fünften Buch Sozialgesetzbuch (SGB V) Beschluss des Gemeinsamen Bundesausschusses vom 5. Juli 2018 über eine Beauftragung des Instituts für Qualität und Wirtschaftlichkeit im Gesundheitswesen: Addendum zur Bewertung von biomarkerbasierten Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mamma-Karzinom
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Trastuzumab Emtansin L01XC14 Kadcyla®	Zugelassenes Anwendungsgebiet: Kadcyla wird als Einzelsubstanz zur adjuvanten Behandlung bei erwachsenen Patienten mit HER2-positivem Brustkrebs im Frühstadium angewendet, die nach einer neoadjuvanten Taxan-basierten und HER2-gerichteten Therapie eine invasive Resterkrankung in der Brust und/oder den Lymphknoten aufweisen.
Antiestrogene	
Tamoxifen L02BA01 generisch	• Adjuvante Therapie nach Primärbehandlung des Mammakarzinoms. • Metastasierendes Mammakarzinom.
Aromatasehemmer	
Anastrozol L02BG03 generisch	• Adjuvante Behandlung postmenopausaler Frauen mit hormonrezeptorpositivem, nicht fortgeschrittenem, invasivem Mammakarzinom. • Adjuvante Behandlung postmenopausaler Frauen mit hormonrezeptorpositivem, nicht fortgeschrittenem Mammakarzinom, die bereits 2 bis 3 Jahre eine adjuvante Behandlung mit Tamoxifen erhalten haben. • Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen.
Letrozol L02BG04 generisch	• Adjuvante Therapie postmenopausaler Frauen mit hormonrezeptor-positivem primärem Mammakarzinom. • Erweiterte adjuvante Therapie des hormonabhängigen primären Mammakarzinoms bei postmenopausalen Frauen nach vorheriger adjuvanter Standardtherapie mit Tamoxifen über 5 Jahre. • First-Line-Therapie des hormonabhängigen fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen. • Behandlung des Mammakarzinoms im fortgeschrittenen Stadium nach Rezidiv oder Progression der Erkrankung bei Frauen, die sich physiologisch oder nach einem künstlichen Eingriff in der Postmenopause befinden und die zuvor mit Antiöstrogenen behandelt wurden. • Neoadjuvante Behandlung postmenopausaler Frauen mit hormonrezeptor-positivem, HER-2-negativem Mammakarzinom, bei denen eine Chemotherapie nicht in Betracht kommt und ein sofortiger chirurgischer Eingriff nicht indiziert ist. Bei Patientinnen mit hormonrezeptor-negativem Mammakarzinom ist die Wirksamkeit nicht belegt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Exemestan L02BG06 Aromasin®	• adjuvante Behandlung eines Östrogenrezeptor-positiven, invasiven, frühen Mammakarzinoms bei postmenopausalen Frauen nach 2 – 3 Jahren adjuvanter Initialtherapie mit Tamoxifen. • Behandlung des fortgeschrittenen Mammakarzinoms bei Frauen mit natürlicher oder induzierter Postmenopause nach Progression unter Antiöstrogenbehandlung. Bei Patientinnen mit negativem Östrogenrezeptor-Status ist die Wirksamkeit nicht belegt.
GnRH-Analoga	
Leuprorelin L02AE02 Enantone-Gyn®	• Mammakarzinom prä- und perimenopausaler Frauen, sofern eine endokrine Behandlung angezeigt ist. • […]
Goserelin L02AE03 Zoladex®	• Behandlung von Patientinnen mit Mammakarzinom (prä- und perimenopausale Frauen), bei denen eine endokrine Behandlung angezeigt ist. • […]
Zytostatika	
Cyclophosphamid L01AA01 generisch	Cyclophosphamid ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: • Adjuvante Therapie des Mammakarzinoms nach Resektion des Tumors beziehungsweise Mastektomie. • […]
Docetaxel L01CD02 generisch	Docetaxel ist in Kombination mit Doxorubicin und Cyclophosphamid angezeigt für die adjuvante Therapie von Patientinnen mit: • operablem, nodal positivem Brustkrebs, • operablem, nodal negativem Brustkrebs. Bei Patientinnen mit operablem, nodal negativem Brustkrebs sollte die adjuvante Therapie auf solche Patientinnen beschränkt werden, die für eine Chemotherapie gemäß den international festgelegten Kriterien zur Primärtherapie von Brustkrebs in frühen Stadien infrage kommen.
Doxorubicin L01DB01 generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: • Mammakarzinom • […] Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Epirubicin L01DB03 generisch	Epirubicin wird zur Behandlung verschiedener Neoplasien eingesetzt, einschließlich: • Mammakarzinom • […]
5-Fluorouracil L01BC02 generisch	• Adjuvante Therapie des primären invasiven Mammakarzinoms • […]
Methotrexat L01BA01 generisch	[…] Mammakarzinome: In Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.
Paclitaxel L01CD01 generisch	[…] Mammakarzinom Im Rahmen einer adjuvanten Therapie ist Paclitaxel zur Behandlung von Patientinnen mit Lymphknoten-positivem Mammakarzinom nach vorangegangener Therapie mit Anthracyclinen und Cyclophosphamid (AC) angezeigt. Die adjuvante Behandlung mit Paclitaxel kann als Alternative zu einer verlängerten AC-Therapie betrachtet werden.
Vincristin L01CA02 generisch	Vincristin wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: • soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom. • […]
HER2-gerichtete Therapien	
Trastuzumab L01XC03 Herceptin®	<u>Brustkrebs im Frühstadium</u> 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.

Pertuzumab L01XC13 Perjeta®	<u>Brustkrebs im Frühstadium (early breast cancer – EBC)</u> Perjeta ist zur Anwendung in Kombination mit Trastuzumab und Chemotherapie indiziert zur: • neoadjuvanten Behandlung von erwachsenen Patienten mit HER2-positivem lokal fortgeschrittenem, entzündlichem oder frühem Brustkrebs mit hohem Rezidivrisiko • adjuvanten Behandlung von erwachsenen Patienten mit HER2-positivem frühem Brustkrebs mit hohem Rezidivrisiko
Proteinkinaseinhibitoren	
Everolimus L01XE10 Afinitor®	Hormonrezeptor-positives, fortgeschrittenes Mammakarzinom: Afinitor wird in Kombination mit Exemestan zur Therapie des Hormonrezeptor-positiven, HER2/neu-negativen, fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen ohne symptomatische viszerale Metastasierung angewendet, nachdem es zu einem Rezidiv oder einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.
Neratinib L01XE45 Nerlynx®	Nerlynx ist indiziert für die erweiterte adjuvante Behandlung von erwachsenen Patienten mit Hormonrezeptor-positivem, HER2-überexprimiertem/amplifiziertem Brustkrebs in einem frühen Stadium, deren vorherige Trastuzumab-basierte adjuvante Therapie seit weniger als einem Jahr abgeschlossen ist.
Lapatinib L01XE07 Tyverb®	Tyverb ist angezeigt zur Behandlung von erwachsenen Patienten mit Brustkrebs, deren Tumore HER2 (ErbB2) überexprimieren; • In Kombination mit Capecitabin bei Patienten mit fortgeschrittener oder metastasierter Erkrankung, die nach vorangegangener Therapie, die Anthrazykline und Taxane sowie in der metastasierten Situation Trastuzumab einschloss, progredient verläuft • […]

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2018-B-232 (Trastuzumab Emtansin)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	15. Januar 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AI	Aromataseinhibitoren
AC	Doxorubicin + Cyclophosphamid
ACE	angiotensin converting enzyme
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
CF	conventional fractionation
CI	Confidence Interval
CHF	congestive heart failure
CMF	cyclophosphamide, methotrexate, and 5-fluorouracil
CNS	zentrales Nervensystem
DAHTA	Deutsche Agentur für Health Technology Assessment
DCIS	ductal carcinoma in situ
DFS	Disease-free-survival
EBC	Early breast cancer
ER	estrogen receptor
ESMO	European Society for Medical Oncology
EXE	Exemestan
FEC	5-Fluorouracil / Epirubicin / Cyclophosphamid
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendation
HER2	human epidermal growth factor receptor 2
HER2/neu	Human Epidermal Growth Factor Receptor 2, also known as Neu
HF	hypofractionation
HR	Hormonrezeptor
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
ITT	Intention to treat

k.A	keine Angaben
LoE	Level of Evidence
LVEF	left ventricular ejection fraction.
MBC	Metastatic breast cancer
NAC	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCCP	National Cancer Control Programme
NCI	U.S. *National Cancer Institute*
NCICTC	National Cancer Institute Common Toxicity Criteria
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NNH	Number needed to harm
OR	Odds Ratio
OS	Overall survival
pCR	pathologic complete response
PEBC	Program in Evidence-Based Care
PFS	Progression free survival
PLD	pegylated liposomal doxorubicin
RR	Relatives Risiko
RT	radiotheraapy
SAE	serious adverse event
SIGN	Scottish Intercollegiate Guidelines Network
TH	Paclitaxel and trastuzumab
TCH	Docetaxel, carboplatin and trastuzumab
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WBI	whole breast irradiation

1 Indikation

Anwendungsgebiet laut Beratungsanforderung:

Kadcyla wird als Einzelsubstanz zur adjuvanten Behandlung bei erwachsenen Patienten mit HER2-positivem Brustkrebs im Frühstadium angewendet, die nach einer neoadjuvanten Taxan-basierten und HER2-gerichteten Therapie eine invasive Resterkrankung in der Brust und/oder den Lymphknoten aufweisen.

Indikation für die Synopse:

Neo-adjuvante und adjuvante Behandlung des HER2-positiven und HER2-/HR-positiven Brustkrebs

Hinweis:

Nicht für diese Synopse berücksichtigt wurden

- alleinige Metastasen- oder Lymphknotenbehandlung,
- Behandlung von oder Therapien zur Vermeidung/ Verminderung von Nebenwirkungen,
- verschiedene Behandlungsregime (Kombination von Wirkstoff – Zeitintervall – Dosierierung sowie Behandlungsabfolgen verschiedener Wirkstoffe sowie Wirkstoff-Zeitintervall-Dosierierung-Kombinationen)

Strahlentherapie, Radiomenolyse und Ovarektomie wurden unabhängig vom HER2-Status aufgenommen, sofern es sich um adjuvante/ neoadjuvante Therapiesituationen handelt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Mammakarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 09.11.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1686 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 48 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2017 [26].

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

1.4.3.1Strahlentherapie nach brusterhaltender Operation

Die perkutane Strahlentherapie verbessert die lokale Tumorkontrolle und das Gesamtüberleben. Eine homogene Nachbestrahlung des verbliebenen Brustgewebes einschließlich der angrenzenden Thoraxwand ist nach brusterhaltendem operativen Vorgehen grundsätzlich indiziert.

Eine zusätzliche lokale Dosisaufsättigung (Boost) des Tumorbettes senkt in allen Altersgruppen die lokale Rezidivrate ohne zu einem signifikanten Überlebensvorteil zu führen.

Bei geringem Rezidivrisiko (ältere Patientinnen) soll unter Abwägung der Vor- und Nachteile (Fibrose) über die Durchführung einer Boostbestrahlung entschieden werden.

1.4.3.2Strahlentherapie nach Mastektomie

Eine postoperative Radiotherapie der Thoraxwand senkt das Risiko eines lokoregionären Rezidivs und verbessert das Gesamtüberleben bei Patientinnen mit hohem Lokalrezidivrisiko. Sie ist insbesondere bei folgenden Konstellationen indiziert:

- bei Patientinnen mit T3/T4- Tumoren, inklusive inflammatorisches Karzinom,

- bei Befall von vier und mehr axillären Lymphknoten,

- bei inkompletter Tumorentfernung (R1-/R2-Resektion).

Nach primärer systemischer Therapie soll sich die Indikation zur Radiotherapie nach der prätherapeutischen T- und N-Kategorie, unabhängig vom Ausmaß des Ansprechens auf die primäre systemische Therapie, richten.

(…)

1.4.4 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 Beratung 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.

Alle anderen Patientinnen haben ein erhöhtes Risiko.

Jede Patientin mit positivem Hormonrezeptorstatus soll eine endokrine Therapie erhalten.

Bei Patientinnen mit erhöhtem Risiko und rezeptornegativem Befund sollte eine Chemotherapie in Betracht gezogen werden. 0Die Chemotherapie muss in ausreichend hoher Dosierung und ausreichend lange erfolgen.

Bei Patientinnen mit erhöhtem Risiko und rezeptorpositivem Befund ist entweder die alleinige endokrine Therapie oder die Kombination von Chemotherapie mit endokriner Therapie zu erwägen.

Bei Patientinnen mit HER2/neu positiven Tumoren (ab Stadium pT1c und/oder LK Befall) soll eine Behandlung mit Trastuzumab erfolgen.

Wirksame Begleitmaßnahmen, insbesondere eine ausreichende Antiemese, sind Bestandteil der systemischen Therapie.

1.4.5 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.

Weitere spezifische Aspekte zur primär systemischen Therapie finden sich auch unter den Ziffern I 1.4.2, I 1.4.2.3 und I 1.4.3.2.

G-BA, 2016 [24].

Beschluss des Gemeinsamen Bundesausschusses über eine Aufhebung der Befristung der Geltungsdauer eines Beschlusses über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Pertuzumab vom 19. Mai 2016

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 19. Mai 2016 beschlossen, die Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008 / 22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), zuletzt geändert am 2. Juni 2016 (BAnz AT 28.06.2016 B3), wie folgt zu ändern:

I. In Anlage XII werden die Regelungen unter Abschnitt II zur Geltungsdauer des Beschlusses über die Nutzenbewertung von Pertuzumab vom 1. Oktober 2013 wie folgt geändert:

1. Die Angabe „1." wird gestrichen.

2. Der Satz „2. Die Geltungsdauer des Beschlusses ist bis zum 1. Oktober 2018 befristet." wird aufgehoben.

(…)

G-BA, 2016 [23].

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 – Pertuzumab (neues Anwendungsgebiet) vom 18.02.2016

Anwendungsgebiet

Zugelassenes Anwendungsgebiet (laut Zulassung vom 28. Juli 2015):

Perjeta® ist in Kombination mit Trastuzumab und Chemotherapie bei erwachsenen Patienten zur neoadjuvanten Behandlung von HER2-positivem lokal fortgeschrittenem, entzündlichem oder frühem Brustkrebs mit hohem Rezidivrisiko indiziert (siehe Abschnitt 5.1).

Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Pertuzumab in Kombination mit Trastuzumab und Chemotherapie, bei erwachsenen Patienten zur neoadjuvanten Behandlung von HER2-positivem, lokal fortgeschrittenem, entzündlichem Brustkrebs oder frühem Brustkrebs mit hohem Rezidivrisiko, als Teil der Therapie des frühen Brustkrebses, ist:

• Ein Therapieschema, Trastuzumab, ein Taxan (Paclitaxel oder Docetaxel) und ggf. ein Anthrazyklin (Doxorubicin oder Epirubicin) enthaltend

Die Kombination von Trastuzumab mit einem Anthrazyklin ist unter Berücksichtigung der kardiovaskulären Risiken abzuwägen und die kardialen Funktionen engmaschig zu überwachen.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [21].

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 Emtansin

Anwendungsgebiet

Trastuzumab Emtansin (Kadcyla®) ist als Einzelsubstanz zur Behandlung von erwachsenen Patienten mit HER2-positivem, inoperablem lokal fortgeschrittenem oder metastasiertem Brustkrebs indiziert, die zuvor, einzeln oder in Kombination, Trastuzumab und ein Taxan erhalten haben. Die Patienten sollten entweder eine vorherige Behandlung gegen die lokal fortgeschrittene oder metastasierte Erkrankung erhalten haben oder ein Rezidiv während oder innerhalb von sechs Monaten nach Beendigung der adjuvanten Behandlung entwickelt haben.

Vergleichstherapie

Teilpopulation a): Patientinnen mit HER2-postivem, inoperablem lokal fortgeschrittenem Brustkrebs:

Zweckmäßige Vergleichstherapie:

- Strahlentherapie (für Patientinnen, die für eine Strahlentherapie in Frage kommen)

oder

- 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)

Teilpopulation b): Patientinnen mit HER2-positivem, metastasiertem Brustkrebs, nach vorangegangener Therapie, Anthrazykline, Taxane und Trastuzumab enthaltend:

Zweckmäßige Vergleichstherapie:

- Lapatinib in Kombination mit Capecitabin

Teilpopulation c): Patientinnen mit HER2-positivem, metastasiertem Brustkrebs, nach vorangegangener Therapie mit Taxanen und Trastuzumab, jedoch ohne Anthrazykline:

Zweckmäßige Vergleichstherapie:

- Eine patientenindividuelle, optimierte Therapie nach Maßgabe des Arztes, grundsätzlich unter Beachtung des jeweiligen Zulassungsstatus der eingesetzten Wirkstoffe

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Teilpopulation a)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Strahlentherapie oder einer patientenindividuellen, optimierten Therapie:

- Da erforderliche Nachweise nicht erbracht worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V).

Teilpopulation b)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer Kombinationstherapie aus Lapatinib und Capecitabin:

- Hinweis auf einen beträchtlichen Zusatznutzen

Teilpopulation c)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber einer patientenindividuellen, optimierten Therapie:

- Da erforderliche Nachweise nicht erbracht worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Absatz 1 Satz 5 SGB V).

G-BA, 2010 [22].

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

Der Gemeinsame Bundesausschuss hat in seiner Sitzung am 20. Mai 2010 beschlossen, die Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie) in der Fassung vom 18. Dezember 2008/22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), zuletzt geändert am 20. Mai 2010 (BAnz. S. 2062), wie folgt zu ändern:

I.

Die Anlage VI wird im Teil B wie folgt ergänzt: „IV. Gemcitabin in der Monotherapie beim Mammakarzinom der Frau“

G-BA, 2009 [25].

Beschluss des Gemeinsamen Bundesausschusses: Protonentherapie beim Mammakarzinom vom 28. Mai 2009

Siehe auch: **G-BA, 2009** [20].

Der Gemeinsame Bundesausschuss gemäß § 91 Absatz 7 in der bis 30. Juni 2008 geltenden Fassung des Fünften Buches Sozialgesetzbuch (SGB V) hat in seiner Sitzung am 16. November 2004 folgenden Beschluss zur Anwendung der Protonentherapie im stationären Bereich gefasst (Anmerkung: der Beschlusstext wurde redaktionell an den aktuellen Stand der Richtlinie angepasst):

Die Protonentherapie bei der Indikation Mammakarzinom erfüllt derzeit weder alleine noch in Kombination mit einer anderen Therapie die Kriterien des §137c SGB V (ausreichend, zweckmäßig, wirtschaftlich) und ist damit nicht Leistung im Rahmen der gesetzlichen Krankenversicherung.

In § 4 der Richtlinie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung) in der Fassung vom 21. März 2006 (BAnz. S.

4466), zuletzt geändert am 19. Juni 2008 (BAnz. S. 3571), wird nach Nummer 3.4 folgende Nummer angefügt:

„3.5 Protonentherapie beim Mammakarzinom“

3.2 Cochrane Reviews

Kindts I et al., 2018 [31].

Tumour bed boost radiotherapy for women after breast-conserving surgery

Fragestellung

Breast-conserving therapy, involving breast-conserving surgery followed by whole-breast irradiation and optionally a boost to the tumour bed, is a standard therapeutic option for women with early-stage breast cancer. A boost to the tumour bed means that an extra dose of radiation is applied that covers the initial tumour site. The rationale for a boost of radiotherapy to the tumour bed is that (i) local recurrence occurs mostly at the site of the primary tumour because remaining microscopic tumour cells are most likely situated there; and (ii) radiation can eliminate these causative microscopic tumour cells. The boost continues to be used in women at high risk of local recurrence, but is less widely accepted for women at lower risk. Reasons for questioning the boost are twofold. Firstly, the boost brings higher treatment costs. Secondly, the potential adverse events are not negligible. In this Cochrane Review, we investigated the effect of the tumour bed boost on local control and side effects.

To assess the effects of tumour bed boost radiotherapy after breast-conserving surgery and whole-breast irradiation for the treatment of breast cancer

Methodik

Population:

- All women with BCS (lumpectomy, wide local excision, quadrantectomy or segmental mastectomy) followed by WBI (any standard schedule).
- We excluded women who had received intraoperative radiotherapy. We allowed systemic treatments such as hormones, chemotherapy, or monoclonal antibodies as long as they were applied equally to women in each arm of the trial.

Intervention:

- additional boost to the tumour bed
- The boost could be delivered with external beam radiation (electrons or photons) or with interstitial brachytherapy.

Komparator:

- not received a boost to the tumour bed

Endpunkte:

Primary outcomes

1. Local control, defined as the time (from randomisation) until the development of any local recurrence during follow-up (time-to-event outcome). We defined local recurrence as recurrence in the ipsilateral breast (i.e. the breast in which cancer had been diagnosed), the skin and parenchyma.

2. Acute toxicity related to radiotherapy, i.e. any toxic event occurring in the breast, skin, lung, and heart within six months of completion of radiotherapy. We intended for acute toxicity to be

classified according to the scales the authors used and, if possible, converted to the score from the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v4.0)

Secondary outcomes

1. Overall survival, defined as the time from randomisation to death from any cause during follow-up.

2. Disease-free survival, defined as the time from randomisation to relapse (local or distant) during follow-up.

3. Late toxicity related to radiotherapy, i.e. any toxic event occurring more than six months after radiotherapy. We classified these according to the scales the authors used, otherwise considering grade 3 or 4 toxic events according to the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE v4.0). In this review, we extracted data at 5, 10, 15, and 20 years.

4. Cosmesis, scored according to the Harvard scale in four classes: excellent, good, fair, and poor (Harris 1979).

5. Quality of life, to be classified according to validated scales the trial authors used or current scores on the EORTC Quality of Life scale (EORTC QoL).

6. Treatment costs, to be classified according to the scales the trial authors used

Recherche/Suchzeitraum:

- 1 March 2017

Qualitätsbewertung der Studien:

- Cochrane's 'Risk of bias' tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 (n=8325)

Charakteristika der Population:

Design

Five studies randomised 8325 women (Budapest; EORTC; Lyon; Nice; SGW). These studies enrolled women from August 1995 to October 1998 (Budapest), May 1989 to June 1996 (EORTC), January 1986 to June 1992 (Lyon), 1987 to 1994 (Nice), and accrual was started in September 1996 without reporting an end date (SGW).

Sample size

Budapest enrolled 627 women; EORTC enolled 5569 participants, of whom 5318 were randomised between a boost and no boost; Lyon enrolled 1028 participants, Nice enrolled 664 participants; and SGW enrolled 688 participants.

Setting

The Budapest and Nice trials were single-centre trials. The Lyon and SGW were conducted in centres in France and Australia, respectively. The EORTC trial was a multicentre trial in nine countries.

Participants

Budapest included women with stage I-II breast cancer excluding bilateral cases. EORTC enrolled 5569 patients with stage I or II (T1-2, N0-1, M0) invasive breast cancer who were younger than 70 years old. All patients in whom the tumour excision was microscopically complete according to the local pathologist (n =5318) were randomised to either a boost and no boost to the tumour bed. Patients were excluded if they had pure carcinoma in situ. Lyon included women with invasive ductal carcinoma ≤ 3 cm and “free” pathological margins (absence of detectable cancer cells at the inked margin) and who were younger than 70 years old. SGW included women with T in situ, T1, T2 N0-3 breast cancer. Nice included patients with invasive breast cancer treated with axillary dissection.

Interventions

Experimental arm

Whole-breast irradiation:

• 50 Gy in 25 fractions in 5 weeks (Budapest;EORTC;Nice)

• 50 Gy in 20 fractions in 5 weeks (Lyon)

• 45 Gy in 25 fractions in 5 weeks (SGW)

plus boost irradiation:

• 16 Gy external beam (Budapest; EORTC; SGW)

• high-dose-rate brachytherapy 12 to 14.25 (Budapest)

• 15 Gy by means of an iridium-192 implant at a dose rate of

0.5 Gy per hour (EORTC)

• 10 Gy in 4 fractions in 1 week (Lyon)

• 10 Gy in 5 fractions in 1 week (Nice)

The BEDs for the experimental arm were 87.8 Gy in Budapest and EORTC, 86.4 Gy in Lyon, 79.9 Gy in Nice, and 78.6 Gy in SGW.

Control arm

Whole-breast irradiation:

• 50 Gy in 25 fractions in 5 weeks (Budapest;EORTC;Nice;SGW) • 50 Gy in 20 fractions in 5 weeks (Lyon)

TheBEDs for the control armwere 66.7Gy inBudapest, EORTC, Nice, and SGW, and 72.1 Gy in Lyon.

Co-interventions

Budapest only provided detailed population information on the first 207 patients with at least 3 years of follow-up: 18% received hormonal therapy alone, 18% chemotherapy alone, and 6% hormonal therapy and chemotherapy. There were no significant differences between the boost and no boost group. In EORTC, participants with axillary lymph node involvement received

adjuvant systemic therapy (7%): premenopausal women received chemotherapy (38%) and postmenopausal women received amoxifen (62%). In Lyon, chemotherapy was administered in 22% of women and endocrine therapy in 30%. Premenopausal women with positive lymph nodes received adjuvant chemotherapy. For postmenopausal women, tamoxifen was always started in node-positive women and sometimes in node-negative women. In SGW, 20% of women received chemotherapy and 39% received endocrine therapy. Nice did not report numbers on systemic therapy.

Qualität der Studien:

- Siehe Ergebnisse

Studienergebnisse:

Boost compared to no boost in breast cancer radiotherapy

Patient or population: breast-conserving radiotherapy for breast cancer
Setting: radiotherapy centres
Intervention: boost
Comparison: no boost

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk without boost	Risk with boost				
Local control: recurrence at 5 years	Study population		HR 0.64 (0.55 to 0.75)	8315 (5 RCTs)	⊕⊕◯◯ LOW [1,2]	Nice did not report 5-year local control.
	70 per 1000	45 per 1000 (39 to 53)				
Overall survival: mortality at 5 years	Study population		HR 1.04 (0.94 to 1.14)	6342 (2 RCTs)	⊕⊕⊕◯ MODERATE [3]	
	91 per 1000	94 per 1000 (86 to 103)				
Disease-free survival: disease progression/ mortality at 5 years	Study population		HR 0.94 (0.87 to 1.02)	6549 (3 RCTs)	⊕⊕◯◯ LOW [4,5]	EORTC did not report 5-year disease-free survival.
	221 per 1000	209 per 1000 (195 to 224)				
Late toxicity, pBRA	Mean pBRA 8.17, range 7.55 to 10	Mean pBRA 8.55, range 8.26 to 9.4	MD 0.38 higher (0.18 lower to 0.93 higher)	1526 (2 RCTs)	⊕◯◯◯ VERY LOW [2,5]	
Cosmesis, panel scored: fair or poor	Study population		OR 1.41 (1.07 to 1.85)	1116 (2 RCTs)	⊕⊕◯◯ LOW [1,2]	
	202 per 1000	263 per 1000 (213 to 319)				
Cosmesis, physician-scored: fair or poor	Study population		OR 1.58 (0.93 to 2.69)	592 (2 RCTs)	⊕◯◯◯ VERY LOW [1,5,6]	
	85 per 1000	128 per 1000 (80 to 200)				
Sensitivity analysis: local control - recurrence at 5 years	Study population		HR 0.62 (0.52 to 0.73)	6963 (3 RCTs)	⊕⊕⊕⊕ HIGH	
	74 per 1000	47 per 1000 (39 to 55)				
Subgroup analysis: local control - > 40 years old, recurrence at 5 years	Study population		HR 0.65 (0.53 to 0.81)	5058 (2 RCTs)	⊕⊕⊕⊕ HIGH	
	59 per 1000	39 per 1000 (32 to 48)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **OR:** odds ratio; **pBRA:** percentage breast retraction assessment; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

[1] High risk of selective reporting in one study.
[2] There was considerable clinical heterogeneity with respect to radiotherapy dose and the use of quality assurance procedures.
[3] One of the two studies has a very wide confidence interval.
[4] There was considerable clinical heterogeneity on statistical testing, but not on visual inspection.
[5] Both studies have wide confidence intervals.
[6] High risk of bias for blinding of outcome assessment in one study.

Local control appeared to be better for women receiving a tumour bed boost compared to no tumour bed boost (hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.55 to 0.75; 5 studies, 8315 women, low-quality evidence). Overall survival did not differ with or without a tumour bed boost (HR 1.04, 95%CI 0.94 to 1.14; 2 studies, 6342 women, moderate-quality evidence). Disease-free survival did not differ with or without a tumour bed boost (HR 0.94, 95% CI 0.87 to 1.02; 3 studies, 6549 women, low-quality evidence).

Late toxicity scored by means of percentage of breast retraction assessment did not differ with or without a tumour bed boost (mean difference 0.38, 95% CI -0.18 to 0.93; 2 studies, 1526 women, very low-quality evidence). Cosmesis scored by a panel was better (i.e. excellent or good compared to fair or poor) in the no-boost group (odds ratio (OR) 1.41, 95% CI 1.07 to 1.85; 2 studies, 1116 women, low-quality evidence). Cosmesis scored by a physician did not differ with or without a tumour bed boost (OR 1.58, 95% CI 0.93 to 2.69; 2 studies, 592 women, very low-quality evidence).

We excluded two studies in a sensitivity analysis of local recurrence (because the biological equivalent dose (BED) to the tumour bed was lower, in situ tumours were included, or there was a high risk of selective reporting bias or blinding of outcome assessment bias), which resulted in a HR of 0.62 (95% CI 0.52 to 0.73; 3 studies, 6963 women, high-quality evidence). Subgroup analysis including women older than 40 years of age yielded a HR of 0.65 (95% CI 0.53 to 0.81; 2 studies, 5058 women, high-quality evidence).

We found no data for the outcomes of acute toxicity, quality of life, or costs.

Anmerkung/Fazit der Autoren

It appears that local control rates are increased with the boost to the tumour bed, but we found no evidence of a benefit for other oncological outcomes. Subgroup analysis including women older than 40 years of age yielded similarly significant results. Objective percentage of breast retraction assessment appears similar between groups. It appears that the cosmetic outcome is worse with the boost to the tumour bed, but only when measured by a panel, not when assessed by a physician.

Hickey BE et al., 2016 [29].

Partial breast irradiation for early breast cancer

Fragestellung

Breast-conserving therapy for women with breast cancer consists of local excision of the tumour (achieving clear margins) followed by radiotherapy (RT). RT is given to sterilize tumour cells that may remain after surgery to decrease the risk of local tumour recurrence. Most true recurrences occur in the same quadrant as the original tumour. Whole breast radiotherapy (WBRT) may not protect against the development of a new primary cancer developing in other quadrants of the breast. In this Cochrane review, we investigated the delivery of radiation to a limited volume of the breast around the tumour bed (partial breast irradiation (PBI)) sometimes with a shortened treatment duration (accelerated partial breast irradiation (APBI)).

To determine whether PBI/APBI is equivalent to or better than conventional or hypo-fractionated WBRT after breast-conserving therapy for early-stage breast cancer.

Methodik

Population:

Women with histologically confirmed early-stage breast cancer who had conservative surgery. Early breast cancer included tumours classified as American Joint Committee on Cancer (AJCC) stage T1-2N0-1M0 (Fleming 1997). Surgery could include lumpectomy and wide local excision or quadrantectomy, with or without axillary dissection, axillary sampling or sentinel node biopsy. Women with a previous diagnosis of breast cancer were not eligible for inclusion.

Intervention:

conservative surgery plus PBI/APBI

Komparator:

conservative surgery plus WBRT

Endpunkte:

Primary outcomes

1. Local recurrence-free survival (LR-FS) in the ipsilateral breast. We defined local recurrence as a recurrence of the same histological type of cancer within the same quadrant of the breast as the primary cancer.
2. Cosmesis (cosmetic outcome or breast appearance).

Secondary outcomes

1. Overall survival (OS, time from date of randomization to death from any cause, or number of deaths from any cause).
2. Toxicity (including acute and late effects of RT, chemotherapy-related toxicity and surgical toxicity; individual protocol-based definitions).
3. New primary tumours in ipsilateral breast, 'elsewhere primary'. We defined a new primary as a lesion arising in a quadrant of the breast that was different from the original cancer or a tumour of a different histological subtype occurring anywhere within the breast.
4. Cause-specific survival (C-SS, deaths due to breast cancer at five years).
5. Distant metastasis-free survival (DM-FS, in isolation or at the same time as local recurrence (the occurrence of metastases at five years)).
6. Relapse-free survival (R-FS, length of time after treatment during which no recurrence was found). Recurrence referred to breast cancer in the ipsilateral breast or elsewhere in the body, excluding a new breast cancer in the contralateral breast.
7. Loco-regional recurrence-free survival (L-RR-FS, comprised local recurrence, "elsewhere" ipsilateral breast primaries (a new primary cancer in the same breast) and regional nodal relapse).
8. Subsequent mastectomy (ipsilateral partial mastectomy, modified radical mastectomy or radical mastectomy).
9. Compliance, defined as the number of women who commenced treatment with PBI/APBI or conventional external beam radiotherapy (EBRT) and completed the treatment course.
10. Costs (monetary costs of PBI versus EBRT) to women, government and insurance companies.

11. Quality of life (using trial-specific instruments). The effects of PBI/APBI and EBRT on global quality of life and the physical, emotional and psychological domains.
12. Consumer preference, that is, did women prefer PBI/APBI or WBRT given the advantages and disadvantages of each approach.

Recherche/Suchzeitraum:

We searched the Cochrane Breast Cancer Group Specialized Register (4 May 2015), the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 5), MEDLINE (January 1966 to 4 May 2015), EMBASE (1980 to 4 May 2015), CINAHL (4 May 2015) and Current Contents (4 May 2015). We searched the International Standard Randomised Controlled Trial Number Register (5 May 2015), the World Health Organization's International Clinical Trials Registry Platform (4 May 2015) and ClinicalTrials.gov (17 June 2015). We searched for grey literature: OpenGrey (17 June 2015), reference lists of articles, several conference proceedings and published abstracts, and applied no language restrictions.

Selection criteria: Randomized controlled trials (RCTs) without confounding

Qualitätsbewertung der Studien:

Cochrane Risk of Bias tool

Ergebnisse

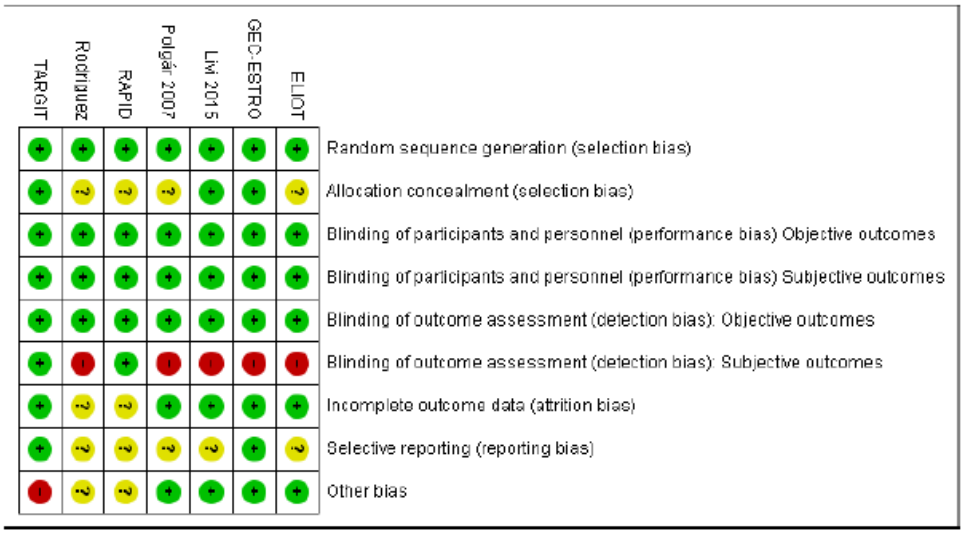
Anzahl eingeschlossener Studien:

6 (n= 8955)

Charakteristika der Population:

Polgár 2007 included womenwith invasive breast cancer after wide local excision of tumour and negative pathologicalmargins (unifocal tumours, tumour size less than 20 mm, clinically or pathologically N0, or single microscopic nodal metastasis (greater than 0.2 mm and less than 2.0 mm), that is, pT1N0-1miM0, Grade I or II; T1N0-N1miM0, Grade I or II. RAPID enrolled women with either invasive ductal carcinoma or ductal carcinoma in situ with tumours 3.3 cm or greater, with negative margins and no involved axillary nodes. Rodriguez included women with pT1-2pN0M0 invasive ductal carcinoma, with tumour size 3 cm or less, with negative margins and Grade I or II histology. ELIOT enrolled women aged 48 to 75 years with early breast cancer, maximum tumour diameter 2.5 cm, "suitable for breast conservation". TARGIT enrolled women aged 45 years or over, with T1 and small T2N0- 1M0 invasive breast cancer, suitable for breast-conserving surgery, available for 10 years' follow-up. Livi 2015 included women aged over 40 years who had wide local excision or quadrantectomy for invasive breast cancer, negative margins and tumour size 2.5 cm or less. GEC-ESTRO included women aged 40 years or more, small T1-2N0-miM0 (less than 3 cm) with negative margins and no lympho-vascular invasion (LVI) and excluded women with multifocal tumours. GEC-ESTRO included Tis.

Qualität der Studien:



Siehe auch Studienergebnisse

Studienergebnisse:

PBI/APBI for women with early breast cancer

Patient or population: women with early breast cancer
Setting: radiotherapy centres
Intervention: PBI/APBI
Comparison: whole breast radiotherapy (WBRT)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with WBRT	Risk with PBI/APBI				
Local recurrence-free survival at 5 years	Study population		HR 1.62 (1.11 to 2.35)	6820 (6 RCTs)	⊕⊕◯◯ Low [3,4,5,6]	-
	10 per 1000[1]	16 per 1000 (11 to 23)				
Cosmesis assessed with 4-point scale Follow-up: range 29-122 months	Study population		OR 1.51 (1.17 to 1.95)	1720 (5 RCTs)	⊕⊕◯◯ Low [6,7,8,9]	Cosmesis was assessed using a 4-point scale. We reported those women with poor/fair cosmesis at final review
	150 per 1000	218 per 1000 (174 to 272)				
Late radiotherapy toxicity (subcutaneous fibrosis) Follow-up: median 36 months	Study population		OR 6.58 (3.08 to 14.06)	766 (1 RCT)	⊕⊕⊕◯ Moderate [5,7,10]	Assessed using National Cancer Institute 3-point scale, events were defined as: Grade II or higher toxicity Physician assessors, at 3 years' follow-up
	22 per 1000	128 per 1000 (64 to 239)				
Cause-specific survival at 5 years	Study population		HR 1.08 (0.73 to 1.58)	6718 (5 RCTs)	⊕⊕⊕◯ Moderate [5,11]	-

	20 per 1000[2]	22 per 1000 (15 to 32)				
Distant metastasis-free survival at 5 years	Study population		HR 0.94 (0.65 to 1.37)	3267 (4 RCTs)	⊕⊕⊕◯ Moderate [5,12]	-
	33 per 1000[2]	31 per 1000 (21 to 44)				
Mastectomy rate Follow-up: range 29-122 months	Study population		OR 1.20 (0.77 to 1.87)	4817 (3 RCTs)	⊕⊕◯◯ Low [5,11,13]	Mastectomy rate reflected both local recurrence and adverse cosmetic outcome
	15 per 1000	18 per 1000 (12 to 28)				
Mortality (follow-up: 5 years survival)	Study population		HR 0.90 (0.74 to 1.09)	6718 (5 RCTs)	⊕⊕⊕⊕ High	Survival advantage from radiotherapy for breast cancer is not apparent before 15 years' follow-up (EBCTCG 2011)
	51 per 1000[2]	46 per 1000 (38 to 55)				

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RCT:** randomized controlled trial.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The baseline risk for the control group was calculated at the 5-year time point from 5 studies.
[2] The baseline risks for the control groups were calculated at the 5-year time point from 4 studies.
[3] There was considerable clinical heterogeneity with respect to radiotherapy dose, technique and use of quality assurance procedures. However, the techniques employed delivered a dose that was the same or higher in the accelerated partial breast irradiation arm than the whole breast radiotherapy arm, which should mean the local recurrence-free survival is better or at least the same.
[4] 38% of the women contributing to this outcome came from a study deemed at high risk of bias for short follow-up.

[5] There were fewer than 300 events.
[6] Confidence intervals did not exclude both clinically important and clinically unimportant harms.
[7] Optimum sample size was not met, therefore downgraded.
[8] There was evidence of considerable heterogeneity on statistical testing (I^2 = 71%; P value < 0.00001).
[9] Less than 30% of events came from studies deemed at high risk of bias for subjective outcomes.
[10] Testing for heterogeneity was not appropriate, given that there was only one study contributing to this outcome.
[11] Confidence intervals did not exclude either clinically significant benefits or harms.
[12] Confidence intervals did not exclude the possibility of clinically significant harms.
[13] One of the two included studies had median follow-up of 29 months, which was too short to report this outcome.

Anmerkung/Fazit der Autoren

It appeared that local recurrence and 'elsewhere primaries' (new primaries in the ipsilateral breast) are increased with PBI/APBI (the difference was small), but we found no evidence of detriment to other oncological outcomes. It appeared that cosmetic outcomes and some late effects were worse with PBI/APBI but its use was associated with less acute skin toxicity. The limitations of the data currently available mean that we cannot make definitive conclusions about the efficacy and safety or ways to deliver of PBI/APBI. We await completion of ongoing trials.

Hickey BE et al., 2018 [28].

Hypofractionated radiation therapy for early breast cancer.

Fragestellung

Shortening the duration of radiation therapy would benefit women with early breast cancer treated with breast conserving surgery. It may also improve access to radiation therapy by improving efficiency in radiation oncology departments globally. This can only happen if the shorter treatment is as effective and safe as conventional radiation therapy. This is an update of a Cochrane Review first published in 2008 and updated in 2009.

To assess the effect of altered radiation fraction size for women with early breast cancer who have had breast conserving surgery.

Methodik

Population:

- Women with histologically confirmed early breast cancer who had undergone breast conserving surgery. Early breast cancer is defined as invasive adenocarcinoma restricted to the breast, plus or minus the local lymph nodes, which can be removed surgically (EBCTCG 2011), that is T1-2, N0-1, M0 (Fleming 1997).
- Surgery could include lumpectomy, wide local excision, quadrantectomy, or segmental resection; with or without axillary dissection, node sampling, or sentinel node biopsy. If a study included the relevant population as a subgroup and the outcomes relating to this group were reported separately, we included those participants eligible for this review (e.g. Saha 2009).

Intervention:

altered fraction size for radiation therapy

Komparator:

conventional fractionation for radiation therapy

Endpunkte:

Primary outcomes

1. Local recurrence-free survival (LR-FS) in the ipsilateral breast (i.e. events defined as cancer detected in the same breast where the cancer had been diagnosed).

2. Appearance or cosmesis (objective and subjective) of the treated breast.

Secondary outcomes

1. Overall survival (OS; time from date of randomisation to death from any cause, or number of deaths from any cause).

2. Toxicity (including acute and late effects of radiation therapy and chemotherapy-related toxicity); we used individual protocol-based definitions.

3. Breast cancer-specific survival (BC-SS; events were: death due to breast cancer).

4. Relapse-free survival (RFS; events included local recurrence, loco-regional recurrence, distant metastasis and death).

5. Mastectomy rate (salvage following local recurrence or unacceptable toxicity).

6. Quality of life (trial-specific instruments).

7. Costs (to women and health services).

Recherche/Suchzeitraum:

We searched the Cochrane Breast Cancer Specialised Register (23 May 2015), CENTRAL (The Cochrane Library 2015, Issue 4), MEDLINE (Jan 1996 to May 2015), EMBASE (Jan 1980 to May 2015), the WHO International Clinical Trials Registry Platform (ICTRP) search portal (June 2010 toMay 2015) and ClinicalTrials.gov (16 April 2015), reference lists of articles and relevant conference proceedings. No language or publication constraints were applied.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

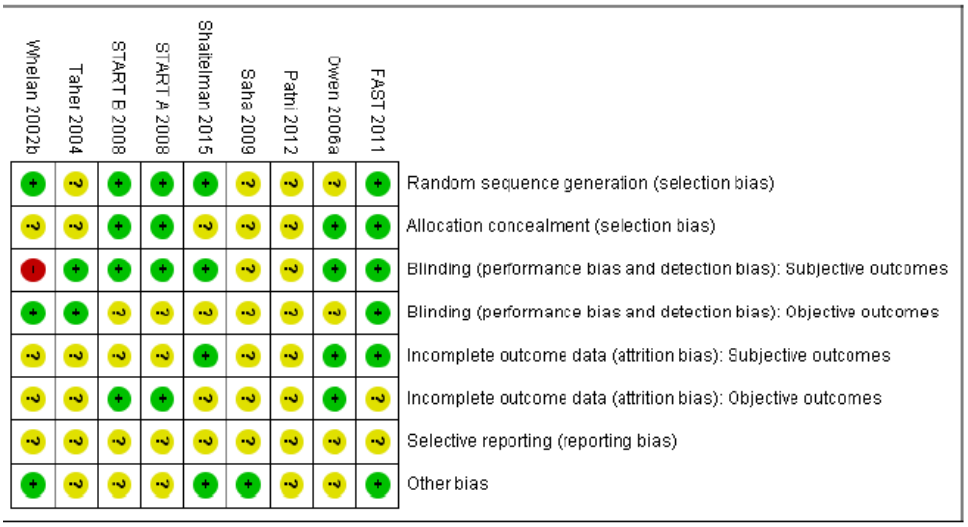
Anzahl eingeschlossener Studien:

9 (n=8228)

Charakteristika der Population:

The women studied in this review were mostly women with early breast cancer (6829/7553 (90.4%)) and 4580 out of 8010 (57%) women were aged 50 or more where reported (FAST 2011; Owen 2006a; STARTA2008; STARTB2008;Whelan2002b). Seventytwo out of 287 (25%) of the women in Shaitelman 2015 and 59 women in Owen 2006a had Stage 0 early breast cancer or ductal carcinoma in situ (DCIS): in total, 131/8228 (0.15%) women had DCIS. Further, 6701/6701 (100%) of the women studied in this review had negative pathological margins, where reported (FAST 2011; Saha 2009; Shaitelman 2015; START A 2008; START B 2008; Taher 2004; Whelan 2002b). Most tumours (3916/6600 (59%)) were 2 cm or less in size, where size was reported (FAST 2011; STARTA 2008; STARTB 2008;Whelan 2002b) and 4457/ 4853 (91%) were 3 cm or less in size (FAST 2011; START A 2008; START B 2008).Women with T3 tumours (that is tumour size greater than 5 cm) were eligible for the START A 2008 and START B 2008 studies. They comprised 1.6% (22/1410) of the women studied in Owen 2006a. T stage was not reported in START A 2008 and START B 2008, but 15% (702/4451) of women had tumours larger than 3 cm. Most women 5040/6135 (82%) studied in this review, had small to medium breasts (where breast size was reported) (FAST 2011; Owen 2006a; START A 2008; STARTB 2008; Whelan 2002b), in Shaitelman 2015 (those with cup sizeDor less). Most women (5332/7824 (68%)) studied in this review were node negative where reported (FAST 2011; Owen 2006a; START A 2008; START B 2008; Whelan 2002b) and most women (7675/8188 (93.7%)) studied were treated with breast conserving surgery. Saha 2009 included 131 women with early breast cancer, we included the 47 women treated with breast conserving surgery, where the results were reported separately.

Qualität der Studien:



Siehe auch: Studienergebnisse

Studienergebnisse:

Hypofractionated radiation therapy compared to conventionally fractionated radiation therapy for women treated with breast conserving therapy for early breast cancer

Patient or population: women treated with breast conserving therapy for early breast cancer
Setting: cancer centres
Intervention: hypofractionated radiation therapy
Comparison: conventionally fractionated radiation therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with conventionally fractionated radiation therapy	Risk with hypofractionated radiation therapy				
Local recurrence-free survival (LR-FS) at 10 years	Study population 70 per 1,000[1]	 66 per 1,000 (54 to 80)	HR 0.94 (0.77 to 1.15)	7095 (4 RCTs)	⊕⊕⊕⊕ HIGH	
Cosmesis assessed with fair/poor on 4-point scale, follow-up: range 42 months-12 years	Study population 311 per 1,000	 280 per 1,000 (252 to 314)	RR 0.90 (0.81 to 1.01)	2103 (4 RCTs)	⊕⊕⊕⊕ HIGH	
Mortality at 10 years	Study population 166 per 1,000[1]	 153 per 1,000 (135 to 171)	HR 0.91 (0.80 to 1.03)	5685 (3 RCTs)	⊕⊕⊕⊕ HIGH	
Late subcutaneous toxicity assessed with ≥ Grade 2 on 4-point scale, follow-up: median 6 years	Study population 4 per 1,000	 4 per 1,000 (3 to 4)	RR 0.93 (0.83 to 1.05)	5130 (4 RCTs)	⊕⊕⊕⊕ HIGH [2]	
Breast cancer-specific survival (BC-SS) at 10 years	Study population 123 per 1,000[1]	 113 per 1,000 (98 to 130)	HR 0.91 (0.78 to 1.06)	5685 (3 RCTs)	⊕⊕⊕⊕ HIGH	
Relapse-free survival (RFS) at 10 years	Study population 224 per 1,000[1]	 210 per 1,000 (188 to 234)	HR 0.93 (0.82 to 1.05)	5685 (3 RCTs)	⊕⊕⊕◯ MODERATE [3]	
Mastectomy rate - not measured	see comment	see comment	not estimable	(studies)	-	We found no data with respect to subsequent mastectomy

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** Hazard ratio; **RR:** risk ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The baseline risks for the control groups were calculated using 10-year event data from the included studies
[2] No blinding for assessment of subjective outcomes (for 5% of events only)
[3] Statistical testing as well as examination of the forest plots suggested there was some heterogeneity

Anmerkung/Fazit der Autoren

We found that using altered fraction size regimens (greater than 2 Gy per fraction) does not have a clinically meaningful effect on local recurrence, is associated with decreased acute toxicity and does not seem to affect breast appearance, late toxicity or patient-reported quality-

of-life measures for selected women treated with breast conserving therapy. These are mostly women with node negative tumours smaller than 3 cm and negative pathological margins.

Goodwin A et al., 2013 [27].

Post-operative radiotherapy for ductal carcinoma in situ of the breasts

Fragestellung

The addition of radiotherapy (RT) following breast conserving surgery (BCS) was first shown to reduce the risk of ipsilateral recurrence in the treatment of invasive breast cancer. Ductal carcinoma in situ (DCIS) is a pre-invasive lesion. Recurrence of ipsilateral disease following BCS can be either DCIS or invasive breast cancer. Randomised controlled trials (RCTs) have shown that RT can reduce the risk of recurrence, but assessment of potential long-term complications from addition of RT following BSC for DCIS has not been reported for women participating in RCTs.

To summarise the data from RCTs testing the addition of RT to BCS for treatment of DCIS to determine the balance between the benefits and harms.

Methodik

Population:

Women with a histological diagnosis ofDCIS for the first time (not recurrent or metastatic disease) with no prior history of malignant disease (other than in situ carcinoma of the cervix, or Basal Cell Carcinoma (BCC) or Squamous Cell Carcinoma (SCC) of the skin).

No invasive breast cancer.

No age limit.

Intervention:

Any trial in which RT (of any kind) was the primary treatment comparison after BCS.

This included: BCS (either lumpectomy, quadrantectomy, or segmental mastectomy) with or without RT (any standard schedule of treatment).

Trials where patients received tamoxifen were included provided this was given in both study arms and patients differed only in respect to receiving radiotherapy or not.

Komparator:

- K.A.

Endpunkte:

- Primary outcomes
- Efficacy:
  - ipsilateral local recurrence (both DCIS and invasive cancer);
  - contralateral breast cancer (both DCIS and invasive cancer);
  - metastatic disease (if reported);
  - breast cancer mortality;
  - all-cause mortality.
- Toxicity:

- long-term complications from radiotherapy;
- vascular mortality (including acute myocardial infarction, sudden cardiac death, congestive cardiac failure, and cerebrovascular disease);
- pulmonary toxicity;
- lung cancer;
- osteoradionecrosis.

- Secondary outcomes

  Quality of life assessment (individual trial instruments), if available.

Recherche/Suchzeitraum:

We searched the Cochrane Breast Cancer Group Specialised Register (2 June 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, Issue 1), MEDLINE (2 June 2011), EMBASE (2 June 2011) and the World Health Organization's InternationalClinical TrialsRegistry Platform(WHOICTRP; 2 June 2011). Reference lists of articles and handsearching of ASCO (2007), ESMO (2002 to 2007), and St Gallen (2005 to 2007) conferences were performed.

Qualitätsbewertung der Studien:

Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

4 (n=3925)

Charakteristika der Population:

The EORTC trial (EORTC 2006): RCT investigating the role of RT after local excision of ductal carcinoma in situ (DCIS) of the breast. Participants in this multicentre trial were 1010 women recruited in Europe betweenMarch 1986 and July 1996. The trial has published data with a median follow up of 10.5 years.

The NSABP trial (NSABP 2001): RCT investigating the role of RT after lumpectomy for DCIS of the breast. Participants in this multicentre trial were 818 women recruited in the United States of America and Canada between October 1985 and December 1990. The trial has a mean follow up of 10.7 years.

The SweDCIS trial (SweDCIS 2008): RCT investigating the role of RT after sector resection for DCIS of the breast. Participants in this multicentre trial were 1067 women recruited in Sweden between September 1987 and December 1999. The trial has a mean follow-up data for a mean of 8.4 years.

The UKCCCR trial (UKCCCR 2003): a multicentre RCT investigating the effectiveness of adjuvant RT and tamoxifen for DCIS of the breast. This trial has a 2 by 2 factorial design. Patients were either randomised to both treatments, or randomised to either one with an elective decision regarding the other treatment. Recruitment from breast screening programmes commenced in May 1990 in the United Kingdom and September 1991 in Australia and New Zealand and concluded in August 1998. In total, 1030 women were randomised to radiotherapy or no radiotherapy in this trial that included 1701 women. The trial has published follow- up data for a median follow up of 4.4 years.

Qualität der Studien:

- The risk of bias was low as the quality of all four included studies was high

Studienergebnisse:

Three trials compared the addition of RT to BCS. One trial was a two by two factorial design comparing the use of RT and tamoxifen, each separately or together, in which participants were randomised in at least one arm. Analysis confirmed a statistically significant benefit from the addition of radiotherapy on all ipsilateral breast events (hazards ratio (HR) 0.49; 95%CI 0.41 to 0.58, P < 0.00001), ipsilateral invasive recurrence (HR 0.50; 95% CI 0.32 to 0.76, p=0.001) and ipsilateral DCIS recurrence (HR 0.61; 95% CI 0.39 to 0.95, P = 0.03). All the subgroups analysed benefited from addition of radiotherapy. No significant long-term toxicity from radiotherapy was found. No information about short-term toxicity from radiotherapy or quality of life data were reported.

Figure 2. Forest plot of comparison: 1 Post-operative radiotherapy versus surgery alone, outcome: 1.1 All ipsilateral recurrence.

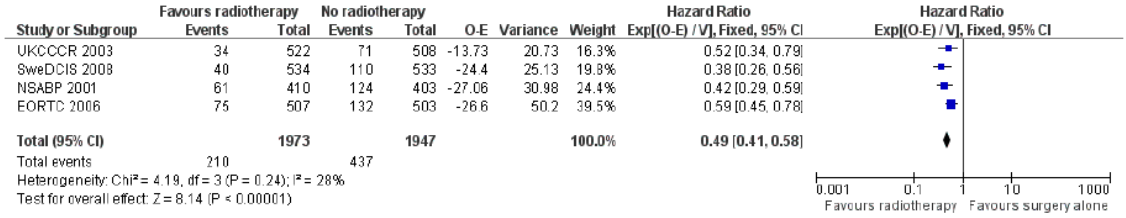


Figure 3. Forest plot of comparison: 1 Post-operative radiotherapy versus surgery alone, outcome: 1.2 Ipsilateral Invasive recurrence.

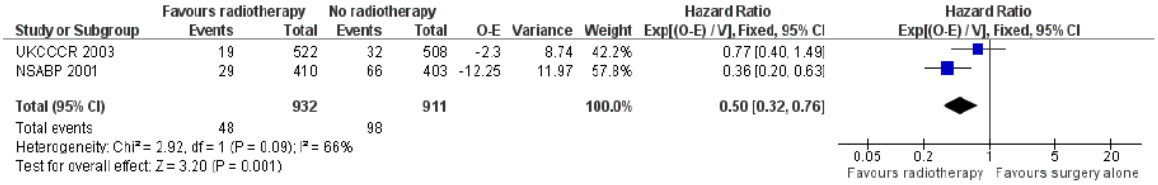


Figure 4. Forest plot of comparison: 1 Post-operative radiotherapy versus surgery alone, outcome: 1.3 Ipsilateral DCIS recurrence.

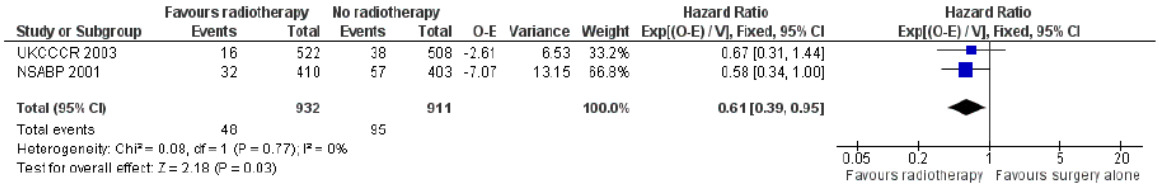


Figure 5. Forest plot of comparison: 1 Post-operative radiotherapy versus surgery alone, outcome: 1.4 Incidence of Ipsilateral recurrence by surgical excision.

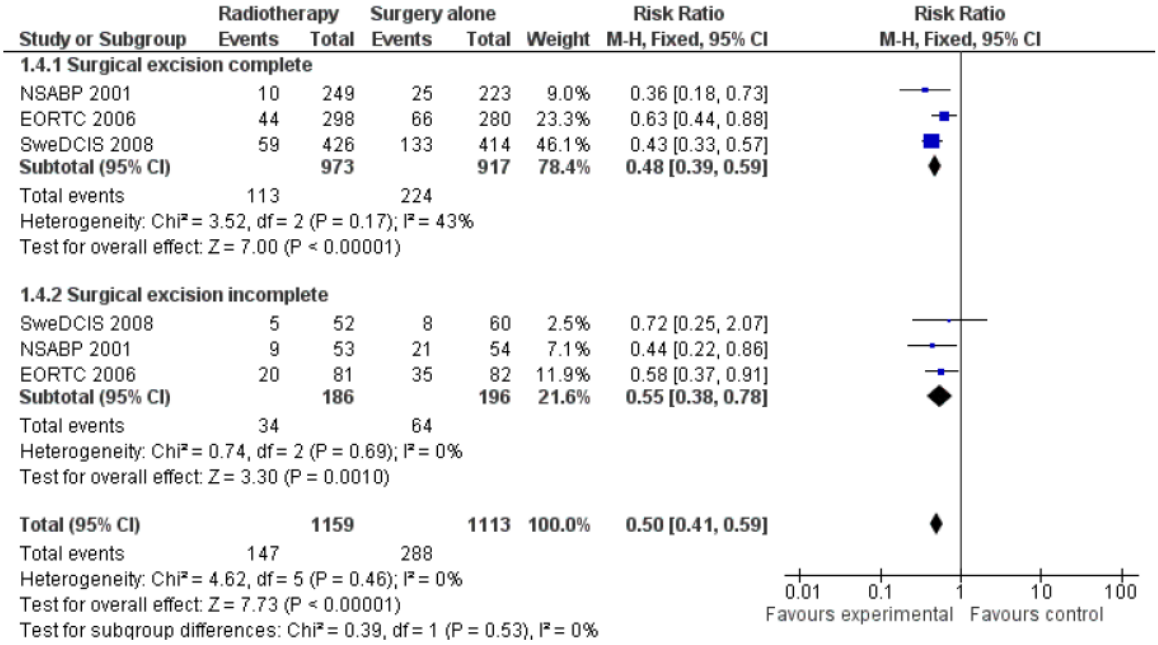
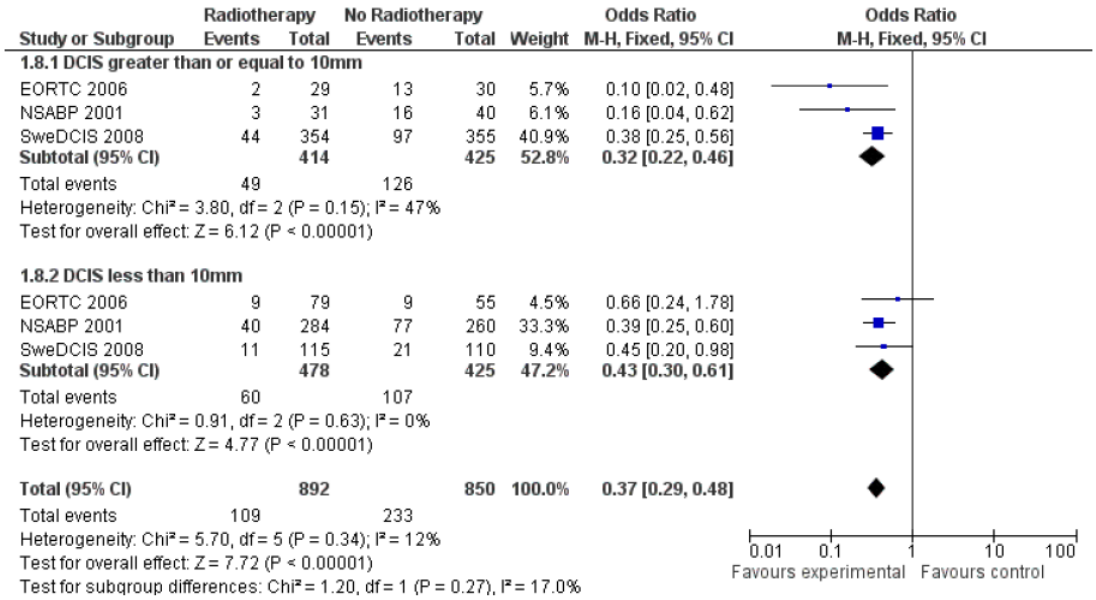


Figure 8. Forest plot of comparison: 1 Post-operative radiotherapy versus surgery alone, outcome: 1.8 Size of DCIS lesion.



Anmerkung/Fazit der Autoren

This review confirms the benefit of adding radiotherapy to breast conserving surgery for the treatment of all women diagnosed with DCIS. No long-term toxicity from use of radiotherapy was identified.

3.3 Systematische Reviews

Zhao B & Zhao H, 2018 [50].

Impact of clinicopathological characteristics on the efficacy of neoadjuvant therapy in patients with human epidermal growth factor receptor-2-positive breast cancer.

Fragestellung

Based on accumulating evidence, in this study, we systematically evaluate the impact of four clinicopathological features, including hormone receptor (HR) status, tumour size, age and nodal status, on the efficacy of neoadjuvant treatment in patients with HER2-positive breast cancer.

Methodik

Population:

at least 100 patients (>18 years of age) with HER2-positive breast cancer

Intervention:

neoadjuvant treatment with HER2-targeted regimens irrespective of dose and duration

Komparator:

k.A.

Endpunkte:

Pathological complete response (pCR)

Recherche/Suchzeitraum:

to April 2017

Qualitätsbewertung der Studien:

K.A.

Ergebnisse

Anzahl eingeschlossener Studien:

11

Charakteristika der Population:

- 3,269 HER2-positive patients. Specifically, 1,810 (55%) of the patients were HR-positive, and the rest of the 1,459 subjects (45%) were HR-negative.

Qualität der Studien:

- K.A.
- All studies were open-label randomized trials conducted in the United States, Canada and Europe.

Studienergebnisse:

Table 1. Characteristics of eligible neoadjuvant studies

Study	Phase	Region	Study period	Clinical stage	Neoadjuvant chemotherapy	Neoadjuvant anti-HER2 agents	Age, median (range)	Duration (weeks)	Definition of pCR	No. of patients		No. of events	
										HR+	HR−	HR+	HR−
CALGB 40601[7]	III	US	2008–2012	II–III	T	Tzmb and/or Lpnb	49(24–75)	16	Absence of residual invasive carcinoma	176	123	68	74
EORTC 10054[8]	II	Europe	2010–2013	II–III	FEC	Tzmb and/or Lpnb	49(25–71)	18	Absence of residual invasive carcinoma	67	60	34	32
GeparQuattro[9]	III	Europe	2005–2006	I–III	EC→ T± Ca	Tzmb	50(22–78)	24	No tumor cells and residual tumor in breast and lymph nodes	261	184	61	80
GEICAM/2006-14[10]	II	Europe	2009–2010	I–III	EC→T	Tzmb and Lpnb	48(30–79)	24	Absence of residual invasive carcinoma	59	43	NR	NR
UPT109096[11]	II	US	2007–2010	II–III	FEC→ T	Tzmb and/or Lpnb	52(21–67)	26	NR	49	51	21	28
NeoALTTO[12]	III	International	2008–2010	T2-T4	T	Tzmb and/or Lpnb	50(42–59)	18	Absence of invasive tumor cells	232	223	62	160
NeoSphere[13]	II	International	2007–2009	T2-T4	T	Tzmb and Pzmb	50(22–80)	12	Absence of invasive tumor cells	146	164	31	72
NSABP B-41[14]	III	US, Canada	2007–2011	T2-T3	AC→ T	Tzmb and/or Lpnb	NR	24	Absence of residual invasive carcinoma	331	198	165	125
TRYPHAENA[15]	II	International	2009–2011	T2-T4	FEC→T	Tzmb and Pzmb	50(24–81)	18	Absence of invasive tumor cells	114	111	55	84
GeparQuinto[16]	III	Europe	2007–2010	T1-T3	EC→T	Tzmb or Lpnb	50(21–74)	24	No evidence of disease in the breast	341	274	NR	NR
Remagus 02[17]	II	Europe	2004–2007	II–III	EC→T	Tzmb	47	24	Absence of residual invasive carcinoma in breast and lymph nodes	34	28	7	9

AC→ T, doxorubicin hydrochloride, cyclophosphamide followed by paclitaxel; Ca, capecitabine; FEC, fluorouracil, epirubicin hydrochloride and cyclophosphamide; T, docetaxel or paclitaxel; Lpnb, lapatinib; Pzmb, pertuzumab; Tzmb, trastuzumab; NR, not reported.

Impact of HR status on pCR

Overall, the pooled model showed that patients with HRnegative breast cancer exhibited significantly more pCR events than those with HR-positive breast cancer after HER2-targeted

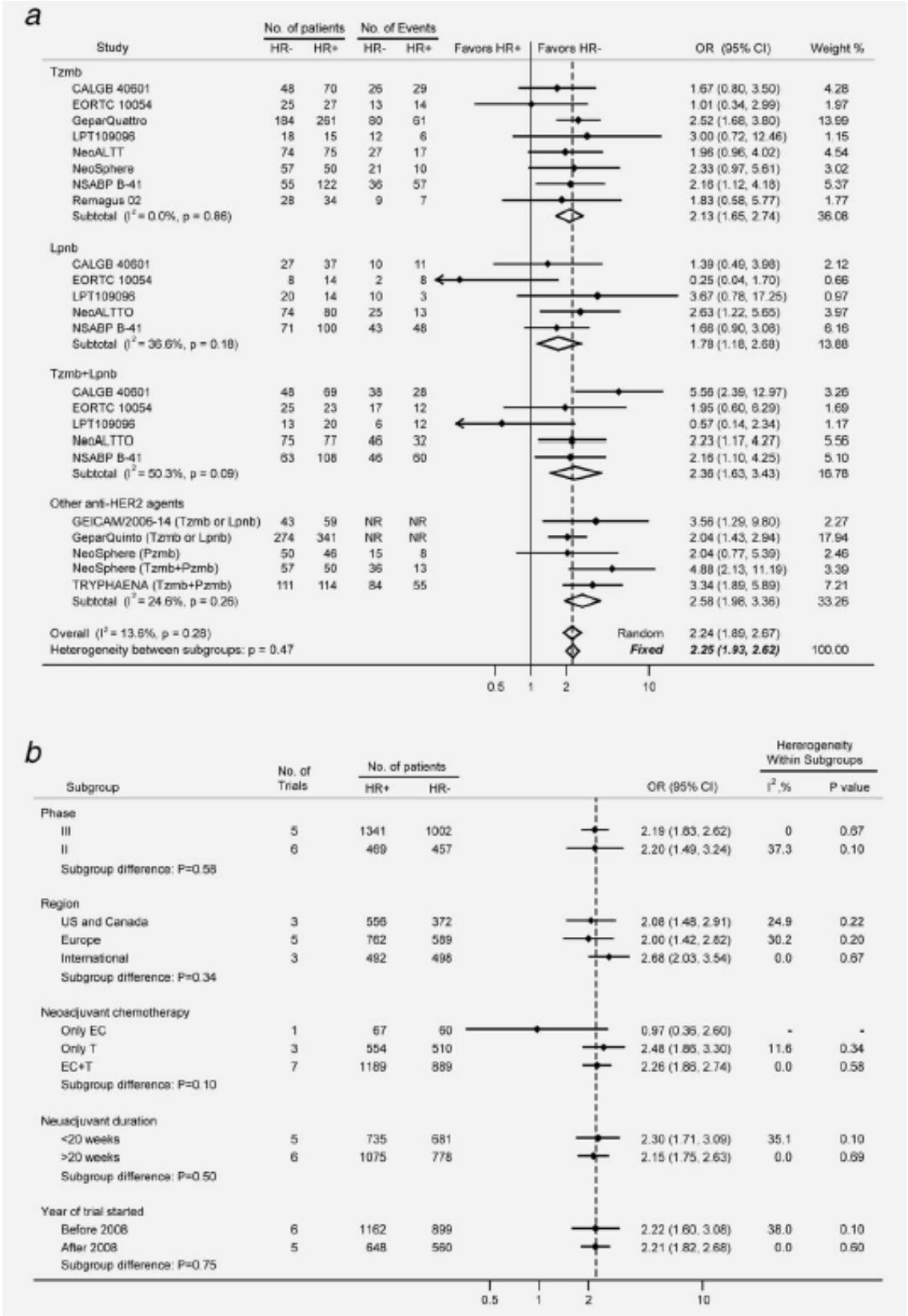
treatment (OR, 2.25; 95% CI, 1.93–2.62; p<0.001; fixed-effects model). No substantial heterogeneity was observed (p50.28, I2513.6%). The advantage of pCR in HRnegative patients stratified by different anti-HER2 agents was further examined (Fig. 2a). HR-negative patients benefited more from trastuzumab (OR, 2.13; 95% CI, 1.65–2.74), lapatinib (OR, 1.78; 95% CI, 1.18–2.68), the combination of trastuzumab and lapatinib (OR, 2.36; 95% CI, 1.63–3.43), and other types of anti-HER2 agents (OR, 2.58; 95% CI, 1.98– .36). No statistically significant difference was observed among these subgroups (heterogeneity between subgroups, p=0.47), which suggested that the greater benefit achieved by HR-negative women over HR-positive women was independent of the anti-HER2 agent given. Moreover, as shown in Figure 2b, the improvement in pCR in HR-negative patients compared with HR-positive patients did not differ by region (subgroup difference, p=0.34), clinical phase (subgroup difference, p50.58), combined

neoadjuvant chemotherapy drugs (subgroup difference, p=0.10), neoadjuvant duration (subgroup difference, p=0.50) or year the trials started (subgroup difference, p=0.75).

Figure 2. Pathological complete response (pCR) analysis by hormone receptor (HR) status (positive versus negative) in HER2-positive breast cancer patients.

(a) pCR analysis of different anti-HER2 agents in a neoadjuvant setting; and

(b) subgroup analysis for pCR according to clinical phase, region, chemotherapy agents, duration of treatment, and year the trials started. Lpnb, lapatinib; NR, not reported; Pzmb, pertuzumab; Tzmb, trastuzumab.


a
Study
No. of patients HR- HR+
No. of Events HR- HR+
Favors HR+
Favors HR-
OR (95% CI)
Weight %
Tzmb
CALGB 40601 48 70 26 29 1.67 (0.80, 3.50) 4.28
EORTC 10054 25 27 13 14 1.01 (0.34, 2.99) 1.97
GeparQuattro 184 251 80 61 2.52 (1.66, 3.80) 13.99
LPT109096 18 15 12 6 3.00 (0.72, 12.46) 1.15
NeoALTT 74 75 27 17 1.96 (0.96, 4.02) 4.54
NeoSphere 57 50 21 10 2.33 (0.97, 5.61) 3.02
NSABP B-41 55 122 36 57 2.16 (1.12, 4.18) 5.37
Remagus 02 28 34 9 7 1.83 (0.58, 5.77) 1.77
Subtotal (I^2 = 0.0%, p = 0.86) 2.13 (1.65, 2.74) 36.08
Lpnb
CALGB 40601 27 37 10 11 1.39 (0.49, 3.98) 2.12
EORTC 10054 8 14 2 8 0.25 (0.04, 1.70) 0.66
LPT109096 20 14 10 3 3.67 (0.78, 17.25) 0.97
NeoALTTO 74 80 25 13 2.63 (1.22, 5.65) 3.97
NSABP B-41 71 100 43 48 1.66 (0.90, 3.06) 6.16
Subtotal (I^2 = 36.6%, p = 0.18) 1.78 (1.18, 2.68) 13.88
Tzmb+Lpnb
CALGB 40601 48 69 38 28 5.56 (2.39, 12.97) 3.26
EORTC 10054 25 23 17 12 1.95 (0.60, 6.29) 1.69
LPT109096 13 20 6 12 0.57 (0.14, 2.34) 1.17
NeoALTTO 75 77 46 32 2.23 (1.17, 4.27) 5.56
NSABP B-41 63 108 46 60 2.16 (1.10, 4.25) 5.10
Subtotal (I^2 = 50.3%, p = 0.09) 2.36 (1.63, 3.43) 16.78
Other anti-HER2 agents
GEICAM/2006-14 (Tzmb or Lpnb) 43 59 NR NR 3.56 (1.29, 9.80) 2.27
GeparQuinto (Tzmb or Lpnb) 274 341 NR NR 2.04 (1.43, 2.94) 17.94
NeoSphere (Pzmb) 50 46 15 8 2.04 (0.77, 5.39) 2.46
NeoSphere (Tzmb+Pzmb) 57 50 36 13 4.88 (2.13, 11.19) 3.39
TRYPHAENA (Tzmb+Pzmb) 111 114 84 55 3.34 (1.89, 5.89) 7.21
Subtotal (I^2 = 24.6%, p = 0.26) 2.58 (1.98, 3.36) 33.26
Overall (I^2 = 13.6%, p = 0.28) Random 2.24 (1.89, 2.67)
Heterogeneity between subgroups: p = 0.47 Fixed 2.25 (1.93, 2.62) 100.00
0.5 1 2 10
b
Subgroup
No. of Trials
No. of patients HR+ HR-
OR (95% CI)
Heterogeneity Within Subgroups I^2,% P value
Phase
III 5 1341 1002 2.19 (1.83, 2.62) 0 0.67
II 6 469 457 2.20 (1.49, 3.24) 37.3 0.10
Subgroup difference: P=0.58
Region
US and Canada 3 556 372 2.06 (1.48, 2.91) 24.9 0.22
Europe 5 762 589 2.00 (1.42, 2.82) 30.2 0.20
International 3 492 498 2.68 (2.03, 3.54) 0.0 0.67
Subgroup difference: P=0.34
Neoadjuvant chemotherapy
Only EC 1 67 60 0.97 (0.36, 2.60) - -
Only T 3 554 510 2.48 (1.86, 3.30) 11.6 0.34
EC+T 7 1189 889 2.26 (1.86, 2.74) 0.0 0.58
Subgroup difference: P=0.10
Neuadjuvant duration
<20 weeks 5 735 681 2.30 (1.71, 3.09) 35.1 0.10
>20 weeks 6 1075 778 2.15 (1.75, 2.63) 0.0 0.69
Subgroup difference: P=0.50
Year of trial started
Before 2008 6 1162 899 2.22 (1.60, 3.08) 38.0 0.10
After 2008 5 648 560 2.21 (1.82, 2.68) 0.0 0.60
Subgroup difference: P=0.75
0.5 1 2 10

Anmerkung/Fazit der Autoren

In summary, for HER2-targeted neoadjuvant treatment, greater benefits are observed in patients with small, HRnegative tumours. The efficacies of anti-HER2 agents are similar in patients of different ages, and the impact of nodal status depends on the anti-HER2 drugs used. These results have important implications for clinical trial design and interpretation, economic analysis, drug development, and treatment strategies for HER2-positive breast cancer.

Yu Z et al., 2018 [49].

Adjuvant endocrine monotherapy for postmenopausal early breast cancer patients with hormone-receptor positive: a systemic review and network meta-analysis

Fragestellung

No comparison among 10-year tamoxifen and AIs can be found, so far. Hence, the Bayesian network meta-analysis, which combines direct evidence and indirect evidence and compares the efficacy of different monotherapies based on disease-free survival and overall survival, thereby providing an optimum regimen for women with estrogen-positive early breast cancer.

Methodik

Population:

postmenopausal women with hormone receptor-positive diagnosed early breast cancer

Intervention:

letrozole, tamoxifen, exemestane, anastrozle, and toremifene

Komparator:

k.A.

Endpunkte:

- disease-free survival (DFS) and
- overall survival (OS)

Recherche/Suchzeitraum:

31st, December 2016

Qualitätsbewertung der Studien:

Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

14

Table 1 Summary of randomized-controlled trials of adjuvant endocrine monotherapy for early breast cancer patients

Study	Intervention arm	HR for DFS	HR for OS	Follow-up time	Patients number	Percentage of post-menopausal	Percentage of HR (+) tumor	Median age (years)
CRC (1996)	20 mg daily Tam for 5 years	0.81 (0.69–0.98)	0.89 (0.69–1.15)	NA	1467	NA	NA	51
	20 mg daily Tam for 2 years				1470			61
ECOG (1996)	20 mg daily Tam for 10 years	0.448 (0.22–0.91)	NA	5.6 years	73	NA	73 (100%)	NA
	20 mg daily Tam for 5 years				67		67 (100%)	
SBCCG (1997)	40 mg daily Tam for 5 years	0.80 (0.66–0.96)	0.83 (0.66–1.05)	5.5 years	1096	1096 (100%)	1096 (100%)	NA
	40 mg daily Tam for 2 years				1114	1114 (100%)	1114 (100%)	
Thierry Delozier (2000)	20–40 mg daily Tam for 10 years	0.79 (0.64–0.98)	NA	70 months	1220	NA	NA	62.8
	20–40 mg daily Tam for 3 years			30 months	1215			
IBCSG (2004)	60 mg daily Tor for 5 years	0.89 (0.68–1.17)	0.94 (0.64–1.37)	5.5 years	399	NA	399 (100%)	70
	20 mg daily Tam for 5 years				374		374 (100%)	
ATAC (2010)	1 mg daily A for 5 years	0.86 (0.78–0.95)	0.95 (0.84–1.06)	10 years	2618	2618 (100%)	2618 (100%)	72
	20 mg daily Tam for 5 years				2598	2598 (100%)	2598 (100%)	
NAFTA (2010)	60 mg daily Tor for 5 years	1.037 (0.72–1.49)	0.951 (0.623–1.451)	59 months	906	860 (94.8%)	906 (100%)	68
	20 mg daily Tam for 5 years				907	864 (95.4%)	907 (100%)	67
BIG 1-98 (2011)	2.5 mg daily L for 5 years	0.86 (0.78–0.96)	0.87 (0.77–0.999)	8.1 years	2463	2463 (100%)	2463 (100%)	61
	20 mg daily Tam for 5 years				2459	2459 (100%)	2459 (100%)	
TEAM (2011)	25 mg daily Tam for 3 years and then 20 mg daily E for 2 years	0.97 (0.88–1.08)	1.00 (0.89–1.14)	5.1 years	4868	4868 (100%)	4860 (99.84%)	64
	20 mg daily Tam for 5 years				4898	4898 (100%)	4888 (99.80%)	
IES (2012)	20–30 mg daily Tam for 3 years and then 20 mg daily E for 2 years	0.81 (0.72–0.91)	0.86 (0.74–0.99)	91 months	2294	2294 (100%)	2303 (97.9%)	NA
	20–30 mg daily Tam for 5 years				2305	2305 (100%)	2314 (97.6%)	
MA.27 (2013)	25 mg daily E for 5 years	1.02 (0.87–1.18)	0.93 (0.77–1.13)	4.1 years	3789	3789 (100%)	3766 (99.39%)	64.2
	1 mg daily A for 5 years				3787	3787 (100%)	3759 (99.26%)	
ATLAS (2013)	20 mg daily Tam for 10 years	0.84 (0.76–0.94)	0.87 (0.78–0.97)	7.6 years	3428	3035 (88.54%)	3428 (100%)	NA
	20 mg daily Tam for 5 years				3418	3044 (89.06%)	3418 (100%)	
aTTom (2013)	Tam for 10 years	0.86 (0.77–0.96)	0.91 (0.80–1.04)	4.2 years	3470	NA	NA	NA
	Tam for 5 years				3486			
Face trial (2016)	2.5 mg daily L for 5 years	0.93 (0.80–1.07)	0.98 (0.82–1.17)	65 months	2061	NA	2028 (98.4%)	62
	1 mg daily A for 5 years				2075		2053 (98.9%)	

Tam tamoxifen, *Tor* toremifene, *A* anastrozole, *L* letrozole, *E* exemestane

Qualität der Studien:

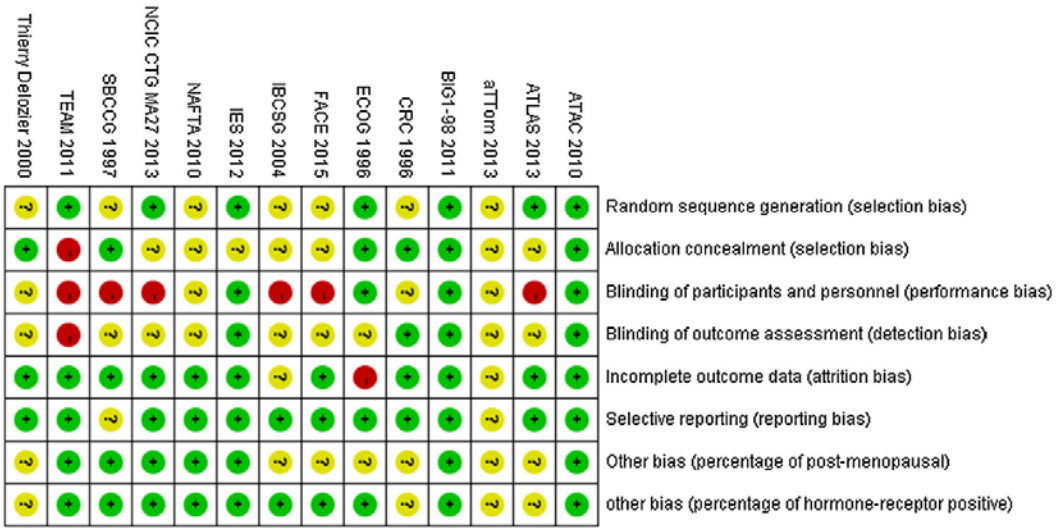


Fig. 2 Cochrane risk of bias tool assessment (+: low risk of bias; −: high risk of bias; ?: unclear risk of bias). Other bias: percentage of post-menopausal and HR(+): low risk: ≧50%; high risk of bias: <50%; unclear risk of bias: not mentioned in the article

Studienergebnisse:

Table 2 The results of direct comparisons and the heterogeneity with I statistics or I2 square of univariate meta-analysis

DFS					OS				
Fixed-effected model HR (95% CI)	Random-effected model HR (95% CI)	Heterogeneity			Fixed-effected model HR (95% CI)	Random-effected model HR (95% CI)	Heterogeneity		
		Q value	I2 square	*P* value			*Q* value	I2 square	*P* value
Tor vs T5									
0.940 (0.756, 1.168)	0.940 (0.756, 1.168)	0.437	0.000	0.509	0.945 (0.712, 1.254)	0.945 (0.712, 1.254)	0.002	0.000	0.968
T10 vs T5									
0.884 (0.780, 0.912)	0.837 (0.747, 0.937)	3.176	37.022	0.204	0.886 (0.815, 0.964)	0.886 (0.815, 0.964)	0.267	0.000	0.605
T5 vs T3									
0.812 (0.722, 0.913)	0.812 (0.722, 0.913)	0.404	0.000	0.841	0.857 (0.721, 1.017)	0.857 (0.721, 1.017)	0.157	0.000	0.692

T3 less than 5 years of tamoxifen, *T5* 5 years of tamoxifen, *T10* 10-year tamoxifen, *Tor* 5-year toremifene

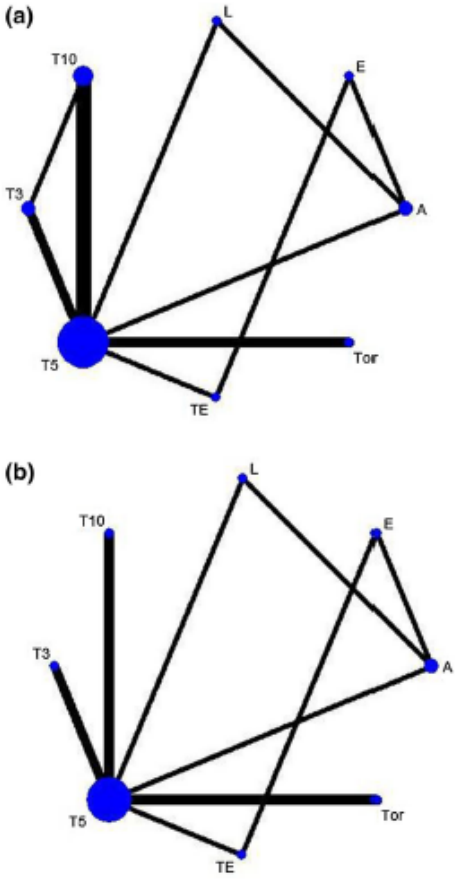


Fig. 3 Network of analyzed comparisons. The notes size of DFS (**a**) and OS (**b**) are thickness of the line corresponding to the number of trial per comparison

Table 3 Pooled hazard ratios for DFS (A) and OS (B) by Bayesian network meta-analysis and pair-wise meta-analysis

A						
T5	0.86 (0.80–0.92)	0.87 (0.80–0.94)	1.20 (1.07–1.34)	0.84 (0.77–0.92)	0.86 (0.76–0.96)	0.95 (0.76–1.17)
	0.84 (0.79–0.91)	*0.86 (0.78–0.95)*	**1.23 (1.09–1.41)**	*0.86 (0.78–0.96)*		**0.94 (0.75–1.17)**
	T10	1.02 (0.91–1.13)	1.40 (1.24–1.58)	0.98 (0.88–1.11)	1.01 (0.88–1.15)	1.11 (0.88–1.39)
			1.27 (1.02–1.56)			
		A	1.38 (1.21–1.58)	0.97 (0.88–1.07)	0.99 (0.88–1.11)	1.09 (0.86–1.36)
				0.93 (0.80–1.07)	*1.02 (0.87–1.18)*	
			T3	0.70 (0.61–0.81)	0.72 (0.61–0.84)	0.79 (0.62–1.00)
				L	1.02 (0.89–1.17)	1.13 (0.89–1.41)
					E	1.1 (0.86–1.41)
						Tor
B						
T5	0.94 (0.85–1.03)	0.89 (0.79–0.99)	0.86 (0.74–1.00)	0.95 (0.70–1.24)	0.89 (0.81–0.96)	1.17 (0.99–1.39)
	0.95 (0.84–1.06)	*0.87 (0.77–0.999)*		**0.95 (0.71–1.26)**	**0.886 (0.81–0.96)**	**1.16 (0.98–1.39)**
	A	0.95 (0.84–1.07)	0.92 (0.80–1.07)	1.02 (0.75–1.35)	0.95 (0.84–1.08)	1.26 (1.03–1.53)
		0.98 (0.82–1.17)	*0.93 (0.77–1.13)*			
		L	0.98 (0.82–1.15)	1.08 (0.78–1.44)	1.00 (0.87–1.15)	1.33 (1.08–1.62)
			E	1.11 (0.79–1.49)	1.03 (0.87–1.21)	1.36 (1.08–1.72)
				Tor	0.95 (0.71–1.27)	1.26 (0.90–1.73)
					T10	1.33 (1.10–1.60)
						T3

The italiced number in one cell is original data from original article. The bold number was the amalgamative HRs which was calculated by pair-wise meta-analysis, if there were two or more articles have HRs of DFS or OS

CI confidence interval for traditional meta-analysis, *CrI* credible interval for Bayesian network meta-analysis, *T3* less than 5 years of tamoxifen, *T5* 5 years of tamoxifen, *T10* 10-year tamoxifen, *E* 5-year exemestane, *L* 5-year letrozole, *A* 5-year anastrozole, *Tor* 5-year toremifene, *TE* 2–3 years of tamoxifen followed by 2–3 years of exemestane

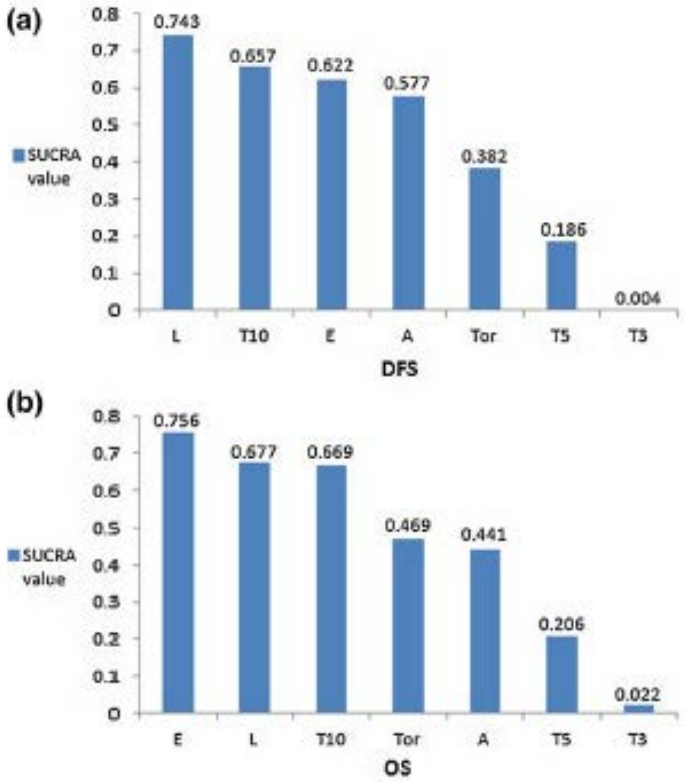


Fig. 4 Ranking of interventions with respect to the DFS (**a**) and OS (**b**): SUCRA values

Anmerkung/Fazit der Autoren

In conclusion, our network meta-analysis suggested that adjuvant endocrine monotherapy with letrozole or exemestane is the optimum endocrine therapy in postmenopausal women with hormone receptor-positive early stage breast cancer. Simultaneously, it is a great possibility

that the efficacy of 10-year tamoxifen for early breast cancer patients is noninferior to 5-year letrozole or 5-year exemestane, and even more effective than 5-year anastrozle.

Wu Y-T et al., 2018 [46].

Efficacy and cardiac safety of the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy for HER2-positive breast cancer: a systematic review and meta-analysis

Fragestellung

The purpose of this study was to evaluate the efficacy and cardiac safety of the concurrent use of trastuzumab and anthracycline-based NAC for human epidermal growth factor receptor 2 (HER2)-positive locally advanced breast cancer.

Methodik

Population:

(HER2)-positive locally advanced breast cancer

Intervention:

Fulvestrant (250 or 500 mg)

Komparator:

aromatase inhibitors (anastrozole, exemestane, letrozole)

Endpunkte:

- The primary outcomes were the absolute rates of pCR and the OR of the pCR, when comparing concurrent use with nonconcurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer. The pCR is defined as the state in which no residual invasive carcinoma is found in the breast and axillary lymph nodes or the breast.
- The secondary outcomes were the absolute rates and OR of cardiac ejection fraction decrease (CED), cardiac failure (CF), complete response (CR), partial response (PR), breast conservation surgery (BCS), recurrence-free survival (RFS), and OS.

Recherche/Suchzeitraum:

- July 1, 2017

Qualitätsbewertung der Studien:

Newcastle–Ottawa scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

13 (n=1391)

- Of the 13 studies, four studies were randomized trials, six studies were prospective cohorts, and three studies were retrospective cohorts.
- Five studies had two arms; meanwhile, eight studies in the meta-analysis were single-armed ones (experimental arm), of which three studies' control groups were abandoned because the patients were not HER2 positive or because the treatment regimen was not suitable for comparing with the experimental group.

Charakteristika der Population:

Of the 13 studies, four studies were randomized trials, six studies were prospective cohorts, and three studies were retrospective cohorts. Five studies had two arms; meanwhile, eight studies in the meta-analysis were single-armed ones (experimental arm), of which three studies' control groups were abandoned because the patients were not HER2 positive or because the treatment regimen was not suitable for comparing with the experimental group.

Qualität der Studien:

We found that all of the included studies were of moderate or high quality, and hence the included studies were reliable. Besides, we assessed the publication bias of the included studies using symmetrical funnel plot analysis and Egger's tests, and the result showed no significant publication bias.

Table S3 Quality assessment of the included studies using the Newcastle-Ottawa scale

	Selection†				Comparability‡	Outcome§			
Study, Year (Reference)	**Representativeness of the exposed cohort (maximum:*)**	**Selection of the non-exposed cohort (maximum:*)**	**Ascertainment of exposure (maximum:*)**	**Demonstration that outcome of interest was not present at start of study (maximum:*)**	**Comparability of cohorts on the basis of the design or analysis (maximum:**)**	**Assessment of outcome (maximum:*)**	**Was follow up long enough for outcomes to occur (maximum:*)**	**Adequacy of follow up of cohorts (maximum:*)**	**Aggregate score**
Uriarte-Pinto et al, 2016	*	NA	*	*	NA	*	*	*	******
Buzdar et al, 2005	*	*	*	*	**	*	*	*	********
Buzdar et al, 2007	*	*	*	*	**	*	*	*	********
Huang et al, 2015	*	*	*	*	**	*	*	/	*******
Bayraktar et al, 2012	*	*	*	*	**	*	*	*	********
Pizzuti et	*	NA	*	*	NA	*	*	*	******

al, 2016									
Dawood et al, 2007	*	NA	*	*	NA	*	*	*	******
Wenzel et al, 2004	*	NA	*	*	NA	*	*	/	*****
Gavila et al, 2015	*	NA	*	*	NA	*	*	*	******
Untch et al, 2010	*	/	*	*	/	*	*	/	*****
Gianni et al, 2010	*	*	*	*	**	*	*	*	******* **
Untch et al, 2012	*	/	*	*	/	*	*	/	*****
Tuxen et al, 2014	*	/	*	*	/	*	*	/	*****

For our main outcome(Pathologic complete response, pCR), the points for confounding were allocated as follows: one point was allocated for controlling for type or duration of chemotherapy and an additional point for age, sex ,country, race. We designated the lowest score for the main outcome(pCR) without controlling all the items. The final comparability score was the minimum score that a study received for all the outcomes.

/=study did not fulfill listed criteria; *=study fulfilled listed criteria; NA=criteria not applicable to the study.

†Representativeness of exposed cohort: *given if the cohort was representative of the average HER2-positive breast cancer patients with concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy; / given if the cohort was selected based on convenience (i.e., volunteers) or if there was no description of the derivation of the cohort. Selection of nonexposed cohort: * given if the nonexposed cohort was drawn from the same community as the exposed cohort; / was given if it was drawn from a different source or there was no description of the cohort derivation. Exposure ascertainment: * given if obtained from secure record (hospital chart); / was given if from a written self-report or no description given.* given if outcome of interest was not present at start of study.

‡ * given if study controlled for or adjusted for type or duration of chemotherapy used; additional * if controlled for age or sex.

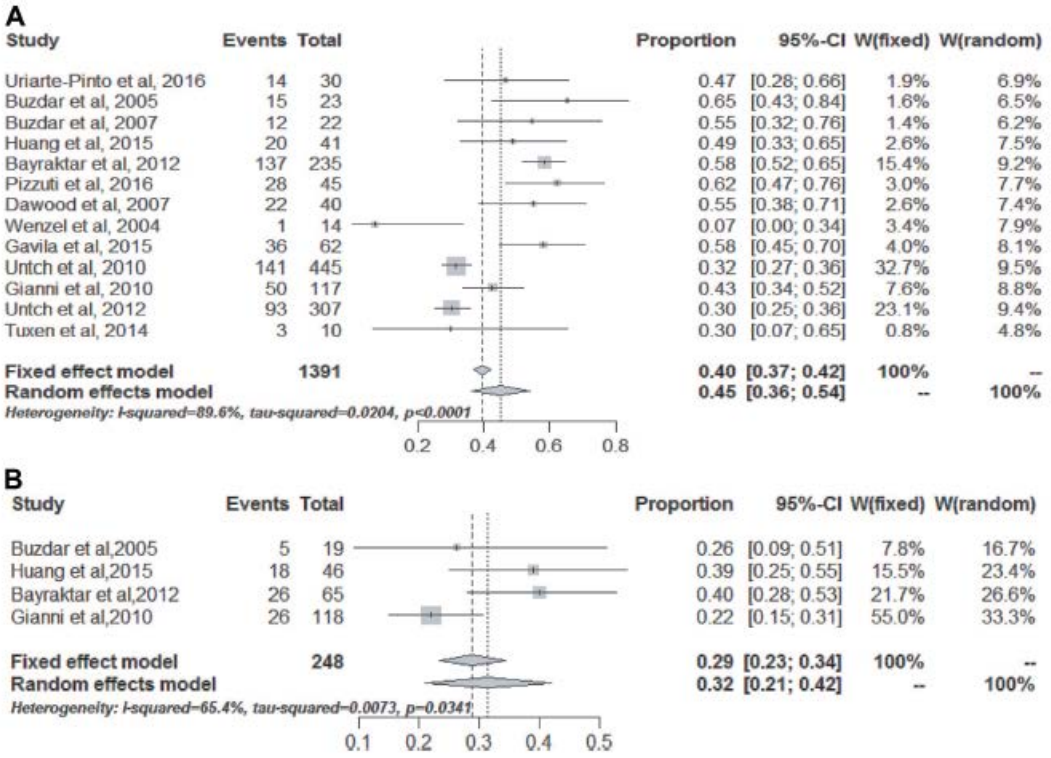
Studienergebnisse:

- pathologic complete response (pCR)

All 13 studies, which included 1,391 patients, were analyzed for the pCR rate after concurrent use of trastuzumab and anthracycline-based NAC in HER2-positive breast cancer patients. The pCR rate ranged from 7% to 65% in the 13 studies, and the pooled absolute rate of pCR was 45% (95% CI: 0.36–0.54)

Figure 2 The pooled absolute rate of pCR for the concurrent (A) and nonconcurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer.

Abbreviations: HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response.



- The CR rate of concurrent vs nonconcurrent use of trastuzumab and anthracycline-based NAC in HER2-positive breast cancer patients

Seven studies reported the CR rate of concurrent use of trastuzumab and anthracycline-based NAC in HER2-positive breast cancer patients. Meanwhile, three studies reported the CR rate of nonconcurrent use of trastuzumab and anthracycline-based NAC in HER2-positive breast cancer patients. The pooled absolute rate of CR was 51% (95% CI: 0.34–0.68) and 37% (95% CI: 0.11–0.63) in the experimental group and the control group, respectively (Figure S1), and the OR was 3.03 (95% CI: 1.50–6.13, P=0.002) (Figure 4).

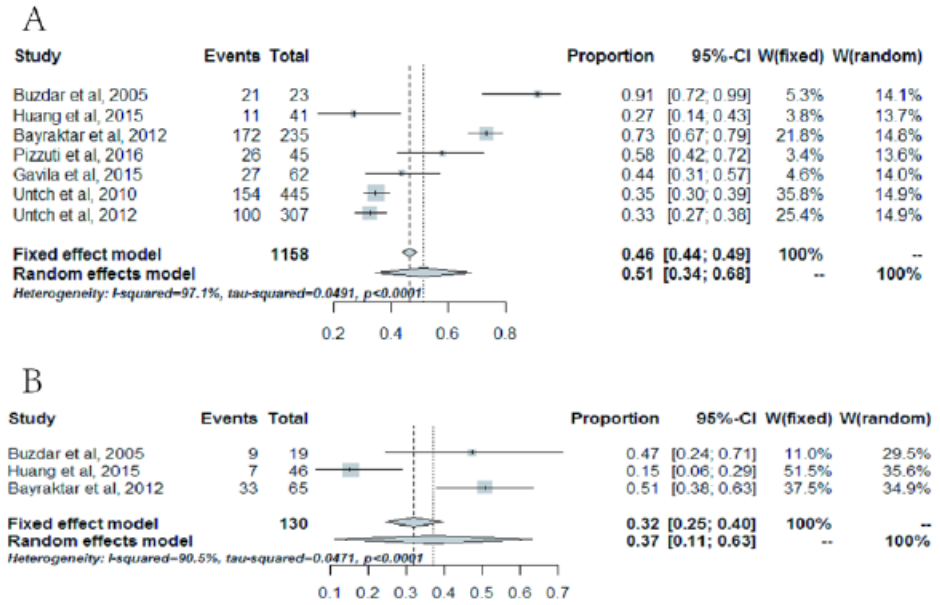


Figure S1 The pooled absolute rate of CR for the concurrent (A) and non-concurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

The PR rate of concurrent vs nonconcurrent use of trastuzumab and anthracycline-based NAC in HER2-positive breast cancer patients

Ten studies analyzed the PR rate for the concurrent combination therapy, and three studies reported the PR rate for nonconcurrent use of trastuzumab and anthracycline-based NAC. The pooled absolute rate of PR was 49% (95% CI: 0.31–0.68) and 47% (95% CI: 0.04–0.91) in the experimental group and the control group, respectively (Figure S2), and the OR was 0.32 (95% CI: 0.11–0.92, P=0.03) (Figure 4).

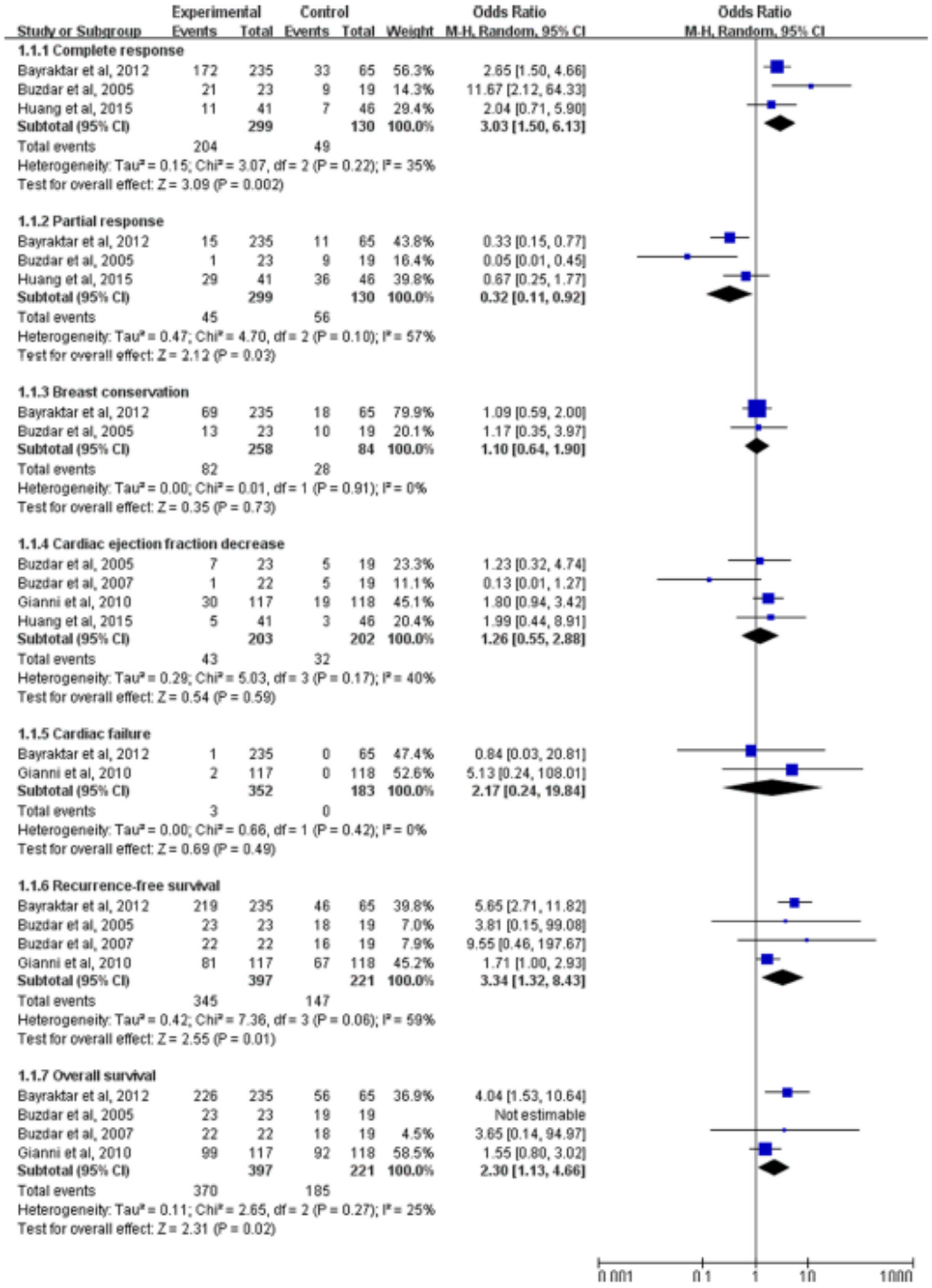


Figure 4 The pooled OR of secondary outcomes for the comparison of the concurrent vs nonconcurrent use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer.
Abbreviations: HER2, human epidermal growth factor receptor 2; NAC, neoadjuvant chemotherapy; pCR, pathologic complete response.

Anmerkung/Fazit der Autoren

Taken together, our study indicates that the concurrent use of trastuzumab and anthracycline-based NAC for HER2-positive locally advanced breast cancer significantly improves the pCR rates without obvious increase in the cardiotoxicity events. During the period of follow-up, the concurrent use of trastuzumab and anthracycline-based NAC was superior to the nonconcurrent use of trastuzumab and anthracycline-based NAC in terms of RFS and OS.

Our results support the efficacy and cardiac safety of the concurrent use of trastuzumab plus anthracycline-based NAC for certain patients with HER2-positive locally advanced breast cancer.

Shen Y et al., 2018 [41].

Comparative efficacy of adjuvant trastuzumab-containing chemotherapies for patients with early HER2-positive primary breast cancer: a network meta-analysis

Fragestellung

Trastuzumab (H) with chemotherapy benefits patients with HER2+ breast cancer (BC); however, we lack head-to-head pairwise assessment of survival or cardiotoxicity for specific combinations. We sought to identify optimal combinations.

Methodik

Population:

To ensure a reasonably homogeneous cohort of patients with early-stage HER2+ breast cancer, we excluded RCTs for patients with stage IV HER2+ breast cancers, trials in neoadjuvant settings, and trials that evaluated H combined with hormonal therapies. For trials represented in multiple publications, we used the publication with the most updated results. To facilitate indirect comparisons and link two separate networks with adjuvant H-containing chemotherapies, we included three RCTs of adjuvant treatments without H for early-stage breast cancer that compared AC versus ACT

Intervention:

anti-HER2 agent, trastuzumab (H)

Komparator:

k.A.

Endpunkte:

The primary outcome was OS, and EFS and cardiotoxicity were secondary outcomes. We define OS as the time from the date of randomization to the date of death or last follow-up; EFS as the time from the date of randomization to the date of first cancer recurrence, including locoregional, contralateral breast cancer, distant recurrence, or death; and SCAEs using the original definition given in each RCT. SCAEs included New York Heart Association class III/ IV heart failure, possible/ probable cardiac death, and discontinuation of treatment due to cardiac toxicities, for which some studies defined cardiac toxicities using significant left ventricular ejection fraction (LVEF) decrease ≥ 10% from baseline and absolute LVEF < 50% or symptomatic heart failure.

Recherche/Suchzeitraum:

We employed a computerized search of PubMed up to October 2013 and updated our search in October 2017

Qualitätsbewertung der Studien:

Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

6 RCT: 13621 HER2+ primary breast cancer patients treated with adjuvant chemotherapy regimens with or without H

3 RCT that compared ACT to AC for 5422 patients with early-stage breast cancer

Charakteristika der Population:

Table 1 Characteristics of studies analyzed for comparing trastuzumab in the setting of adjuvant chemotherapy

Study	Journal/year published	Median follow-up (months)	Age[a] (years)	# per arm (# analyzed)	Adjuvant treatment	Dose of trastuzumab (H)	Duration of H (weeks)
NSABP B-31 [19–21]	JCO/2005 JCO/2012 JCO/2014	101[b]	22–80	1024 (814)	ACT	None	NA
				1019 (850)	ACT+H	4 mg/kg loading 2 mg/kg q. wk	52
FinHer [31]	JCO/2009	62	NA	58	ACT	None	NA
				54	ACT+H	4 mg/kg loading 2 mg/kg q. wk	9
PACS-04 [32]	JCO/2009	47	48	268	AC	None	NA
				260	AC-H	8 mg/kg loading 6 mg/kg q. 3 wk	52
BCIRG 006 [33]	NEJM/2011	65	49	1073	ACT	None	NA
				1074	ACT+H	Not reported	52
				1075	TC+H	Not reported	52
N9831 [20, 22]	JCO/2011	72	22–80	819	ACT	None	NA
				981	ACT-H	4 mg/kg loading 2 mg/kg q. wk	52
				814	ACT+H	4 mg/kg loading 2 mg/kg q. wk	52
HERA [34, 35]	Lancet/2013 Lancet/2017	132	49	1698 (1697)	AC	None	NA
				1703 (1702)	AC-H	8 mg/kg loading 6 mg/kg q. 3 wk	52
				1701 (1700)	AC-H2y	8 mg/kg loading 6 mg/kg q. 3 wk	104
NABCTTE 2197 [36]	JCO/2008	79.4	51	1476 (1441)	ACT	NA	NA
				1476 (1441)	AC	NA	NA
ADNPBC [37]	NEJM/2005	55	49	745 (744)	ACT	NA	NA
				746 (736)	AC	NA	NA
ADHRNNBC [38]	NEJM/2010	77	23–74	521	ACT	NA	NA
				539	AC	NA	NA

NABCTTE North American Breast Cancer Intergroup Trial E 2197, *ADNPBC* adjuvant docetaxel for node-positive breast cancer, *ADHRNNBC* adjuvant docetaxel for high-risk, node-negative breast cancer, *NSABP B-31* doxorubicin plus cyclophosphamide (60 mg/m^2 and 600 mg/m^2, respectively, every 21 days for 4 cycles) followed by paclitaxel (175 mg/m^2 every 21 days for 4 cycles), *FinHer* docetaxel (100 mg/m^2 every 3 weeks for 3 cycles) followed by fluorouracil plus epirubicin plus cyclophosphamide (600 mg/m^2, 60 mg/m^2, and 600 mg/m^2, respectively, every 3 weeks for 3 cycles), *PACS-04* fluorouracil plus epirubicin plus cyclophosphamide (FE100C: F and C 500 mg/m^2, E 100 mg/m^2) every 3 weeks for 6 cycles, or epirubicin plus docetaxel (both 75 mg/m^2) every 3 weeks for 6 cycles, *BCIRG 006* doxorubicin plus cyclophosphamide (60 mg/m^2 and 600 mg/m^2, respectively, every 3 weeks for 4 cycles) followed by docetaxel (100 mg/m^2 every 3 weeks for 4 cycles), docetaxel plus carboplatin (both 75 mg/m^2 every 3 weeks for 6 cycles), *N9831* doxorubicin plus cyclophosphamide (60 mg/m^2 and 600 mg/m^2, respectively, every 21 days for 4 cycles) followed by paclitaxel (80 mg/m^2 weekly for 12 doses), *HERA* anthracyclines alone (68% of patients in each group), anthracyclines plus taxanes (26% of patients in each group) or a regimen without anthracyclines, including cyclophosphamide, methotrexate, and fluorouracil (6% of patients in each group), *AC* Anthracycline-containing regimen without taxane, *ACT*: anthracycline with sequential or concurrent taxane, *ACT+H* ACT with concurrent trastuzumab, *ACT-H* ACT followed by sequential trastuzumab, *AC-H* AC followed by sequential trastuzumab, *AC-H2y* AC with sequential trastuzumab for 2 years, *TC+H* docetaxel and carboplatin (TC) with concurrent trastuzumab

[a]Age: median, mean, or range in years

[b]The joint analysis of B31 and N9831 based on results reported in JCO 2014 [20]

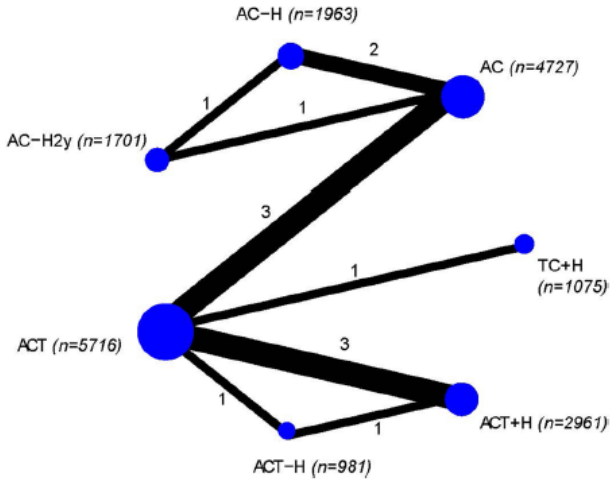


Fig. 1 Network of meta-analysis comparisons. *AC* anthracycline-containing regimen without taxane, *ACT* anthracycline with sequential or concurrent taxane, *ACT+H* ACT with concurrent trastuzumab, *ACT-H* ACT followed by sequential trastuzumab, *AC-H* AC followed by sequential trastuzumab, *AC-H2y* AC with sequential trastuzumab of 2 years, *TC+H* docetaxel, and carboplatin with concurrent trastuzumab

Qualität der Studien:

Table S1. Cochrane risk-of-bias tool for quality assessment of 7 randomized controlled trials.

Study publication	Sequence generation	Allocation concealment	Blinding	Blinding outcome	Incomplete outcome data	Selective outcome reporting	Other source of bias
Tan-Chiu, JCO, 2005[19]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes
Goldhirsch, Lancet, 2013[34]	Yes	Yes	No	No	Yes	Yes	Yes
Joensuu, JCO, 2009[31]	Yes	Yes	No	No	Yes	Yes	Yes
Spielmann, JCO, 2009[32]	Unclear	Unclear	No	No	Yes	Yes	Yes
Perez, JCO, 2011[20]	Unclear	Unclear	No	No	Yes	Yes	Yes
Perez, JCO, 2011[22] Sequential versus concurrent	Yes	Yes	No	No	Yes	Yes	Yes
Slamon, NEJM, 2011[33]	Unclear	Unclear	No	No	Yes	Yes	Yes

Yes: Low risk of bias; No: High risk of bias; Unlcear: Unlcear risk of bias

Studienergebnisse:

- Summary of direct comparisons

Figure S2a: Hazards ratios and 95% confidence intervals (CIs) to compare overall survival times between treatments in each study

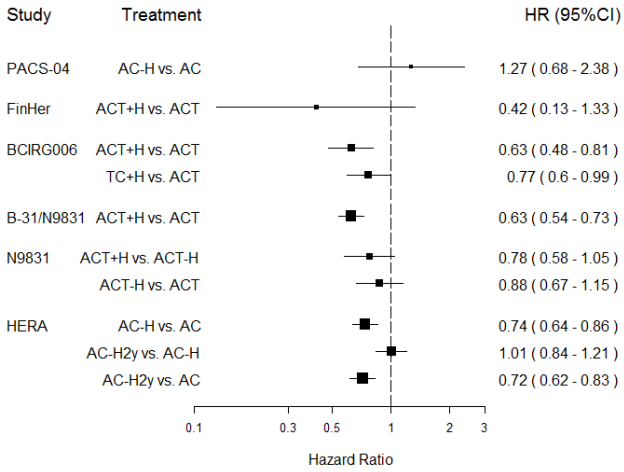
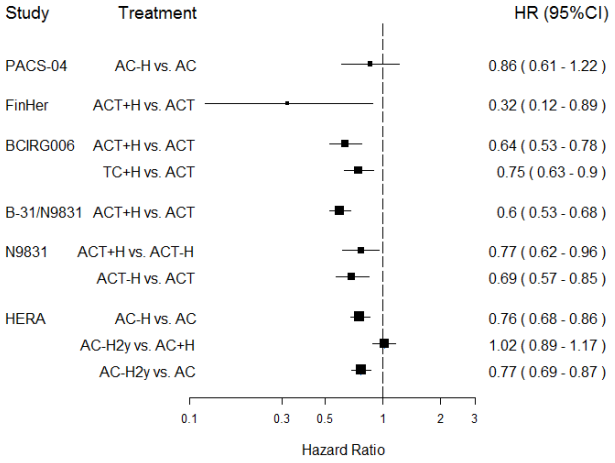


Figure S2b: Hazards ratios and 95% confidence intervals (CIs) to compare event-free survival times between treatments in each study



Table·S2.·Estimated·hazard·ratio·of·pairwise·comparison·of·overall·survival·times·between·treatments.·¶

*¤	AC¤	AC-H¤	AC-H2y¤	ACT¤	ACT-H¤	ACT+H¤	TC+H¤
AC¤	1·(·1·,··1·)·¤	1.31·(·1.12·,··1.55·)·¤	1.36·(·1.15·,··1.61·)·¤	1.21·(·1.02·,··1.43·)·¤	1.42·(·1.08·,··1.88·)·¤	1.91·(·1.54·,··2.37·)·¤	1.57·(·1.15·,··2.14·)·¤
AC-H¤	0.76·(·0.65·,··0.9·)·¤	1·(·1·,··1·)·¤	1.04·(·0.85·,··1.26·)·¤	0.92·(·0.73·,··1.16·)·¤	1.08·(·0.79·,··1.49·)·¤	1.45·(·1.11·,··1.91·)·¤	1.19·(·0.84·,··1.7·)·¤
AC-H2y¤	0.73·(·0.62·,··0.87·)·¤	0.96·(·0.79·,··1.18·)·¤	1·(·1·,··1·)·¤	0.89·(·0.7·,··1.12·)·¤	1.05·(·0.76·,··1.44·)·¤	1.4·(·1.06·,··1.84·)·¤	1.15·(·0.81·,··1.64·)·¤
ACT¤	0.83·(·0.7·,··0.98·)·¤	1.09·(·0.86·,··1.38·)·¤	1.13·(·0.89·,··1.43·)·¤	1·(·1·,··1·)·¤	1.18·(·0.95·,··1.47·)·¤	1.58·(·1.38·,··1.81·)·¤	1.3·(·1·,··1.69·)·¤
ACT-H¤	0.7·(·0.53·,··0.92·)·¤	0.92·(·0.67·,··1.27·)·¤	0.96·(·0.69·,··1.32·)·¤	0.85·(·0.68·,··1.05·)·¤	1·(·1·,··1·)·¤	1.34·(·1.07·,··1.67·)·¤	1.1·(·0.78·,··1.55·)·¤
ACT+H¤	0.52·(·0.42·,··0.65·)·¤	0.69·(·0.52·,··0.9·)·¤	0.71·(·0.54·,··0.94·)·¤	0.63·(·0.55·,··0.72·)·¤	0.75·(·0.6·,··0.93·)·¤	1·(·1·,··1·)·¤	0.82·(·0.61·,··1.1·)·¤
TC+H¤	0.64·(·0.47·,··0.87·)·¤	0.84·(·0.59·,··1.19·)·¤	0.87·(·0.61·,··1.24·)·¤	0.77·(·0.59·,··1·)·¤	0.91·(·0.65·,··1.28·)·¤	1.22·(·0.91·,··1.64·)·¤	1·(·1·,··1·)·¤

Table S3. Estimated hazard ratios of pairwise comparisons of event-free survival times between treatments.

	AC	AC-H	AC-H2y	ACT	ACT-H	ACT+H	TC+H
AC	1 (1, 1)	1.28 (1.06, 1.55)	1.28 (1.04, 1.58)	1.23 (1.04, 1.45)	1.69 (1.29, 2.21)	2.07 (1.65, 2.59)	1.64 (1.21, 2.22)
AC-H	0.78 (0.65, 0.94)	1 (1, 1)	1 (0.8, 1.24)	0.96 (0.75, 1.23)	1.32 (0.95, 1.83)	1.61 (1.2, 2.17)	1.28 (0.89, 1.83)
AC-H2y	0.78 (0.63, 0.96)	1 (0.8, 1.25)	1 (1, 1)	0.96 (0.73, 1.25)	1.32 (0.94, 1.85)	1.62 (1.19, 2.2)	1.28 (0.89, 1.85)
ACT	0.81 (0.69, 0.96)	1.04 (0.81, 1.34)	1.04 (0.8, 1.36)	1 (1, 1)	1.38 (1.12, 1.7)	1.69 (1.45, 1.96)	1.33 (1.04, 1.72)
ACT-H	0.59 (0.45, 0.77)	0.76 (0.55, 1.05)	0.76 (0.54, 1.06)	0.73 (0.59, 0.9)	1 (1, 1)	1.22 (0.99, 1.51)	0.97 (0.7, 1.35)
ACT+H	0.48 (0.39, 0.61)	0.62 (0.46, 0.83)	0.62 (0.45, 0.84)	0.59 (0.51, 0.69)	0.82 (0.66, 1.01)	1 (1, 1)	0.79 (0.59, 1.06)
TC+H	0.61 (0.45, 0.83)	0.78 (0.55, 1.12)	0.78 (0.54, 1.13)	0.75 (0.58, 0.97)	1.03 (0.74, 1.43)	1.26 (0.94, 1.7)	1 (1, 1)

Table S4. Estimated odds ratios of pairwise comparisons of cardiotoxicities between treatments.

Treatment	AC	AC-H	AC-H2y	ACT	ACT-H	ACT+H	TC+H
AC	1 (1, 1)	0.16 (0.04, 0.58)	0.14 (0.03, 0.67)	0.46 (0.23, 0.91)	0.12 (0.04, 0.41)	0.11 (0.04, 0.29)	0.81 (0.18, 3.69)
AC-H	6.37 (1.74, 23.36)	1 (1, 1)	0.87 (0.35, 2.16)	2.92 (0.67, 12.7)	0.78 (0.13, 4.56)	0.69 (0.14, 3.52)	5.15 (0.7, 37.97)
AC-H2y	7.33 (1.5, 35.84)	1.15 (0.46, 2.86)	1 (1, 1)	3.36 (0.59, 18.94)	0.89 (0.12, 6.54)	0.8 (0.12, 5.14)	5.92 (0.66, 53.25)
ACT	2.18 (1.1, 4.36)	0.34 (0.08, 1.49)	0.3 (0.05, 1.68)	1 (1, 1)	0.27 (0.1, 0.71)	0.24 (0.12, 0.47)	1.77 (0.46, 6.82)
ACT-H	8.21 (2.46, 27.32)	1.29 (0.22, 7.56)	1.12 (0.15, 8.2)	3.76 (1.4, 10.05)	1 (1, 1)	0.89 (0.4, 1.98)	6.63 (1.24, 35.31)
ACT+H	9.17 (3.47, 24.26)	1.44 (0.28, 7.29)	1.25 (0.19, 8.05)	4.2 (2.12, 8.33)	1.12 (0.5, 2.48)	1 (1, 1)	7.41 (1.63, 33.73)
TC+H	1.24 (0.27, 5.65)	0.19 (0.03, 1.43)	0.17 (0.02, 1.52)	0.57 (0.15, 2.19)	0.15 (0.03, 0.8)	0.13 (0.03, 0.61)	1 (1, 1)

- Network meta- analysis

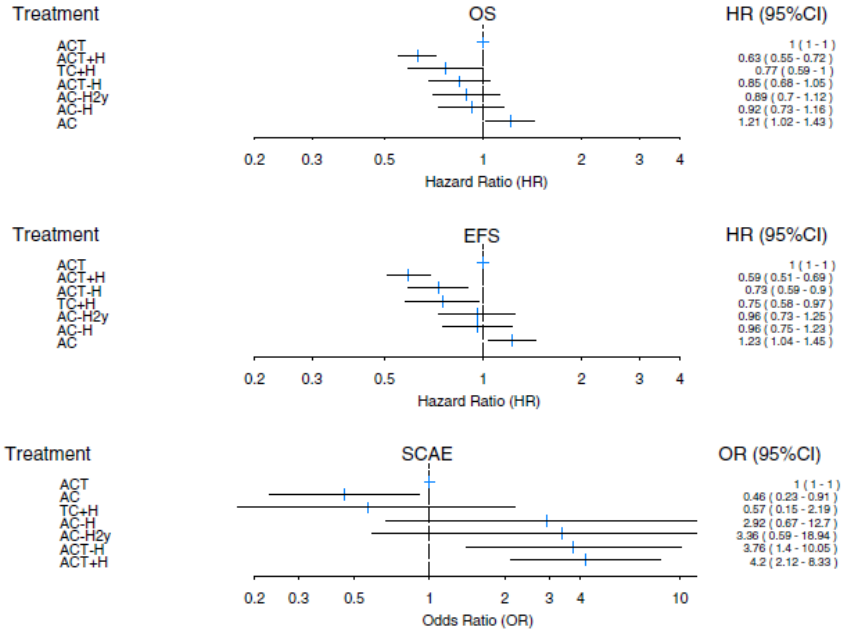


Fig. 2 Network meta-analysis estimated hazard ratios (HRs) for comparison of overall survival (OS) or event-free survival (EFS) between each adjuvant therapy and ACT and odds ratios (ORs) for comparison of incidence of severe cardiac adverse events (SCAEs) between each adjuvant therapy and ACT

Table S5. P-scores to rank treatment agents based on overall survival (OS), event-free survival (EFS) and cardiotoxicity

Treatment¤	OS¤	EFS¤	Cardiotoxicity¤
ACT+H¤	0.9812¤	0.9845¤	0.189¤
TC+H¤	0.7324¤	0.7146¤	0.843¤
ACT-H¤	0.586¤	0.7502¤	0.245¤
AC-H2y¤	0.5174¤	0.3762¤	0.278¤
AC-H¤	0.4327¤	0.3779¤	0.339¤
ACT¤	0.2464¤	0.2926¤	0.675¤
AC¤	0.004¤	0.004¤	0.931¤

A bigger p-score corresponds to better treatment for the corresponding outcome. The highest p-score indicates the best treatment. For example, ACT+H is ranked the best in terms of OS and EFS

SCAEs

ACT+H was associated with the highest SCAE risk compared to ACT alone (OR 4.2, 95% CI 2.12, 8.33), and ACT-H had the second highest OR (OR 3.76, 95%CI 1.4, 10.5) (Fig. 2). TC+H had the lowest SCAE risk compared with ACT alone (OR 0.57, 95% CI 0.15, 2.19). Among the H-containing chemotherapies in the pairwise comparisons, TC+H had a statistically significant lower SCAE risk than ACT+H (OR 0.13, 95% CI 0.03, 0.61) and ACT-H (OR 0.15, 95 CI 0.03, 0.8), and had non-significant lower risks than the other two H-containing adjuvant therapies (Supplementary Table S4).

Fig. 2 Network meta-analysis estimated hazard ratios (HRs) for comparison of overall survival (OS) or event-free survival (EFS) between each adjuvant therapy and ACT and odds ratios (ORs) for comparison of incidence of severe cardiac adverse events (SCAEs) between each adjuvant therapy and ACT

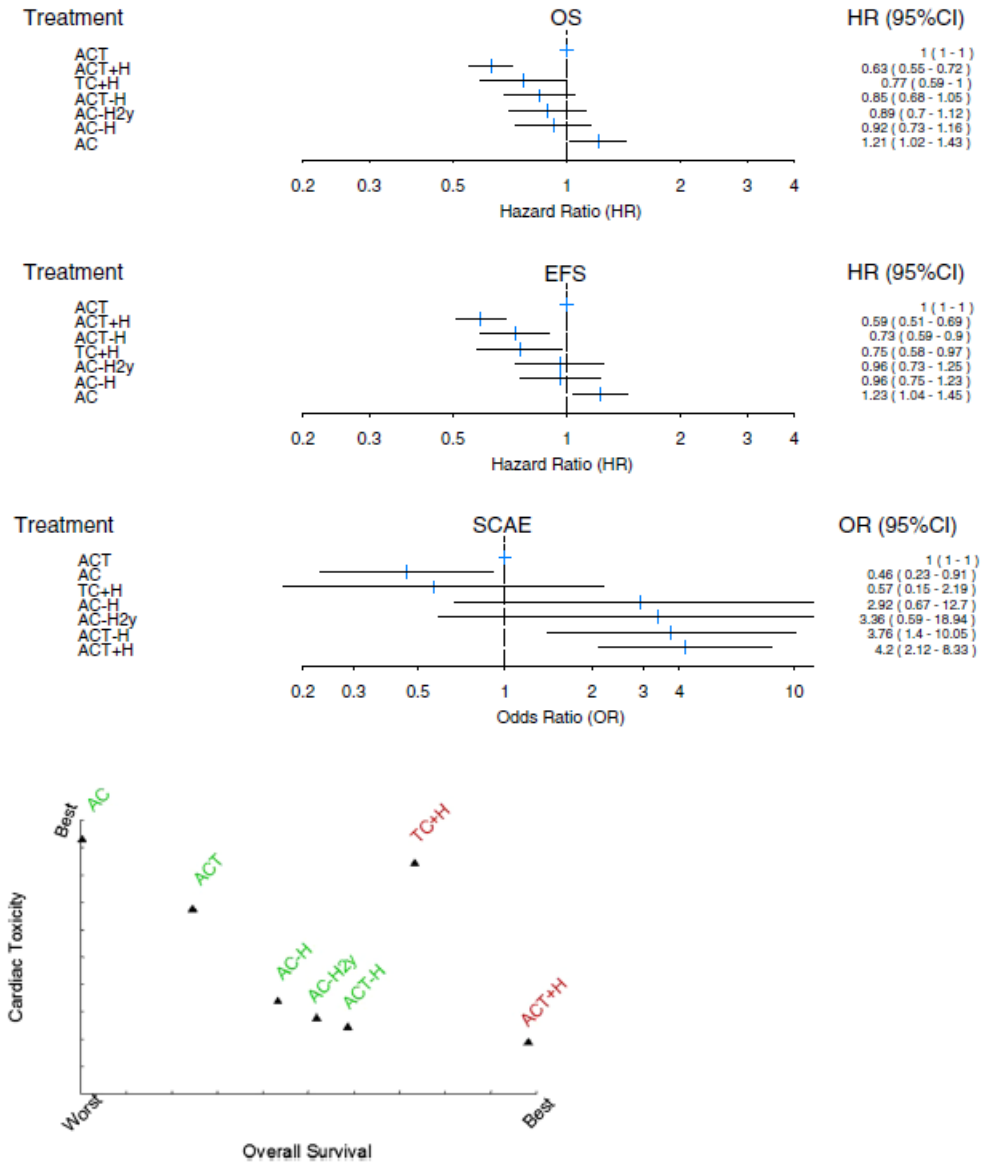


Fig. 3 Ranking of treatments in terms of overall survival and cardiotoxicity

Anmerkung/Fazit der Autoren

Concurrent H with ACT or TC showed most clinical benefit for early-stage HER2+ BC; TC+H had lowest cardiotoxicity.

Kommentare zum Review

Die Literatursuche fand nur in PubMed statt.

Die methodische Güte der NMA ist nicht abschließend beurteilbar. Es handelt sich ohnehin um indirekte Vergleiche, die gegenüber direkten Vergleiche ein höheres Verzerrungspotezial aufweisen. Deshalb sind die Ergebnisse auch der direkten Vergleiche dargestellt.

Nakashoji A et al., 2018 [36].

The updated network meta-analysis of neoadjuvant therapy for HER2-positive breast cancer

(Erstanalyse hierzu war publiziert worden in: **Nagayama A et al., 2014 [14]**.)

Fragestellung

We previously described a systematic assessment of the neoadjuvant therapies for human epidermal growth factor receptor-2 (HER2) positive breast cancer, using network meta-analysis. Accumulation of new clinical data has compelled us to update the analysis.

Methodik

Population:

HER2-positive breast cancer patients in the neoadjuvant settings

Intervention/ Komparator:

All randomized trials that compared at least two arms of different treatment regimens involving CT and/or anti-HER2 agents in HER2-positive breast cancer patients in the neoadjuvant settings were considered. All cytotoxic CT regimens were considered eligible for the meta-analysis.

Endpunkte:

- The primary outcome in this study was the number of patients who achieved pCR, which was defined as the absence of invasive residual cancer in the breast tissue and nodes (ypT0/is ypN0); noninvasive breast residuals were allowed. Other definitions of pCR were substituted if not reported.
- Secondary outcomes were the number of patients who completed the treatment as planned and the number of patients who had grade 3 or 4 adverse events, including diarrhea, neutropenia, and skin disorders. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria (NCI-CTC) version 4.0. If adverse events were not graded as per the NCI-CTC, the corresponding numbers of the adverse events were used. Cardiac events, including asymptomatic events, such as less than 50% left ventricular ejection fraction or a drop of at least 10% from baseline, and symptomatic events, such as congestive heart failure or cardiac deaths were reported separately.
- However, outcomes, such as overall survival (OS) and disease-free survival (DFS), were not analyzed because of insufficient data.

Recherche/Suchzeitraum:

11/2016

Qualitätsbewertung der Studien:

Cochrane Collaboration risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

13

Charakteristika der Population:

From the eligible studies, 10 direct comparisons were made

- CT vs CT + tzmb [27–31]
- CT + tzmb vs CT + lpnb [21–23,25,26,32,33]
- CT + tzmb vs CT + pzmb [24]
- CT + tzmb vs tzmb + pzmb [24]
- CT + tzmb vs CT + tzmb + lpnb [21–23,25,26]
- CT + tzmb vs CT + tzmb + pzmb [24]
- CT + lpnb vs CT + tzmb + lpnb [21–23,25,26]
- CT + pzmb vs tzmb + pzmb [24]
- CT + pzmb vs CT + tzmb + pzmb [24]
- CT + tzmb + pzmb vs tzmb + pzmb [24]

Table 1
Characteristics of eligible studies.

	No. of pts	Clinical stage	Neoadjuvant chemotherapy	Neo-adjuvant anti-HER2 agent	Arms	HR positive pts (%)	Duration (week)	Adjuvant therapy
Buzdar (27)	64	II-IIIA	Paclitaxel → FEC	tzmb	23	13 (56)	24	None
				–	19	11 (58)		
NOAH (29)	235	T3N1, T4, any T N2-3	AP → paclitaxel → CMF	tzmb	117	40 (35)	33	tzmb
				–	118	40 (35)		None
Pierga (30)	120	II-III	EC → docetaxel	tzmb	62	34 (55)	24	tzmb ± 5FU ± vinorelbine
				–	58	37 (63)		
NeoSphere (24)	417	T2-4	Docetaxel	tzmb	107	50 (47)	12	tzmb + FEC
			Docetaxel	tzmb + pzmb	107	50 (47)		tzmb + FEC
			–	tzmb + pzmb	107	51 (48)		tzmb + docetaxel → FEC
			Docetaxel	pzmb	96	46 (48)		tzmb + FEC
Neo ALTTO (25)	455	T2-4	Paclitaxel	tzmb	149	75 (50)	18	tzmb + FEC
				lpnb	154	80 (52)		lpnb + FEC
				tzmb + lpnb	152	77 (51)		tzmb + lpnb + FEC
Gepar Quinto (32)	615	T1 pNSLN+, T2 cN+,T3-4, HR negative	EC → docetaxel	tzmb	307	170 (55)	24	tzmb
				lpnb	308	171 (56)		
CHER-LOB (26)	121	II-IIIA	Paclitaxel → FEC	tzmb	36	21 (58)	26	tzmb
				lpnb	39	24 (62)		
				tzmb + lpnb	46	28 (61)		
H2269s (28)	29	T2-4	Docetaxel + carboplatin	tzmb	15	NR	12	Docetaxel + carboplatin + tzmb
				–	14	NR		
ABCSG-24 (31)	89	T1-4	Epirubicin + docetaxel + capecitabine	tzmb	44	26 (59)	18	NR
				–	49	30 (61)		
GEICAM 2006-14 (33)	102	T2-4	EC → docetaxel	tzmb	50	30 (60)	24	NR
				lpnb	52	31 (60)		
CALGB 40601 (23)	295	II-III	Paclitaxel	tzmb	117	69 (59)	16	tzmb + TC
				lpnb	62	35 (56)		
				tzmb + lpnb	116	69 (59)		
EORTC 10054 (22)	123	IIA-IIIC	Docetaxel + carboplatin → FEC	tzmb	53	27 (51)	18	tzmb
				lpnb	22	14 (64)		
				tzmb + lpnb	48	23 (48)		
NSABP B-41 (21)	519	IIA-IIIA	AC → paclitaxel	tzmb	177	122 (69)	28	tzmb
				lpnb	171	100 (58)		
				tzmb + lpnb	171	108 (63)		

HR = hormone receptor; tzmb = trastuzumab; lpnb = lapatinib; pzmb = pertuzumab; NR = not reported; FEC = fluorouracil-epirubicin-cyclophosphamide; AP = doxorubicin-paclitaxel; CMF = cyclophosphamide-methotrexate-fluorouracil; EC = epirubicin-cyclophosphamide.

Qualität der Studien:

Supplementary Table 1. Risk of bias summary

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
ABCSG-24 (31)	?	?	-	?	?	+	?
Buzdar (27)	+	+	?	?	?	+	-
CHER-LOB (26)	+	?	?	?	+	+	?
GEICAM 2006-14 (33)	?	?	-	?	?	+	?
GeparQuinto (32)	+	+	-	+	+	+	-
H2269s (28)	?	?	-	?	-	-	?
NeoALTTO (25)	+	+	-	+	+	+	+
NeoSphere (24)	+	?	-	?	+	+	+
NOAH (29)	+	+	-	?	+	+	+
Pierga (30)	?	?	?	+	+	+	+
CALBG40601(23)	+	?	?	?	+	+	+
EORTC 10054(22)	+	+	?	?	-	+	+
NSASBP B-41 (21)	+	+	-	?	+	+	+

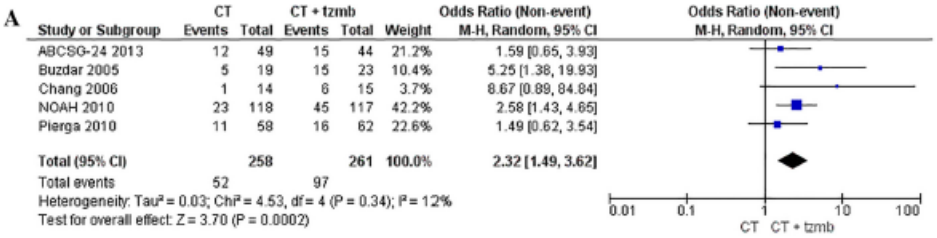
* + = low risk of bias; - = high risk of bias; ? = unclear risk of bias.

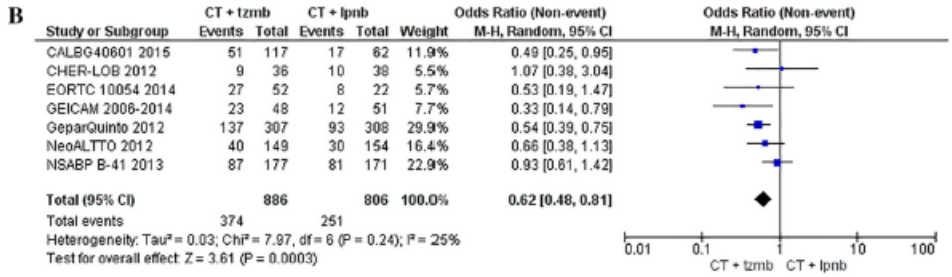
† Other bias is defined as the manner of diagnosis of HER2 positivity (i.e., whether it is confirmed centrally).

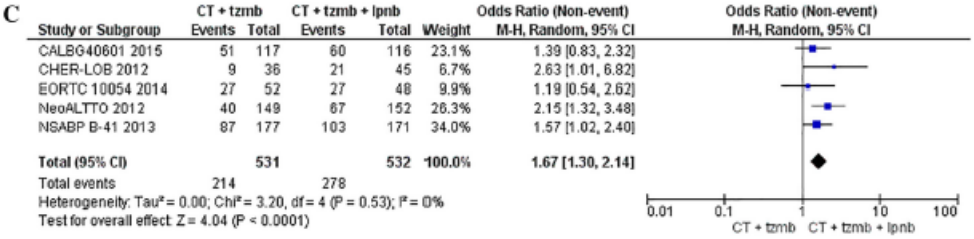
‡ Risk of bias tool, developed by the Cochrane Collaboration, to assess the potential limitations in randomized trials separates a judgment about risk of bias from a description of the support for that judgment, for a series of items covering different domains of bias.

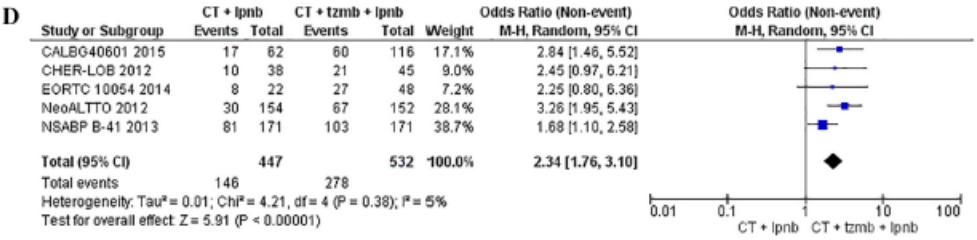
Studienergebnisse:

Fig. 1. Forest plots of odds ratios (ORs) for pathologic complete response (pCR) comparing different anti-human epidermal growth factor receptor-2 treatment arms. The reference for OR is a treatment arm in the left. ORs for each trial are represented by the squares and the horizontal lines crossing the square represent the 95% confidence intervals (CI). The diamonds represent the estimated overall effect based on the DerSimonian-Laird random effects model. All statistical tests were two-sided. (A) Forest plot of OR comparing pCR in CT and CT + trastuzumab (tzmb). (B) Forest plot of OR comparing pCR in CT + tzmb and CT + lapatinib (lpnb). (C) Forest plot of OR comparing pCR in CT + tzmb and CT + tzmb + lpnb. (D) Forest plot of OR comparing pCR in CT + lpnb and CT + tzmb + lpnb.


A
CT
CT + tzmb
Odds Ratio (Non-event)
Odds Ratio (Non-event)
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
ABCSG-24 2013 12 49 15 44 21.2% 1.59 [0.65, 3.93]
Buzdar 2005 5 19 15 23 10.4% 5.25 [1.38, 19.93]
Chang 2006 1 14 6 15 3.7% 8.67 [0.89, 84.84]
NOAH 2010 23 118 45 117 42.2% 2.58 [1.43, 4.65]
Pierga 2010 11 58 16 62 22.6% 1.49 [0.62, 3.54]
Total (95% CI) 258 261 100.0% 2.32 [1.49, 3.62]
Total events 52 97
Heterogeneity: Tau² = 0.03; Chi² = 4.53, df = 4 (P = 0.34); I² = 12%
Test for overall effect: Z = 3.70 (P = 0.0002)
0.01 0.1 1 10 100
CT CT + tzmb


B
CT + tzmb
CT + lpnb
Odds Ratio (Non-event)
Odds Ratio (Non-event)
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
CALBG40601 2015 51 117 17 62 11.9% 0.49 [0.25, 0.95]
CHER-LOB 2012 9 36 10 38 5.5% 1.07 [0.38, 3.04]
EORTC 10054 2014 27 52 8 22 5.7% 0.53 [0.19, 1.47]
GEICAM 2006-2014 23 48 12 51 7.7% 0.33 [0.14, 0.79]
GeparQuinto 2012 137 307 93 308 29.9% 0.54 [0.39, 0.75]
NeoALTTO 2012 40 149 30 154 16.4% 0.66 [0.38, 1.13]
NSABP B-41 2013 87 177 81 171 22.9% 0.93 [0.61, 1.42]
Total (95% CI) 886 806 100.0% 0.62 [0.48, 0.81]
Total events 374 251
Heterogeneity: Tau² = 0.03; Chi² = 7.97, df = 6 (P = 0.24); I² = 25%
Test for overall effect: Z = 3.61 (P = 0.0003)
0.01 0.1 1 10 100
CT + tzmb CT + lpnb


C
CT + tzmb
CT + tzmb + lpnb
Odds Ratio (Non-event)
Odds Ratio (Non-event)
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
CALBG40601 2015 51 117 60 116 23.1% 1.39 [0.83, 2.32]
CHER-LOB 2012 9 36 21 45 6.7% 2.63 [1.01, 6.82]
EORTC 10054 2014 27 52 27 48 9.9% 1.19 [0.54, 2.62]
NeoALTTO 2012 40 149 67 152 26.3% 2.15 [1.32, 3.48]
NSABP B-41 2013 87 177 103 171 34.0% 1.57 [1.02, 2.40]
Total (95% CI) 531 532 100.0% 1.67 [1.30, 2.14]
Total events 214 278
Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 4.04 (P < 0.0001)
0.01 0.1 1 10 100
CT + tzmb CT + tzmb + lpnb


D
CT + lpnb
CT + tzmb + lpnb
Odds Ratio (Non-event)
Odds Ratio (Non-event)
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
CALBG40601 2015 17 62 60 116 17.1% 2.84 [1.46, 5.52]
CHER-LOB 2012 10 38 21 45 9.0% 2.45 [0.97, 6.21]
EORTC 10054 2014 8 22 27 48 7.2% 2.25 [0.80, 6.36]
NeoALTTO 2012 30 154 67 152 28.1% 3.26 [1.95, 5.43]
NSABP B-41 2013 81 171 103 171 38.7% 1.68 [1.10, 2.58]
Total (95% CI) 447 532 100.0% 2.34 [1.76, 3.10]
Total events 146 278
Heterogeneity: Tau² = 0.01; Chi² = 4.21, df = 4 (P = 0.38); I² = 5%
Test for overall effect: Z = 5.91 (P < 0.00001)
0.01 0.1 1 10 100
CT + lpnb CT + tzmb + lpnb

AE

Table 2
The odds ratios and heterogeneity for direct comparisons.*

Outcome	No. of studies	Events	Total	Events	Total	OR [95% CI]	P	I^2 (%)
		CT		CT + tzmb				
pCR	5	52	258	97	261	2.32 [1.49, 3.62]	<0.01	12
Completion	2	104	118	111	117	2.49 [0.92, 6.72]	0.07	–
Diarrhea	2	4	171	1	177	0.24 [0.03, 2.17]	0.44	28
Neutropenia	3	54	190	60	200	1.28 [0.33, 4.29]	0.79	67
Cardiac events	4	19	239	26	244	1.33 [0.70, 2.53]	0.38	0
Skin disorder	2	9	107	5	106	0.55 [0.18, 1.72]	0.31	0
		CT + tzmb		CT + lpnb				
pCR	7	374	886	251	806	0.62 [0.48, 0.81]	<0.01	25
Completion	7	779	890	542	797	0.28 [0.16, 0.48]	<0.01	66
Diarrhea	7	21	890	146	809	8.56 [5.33, 13.75]	<0.01	53
Neutropenia	7	314	890	318	809	1.59 [0.87, 2.91]	0.13	74
Cardiac events	7	63	890	49	809	0.78 [0.52, 1.15]	0.2	0
Skin disorder	7	9	890	57	808	7.04 [3.35, 14.80]	<0.01	0
		CT + tzmb		CT + pzmb				
pCR	1	23	96	17	107	0.79 [0.39–1.58]	0.5	–
Completion	1	102	107	90	96	0.74 [0.22, 2.49]	0.62	–
Diarrhea	1	4	107	4	94	1.14 [0.28, 4.71]	0.85	–
Neutropenia	1	61	107	52	94	0.93 [0.53, 1.63]	0.81	–
Cardiac events	1	1	107	1	94	1.14 [0.07, 18.48]	0.93	–
Skin disorder	1	2	107	2	94	1.14 [0.16, 8.26]	0.9	–
		CT + tzmb		tzmb + pzmb				
pCR	1	23	107	12	107	0.46 [0.22, 0.98]	0.05	–
Completion	1	102	107	93	107	0.33 [0.11, 0.94]	0.04	–
Diarrhea	1	4	107	0	108	0.11 [0.01, 1.99]	0.13	–
Neutropenia	1	61	107	1	108	0.01 [0.00, 0.05]	<0.01	–
Cardiac events	1	1	107	1	108	0.99 [0.06, 16.05]	0.99	–
Skin disorder	1	2	107	0	108	0.19 [0.01, 4.10]	0.29	–
		CT + tzmb		CT + tzmb + lpnb				
pCR	5	214	531	278	532	1.67 [1.30, 2.14]	<0.01	0
Completion	5	467	533	370	529	0.29 [0.14, 0.60]	<0.01	71
Diarrhea	5	12	533	134	535	14.36[7.84,26.32]	<0.01	0
Neutropenia	5	72	533	92	535	1.37 [0.89, 2.10]	0.15	18
Cardiac events	5	28	533	25	535	1.31 [0.33, 5.26]	0.71	58
Skin disorder	5	7	533	33	535	4.11 [1.78, 9.51]	<0.01	0
		CT + tzmb		CT + tzmb + pzmb				
pCR	1	23	107	42	107	2.36 [1.29, 4.31]	<0.01	–
Completion	1	102	107	102	107	1.00 [0.28, 3.56]	1	–
Diarrhea	1	4	107	6	107	1.53 [0.42, 5.58]	0.52	–
Neutropenia	1	61	107	48	107	0.61 [0.36, 1.05]	0.08	–
Cardiac events	1	1	107	3	107	3.06 [0.31, 29.87]	0.34	–
Skin disorder	1	2	107	2	107	1.00 [0.14, 7.23]	1	–
		CT + lpnb		CT + tzmb + lpnb				
pCR	5	146	447	278	532	2.34 [1.76, 3.10]	<0.01	5
Completion	5	294	437	370	529	1.17 [0.59, 2.29]	0.65	77
Diarrhea	4	65	297	96	386	1.23 [0.85, 1.78]	0.27	0
Neutropenia	5	86	449	92	535	0.80 [0.54, 1.21]	0.29	22
Cardiac events	5	25	449	22	535	0.94 [0.22, 3.99]	0.93	60
Skin disorder	5	31	449	33	535	0.76 [0.44, 1.30]	0.31	0
		CT + pzmb		tzmb + pzmb				
pCR	1	17	96	12	107	0.59 [0.26, 1.30]	0.19	–
Completion	1	90	96	93	107	0.44 [0.16, 1.20]	0.11	–
Diarrhea	1	4	94	0	108	0.09 [0.00, 1.74]	0.11	–
Neutropenia	1	52	94	1	108	0.01 [0.00, 0.06]	<0.01	–
Cardiac events	1	1	94	1	108	0.87 [0.05, 14.09]	0.92	–
Skin disorder	1	2	94	0	108	0.17 [0.01, 3.60]	0.26	–
		CT + pzmb		CT + tzmb + pzmb				
pCR	1	17	96	42	107	3.00 [1.56, 5.76]	<0.01	–
Completion	1	90	96	102	107	1.36 [0.40, 4.61]	0.49	–
Diarrhea	1	4	94	6	107	1.34 [0.37, 4.89]	0.66	–
Neutropenia	1	52	94	48	107	0.66 [0.38, 1.15]	0.14	–
Cardiac events	1	1	94	3	107	2.68 [0.27, 26.24]	0.4	–
Skin disorder	1	2	94	2	107	0.88 [0.12, 6.35]	0.9	–
		CT + tzmb + pzmb		tzmb + pzmb				
pCR	1	42	107	12	107	5.12 [2.50, 10.46]	<0.01	–
Completion	1	102	107	93	107	3.07 [1.06, 8.86]	0.04	–
Diarrhea	1	6	107	0	108	13.90[0.77, 249.83]	0.07	–
Neutropenia	1	48	107	1	108	87.05[11.72,646.85]	<0.01	–
Cardiac events	1	3	107	1	108	3.09 [0.32, 30.15]	0.33	–
Skin disorder	1	2	107	0	108	5.14 [0.24, 108.38]	0.29	–

OR = odds ratio; CT = chemotherapy; lpnb = lapatinib; pzmb = pertuzumab; pCR = pathological complete response; tzmb = trastuzumab.

NMA

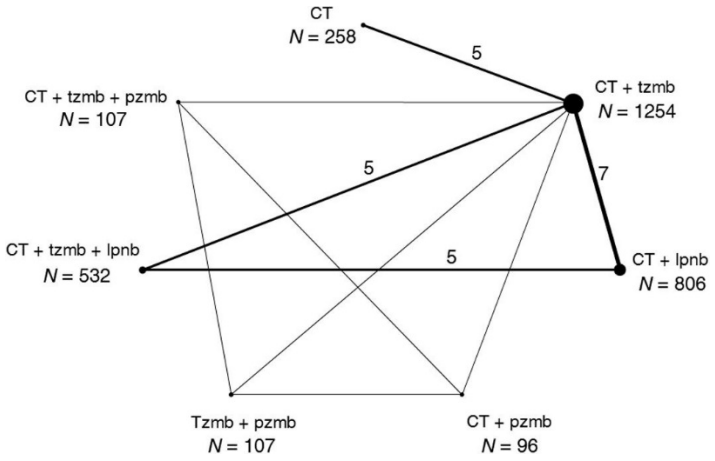


Table 3
The odds ratio and 95% credibility intervals calculated by Bayesian network meta-analysis.*

		1 CT	2 CT + tzmb	3 CT + lpnb	4 CT + pzmb	5 tzmb + pzmb	6 CT + tzmb + lpnb	7 CT + tzmb + pzmb
1	**CT**							
2	**CT + tzmb**	**2.37 [1.51–3.79]**						
3	**CT + lpnb**	1.45 [0.85–2.52]	**0.61 [0.46–0.81]**					
4	**CT + pzmb**	1.86 [0.7–4.79]	0.78 [0.34–1.78]	1.28 [0.53–3.07]				
5	**tzmb + pzmb**	1.08 [0.4–2.84]	**0.46 [0.19–1.06] $P = 0.034$**	0.74 [0.3–1.82]	0.58 [0.23–1.43]			
6	**CT + tzmb + lpnb**	**3.73 [2.16–6.55]**	**1.58 [1.15–2.16]**	**2.57 [1.84–3.59]**	2.01 [0.83–4.93]	**3.45 [1.4–8.80]**		
7	**CT + tzmb + pzmb**	**5.59 [2.32–13.64]**	**2.36 [1.13–5.03]**	**3.85 [1.74–8.65]**	**3.01 [1.30–6.71]**	**5.17 [2.27–12.32]**	1.5 [0.67–3.38]	

CT = chemotherapy; lpnb = lapatinib; pzmb = pertuzumab; pCR = pathological complete response; tzmb = trastuzumab.
* The reference of odds ratio is treatment arm in the left column. Comparisons which presented statistical differences are shown in bold numbers. The model applied to analyze the data is a Bayesian consistency model as described in Ref. [9]. All statistical tests were two-sided.

Fig. 2. Heat map of the overall efficacy based on the surface under the cumulative ranking probability curve (SUCRA). Comparative strengths and limitations of each treatment arm are shown. The thickness of colors indicates higher SUCRA values. The green color indicates higher SUCRA values for pathologic complete response (pCR) and treatment completion. The red color indicates higher SUCRA values for incidences of adverse events. The SUCRA values are shown in each box. Chemotherapy (CT) + trastuzumab (tzmb) + lapatinib (lpnb) and CT + tzmb + pertuzumab (pzmb) are the most effective treatment arms. CT + tzmb has the best result for treatment completion and the second best for diarrhea. Lpnb-containing treatment arms have lower SUCRA values for treatment completion, higher SUCRA values for incidence of diarrhea, neutropenia, and skin disorders compared to the other treatment arms. Tzmb + pzmb has low SUCRA values for incidence of diarrhea, neutropenia, and skin disorder. All statistical tests were two-sided.

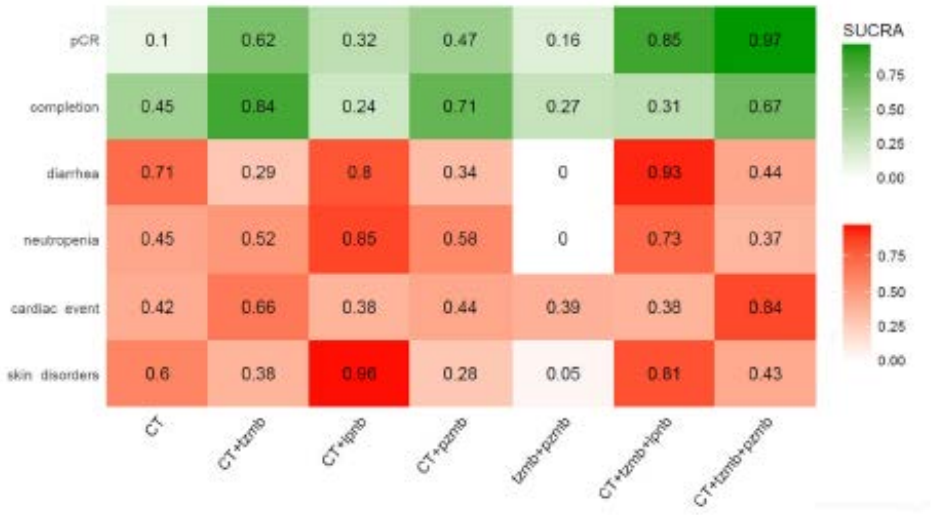
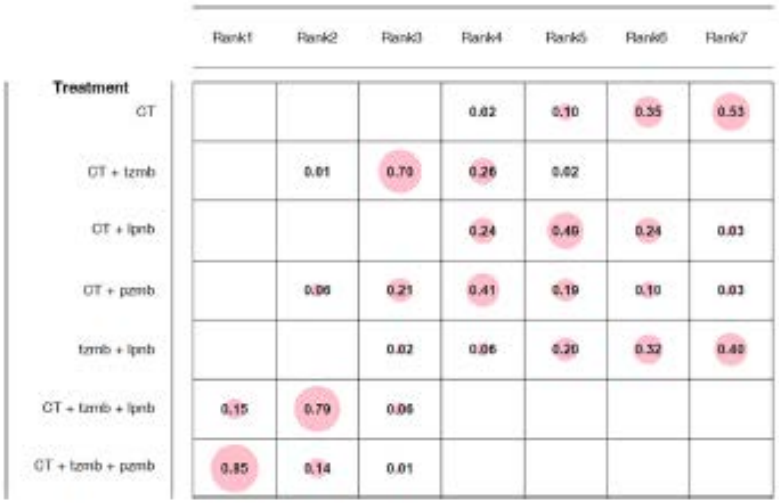


Fig. 3. Ranking for the pathologic complete response (pCR). Each value represents the probability of each treatment to be a specific rank. The pink balloon area is proportional to the probability. For example, the probability of chemotherapy (CT) + trastuzumab (tzmb) + pertuzamab (pzmb) to have the largest number of patients with pCR among all treatments is 85%, and the probability of CT to have the smallest number of patients with pCR is 53%. All statistical tests were two-sided. lpnb = lapatinib. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



Anmerkung/Fazit der Autoren

Network meta-analysis using new clinical data firmly establish that combining two anti- HER2 agents with CT is most effective against HER2-positive breast cancer in the neoadjuvant setting. New pzmb related trials are required to fully determine the best neoadjuvant dual-HER2 blockade regimen.

Kommentare zum Review

Die methodische Güte der NMA ist nicht abschließend beurteilbar. Es handelt sich ohnehin um indirekte Vergleiche, die gegenüber direkten Vergl eiche ein höheres Verzerrungspotezial aufweisen. Desahlab sind die Ergebnisse auch der direkten Vergleiche dargestellt.

Abkürzungen: HR = hormone receptor; tzmb = trastuzumab; lpnb = lapatinib; pzmb = pertuzumab; NR = not reported; FEC = fluorouracil-epirubicin-cyclophosphamide; AP = doxorubicinpaclitaxel; CMF = cyclophosphamide-methotrexate-fluorouracil; EC = epirubicin-cyclophosphamide.

Matthews A et al., 2018 [35].

Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: systematic review

Fragestellung

To investigate the effect of endocrine therapies on a wide range of specific clinical cardiovascular disease outcomes in women with a history of non-metastatic breast cancer.

Methodik

Population:

women with a history of non-metastatic breast cancer

Intervention/ Komparator:

tamoxifen or an aromatase inhibitor, or compared the two treatments

Endpunkte:

risk of a specific cardiovascular disease outcome

Recherche/Suchzeitraum:

06/2018

Qualitätsbewertung der Studien:

Cochrane Collaboration’s tool

Ergebnisse

Anzahl eingeschlossener Studien:

The final 26 included studies consisted of 15 randomised controlled trials and 11 observational studies.

Charakteristika der Population:

Table 1 | Overview of characteristics of studies included in systematic review. Values are numbers (percentages)	
	Value (n=26)
Study type	
Randomised controlled trial	15 (58)
Observational	11 (42)
Case-control	4 (15)
Cohort	7 (27)
Country/region	
North America	8 (31)
Canada	2 (8)
USA	5 (19)
USA and Canada	1 (4)
Europe	11 (42)
Denmark	2 (8)
Germany	1 (4)
Italy	1 (4)
Scotland	1 (4)
Sweden	1 (4)
UK	3 (12)
Europe-wide	2 (8)
Rest of world	3 (12)
Taiwan	2 (8)
Egypt	1 (3)
International	4 (15)
Study population	
<80 years old	1 (4)
<70 years old	1 (4)
35-70 years old	1 (4)
45-69 years old	2 (8)
All women	7 (27)
Postmenopausal	13 (50)
Premenopausal	1 (4)
Year of study	
Before 2000	4 (15)
2000-10	13 (50)
After 2010	9 (35)
Outcomes*	
Vascular disease	
Myocardial infarction	14 (54)
Stroke	12 (46)
Angina	4 (15)
Peripheral vascular disease	1 (4)
Myocardial disease	
Heart failure	4 (15)
Arrhythmia	1 (4)
Thromboembolic events	15 (58)

*Individual studies often included more than one outcome.

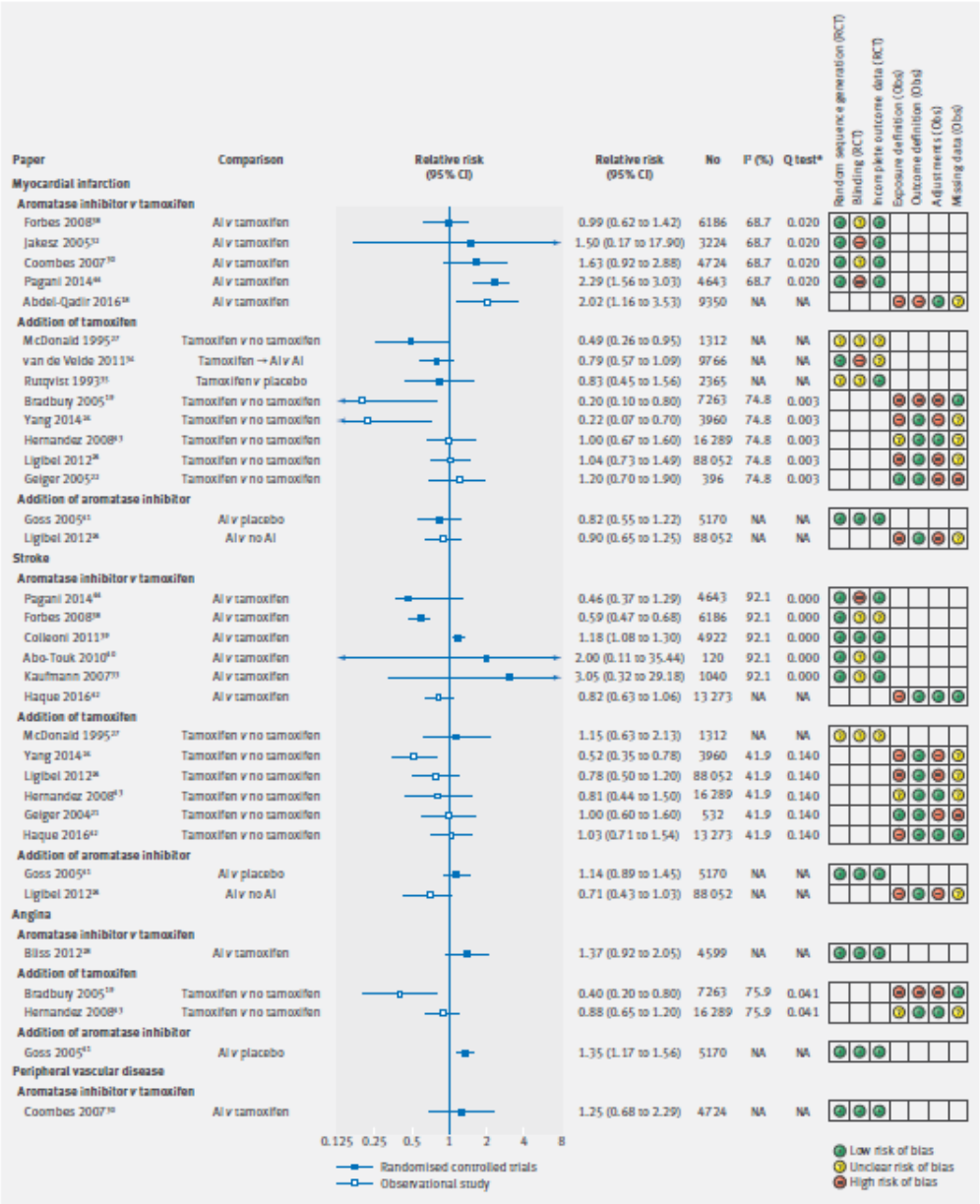
Qualität der Studien:

Table 2 | Risk of bias assessment overview: observational studies							
Paper	**Study design**	**Exposure definition**	**Outcome/case definition**	**Control selection**	**Confounding**	**Missing data**	**Censoring**
Abdel-Qadir 2016	Cohort	High	High	NA	Low	Unknown	Low
Chen 2014	Cohort	High	Low	NA	High	Unknown	Low
Haque 2016	Cohort	High	Low	NA	Low	Low	Low
Hernandez 2008	Cohort	Unknown	Low	NA	Low	Unknown	Low
Hernandez 2009	Cohort	Unknown	Low	NA	Low	High	Low
Ligibel 2012	Cohort	High	Low	NA	High	Unknown	Low
Yang 2014	Cohort	High	Low	NA	High	Unknown	Unknown
Bradbury 2005	Case-control	High	High	Low	High	Low	NA
Geiger 2004	Case-control	Low	Low	Low	High	High	NA
Geiger 2005	Case-control	Low	Low	Low	High	High	NA
Meier 1998	Case-control	Low	Low	Low	High	High	NA

NA=not applicable

Studienergebnisse:

Fig 2 | Estimated relative risk (95% CI) for studies examining use of endocrine therapy and risk of specific vascular diseases, with corresponding I2 tests, Q tests, and assessment of bias according to prespecified criteria. *P value. AI=aromatase inhibitor; NA=not applicable



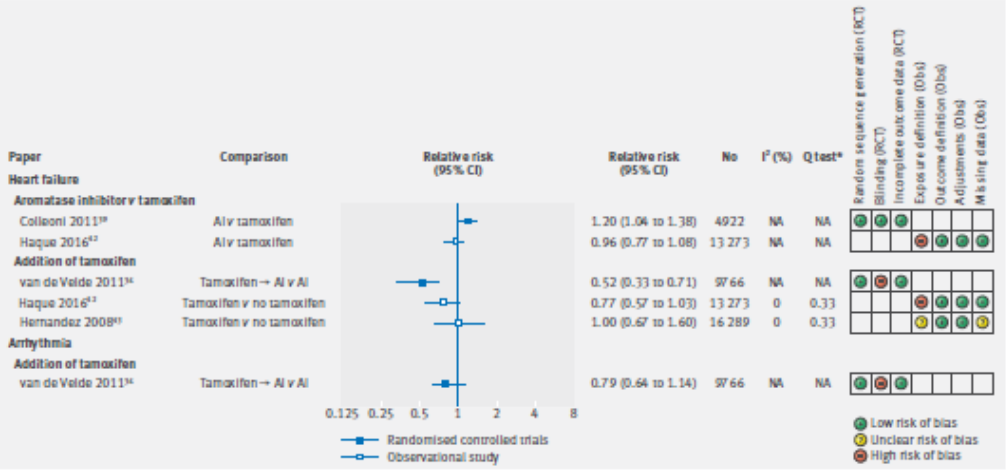
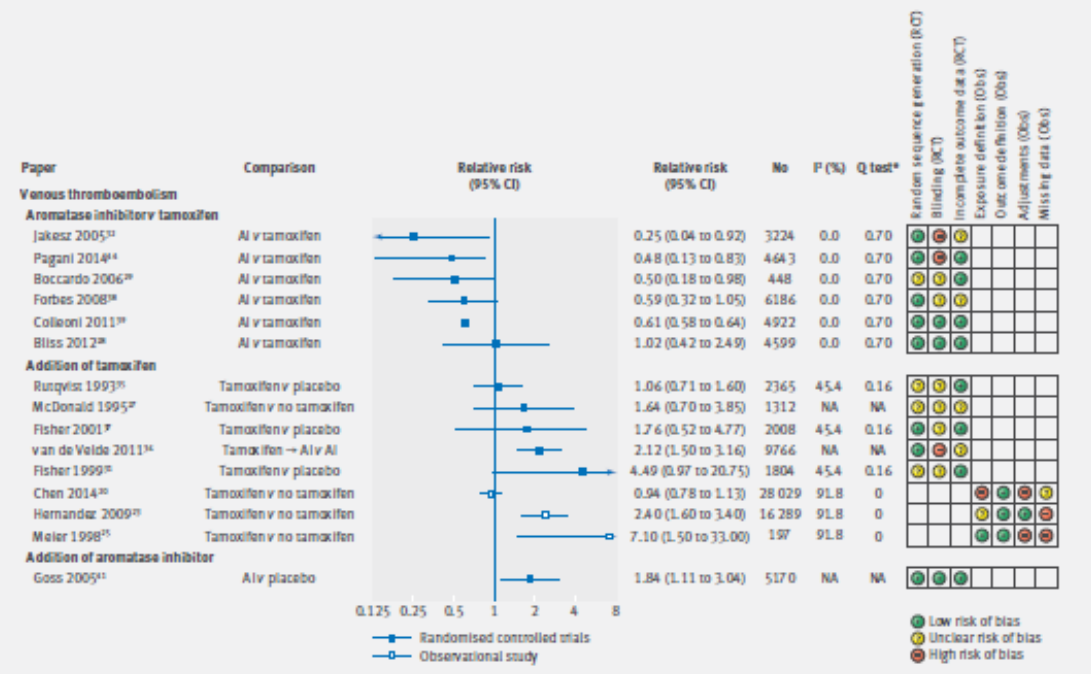


Fig 3 | Estimated relative risk (95% CI) for studies examining use of endocrine therapy and risk of specific myocardial diseases, with corresponding I^2 tests, Q tests and assessment of bias according to prespecified criteria

Fig 4 | Estimated relative risk (95% CI) for studies examining use of endocrine therapy and risk of venous thromboembolism, with corresponding I^2 tests, Q tests, and assessment of bias according to prespecified criteria



Anmerkung/Fazit der Autoren

This review has collated substantial randomised controlled trial and observational evidence on the effect of endocrine therapies on several specific cardiovascular disease outcomes including venous thromboembolism and myocardial infarction, progressing knowledge. Although the choice of aromatase inhibitor or tamoxifen will primarily be based on the effectiveness against the recurrence of breast cancer, this review shows that the individual patient's risk of venous or arterial vascular disease should be an important secondary consideration.

Debiasi M et al., 2018 [12].

Efficacy of Anti-HER2 Agents in Combination With Adjuvant or Neoadjuvant Chemotherapy for Early and Locally Advanced HER2-Positive Breast Cancer Patients: A Network Meta-Analysi

Fragestellung

Several (neo)adjuvant treatments for patients with HER2-positive breast cancer have been compared in different randomized clinical trials. Since it is not feasible to conduct adequate pairwise comparative trials of all these therapeutic options, network meta-analysis offers an opportunity for more detailed inference for evidence-based therapy.

Network meta-analysis (also commonly referred to as multiple treatment comparison—MTC) is a generalization of classic metaanalysis that combines direct and indirect evidence to compare multiple treatment arms across studies with similar populations and outcomes with the proviso that there is at least one linkingarm between them (22). Direct evidence is defined as the

headto- head comparison between two treatment arms in a clinical trial, while indirect evidence is the estimation of the relative effect between two arms that is obtained indirectly through one or more common comparators.

Methodik

Population:

- patients with HER2-positive breast cancer
- in the adjuvant or neoadjuvant settings

Intervention/ Komparator:

CT plus any anti-HER2 therapy with CT alone or any different combination of CT plus anti-HER2 therapy

In order to organize the existing treatment options tested in clinical trials in clinically meaningful arms, some general pre-specified criteria were used to gather the treatment arms as follows:

- ARM 1. chemotherapy alone1
- ARM 2. chemotherapy (see text footnote 1) + trastuzumab 12 months
- ARM 3. chemotherapy (see text footnote 1) + trastuzumab ≤ 6 months
- ARM 4. chemotherapy (see text footnote 1) (taxane + carboplatin) + trastuzumab 12 months
- ARM 5. chemotherapy (see text footnote 1) + lapatinib 12 months
- ARM 6. chemotherapy (see text footnote 1) + trastuzumab 3 months (sequential to trastuzumab)
- ARM 7. chemotherapy (see text footnote 1) + trastuzumab 12 months + lapatinib2 (concomitant with trastuzumab)
- ARM 8. chemotherapy (see text footnote 1) + trastuzumab 12 months + pertuzumab (see text footnote 2) (concomitant with trastuzumab)
- ARM 9. chemotherapy (see text footnote 1) + trastuzumab 12 months months (sequential to trastuzumab)

☐ lapatinib 9 m

☐ neratinib 1

Endpunkte:

- Overall survival was the primary outcome of this study and was similarly defined among studies as the time from randomization until death, using an intention to treat analysis.
- DFS was defined as time from randomization to death or any DFS event.

Recherche/Suchzeitraum:

2005 – 2017

Qualitätsbewertung der Studien:

Cochrane Collaboration risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

17 clinical trials met our eligibility criteria. Two different networks of trials were created based on the availability of the outcomes: OS network (15 trials: 37,837 patients); and DFS network (17 trials: 40,992 patients). Two studies—the ExteNET and the NeoSphere trials—were included only in this DFS network because OS data have not yet been reported.

Charakteristika der Population:

STUDY	Chemo setting	Industry sponsored	Which industry	Phase	Number of patients	Multicentric	N Countries
ALTTO [40-42]	Adj*	Yes: fully	GSK / Novartis	III	8381	Yes	44
APHINITY [11]	Adj*	Yes: fully	Roche / Genentech	III	4805	Yes	43
BCIRG006 [43-45]	Adj*	Yes: fully	More than one industry	III	3222	Yes	41
CALGB40601 [46-47]	Adj*	Yes: fully	Schering-Plough	II	179	Yes	N/A
E-2198 [48]	Adj*	No	----	II	227	Yes	1
EXTENET [34-35]	Adj*	Yes: fully	Puma Biotech	III	2840	Yes	40
FINHER [49-50]	Adj*	Yes: partially	More than one industry	III	232	Yes	N/A
HERA/BIG01-01 [13, 51-56]	Adj*	Yes: fully	Roche	III	3401	Yes	39
MAVROUDIS [57-58]	Adj*	No	----	N/A	481	Yes	1
NCCTG N9831 [59-65]	Adj*	Yes: partially	Genentech	III	2184	N/A	N/A
NSABP B31 [60-61, 64-67]	Adj*	Yes: partially	Genentech	III	1736	N/A	N/A
NEOALTO [68-71]	Neo**	Yes: fully	GSK	III	455	1	23
NEOSPHERE [72-73]	Neo**	Yes: fully	Roche	II	417	Yes	16
PACS 04 [74]	Adj*	Yes: partially	Roche	III	528	Yes	2
PHARE [75-76]	Adj*	No	----	III	3380	Yes	1
SHORTHER [77-78]	Adj*	No	----	III	1253	Yes	1
SOLD [79]	Adj*	No	----	III	2176	Yes	5
TEACH [80-81]	Adj*	Yes: fully	GSK	III	3147	Yes	33

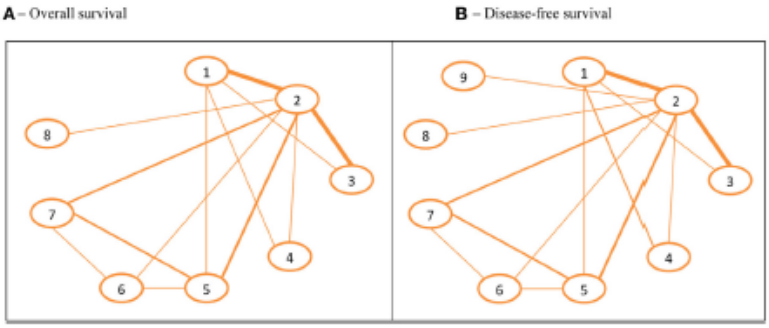


FIGURE 2 | Networks for overall survival (OS) and disease-free survival (DFS). **(A)** OS. **(B)** DFS. The width of the lines represents the relative weight of the direct evidence for a given comparison, based on the number of patients included in trials. ARM 1, chemotherapy alone. ARM 2, chemotherapy + trastuzumab 12 months. ARM 3, chemotherapy + trastuzumab ≤ 6 months. ARM 4, chemotherapy (taxane + carboplatin) + trastuzumab 12 months. ARM 5, chemotherapy + lapatinib 12 months. ARM 6, chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab). ARM 7, chemotherapy + trastuzumab 12 months + lapatinib (concomitant with trastuzumab). ARM 8, chemotherapy + trastuzumab 12 months + pertuzumab (concomitant with trastuzumab). ARM 9, chemotherapy + trastuzumab 12 months → NERATINIB 12 months (sequential to trastuzumab).

Qualität der Studien:

STUDY	RISK OF BIAS EVALUATION DOMINIUM (21)				
	Allocation sequence	Allocation conceal	Blinding	Incomplete outcome	Selective Reporting
ALTTO	Unclear	Unclear	High risk	Unclear	Unclear
APHINITY	Low risk	Low risk	Low risk	Low risk	Low risk
BCIRG006	Unclear	Unclear	High risk	Low risk	Low risk
CALGB40601	Unclear	Unclear	High risk	Low risk	Low risk
E-2198	Low risk	Low risk	High risk	Low risk	Low risk
EXTENET	Unclear	Unclear	Unclear	Unclear	Unclear
FINHER	Low risk	Low risk	High risk	Low risk	Low risk
HERA/BIG01-01	Unclear	Unclear	High risk	Low risk	Low risk
MAVROUDIS	Low risk	Low risk	High risk	Low risk	Low risk
NCCTG N9831	Unclear	Unclear	High risk	Low risk	Low risk
NEOALTO	Low risk	Low risk	High risk	Low risk	Low risk
NEOSPHERE	Low risk	Low risk	High risk	Low risk	Low risk
NSABP B31	Unclear	Unclear	High risk	Low risk	Low risk
PACS 04	Unclear	Unclear	High risk	Low risk	Low risk
PHARE	Low risk	Low risk	High risk	Low risk	Low risk
SHORTHER	Unclear	Unclear	High risk	Low risk	Low risk
SOLD	Unclear	Unclear	High risk	Low risk	Low risk
TEACH	Low risk	Low risk	Low risk	Low risk	Low risk

Studienergebnisse:

STUDY	COMPARISON BETWEEN ARMS	HR	COMPARISON BETWEEN ARMS	HR	COMPARISON BETWEEN ARMS	HR
BCIRG006	2 vs. 1	0.59 (0.42-0.85)	4 vs. 1	0.66 (0.47-0.93)	----------	--
HERA	2 vs. 1	0.66 (0.47-0.91)	----------	--	----------	--
NSABP_B31 AND NCCTGN9831	2 vs. 1	0.61 (0.50-0.75)	----------	--	----------	--
PACS 04	2 vs. 1	1.27 (0.68-2.38)	----------	--	----------	--
FINHER	3 vs. 1	0.41 (0.16-1.08)	----------	--	----------	--
TEACH	5 vs. 1	0.99 (0.74-1.31)	----------	--	----------	--
E2198	3 vs. 2	1.37 (0.46-3.13)	----------	--	----------	--
MAVROUDIS	3 vs. 2	1.45 (0.57-3.67)	----------	--	----------	--
PHARE	3 vs. 2	1.46 (1.06-2.01)	----------	--	----------	--
SHORTHER	3 vs. 2					
SOLD	3 vs. 2					
ALTTO	5 vs. 2	1.36 (1.09-1.72)	6 vs. 2	0.91 (0.71-1.16)	7 vs. 2	0.80 (0.62-1.03)
CALGB40601	5 vs. 2	0.82 (0.32-2.06)	7 vs. 2	0.22 (0.06-0.76)	----------	--
NEOALTTO	5 vs. 2	0.86 (0.45-1.63)	7 vs. 2	0.62 (0.30-1.25)	----------	--
APHINITY	8 vs. 2	0.89 (0.66-1.21)	----------	--	----------	--

Legend for treatment arms

ARM 1. CHEMOTHERAPY* ALONE*
ARM 2. CHEMOTHERAPY* + TRASTUZUMAB 12 months
ARM 3. CHEMOTHERAPY * + TRASTUZUMAB ≤6 months
ARM 4. CHEMOTHERAPY (TAXANE + CARBOPLATIN) + TRASTUZUMAB 12 months
ARM 5. CHEMOTHERAPY* + LAPATINIB 12months
ARM 6. CHEMOTHERAPY* + TRASTUZUMAB 3 months → LAPATINIB 9months (sequential to trastuzumab)
ARM 7. CHEMOTHERAPY* + TRASTUZUMAB 12 months + LAPATINIB (concomitant with trastuzumab)
ARM 8. CHEMOTHERAPY* + TRASTUZUMAB 12 months + PERTUZUMAB (concomitant with trastuzumab)

SUPPLEMENTARY MATERIAL G: Network for disease-free survival

STUDY	COMPARISON BETWEEN ARMS	HR	COMPARISON BETWEEN ARMS	HR	COMPARISON BETWEEN ARMS	HR
BCIRG006	2 vs. 1	0.61 (0.48-0.76)	4 vs. 1	0.67 (0.54-0.83)	----------	--
HERA	2 vs. 1	0.64 (0.54-0.76)	----------	--	----------	--
NSABP_B31 AND NCCTGN9831	2 vs. 1	0.52 (0.45-0.60)	----------	--	----------	--
PACS 04	2 vs. 1	0.86 (0.61-1.22)	----------	--	----------	--
FINHER	3 vs. 1	0.42 (0.21-0.83)	----------	--	----------	--
TEACH	5 vs. 1	0.83 (0.70-1.00)	----------	--	----------	--
E2198	3 vs. 2	1.31 (0.79-2.12)	----------	--	----------	--
MAVROUDIS	3 vs. 2	1.58 (0.86-2.10)	----------	--	----------	--
PHARE	3 vs. 2	1.28 (1.05-1.56)	----------	--	----------	--
SHORTHER	3 vs. 2	1.15 (0.91-1.46)	----------	--	----------	--
SOLD	3 vs. 2	1.39 (1.12-1.72)	----------	--	----------	--
ALTTO	5 vs. 2	1.34 (1.13-1.60)	6 vs.2	0.96 (0.80-1.15)	7 vs. 2	0.84 (0.70-1.02)
CALGB40601	5 vs. 2	1.24 (0.61-2.51)	7 vs. 2	0.35 (0.15-0.83)	----------	--
NEOALTTO	5 vs. 2	1.06 (0.66-1.65)	7 vs. 2	0.78 (0.47-1.28)	----------	--
NEOSPHERE	8 vs. 2	0.60 (0.28-1.27)	----------	--	----------	--
APHINITY	8 vs. 2	0.81 (0.66-1.00)	----------	--	----------	--
EXTENET	9 vs. 2	0.67 (0.50-0.91)	----------	--	----------	--

Legend for treatment arms

ARM 1. CHEMOTHERAPY ALONE*
ARM 2. CHEMOTHERAPY + TRASTUZUMAB 12 months
ARM 3. CHEMOTHERAPY + TRASTUZUMAB ≤6 months
ARM 4. CHEMOTHERAPY (TAXANE + CARBOPLATIN) + TRASTUZUMAB 12 months
ARM 5. CHEMOTHERAPY + LAPATINIB 12months
ARM 6. CHEMOTHERAPY + TRASTUZUMAB 3 months → LAPATINIB 9months (sequential to trastuzumab)
ARM 7. CHEMOTHERAPY + TRASTUZUMAB 12 months + LAPATINIB (concomitant with trastuzumab)
ARM 8. CHEMOTHERAPY + TRASTUZUMAB 12 months + PERTUZUMAB (concomitant with trastuzumab)
ARM 9. CHEMOTHERAPY + TRASTUZUMAB 12 months → NERATINIB 12 months (sequential to trastuzumab)

Overall Survival Network

Fifteen trials published from 2005 to 2017 accounting for 37,837 patients were included in this network, which is described in the Supplementary Material F and in the Figure 2A. The eight treatment arms that constitute this network are ranked in Table 1. Based on the ordered ranks, the regimens containing CT associated with trastuzumab and lapatinib (CT + T + L) for 12 months are probably the best option for OS, with 62.47% of posterior probability of being the best, followed by CT + T + P with 22.06%. On the other hand, arms containing chemotherapy without any anti-HER2-targeted therapy or CT with lapatinib (with no trastuzumab) or CT with trastuzumab for no longer than 6 months are probably the worst options, with posterior probabilities of being the worst of 85, 6.46, and 4.48%, respectively.

All HRs between treatment arms and their 95% CrI for this network are shown in Table 2. This analysis shows that the combination of CT plus 12 months of dual blockade with trastuzumab and lapatinib almost achieved the significance threshold for superiority when compared to the standard regimen of CT + T for 12 months (HR 0.75; 95% CrI: 0.51–1.01). The comparison between the two dual blockade strategies included in this network (CT + T + L versus CT + T + P) favored the lapatinib arm but was not significant (HR 1.18; 95% CrI: 0.71–2.14). Other important findings yielded by this analysis are: the OS and the omission of anthracycline did not seem to jeopardize treatment efficacy. Six months of anti-HER2 therapy is probably inferior to 12 months with an estimated 27% increase in the probability of death (HR 1.27; 95% CrI: 0.99–1.59). On the other hand, the schedule composed of a taxane without anthracycline plus trastuzumab for 1 year (TCH—arm 4) had similar efficacy when compared to the standard regimen of CT + T for 12 months (HR 1.00; 95% CrI: 0.71–1.64). It is important to emphasize that more than 90% of patients included in the CT + T for 12 months arm in this comparison did receive an anthracycline-containing regimens.

DFS Network

This network is composed of 17 trials, published from 2005 to 2017, and includes 40,992 patients. The design of this network as well as the trials included are summarized in Figure 2B and Supplementary Material F, respectively. The ranking of the nine included arms and their HRs are summarized in Tables 1 and 2. Two studies—the ExteNET and the NeoSphere trials—were included only in this network, and not in the OS network, because they only reported DFS data (13, 32, 33). The inclusion of the ExteNET trial to this network brought up that using an additional year of neratinib after the standard chemotherapy plus 1 year

TABLE 1 | OS and DFS rankings for the (neo)adjuvant treatment strategies available for early and locally advanced HER2 + breast cancer.*

	Rank	ARM 1 (%)	ARM 2 (%)	ARM 3 (%)	ARM 4 (%)	ARM 5 (%)	ARM 6 (%)	ARM 7 (%)	ARM 8 (%)	ARM 9 (%)
Disease-free survival	Rank 9	95.88	0.00	1.72	0.65	1.61	0.08	0.00	0.01	0.04
	Rank 8	3.67	0.00	42.29	6.45	47.08	0.32	0.01	0.05	0.13
	Rank 7	0.40	0.39	45.66	11.50	40.31	1.27	0.01	0.22	0.23
	Rank 6	0.05	18.28	9.30	48.34	9.83	11.34	0.48	1.23	1.15
	Rank 5	0.00	56.38	0.88	16.42	0.91	19.11	1.37	2.71	2.20
	Rank 4	0.00	22.80	0.11	10.75	0.24	41.08	7.38	10.89	6.76
	Rank 3	0.00	2.04	0.03	4.13	0.01	18.17	35.39	25.51	14.71
	Rank 2	0.00	0.10	0.00	1.40	0.01	6.75	34.73	32.78	24.23
	Rank 1	0.00	0.01	0.00	0.37	0.00	1.87	20.62	28.59	50.55
Overall survival	Rank 1	0.00	0.35	0.09	3.68	0.03	11.32	62.47	22.06	N/A
	Rank 2	0.01	5.02	0.37	7.98	0.25	35.09	26.76	24.51	N/A
	Rank 3	0.01	26.30	1.28	12.92	1.08	28.63	7.81	21.97	N/A
	Rank 4	0.11	48.01	4.29	15.36	2.87	13.82	2.00	13.53	N/A
	Rank 5	0.43	18.66	19.30	31.87	10.62	8.11	0.76	10.24	N/A
	Rank 6	2.05	1.54	42.90	15.69	31.03	2.26	0.16	4.37	N/A
	Rank 7	12.39	0.12	27.29	9.70	47.65	0.56	0.03	2.26	N/A
	Rank 8	85.00	0.00	4.48	2.80	6.46	0.22	0.00	1.05	N/A

*This table indicates the posterior estimates of the probability of each treatment arm being the best (green squares—rank 1) or the worst (red squares—rank 9 for DFS or rank 8 for OS).

ARM 1, chemotherapy alone. ARM 2, chemotherapy + trastuzumab 12 months. ARM 3, chemotherapy + Trastuzumab ≤ 6 months. ARM 4, chemotherapy (taxane + carboplatin) + trastuzumab 12 months. ARM 5, chemotherapy + lapatinib 12 months. ARM 6, chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab). ARM 7, chemotherapy + trastuzumab 12 months + lapatinib (concomitant with trastuzumab). ARM 8, chemotherapy + trastuzumab 12 months + pertuzumab (concomitant with trastuzumab). ARM 9, chemotherapy + trastuzumab 12 months → neratinib 12 months (sequential to trastuzumab).

TABLE 2 | Mixed treatment comparison hazard ratios (HRs) and their respective 95% CrI for overall survival and disease-free survival (DFA) comparing the (neo)adjuvant treatment strategies available for early and locally advanced breast cancer.[a,b]

	DFS								
	1	0.62 (0.55–0.72)	0.80 (0.66–0.99)	0.68 (0.51–0.90)	0.81 (0.66–0.98)	0.58 (0.44–0.77)	0.49 (0.37–0.63)	0.49 (0.35–0.66)	0.45 (0.32–0.66)
Overall survival	0.62 (0.52–0.78)	2	1.29 (1.10–1.50)	1.08 (0.82–1.44)	1.30 (1.06–1.55)	0.93 (0.70–1.20)	0.79 (0.61–0.99)	0.78 (0.58–1.02)	0.73 (0.52–1.02)
	0.79 (0.59–1.07)	1.27 (0.99–1.59)	3	0.84 (0.61–1.17)	1.01 (0.78–1.27)	0.73 (0.53–0.97)	0.61 (0.45–0.80)	0.61 (0.43–0.83)	0.57 (0.39–0.82)
	0.68 (0.45–1.04)	1.00 (0.71–1.64)	0.86 (0.53–1.39)	4	1.20 (0.85–1.65)	0.86 (0.58–1.25)	0.73 (0.49–1.04)	0.72 (0.47–1.06)	0.67 (0.43–1.05)
	0.83 (0.61–1.09)	1.34 (0.97–1.69)	1.05 (0.72–1.47)	1.22 (0.74–1.95)	5	0.72 (0.55–0.94)	0.61 (0.48–0.77)	0.60 (0.43–0.84)	0.56 (0.39–0.85)
	0.55 (0.37–0.81)	0.89 (0.59–1.24)	0.70 (0.44–1.06)	0.81 (0.47–1.37)	0.66 (0.47–0.97)	6	0.85 (0.63–1.12)	0.84 (0.57–1.22)	0.78 (0.52–1.22)
	0.47 (0.31–0.66)	0.75 (0.51–1.01)	0.59 (0.38–0.87)	0.69 (0.40–1.13)	0.56 (0.41–0.77)	0.85 (0.57–1.21)	7	0.99 (0.69–1.45)	0.92 (0.62–1.43)
	0.55 (0.35–0.92)	0.89 (0.57–1.38)	0.70 (0.43–1.17)	0.82 (0.45–1.53)	0.67 (0.41–1.16)	1.00 (0.58–1.82)	1.18 (0.71–2.14)	8	0.93 (0.61–1.47)
	–	–	–	–	–	–	–	–	9

[a]In this table, the diagonal squares numbered 1–9 represent the nine treatment arms included in the OS and/or DFS networks. By crossing the row and the column of two treatment arms in the table, the reader will find the HR for the comparison of these two arms in the corresponding square. HRs were computed considering the hazard of the treatment arm assigned the higher number as the numerator and the hazard of the treatment arm assigned the lower number as the denominator (e.g., when comparing the treatment arms 1 and 2; the reader must consider that it is the hazard of the arm 2 over the hazard of the arm 1).

[b]CrI that do not cross the non-significance threshold (value 1,0) are highlighted in red.

ARM 1, chemotherapy alone.[a] ARM 2, chemotherapy + trastuzumab 12 months. ARM 3, chemotherapy + trastuzumab ≤ 6 months. ARM 4, chemotherapy (taxane + carboplatin) + trastuzumab 12 months. ARM 5, chemotherapy + lapatinib 12 months. ARM 6, chemotherapy + trastuzumab 3 months → lapatinib 9 months (sequential to trastuzumab). ARM 7, chemotherapy + trastuzumab 12 months + lapatinib (concomitant with trastuzumab). ARM 8, chemotherapy + trastuzumab 12 months + pertuzumab (concomitant with trastuzumab). ARM 9, chemotherapy + trastuzumab 12 months → neratinib 12 months (sequential to trastuzumab).

Anmerkung/Fazit der Autoren

Conclusion: This network meta-analysis suggests that dual anti-HER2 blockade with trastuzumab plus either lapatinib or pertuzumab are probably the best treatment options in the (neo)adjuvant setting for HER2-positive breast cancer patients in terms of OS gain. Mature OS results are still expected for the Aphinity trial and for the sequential use of trastuzumab followed by neratinib, the treatment that showed the best performance in terms of DFS in our analysis

Kommentare zum Review

Die methodische Güte der NMA ist nicht abschließend beurteilbar. Es handelt sich ohnehin um indirekte Vergleiche, die gegenüber direkten Vergl eiche ein höheres Verzerrungspotezial aufweisen. Desahlab sind die Ergebnisse auch der direkten Vergleiche dargestellt.

Davari M et al., 2017 [11].

Effectiveness of trastuzumab as adjuvant therapy in patients with early stage breast cancer: A systematic review and meta-analysis

Fragestellung

Trastuzumab in combination with chemotherapy has long been established as a standard treatment for HER2-positive patients in early stage breast cancer (BC). The present study aimed at assessing the effectiveness of trastuzumab adjuvant therapy in early stage BC in overall survival (OS) and disease-free survival (DFS).

Methodik

Population:

women with early BC

Intervention:

trastuzumab as adjuvant therapy

Komparator:

basic treatment without trastuzumab.

Endpunkte:

Overall survival (OS) and

disease- free survival (DFS)

Recherche/Suchzeitraum:

PubMed, Cochrane library, Web of Science, Embase, and Google Scholar databases were searched from the beginning to February 2017.

Qualitätsbewertung der Studien:

Cochrane Risk of Bias Tool and Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 (20 924 patients)

Charakteristika der Population:

Table 1. Study characteristics

No.	Study	N	Duration	Intervention	Comparison	Jadad scale
1	B31(10)	394	>6 months	Trastuzumab	Without Trastuzumab	2
2	BCIRG006(11)	1703	>6 months	Trastuzumab	Without Trastuzumab	1
3	Buzdar(12)	42	6 months	Trastuzumab	Without Trastuzumab	3
4	Finher(13)	1010	<6 months	Trastuzumab	Without Trastuzumab	3
5	Hera(14)	5081	>6 months	Trastuzumab	Without Trastuzumab	3
6	Noah(15)	235	>6 months	Trastuzumab	Without Trastuzumab	3
7	Pacs-04(16)	528	>6 months	Trastuzumab	Without Trastuzumab	1
8	Goldhirsch(17)	5102	>6 months	Trastuzumab	Without Trastuzumab	3
9	Joensuu(18)	1500	<6 months and >6 months	Trastuzumab	Chemotherapy without Trastuzumab	2
10	Schneider(19)	227	<6 months and >6 months	Trastuzumab	1 year or 12 weeks Trastuzumab	3
11	Gianni(20)	5102	>6 months	Trastuzumab	Without trasuzumab	3

Qualität der Studien:

- Siehe Charakteristika der Population sowie:

Table 4. The summary of risk of BIAS results

Study	Sequence generation	Allocation concealment	Blinding of participants	Incomplete outcome data	Selective outcome reporting
B31	Low	Unclear	High	High	Unclear
BCIRG006	Unclear	Unclear	Unclear	Unclear	High
Buzdar	Low	Low	High	Low	High
FinHer	Low	Low	High	Low	High
HERA	Low	Unclear	High	Low	Unclear
NOAH	Low	Unclear	High	Low	Low
PACS-04	Unclear	Unclear	High	Low	Unclear
Gianni	Low	Unclear	High	Low	Low
Goldhirsch	Low	Unclear	High	Low	Low
Joensuu	Low	Unclear	High	Low	Low
Schneider	Low	Unclear	High	Low	Low

Studienergebnisse:

- Our findings and meta-analysis results revealed that trastuzumab is effective in increasing OS (OS hazard ratio: -0.286 ± 0.049, 95%CI (-0.381, - 0.191)) and improving DFS (DFS hazard ratio: -0.419± 0.077, 95%CI (-0.569, -0.269)). The most serious but negligible side effect of trastuzumab is congestive heart failure
- OS

The results of the Cochran`s Q test revealed that the homogeneity between selected studies was appropriate (Cochran`s Q= 12.3437, I^2= 0.35%)

Table 2. The results of the meta-analysis of OS outcome

Study	$Ln(HR)$	$SE(Ln(HR))$	Confidence interval	Weight
B31	-0.4	0.17	(-0.733,-0.067)	8.16
BCIRG006	-0.46	0.13	(-0.715,-0.205)	13.95
Finher	-0.6	0.36	(-1.3,0.106)	1.82
Hera	-0.46	0.17	(-0.793,-0.127)	8.16
Noah	-0.48	0.3	(-1.07,0.108)	2.62
Pacs-04	0.24	0.32	(-0.387,0.867)	2.3
Goldhirsch	-0.274	0.079	(-0.429,-0.120)	37.96
Schneider	0.336	0.325	(-0.299,0.973)	2.24
Gianni	-0.162	0.102	(-0.362,0.037)	22.79
Overall effect	-0.286	0.049	(-0.381,-0.191)	
Directional Zero-Effect Test	$\chi^2 = 34.689,\ df = 1,\ P-value = 0.000$			

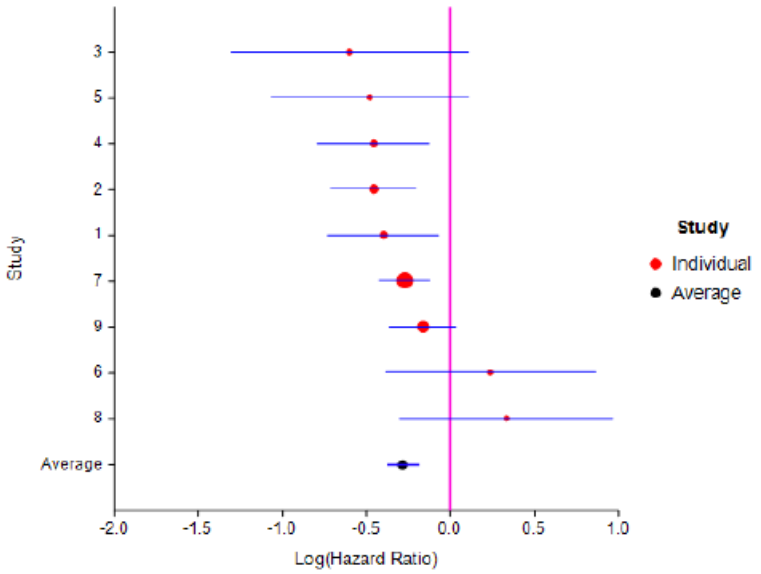


Fig. 3. Forest plot for meta-analysis of OS studies

DFS

The results of the Cochran`s Q test indicated that homogeneity was not met among the selected studies(Cochran`s Q= 32.9034, I^2= 0.69%).

Table 3. The results of meta-analysis of DFS outcome

Study	$Ln(HR)$	$SE(Ln(HR))$	Confidence interval	Weight
B31	-0.73	0.11	(-0.946,-0.514)	12.49
Bcirg006	-0.45	0.1	(-0.646,-0.254)	13.07
Buzdar	-2.27	1.11	(-4.44,-0.094)	0.462
Finher	-0.87	0.35	(-1.56,-0.184)	3.72
Hera	-0.46	0.09	(-0.636,-0.284)	13.65
Noah	-0.53	0.22	(-0.961,-0.099)	7.04
Pacs-04	-0.15	0.18	(-0.503,0.203)	8.72
Goldhirsch	-0.274	0.07	(-0.412,-0.137)	14.75
Joensuu	-0.892	0.271	(-1.423,-0.514)	5.51
Schneider	0.262	0.253	(-0.234,0.758)	5.93
Gianni	-0.274	0.07	(-0.412,-0.137)	14.75
Overall effect	-0.419	0.077	(-0.569,-0.269)	
Directional Zero-Effect Test	$\chi^2 = 116.915,\ df = 1,\ P-value = 0.000$			

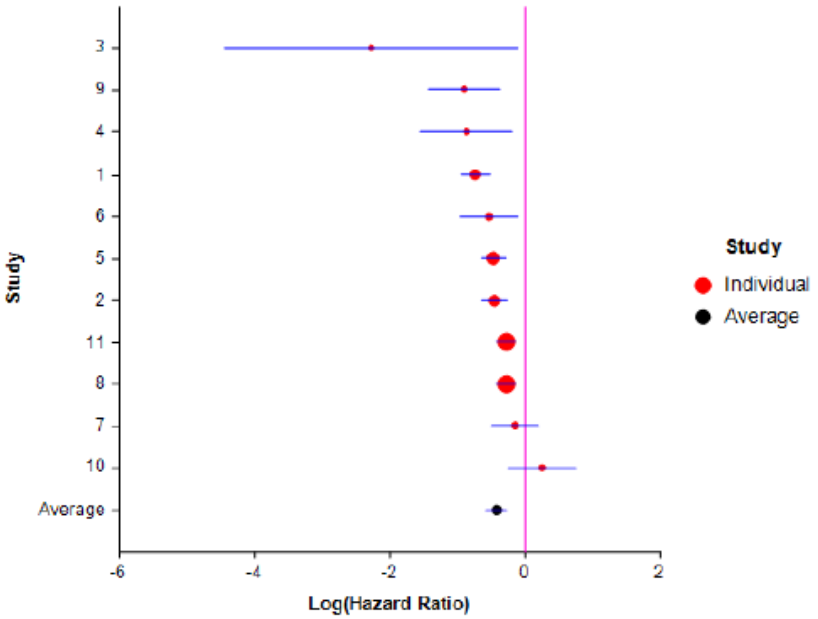


Fig. 5. Forest plot for meta-analysis of DFS studies

Anmerkung/Fazit der Autoren

The addition of trastuzumab as adjuvant therapy in early stages of BC in HER2 positive patients could increase OS and DFS of the patients effectively. The result of FinHer study encourage conducting further studies on this treatment protocol to manage BC.

Chen G et al., 2017 [7].

Clinical Value of Capecitabine-Based Combination Adjuvant Chemotherapy in Early Breast Cancer: A Meta-Analysis of Randomized Controlled TrialsTitel des Reviews

Fragestellung

No consensus has been reached on the role of capecitabine-based combination adjuvant chemotherapy in EBC. This topic was intensely debated at the annual meeting of ASCO in 2016 and has attracted considerable attention. Accordingly, we systematically analyzed the existing evidence on the clinical value of capecitabine-based combination adjuvant chemotherapy in EBC.

Methodik

Population:

- Patients with operable, nonmetastatic BC
- adjuvant chemotherapy setting

Intervention:

capecitabine-based regimens

Komparator:

capecitabine-free regimens

Endpunkte:

sufficient efficacy and safety data for analysis.

Recherche/Suchzeitraum:

To identify potential articles, the Web of Science, Cochrane Library, PubMed, and annual conference proceedings, including the San Antonio Breast Cancer Symposium (SABCS) and ASCO, were searched from the earliest record to December 2016.

Qualitätsbewertung der Studien:

- Cochrane’s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- eight RCTs that included 14,072 patients

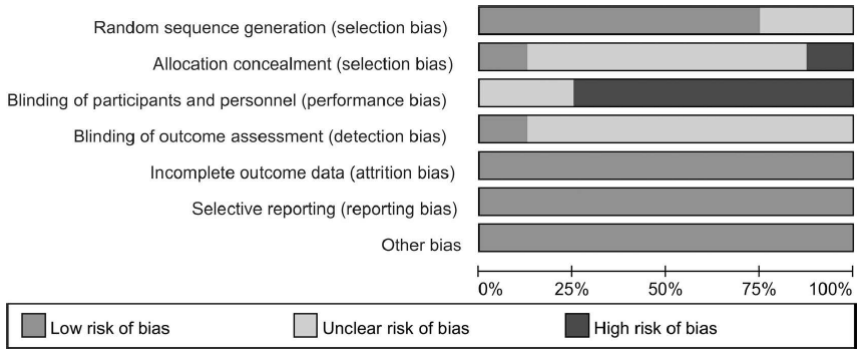
Charakteristika der Population:

Table 1. Characteristics of the Included Studies

Study	Year	Location	No. of Patients	Trial Phase	Capecitabine Based	Capecitabine Free	Capecitabine Schedule (mg/m^2, Cycles)	Follow-Up (Median Years)
CBCSG-10[21]	2016	China	561	III	TX-XEC	T-FEC	1,000, 6	2.5
FinXX[20]	2016	Finland	1,495	III	TX-CEX	T-CEF	900, 6	10.3
GAIN[24]	2014	Germany	2,994	III	EC-TX	ETC/idd-ETC	1,000–1,250, 4	6.2
GEICAM/2003-10[19]	2015	Spain	1,384	III	ET-X	EC-T	1,250, 4	6.6
ICE II-GBC 52[23]	2015	Germany	391	II	nPX/PX	EC/CMF	1,000, 6	2
TACT2[22]	2014	UK	4,358	III	E-X	E-CMF	1,250, 4	5
USON 01062[18]	2015	USA	2,611	III	AC→TX	AC→T	825, 4	5
XH Zhang et al.[25]	2015	China	278	II	AX	AC	1,000, 4	4

T, docetaxel; X, Xeloda/capecitabine; E, epirubicin; F, fluorouracil; C, cyclophosphamide; ST, standard treatment; M, methotrexate; A, doxorubicin; idd, intense dose-dense; I, ibandronate; P, paclitaxel; nP, nab-paclitaxel.

Qualität der Studien:



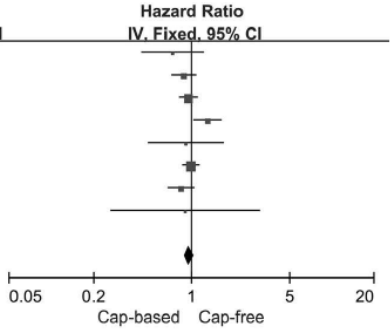
Studienergebnisse:

DFS und OS

a

Study or Subgroup	log[Hazard Ratio]	SE	Cap-based Total	Cap-free Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	-0.3147	0.2622	273	288	2.4%	0.73 [0.44, 1.22]
FinXX	-0.1278	0.107	751	744	14.6%	0.88 [0.71, 1.09]
GAIN	-0.0513	0.0804	1496	1498	25.9%	0.95 [0.81, 1.11]
GEICAM/2003-10	0.2624	0.1186	715	669	11.9%	1.30 [1.03, 1.64]
ICE II-GBC 52	-0.0943	0.3188	193	198	1.6%	0.91 [0.49, 1.70]
TACT2	-0.0101	0.0741	2180	2178	30.4%	0.99 [0.86, 1.14]
USON 01062	-0.1744	0.1146	1307	1304	12.7%	0.84 [0.67, 1.05]
XH Zhang, et al	-0.1054	0.6276	139	139	0.4%	0.90 [0.26, 3.08]
Total (95% CI)			**7054**	**7018**	**100.0%**	**0.96 [0.89, 1.05]**

Heterogeneity: Chi² = 9.86, df = 7 (P = 0.20); I² = 29%
Test for overall effect: Z = 0.87 (P = 0.38)



b

Study or Subgroup	log[Hazard Ratio]	SE	Cap-based Total	Cap-free Total	Weight	Hazard Ratio IV, Fixed, 95% CI
CBCSG-10	0.8654	0.5459	273	288	0.9%	2.38 [0.82, 6.93]
FinXX	-0.1744	0.1233	751	744	17.8%	0.84 [0.66, 1.07]
GAIN	-0.1625	0.1047	1496	1498	24.7%	0.85 [0.69, 1.04]
GEICAM/2003-10	0.1222	0.1624	715	669	10.3%	1.13 [0.82, 1.55]
ICE II-GBC 52	0.1655	0.4155	193	198	1.6%	1.18 [0.52, 2.66]
TACT2	0	0.091	2180	2178	32.6%	1.00 [0.84, 1.20]
USON 01062	-0.3857	0.1515	1307	1304	11.8%	0.68 [0.51, 0.92]
XH Zhang, et al	-0.8916	0.8104	139	139	0.4%	0.41 [0.08, 2.01]
Total (95% CI)			**7054**	**7018**	**100.0%**	**0.91 [0.82, 1.00]**

Heterogeneity: Chi² = 11.84, df = 7 (P = 0.11); I² = 41%
Test for overall effect: Z = 1.87 (P = 0.06)

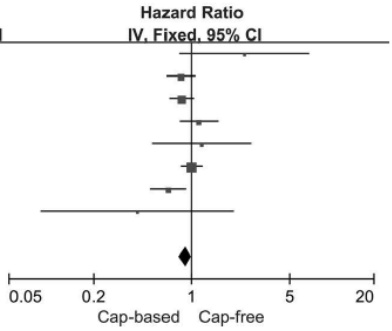


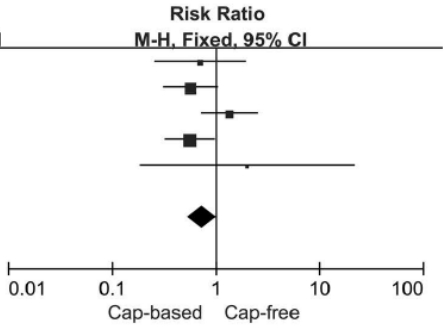
Figure 3. Capecitabine-based versus capecitabine-free combination adjuvant chemotherapy: (a) meta-analysis of disease-free survival (DFS) and (b) overall survival (OS).

Recurrence and distant metastasis

a

Study or Subgroup	Cap-based Events	Cap-based Total	Cap-free Events	Cap-free Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CBCSG-10	6	273	9	288	9.9%	0.70 [0.25, 1.95]
FinXX	16	751	28	744	31.8%	0.57 [0.31, 1.04]
GEICAM/2003-10	23	715	16	669	18.7%	1.35 [0.72, 2.52]
USON 01062	19	1307	34	1304	38.5%	0.56 [0.32, 0.97]
XH Zhang, et al	2	139	1	139	1.1%	2.00 [0.18, 21.80]
Total (95% CI)		**3185**		**3144**	**100.0%**	**0.74 [0.54, 1.01]**
Total events	66		88			

Heterogeneity: Chi² = 5.88, df = 4 (P = 0.21); I² = 32%
Test for overall effect: Z = 1.88 (P = 0.06)



b

Study or Subgroup	Cap-based Events	Cap-based Total	Cap-free Events	Cap-free Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CBCSG-10	16	273	26	288	6.2%	0.65 [0.36, 1.18]
FinXX	128	751	136	744	33.7%	0.93 [0.75, 1.16]
GEICAM/2003-10	108	715	88	669	22.4%	1.15 [0.88, 1.49]
USON 01062	115	1307	145	1304	35.8%	0.79 [0.63, 1.00]
XH Zhang, et al	6	139	7	139	1.7%	0.86 [0.30, 2.49]
Total (95% CI)		**3185**		**3144**	**100.0%**	**0.91 [0.80, 1.04]**
Total events	373		402			

Heterogeneity: Chi² = 5.71, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 1.39 (P = 0.17)

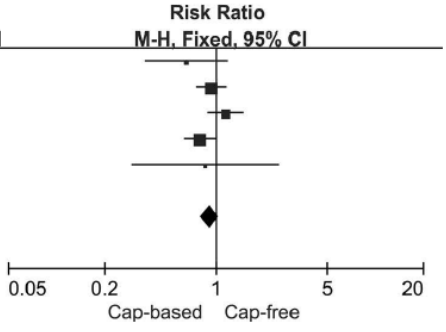


Figure 4. Capecitabine-based versus capecitabine-free combination adjuvant chemotherapy: (a) meta-analysis of local recurrence and b) distant metastasis.

Breast specific survival

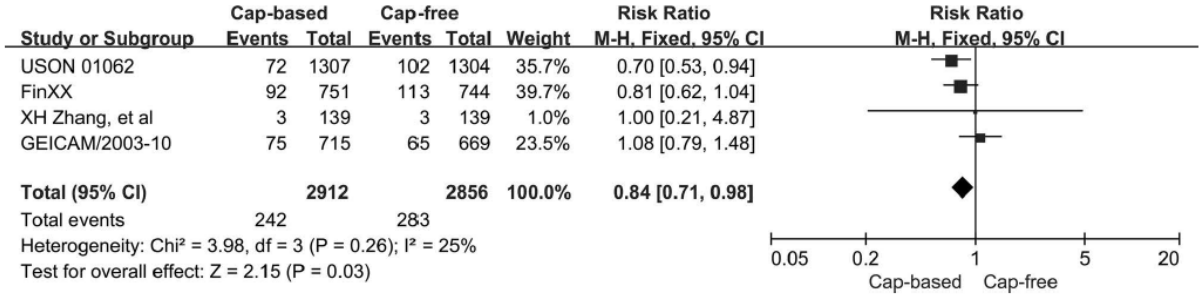


Figure 5. Capecitabine-based versus capecitabine-free combination adjuvant chemotherapy: meta-analysis of breast cancer-specific survival.

Figure 6. Capecitabine-based versus capecitabine-free combination adjuvant chemotherapy: meta-analysis of the subgroups based on hormone receptor (HR) and HER2 status.

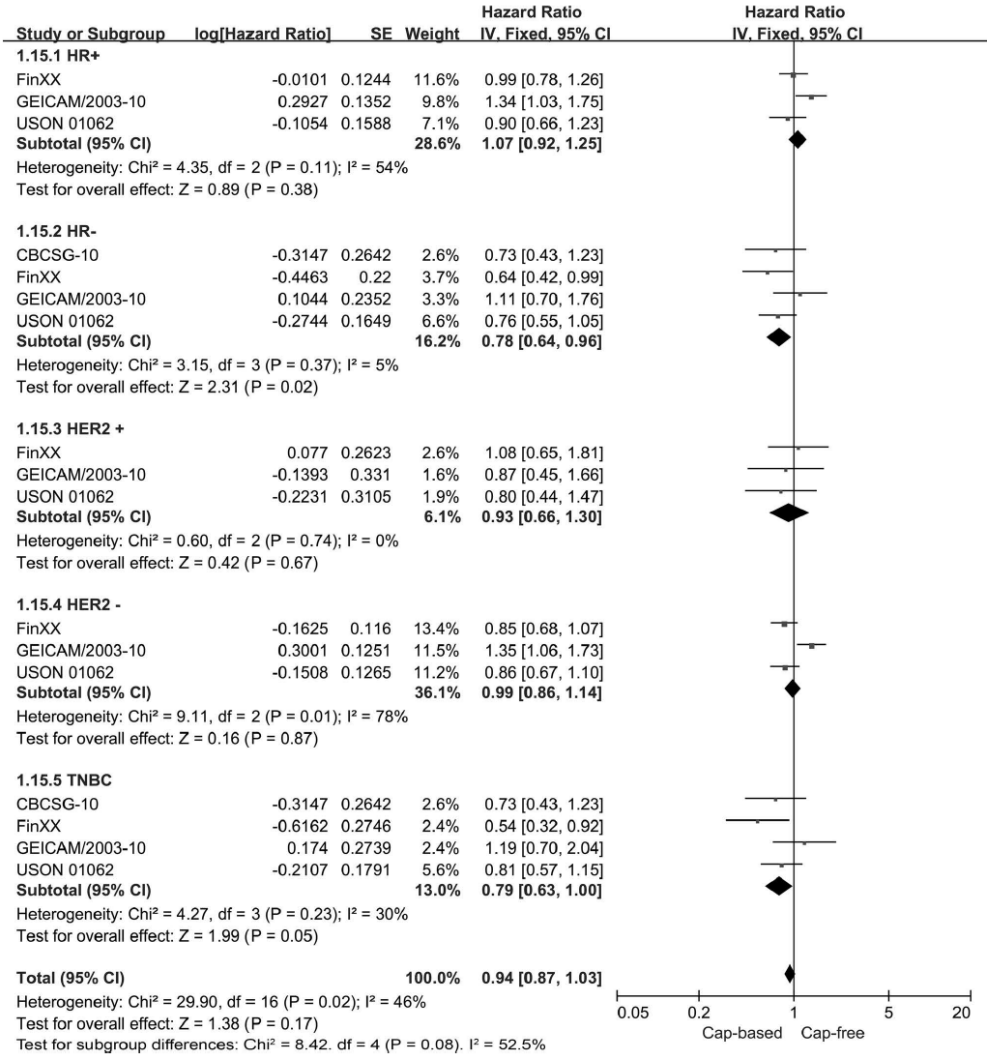
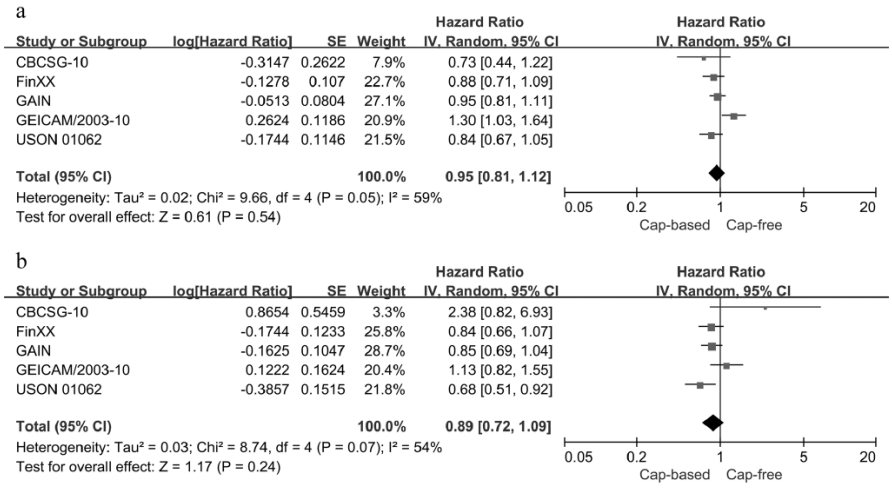


Figure 9. Capecitabine-based versus capecitabine-free combination adjuvant chemotherapy: (a) meta-analysis of DFS and (b) OS in an anthracycline-/taxane-based adjuvant setting



AE

Table 2. Outcomes of Grades 3–5 Drug-Related Adverse Events for Capecitabine-Based Versus Capecitabine-Free Combination Adjuvant Chemotherapy in Early Breast Cancer

Grades 3–5 AEs	No. of Studies	Capecitabine Based *n/N*	Capecitabine Free *n/N*	OR [95% CI]	*p*
Hematologic					
Neutropenia	7	1,977/4,839	2,460/4,836	0.53 (0.31–0.91)	0.02
Febrile neutropenia	5	321/4,507	323/4,499	0.98 (0.54–1.79)	0.94
Anemia	3	56/2,972	92/3,001	0.61 (0.43–0.85)	0.03
Thrombocytopenia	4	44/2,706	11/2,725	3.39 (0.67–17.17)	0.14
Gastrointestinal					
Nausea	5	111/2,632	117/2,671	0.96 (0.73–1.25)	0.76
Vomiting	6	120/3,343	159/3,338	0.74 (0.58–0.94)	0.01
Diarrhea	6	224/3,343	89/3,338	2.77 (1.64–4.67)	0.0001
Others					
HFS	7	672/4,839	80/4,836	13.47 (6.96–26.07)	<0.001
Fatigue	5	311/3,204	309/3,199	1.05 (0.79–1.39)	0.76
Mucositis	5	208/3,204	115/3,199	2.24 (1.17–4.30)	0.02
Myalgia	5	72/3,204	181/3,199	0.42 (0.23–0.76)	0.004

AEs, adverse events; HFS, hand–foot syndrome.

Anmerkung/Fazit der Autoren

Capecitabine-based combination adjuvant chemotherapy might provide some BCSS benefit compared with capecitabine-free regimens in EBC, but the absolute survival gain is small, and the survival benefit appears to be restricted to patients with HR− EBC, which may indicate a target population for capecitabine-based combination adjuvant chemotherapy.

Xin Y et al., 2016 [47].

Effects of lapatinib or trastuzumab, alone and in combination, in human epidermal growth factor receptor 2-positive breast cancer: a meta-analysis of randomized controlled trials

Fragestellung

A meta-analysis

of all relevant published randomized, controlled trials (RCTs) was performed to compare the efficiency and safety of lapatinib and trastuzumab, alone or in combination, administered with neoadjuvant chemotherapy in patients with HER2-positive breast cancer

Methodik

Population:

- pathologically confirmed breast cancer and HER2 positivity
- patients aged over 18 years
- chemotherapy tolerance,
- expected lifetime of more than 3 months

Intervention:

- trastuzumab with lapatinib or trastuzumab

Komparator:

- combination therapy

Endpunkte:

- Several outcomes were measured: pCR, neutropenia, diarrhea, dermatologic toxicity, and congestive heart failure (CHF). pCR was defined as the absence of any invasive component in the resected breast specimen. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria Version 3.0. The number of patients with grade 3–4 adverse events was determined from the articles. Disagreement regarding data extraction was resolved by discussion and consensus among the investigators.

Recherche/Suchzeitraum:

- The search strategy consisted of a systematic review of the literature for RCTs over the last 5 years in any language in the Wanfang Data, PubMed, the Cochrane Library, Medline, and EBSCO databases. The publication time searched was from March 2011 to March 2016

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 (n= 2350)

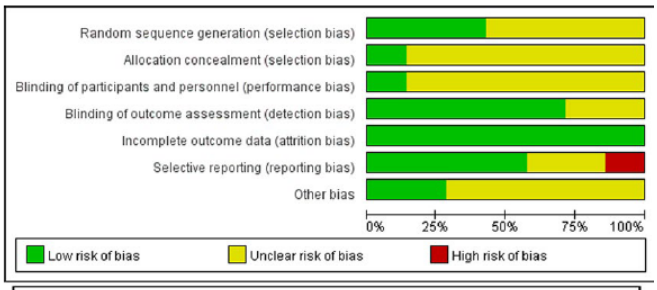
Charakteristika der Population:

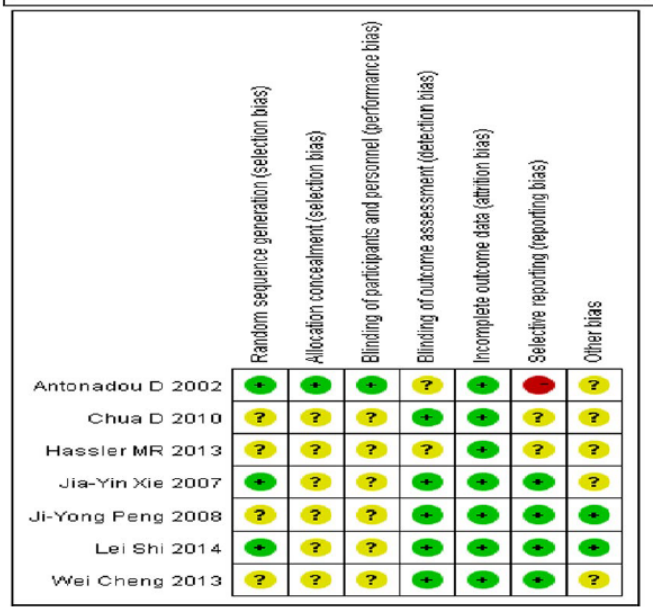
- Of these patients, 837 received lapatinib, 913 received trastuzumab, and 555 received the combination therapy. Each RCT applied different modes of neoadjuvant therapy and different
- doses of experimental drugs. Table 1 presents the characteristics of the RCTs.

Table 1. Characteristics of the eight RCTs (L: lapatinib; T: trastuzumab).

Author	Phase	Groups	No. of patients per group	Neoadjuvant anti-HER2 therapy	Duration of anti-HER2 therapy
Bonnefoi H (17)	II	L	22	1000mg daily	12weeks
		T	53	4mg/kg → 2mg/kg weekly	12weeks
		L+T	50	L:1000mg daily + T:2mg/kg weekly	12weeks
Baselga J (18)	III	L	154	1500mg daily	18weeks
		T	149	4mg/kg → 2mg/kg weekly	18weeks
		L+T	152	L:1000mg daily + T:2mg/kg weekly	18weeks
Untch M (15)	III	L	308	1250mg daily	24weeks
		T	307	8mg/kg → 6mg/kg every 3 weeks	24weeks
GuarneriV (3)	II	L	38	1500mg daily	26weeks
		T	36	4mg/kg → 2mg/kg weekly	26weeks
		L+T	45	L:1000mg daily + T:2mg/kg weekly	26weeks
Robidoux A (6)	III	L	171	1250mg daily	16weeks
		T	177	4mg/kg → 2mg/kg weekly	16weeks
		L+T	171	L:750mg daily + T:2mg/kg weekly	16weeks
Holmes FA (19)	II	L	26	1250mg daily	26weeks
		T	29	4mg/kg → 2mg/kg weekly	26weeks
		L+T	23	L:750mg daily + T:2mg/kg weekly	26weeks
Carey L (16)	III	L	64	1500mg daily	16weeks
		T	118	4mg/kg → 2mg/kg weekly	16weeks
		L+T	117	L:1000mg daily + T:2mg/kg weekly	16weeks
Alba E (20)	II	L	52	1250mg daily	12weeks
		T	50	8mg/kg → 6mg/kg every 3 weeks	12weeks

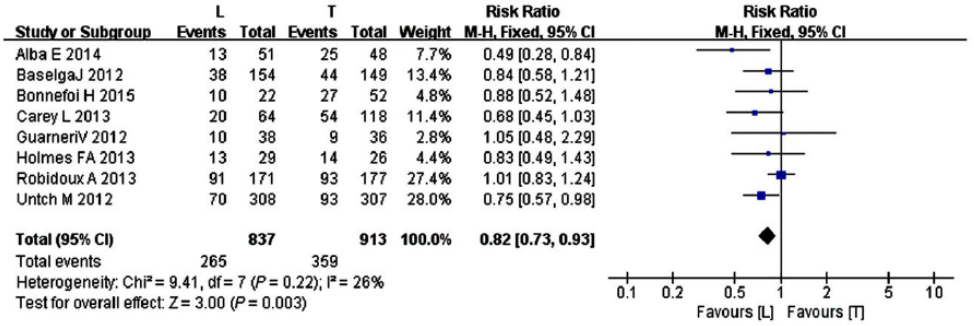
Qualität der Studien:

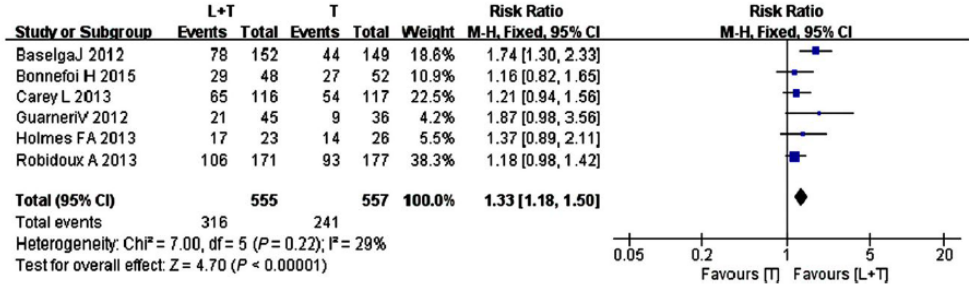




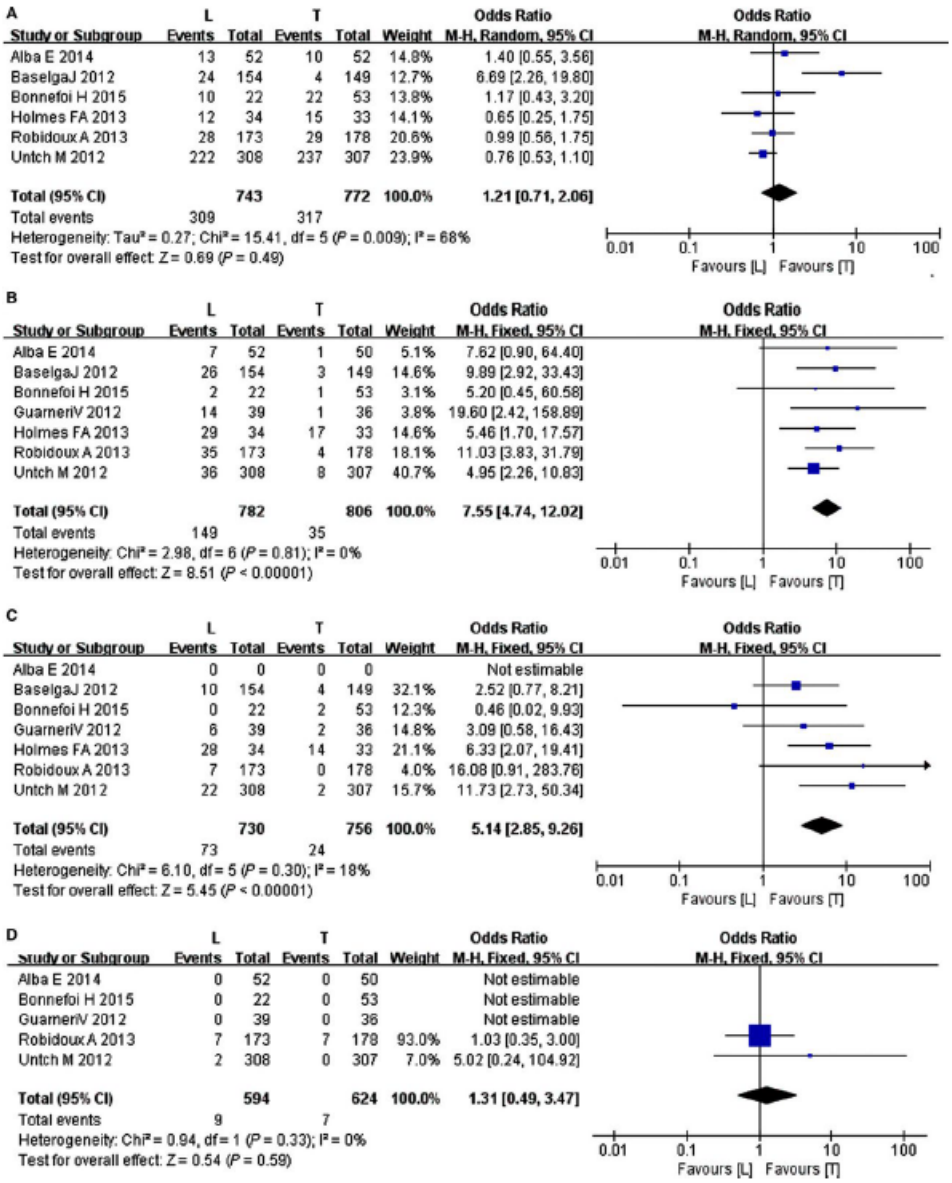
Studienergebnisse:

- pCR


L
T
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Alba E 2014 13 51 25 48 7.7% 0.49 [0.28, 0.84]
BaselgaJ 2012 38 154 44 149 13.4% 0.84 [0.58, 1.21]
Bonnefoi H 2015 10 22 27 52 4.8% 0.88 [0.52, 1.48]
Carey L 2013 20 64 54 118 11.4% 0.68 [0.45, 1.03]
GuarneriV 2012 10 38 9 36 2.8% 1.05 [0.48, 2.29]
Holmes FA 2013 13 29 14 26 4.4% 0.83 [0.49, 1.43]
Robidoux A 2013 91 171 93 177 27.4% 1.01 [0.83, 1.24]
Untch M 2012 70 308 93 307 28.0% 0.75 [0.57, 0.98]
Total (95% CI) 837 913 100.0% 0.82 [0.73, 0.93]
Total events 265 359
Heterogeneity: Chi² = 9.41, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 3.00 (P = 0.003)
0.1 0.2 0.5 1 2 5 10
Favours [L] Favours [T]


L+T
T
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
BaselgaJ 2012 78 152 44 149 18.6% 1.74 [1.30, 2.33]
Bonnefoi H 2015 29 48 27 52 10.9% 1.16 [0.82, 1.65]
Carey L 2013 65 116 54 117 22.5% 1.21 [0.94, 1.56]
GuarneriV 2012 21 45 9 36 4.2% 1.87 [0.98, 3.56]
Holmes FA 2013 17 23 14 26 5.5% 1.37 [0.89, 2.11]
Robidoux A 2013 106 171 93 177 38.3% 1.18 [0.98, 1.42]
Total (95% CI) 555 557 100.0% 1.33 [1.18, 1.50]
Total events 316 241
Heterogeneity: Chi² = 7.00, df = 5 (P = 0.22); I² = 29%
Test for overall effect: Z = 4.70 (P < 0.00001)
0.05 0.2 1 5 20
Favours [T] Favours [L+T]

- AE



igure 5. Forest plot of the adverse events for lapatinib and trastuzumab: (A) neutropenia, (B) diarrhea, (C) dermatologic toxicity, (D) congestive heart ailure.

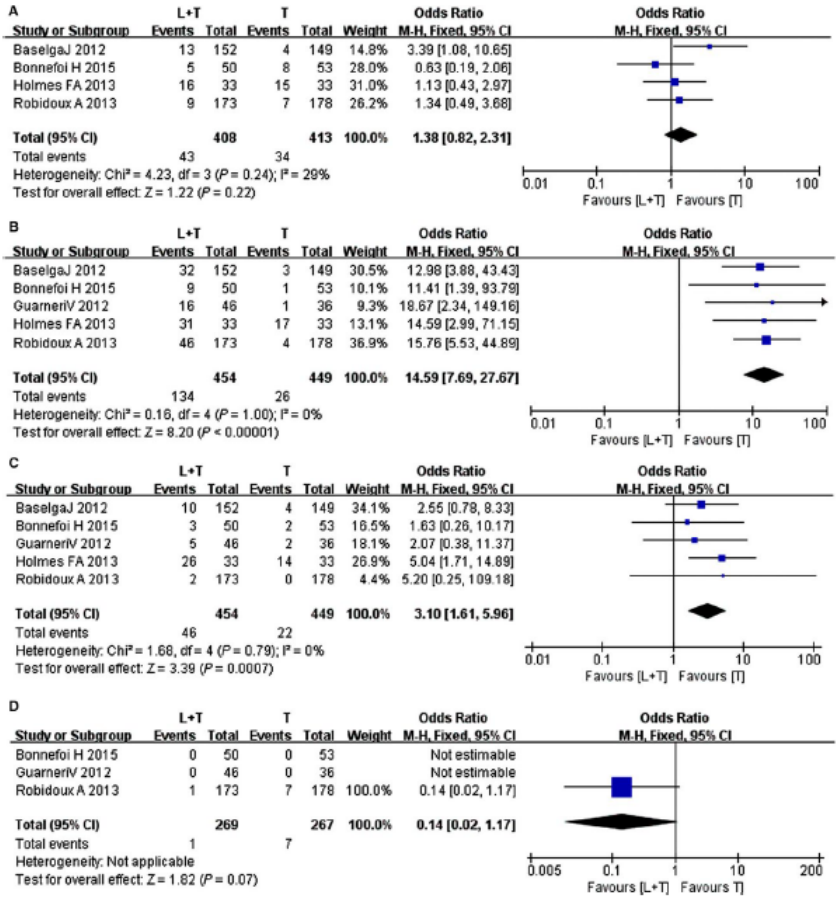


Figure 6. Forest plot of the adverse events for trastuzumab and combination therapy: (A), neutropenia, (B) diarrhea, (C) dermatologic toxicity, (D) congestive heart failure.

A significant difference was found between lapatinib and trastuzumab for pCR (RR = 0.82, 95% CI: 0.73–0.93; Z = 3.00; P = 0.003). In six studies, a significant difference was found between trastuzumab and combination therapy for pCR (RR = 1.33, 95% CI: 1.18–1.50; Z = 4.70; P < 0.00001), diarrhea (RR = 14.59, 95% CI: 7.69–27.67; Z = 8.20; P < 0.00001), and dermatologic toxicity (RR = 3.10, 95% CI: 1.61–5.96; Z = 3.39; P = 0.007), but none was found for neutropenia (RR = 1.38, 95% CI: 0.82–2.31; Z = 1.22; P = 0.22) or CHF (RR = 0.14, 95% CI: 0.02–1.17; Z = 1.02; P = 0.07)

Anmerkung/Fazit der Autoren

Combination therapy compared to trastuzumab alone increases the pCR rate of HER2-positive breast cancer patients with no additional cardiac events. Trastuzumab, which is still the first-line therapy in breast cancer, increases the pCR rate more than lapatinib.

Clavvarezza M et al., 2016 [10].

Dual Block with Lapatinib and Trastuzumab Versus Single-Agent Trastuzumab Combined with Chemotherapy as Neoadjuvant Treatment of HER2-Positive Breast Cancer: A Meta-analysis of Randomized Trials

Fragestellung

(Neo)adjuvant treatment with chemotherapy plus trastuzumab reduces recurrence and death risk in HER2-positive (HER2þ) breast cancer. Randomized trials assessed HER2 dual block

by adding lapatinib to trastuzumab and chemotherapy in the neoadjuvant setting using pathologic complete response (pCR) as the outcome measure. We conducted ametaanalysis of randomized trials testing neoadjuvant dual block with lapatinib and trastuzumab versus trastuzumab alone in HER2+ breast cancer.

Methodik

Population:

- neoadjuvant treatment of HER2þ breast cancer

Intervention:

- HER2 dual block with trastuzumab plus lapatini

Komparator:

- single-agent trastuzumab, all arms combined with chemotherapy

Endpunkte:

- primary endpoint: pCR
  pathologic complete response (pCR) rate as surrogate biomarker

Recherche/Suchzeitraum:

- Studies were identified by searching Medline (PubMed), ISI Web of Science (Science Citation Index Expanded), Embase, and the Cochrane library, by examining the reference lists of published studies, review articles, and editorials and by hand-searched reports from the following major cancer associations/symposia reports: American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), San Antonio Breast Cancer Symposium (SABCS)
- published through March 30, 2016

Qualitätsbewertung der Studien:

Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

6 (n= 1155)

Charakteristika der Population:

483 (41.8%) were hormone receptor–negative, 672 (58.2%) hormone receptor–positive, 534 (46.2%) received taxanes alone, and 621 (53.8%) anthracyclines plus taxanes or the docetaxel–carboplatin regimen.

Table 1. Characteristics of the identified studies in the meta-analysis

Trial	Chemo	HER2 therapy	*N*	*N* HoRe−	*N* HoRe+	% pCR All	% pCR HoRe−	% pCR HoRe+	% Difference All	% Difference HoRe−	% Difference HoRe+
Taxane-alone											
NEOALTTO[a]	wP ×12	L + T	152	75	77	51%	61%	42%	22%	25%	19%
		T	149	74	75	29%	36%	23%			
CALGB 40601[a]	wP ×16	L + T	116	47	69	56%	79%	41%	10%	25%	0%
		T	117	48	69	46%	54%	41%			
Polychemotherapy											
NSABP B-41[a]	AC ×4 – wP ×12	L + T	171	63	108	62%	73%	56%	10%	8%	9%
		T	177	55	122	52%	65%	47%			
EORTC 10054[a]	D ×3 – FEC ×3	L + T	48	25	23	60%	68%	52%	8%	16%	0%
		T	52	25	27	52%	52%	52%			
TRIO-US B07[b]	DCa ×6	L + T	58	24	34	52%	67%	40%	5%	10%	0%
		T	34	14	20	47%	57%	40%			
CHERLOB[b]	wP ×12 – FEC ×4	L + T	45	UNK		46%	UNK		21%	UNK	
		T	36	UNK		25%					

Abbreviations: D, docetaxel every 3 weeks; wP, weekly paclitaxel; AC, doxorubicin-cyclophosphamide; DCa, docetaxel–carboplatin; FEC, fluorouracil–epirubicin–cyclophosphamide; T, trastuzumab; L, lapatinib; HoRe−, hormone receptor negative; HoRe+, hormone receptor positive; UNK, unknown.
[a]pCR: ypT0/is.
[b]pCR: ypT0/is and ypN0.

Qualität der Studien:

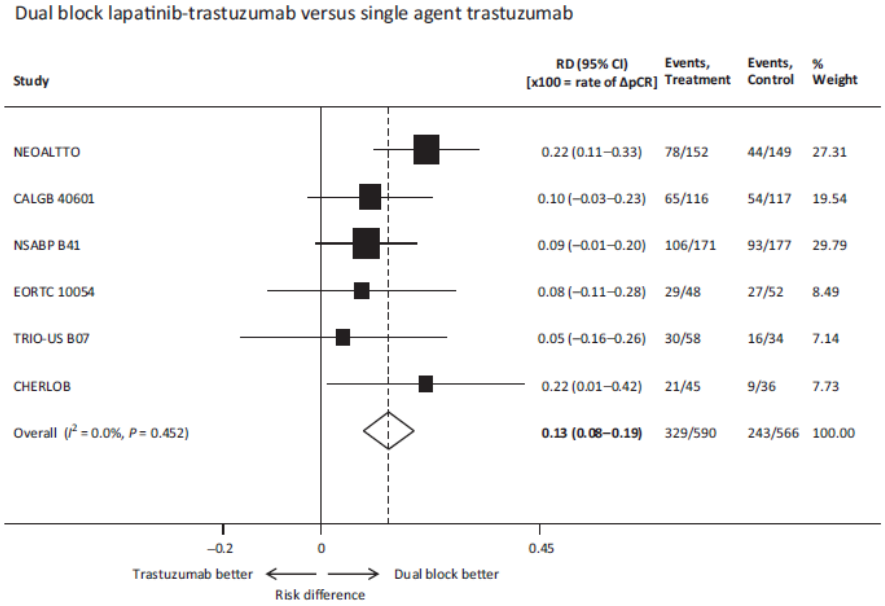
Supplementary Table S1. Results of assessment risk of bias, based on the domain-based evaluation of the Cochrane risk of bias tool*. Low, unclear, and high risk of bias are the 3 possible judgments for each item considered of each of the study assessed

Study	Random sequence generation (selection bias)	Allocation sequence concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)	Other potential sources of bias
NEOALTTO[39]	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
CALGB 40601[40]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
NSABP B-41[41]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
EORT C10054[42]	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
TRIO-US B07[43]	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Unclear risk
CHERLOB[44]	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk

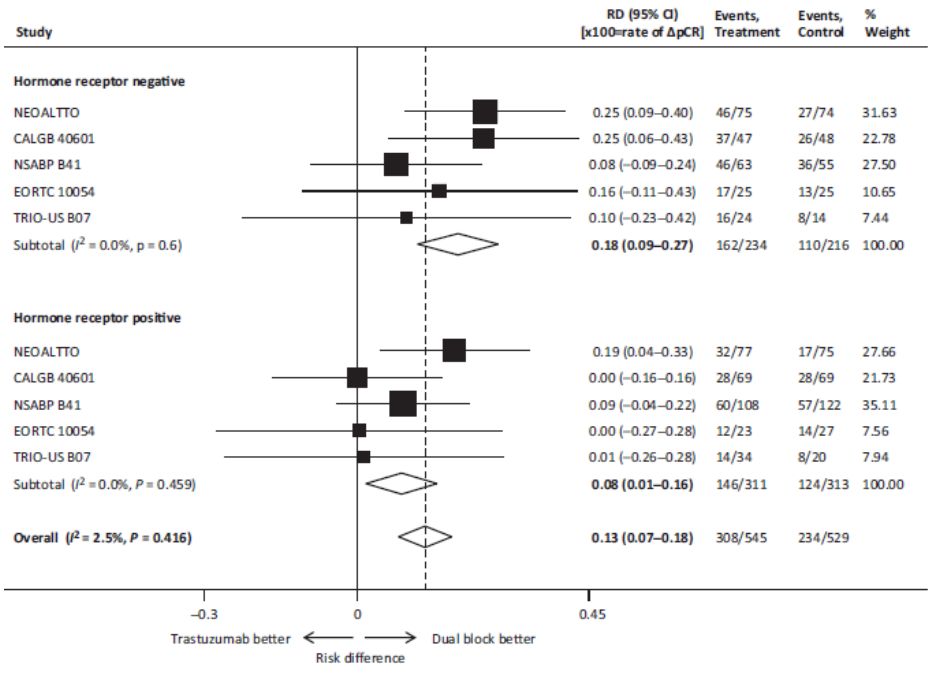
*Reference: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Studienergebnisse:

pCR rate by dual block versus single-agent trastuzumab in HER2þ breast cancer women in the neoadjuvant setting: overall effect.



Subgroup analysis by hormone receptor status (negative vs. positive), $P_{interaction}$ = 0.157.



Anmerkung/Fazit der Autoren

On the basis of DpCR data, the dual block with trastuzumab and lapatinib plus chemotherapy is a very active treatment only in HER2þ and hormone receptor–negative breast cancer treated with taxane monochemotherapy.

Kommentare zum Review

Das SR untersuchte lediglich pCR als Endpunkt. Es ist unklar, ob pCR einen validierten patientenrelevanten Endpunkt darstellt.

Hier dargestellt sind nur die Gesamtergebnisse und die Subgruppenergebnisse nach HER2-Status. Andere Subgruppenauswertungen sind in dieser Synopse nicht abgebildet.

Chen Z-L et al., 2016 [9].

The efficiency and safety of trastuzumab and lapatinib added to neoadjuvant chemotherapy in Her2-positive breast cancer patients: a randomized meta-analysis

Fragestellung

The addition of human epidermal growth factor receptor 2 (Her2) therapies to neoadjuvant chemotherapy (NAC) during treatment of Her2-positive breast cancer has been proposed as an effective way to improve the prognosis. However, the treatment outcomes of adding trastuzumab, lapatinib, or both to NAC were not unequivocal in randomized clinical trials.

The main objective was to evaluate the efficiency and safety of trastuzumab and lapatinib added to NAC for treatment of Her2-positive breast cancer.

Methodik

Population:

Her2-positive operable breast cancer

Intervention/ Komparator:

NAC with trastuzumab, lapatinib, or both

Endpunkte:

- The main objective of this analysis was to determine the pCR rate after adding trastuzumab, lapatinib, or both to NAC, to estimate the efficacy of different methods in anti-Her2 therapy. Two definitions of pCR were used in the included studies, no invasive tumors in breast only, or in breast and axillary nodes. We therefore adopted both as the endpoints.
- Other objectives, such as evaluating the safety of the drug, the influence of HR status, comparing the clinical responses, and the rates of breast conservation were also included.

Recherche/Suchzeitraum:

k.A.

Qualitätsbewertung der Studien:

Jadad scoring

Ergebnisse

Anzahl eingeschlossener Studien:

8 (n= 2349)

Table 1 Baseline characteristics of the eight clinical trials

Clinical trial	Recruitment period	No of patients	Her2 status	Chemotherapy	Arms	HR status (no of patients)		Anti-Her2 therapy
						Positive	Negative	
CHER-LOB[13]	August 2006–November 2010	121	IHC 3+ or FISH +	Weekly P 12 weeks→FEC ×4 (every 3 weeks), totally 26 weeks	T group	21	15	T 4 mg/kg→2 mg/kg once weekly
					L group	24	15	L 1,500 mg orally daily
					T+L group	28	18	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
EORTC 10054[9]	October 2010–January 2013	128	IHC 3+/2+and FISH +, or FISH + only	Doc ×3 weekly→FEC ×3 (every 3 weeks)	T group	27	26	T 4 mg/kg→2 mg/kg once weekly
					L group	15	8	L 1,000 mg orally daily
					T+L group	25	26	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
Holmes et al[23] (2013)	August 2007–February 2010	100	IHC 3+ or FISH (ratio >2.2)	FEC ×4 (every 3 weeks)→ weekly P 12 weeks	T group	15	18	T 4 mg/kg→2 mg/kg once weekly
					L group	14	20	L 1,500 mg→1,250 mg orally daily
					T+L group	20	13	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
GEICAM[11]	February 2009–October 2010	102	IHC 3+ or FISH +	EC ×4→doc ×4 weekly	T group	30	20	T 8 mg/kg→6 mg/kg once weekly
					L group	31	21	L 1,250 mg orally daily
GeparQuinto, GBG44[12]	November 2007–July 2010	614	HercepTest or in-situ hybridization (ratio ≥2.0)	EC ×4→doc ×4 weekly	T group	170	137	T 8 mg/kg→6 mg/kg once weekly
					L group	171	137	L 1,250 mg orally daily
NeoALTTO[14]	January 2008–May 2010	455	IHC 3+ or FISH +	Weekly P 12 weeks	T group	75	74	T 4 mg/kg→2 mg/kg once weekly
					L group	80	774	L 1,500 mg orally daily
					T+L group	77	75	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
NSABP[24]	July 2007–June 2011	524	FISH or CISH, or IHC 3+	AC ×4→weekly P	T group	122	59	T 4 mg/kg→2 mg/kg once weekly
					L group	101	73	L 1,500 mg→1,000 mg orally daily
					T+L group	108	66	T 4 mg/kg→2 mg/kg + L 1,000 mg orally daily
CALGB 40601[7]	December 2008–February 2012	305	IHC 3+ or FISH +	Weekly P 16 weeks	T group	70	48	T 4 mg/kg→ 2 mg/kg once weekly
					L group	37	27	L 1,500 mg orally daily
					T+L group	69	48	T 4 mg/kg→ 2 mg/kg + L 1,000 mg orally daily

Abbreviations: AC, doxorubicin-cyclophosphamide; CISH, chromogenic in situ hybridization; doc, docetaxel; EC, epirubicine–cyclophosphamide; FEC, fluorouracil–epirubicine–cyclophosphamide; FISH, fluorescent in situ hybridization; Her2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; kg, kilogram; L, lapatinib; mg, milligram; No, number; P, paclitaxel; T, trastuzumab; HR, hormone receptor.

Qualität der Studien:

Table 2 The Jadad scale

Clinical trials	CHER-LOB[13]	EORTC 10054[10]	Holmes et al[23]	GEICAM[11]	GeparQuinto, GBG44[12]	NeoALTTO[14]	NSABP[24]	CALGB 40601[27]
Randomization	2	2	2	1	2	2	2	1
Concealment of allocation	2	2	0	0	2	2	2	0
Double blinding	2	2	2	2	2	2	2	2
Withdrawals and dropouts	0	1	1	1	1	1	1	1
Jadad score[a]	6	7	5	4	7	7	7	4

Notes: [a]Methodological quality of meditative movements studies reviewed using Jadad scoring criteria. Total score is 7. Scores 1–3 considered as low quality; Scores 4–7 considered as high quality.

Studienergebnisse:

Figure 2 Forest plots of **pCR rates**: trastuzumab versus lapatinib, defined as no invasive disease in the breast only (A) or no invasive disease in the breast and lymph nodes (B).

Abbreviations: CI, confidence interval; df, degrees of freedom; M–H, Mantel–Haenszel; pCR, pathologically complete response.

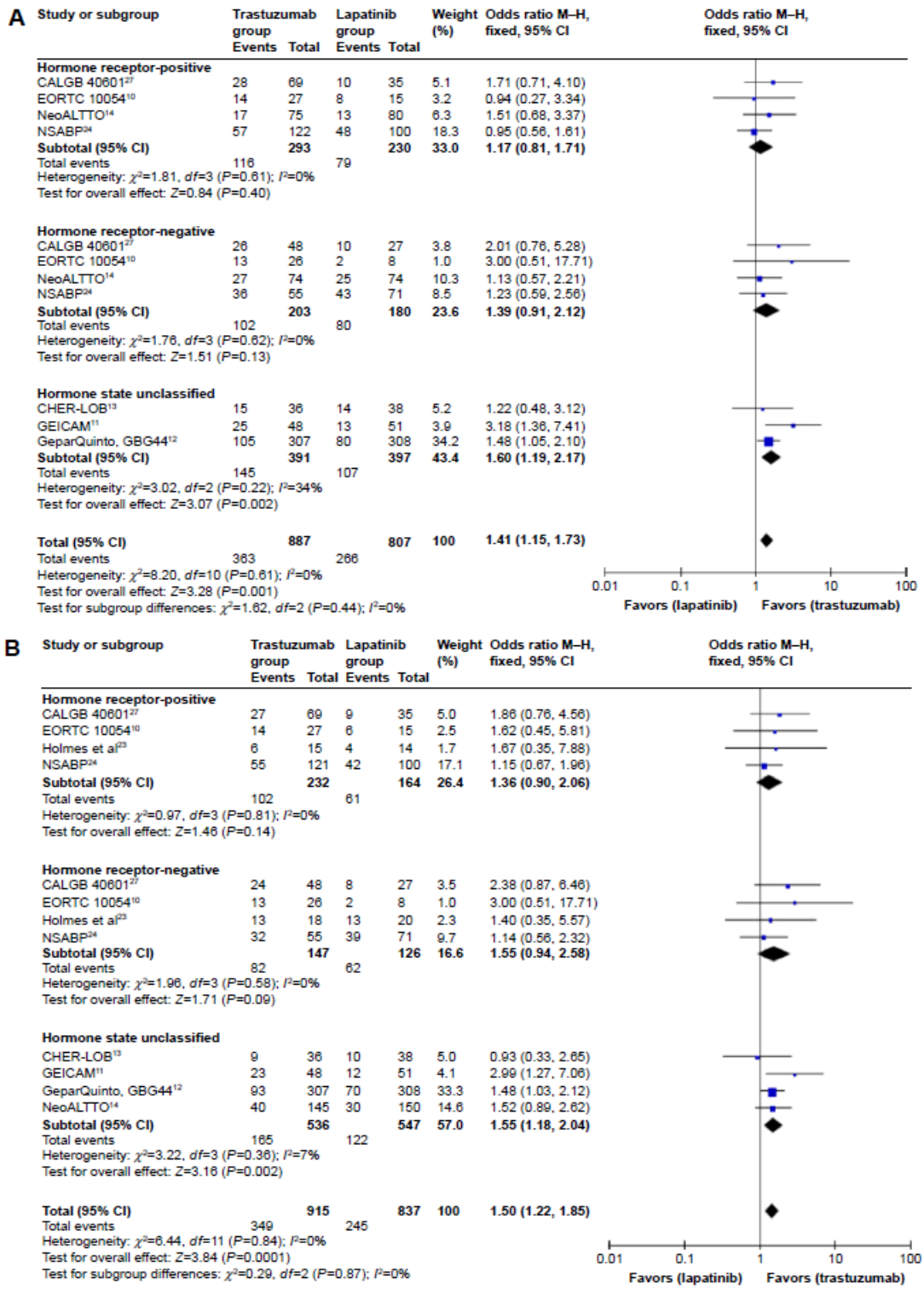


Figure 3 Forest plots of **pCR rates**: combination versus trastuzumab, defined as no invasive disease in the breast only (A) or no invasive disease in the breast and lymph nodes (B).

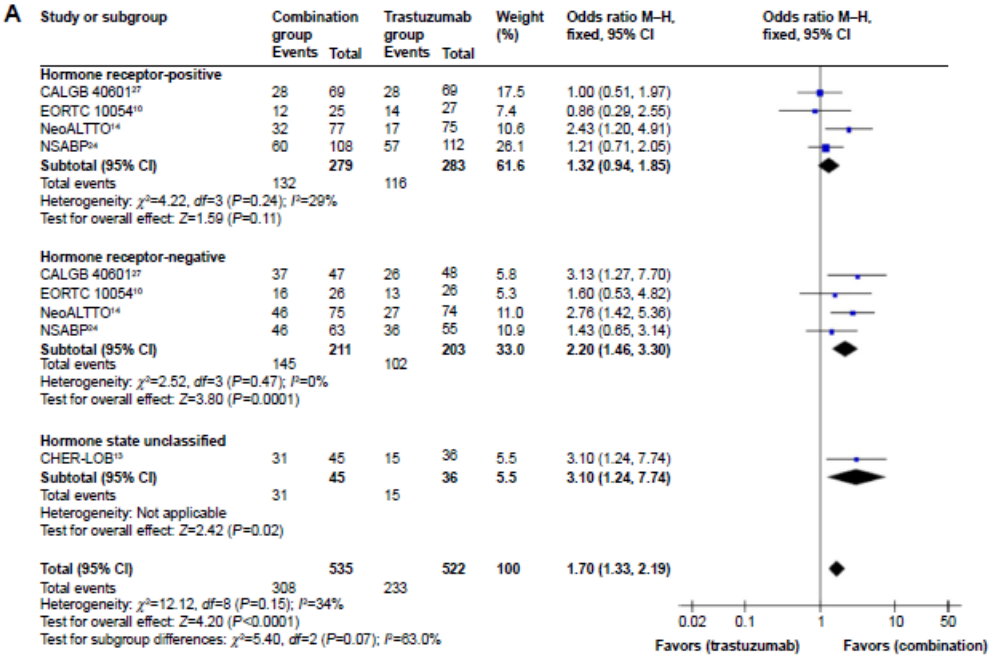


Figure 4 Forest plots of clinical **complete response rates**: trastuzumab versus lapatinib (A); combination versus trastuzumab (B).

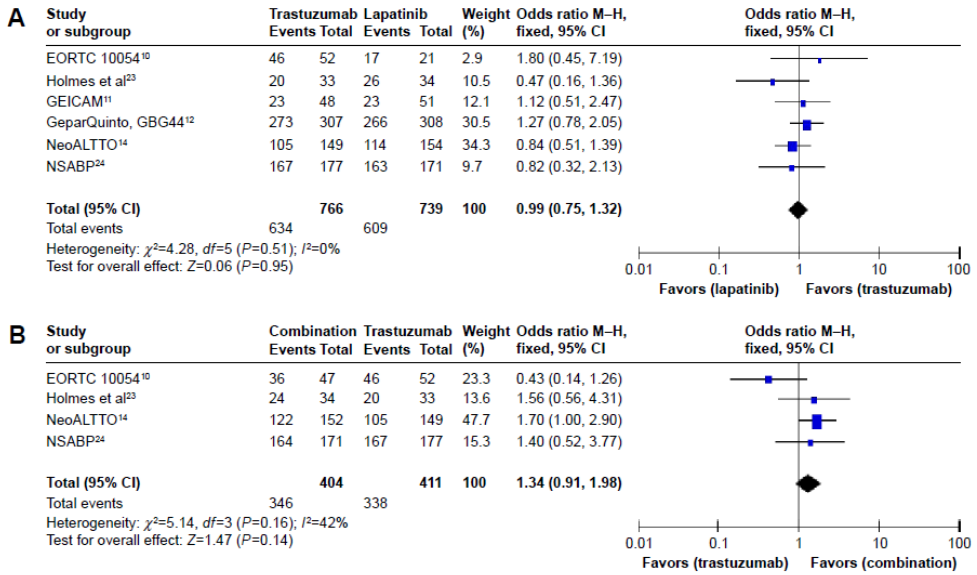
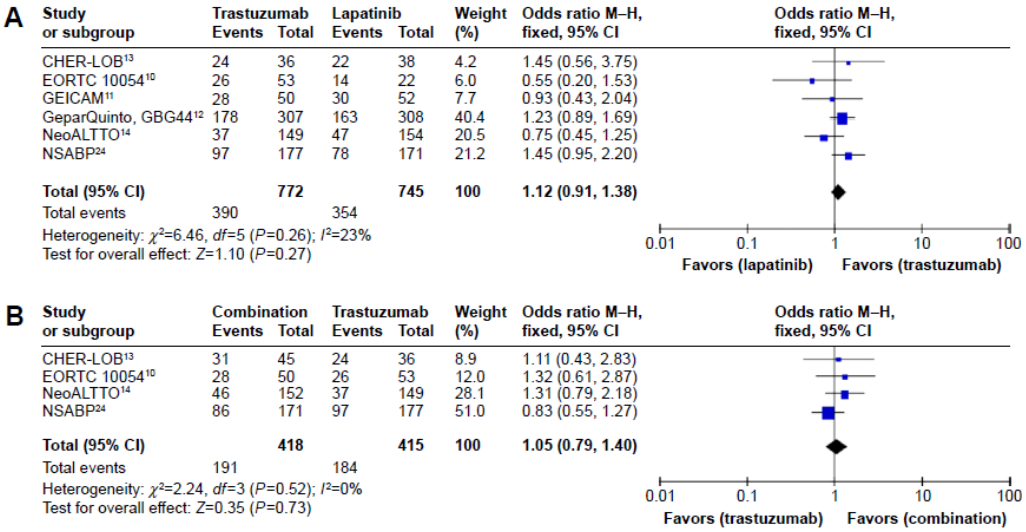


Figure 5 Forest plots of the **rate of breast conservation**: trastuzumab versus lapatinib (A); combination versus trastuzumab (B).



AE

Table 3 Selected toxic effects in the trastuzumab group and lapatinib group

Toxic effect	Studies	Participants	Odds ratio (M–H, fixed, 95% CI)
Diarrhea	8	1,769	0.11* (0.07, 0.18)
Other digestive tract symptoms	6	1,284	0.92 (0.59, 1.44)
Febrile neutropenia	5	1,289	0.85 (0.54, 1.34)
Neutropenia	7	1,694	0.90 (0.69, 1.15)
Hepatic	8	1,769	0.60* (0.39, 0.92)
Skin disorder	7	1,703	0.14* (0.08, 0.26)
CHF	3	1,041	0.76 (0.29, 2.03)
Hemoglobin	4	1,107	0.93 (0.57, 1.50)
LVSD	4	1,143	1.66 (0.98, 2.81)
Fatigue	5	1,218	0.83 (0.55, 1.26)
Dehydration	2	417	0.25 (0.03, 2.24)
Infection and inflammation	6	1,284	0.52* (0.29, 0.94)
Neuropathy sensory	5	1,298	0.69 (0.36, 1.31)
Dyspnea	3	492	1.27 (0.34, 4.71)

Note: *$P<0.05$.
Abbreviations: CHF, congestive heart failure; CI, confidence interval; LVSD, left ventricular systolic dysfunction; M–H, Mantel–Haenszel.

Table 4 Selected toxic effects in the combination group and trastuzumab group

Toxic effect	Studies	Participants	Odds ratio (M–H, fixed, 95% CI)
Diarrhea	6	1,135	14.38* (8.02, 25.78)
Other digestive tract symptoms	4	599	2.11* (1.17, 3.82)
Febrile neutropenia	4	517	0.92 (0.46, 1.85)
Neutropenia	5	1,053	1.37 (0.93, 2.02)
Hepatic	6	1,135	2.63* (1.51, 4.59)
Skin disorder	5	1,072	4.97* (2.56, 9.61)
CHF	2	454	0.14 (0.02, 1.17)
Hemoglobin	3	517	2.80 (0.74, 10.67)
LVSD	2	454	0.73 (0.28, 1.90)
Fatigue	3	536	1.01 (0.51, 2.01)
Dehydration	3	517	3.15 (0.32, 30.76)
Infection and inflammation	4	599	2.26 (0.82, 6.29)
Neuropathy sensory	4	771	1.97 (0.95, 4.11)
Dyspnea	3	517	0.84 (0.24, 2.96)

Note: *$P<0.05$.
Abbreviations: CHF, congestive heart failure; CI, confidence interval; LVSD, left ventricular systolic dysfunction; M–H, Mantel–Haenszel.

Anmerkung/Fazit der Autoren

The combination of trastuzumab and lapatinib was superior to single-agent treatment for improved pCR rate. However, combination treatment was not effective in improving the rate of breast conservation. Furthermore, a higher risk for toxicity was associated with combined administration.

Chen Y-Y et al., 2016 [8].

Efficacy, safety and administration timing of trastuzumab in human epidermal growth factor receptor 2 positive breast cancer patients: A meta-analysis

Fragestellung

based on the publication of several high quality RCTs in recent years, an updated meta‐analysis was performed in the present study in order to evaluate the prognostic effects and the magnitude of AEs caused by trastuzumab in adjuvant and neoadjuvant settings

Methodik

Population:

patients with HER‐2 positive BC

Patients included in the current study required a good performance status (defined as a World Health Organization performance status of 0 or 1), adequate left ventricular ejection fraction (LVEF; as assessed by multiple‐gated acquisition or echocardiography scan, and was required to be within the institutional normal range, and within the lower limit of normal), and normal bone marrow (a blood leukocyte count >3.0×109 cells/l; neutrophil count >1.5×109 cells/l; platelet count >100×109 cells/l; hemoglobin >10 g/dl), liver and renal function laboratory results.

Intervention:

chemotherapy with trastuzumab

Komparator:

k.A.

Endpunkte:

- The primary endpoint was the number of disease‐free survival (DFS) patients, which was defined by events from the random assignment to the first documented disease progression (local, regional, distant recurrence or morality).
- Secondary endpoints included OS, tumor response and AEs. OS was defined as events from random assignment to mortality. The effects of treatment were assessed by the clinical response of the patient in an adjuvant setting, which included the complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). The overall response (OR) was defined as CR plus PR. The effects of treatment in a neoadjuvant setting were divided into pathological CR (pCR) and non‐pCR.
- AEs were graded according to the National Cancer Institute Common Toxicity Criteria (NCI‐CTC) version 2.0 (23). Serious AEs were defined as grade 3‐4 and fatal AEs were also included in the present study.

Recherche/Suchzeitraum:

PubMed, Embase and Science Direct databases were used to identify eligible studies published between January 1995 and March 2014.

Qualitätsbewertung der Studien:

Cochrane Collaboration's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 (n= 14056)

Charakteristika der Population:

Table I. Baseline characteristics of the 15 randomized control trials included in the meta-analysis.

Author, year	Patients (n)		T	T-group treatment	C-group treatment	Follow-up (months)[a]	(Refs.)
	T-group	C-group					
Adjuvant chemotherapy							
Slamon *et al*, 2011	2,149	1,073	Concurrent	(q3w) (Dox+Cyc+Doc)→(w→q3w) T	(q3w) (Dox+Cyc+Doc) (q3w) Doc+Car+(w→q3w) T	65.0	(31)
Perez *et al*, 2011	2,028	2,017	Concurrent	(q3w) (Dox+Cyc)+wP+ wT	(q3w) (Dox+Cyc)+wP	46.8	(32)
Gianni *et al*, 2011	3,397	1,698	Sequential	(q3w) T for 1 year	Observation (q3w) T for 2 years	48.4	(33)
von Minckwitz *et al*, 2009	78	78	Concurrent	Cap+(q3w) T	Cap	15.6	(34)
Spielman *et al*, 2009	260	268	Sequential	(q3w)T+(F+E+Cyc)/(E+Doc)	(F+E+Cyc)/(E+Doc)	47.0	(35)
Joensuu *et al*, 2009	116	116	Concurrent	Doc+F+E+Cyc+T V+F+E+Cyc+T	Doc+F+E+Cyc V+F+E+Cyc	62.0	(36)
Gasparini *et al*, 2007	63	60	Sequential	wP+wT	wP	16.6	(37)
Marty *et al*, 2005	92	94	Concurrent	(q3w) Doc+wT	(q3w) Doc	40.9/35.9[b]	(38)
Slamon *et al*, 2001	235	234	Concurrent (q3w) P+T	(q3w) (A+Cyc)+wT (q3w) P	(q3w) (A+Cyc)	35.0	(39)
Neoadjuvant chemotherapy							
Steger *et al*, 2014	44	49	Concurrent	(q3w) (E+Doc±Cap)+T	(q3w) (E+Doc±Cap)	NR	(40)
Pierga *et al*, 2010	62	58	Concurrent	(q3w) (E+Cyc+Doc)→(q3w) T	(q3w) (E+Cyc+Doc)	NR	(41)
Gianni *et al*, 2010	117	118	Concurrent (Cyc+M+F)→(q3w) T	(q3w) (Dox+P)→(q4w)	(q3w) (Dox+P)→(q4w) (Cyc+M+F)	38.4	(42)
Buzdar *et al*, 2007	23	19	Concurrent	P+F+E+Cyc+wT	P+F+E+Cyc	36.1	(43)

[a]Median value; [b]follow-up for T-group and C-group are 40.9 and 35.9 months. T-group, trastuzumab plus chemotherapy group; C-group, chemotherapy alone group; A, anthracycline; Cap, capecitabine; Cyc, cyclophosphamide; Car, carboplatin; Dox, doxorubicin; Doc, docetaxel; E, epirubicin; F, fluorouracil; M, methotrexate; P, paclitaxel; V, vinorelbine; T, trastuzumab; w, weekly; q3w, every 3-weeks; NR, no report.

Qualität der Studien:

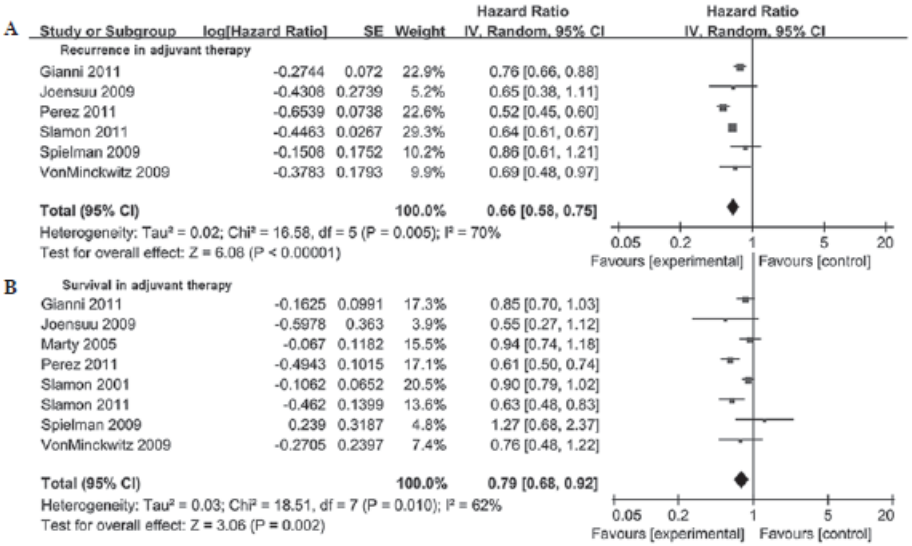
Each trial included a statement regarding randomization and a detailed description was included in 7 trials. One study was randomized using a code envelope (37), two by computer program (40,41), and four via block method (34,36,38,43). Two trials utilized the blind method (38,42). All trials published as full text articles were judged to be grade B.

Studienergebnisse:

- Efficacy and overall analysis of trastuzumab on DFS and OS in an adjuvant setting.

  In an adjuvant setting, 6 trials (31‑36) with 10,503 patients reported disease recurrence. The random effects model (I2=70%) indicated that the disease recurrence risk in C group (26.1%; 1,370/5,246) was higher compared that in the T group [18.8%; 987/5,257; HR=0.66; 95% CI (0.58‑0.75), P<0.00001; Fig. 2A]. There were 8 studies (30‑35,37,38) with complete information on OS. In comparison with the C‑group, there was a significant relative reduction in the risk of mortality in the T‑group [21%; HR=0.79; 95% CI (0.68‑0.92); P=0.002; I2=62%; Fig. 2B].

Figure 2. Forest‑plot of the efficacy of trastuzumab in an adjuvant setting. Analysis of (A) recurrence and (B) survival between trastuzumab and the control group.



- Overall analysis of trastuzumab on DFS and OS in a neoadjuvant setting.

  Only 2 RCTs contained survival analysis data in a neoadjuvant setting. The NOAH trial (42) demonstrated that the addition of trastuzumab could reduce the risk of relapse and mortality in comparison with the C‑group. Buzdar et al observed that the DFS at 1 and 3 years was 100% in the T‑group (P=0.041) (43). The data required to evaluate DFS and OS in neoadjuvant treatment groups was not available.

- Response rates in adjuvant and neoadjuvant settings.

  Tumor response data was available in 4 adjuvant and 4 neoadjuvant trials. Among these, 3 trials (37‑39) adopted the World Health Organization criteria (45) for the response measurement, 2 trials (34,42) used the response evaluation criteria in solid tumors and 1 (41) adopted chevalier criteria. The criteria in a further 2 trials were unclear (40,43). These studies (34,37‑43)were incorporated in the response analysis for relatively high concordance among these criteria (46). The OR, SD and PD was analyzed in 4, 3 and 2 adjuvant setting trials, respectively. The rate of OR was significantly higher in the T‑group in comparison with the C‑group [RR=1.58; 95% CI (1.37‑1.83); P<0.00001; Fig. 4A). However, the rate of SD in the T‑group was significantly lower than that in the C‑group

[RR=0.74, 95% CI (0.55‑0.99), P=0.04; Fig. 4B]. There was no statistical difference between the rate of PD between the two groups [RR=0.72; 95% CI (0.18‑2.88); P=0.64; Fig. 4C]. The estimated pCR in 4 neoadjuvant trials demonstrated that the pCR in the T‑group (61%; 150/246) was significantly higher compared with the C‑group [48%; 116/244; RR=1.29; 95% CI (1.12‑1.49); P=0.0005; Fig. 4D].

- AE

Table III. Relative risk of cardiac toxicity in patients with human epidermal growth factor receptor-2-positive breast cancer treated with adjuvant trastuzumab, stratified by timing.

		T-group (n)		C-group (n)			
Treatment	Trials (n)	Cardiac events	Total	Cardiac events	Total	RR (95% CI)	P-value
LVEF reduction							
Concurrent	5	240	1,890	155	1,948	1.54 (1.27-1.86)	<0.00001
Sequential	2	91	1,942	20	1,987	4.66 (2.89-7.53)	<0.00001
Weekly	3	45	771	41	856	1.16 (0.77-1.76)	0.47
Every 3 weeks	3	92	2,019	20	2,061	4.62 (2.88-7.41)	<0.00001
CHF							
Concurrent	5	75	2,740	15	2,762	4.79 (2.80-8.17)	<0.00001
Sequential	2	37	1,942	3	1,987	12.63 (3.90-40.92)	<0.0001
Weekly	3	53	1621	8	1670	3.34 (0.55-20.44)	0.19
Every 3 weeks	3	38	2,019	3	2,061	11.2 (3.76-33.35)	<0.0001

LVEF, left ventricular ejection fraction; CHF, congestive heart failure; RR, risk ratio; CI, confidence interval; T-group, trastuzumab plus chemotherapy group; C-group, chemotherapy alone group.

Anmerkung/Fazit der Autoren

In conclusion, the present meta‑analysis supports the clinical practice of treating patients with HER‑2 positive BC with a combination of trastuzumab and chemotherapy. AEs resulting from trastuzumab treatment were acceptable and manageable both in adjuvant and neoadjuvant settings. Furthermore, with regards to survival and cardiac toxicity, concurrent and weekly administration of trastuzumab has been demonstrated to be more effective than treatment with trastuzumab sequentially and every 3 weeks. Further research is required to confirm the findings of the present study and support the use of trastuzumab in clinical practice.

Fujii T et al., 2015 [18].

Effectiveness of an Adjuvant Chemotherapy Regimen for Early-Stage Breast Cancer: A Systematic Review and Network Meta-analysis

Fragestellung

Different adjuvant chemotherapy regimens are available for early-stage breast cancer. Because conventional meta-analysis does not allow comparing all regimens, we performed a network meta-analysis to identify the most effective adjuvant chemotherapy regimen.

To find the most effective adjuvant therapy regimen for early-stage breast cancer.

Methodik

Population:

- early-stage breast cancer
- Early-stagebreast cancer was defined as pathological stage I to III.
- adjuvant treatments

Intervention:

- no adjuvant chemotherapy;
- sequential anthracycline-cyclophosphamide and taxane (AC-T);
- concurrent anthracycline-cyclophosphamide and taxane (ACT);
- anthracycline-cyclophosphamide without taxane (AC);
- docetaxel and cyclophosphamide (TC);
- cyclophosphamide,
- methotrexate, and fluorouracil (CMF); and
- platinum-containing regimens

Komparator:

analog Intervention

Endpunkte:

- OS
- event-free survival (EFS),
- unacceptable AEs, which were defined as AEs grade 3 or greater that can require dose reduction or schedule delay

Recherche/Suchzeitraum:

We searched MEDLINE, Embase, and the Cochrane Library for articles published before June 2015; the American Society of Clinical Oncology annual meeting abstracts from January 1983 through December 2014; and the American Association for Cancer Research annual meeting abstracts from January 1916 through December 2014. Additionally, we manually searched bibliographies for related references.

Qualitätsbewertung der Studien:

Cochrane risk-of-bias method

Ergebnisse

Anzahl eingeschlossener Studien:

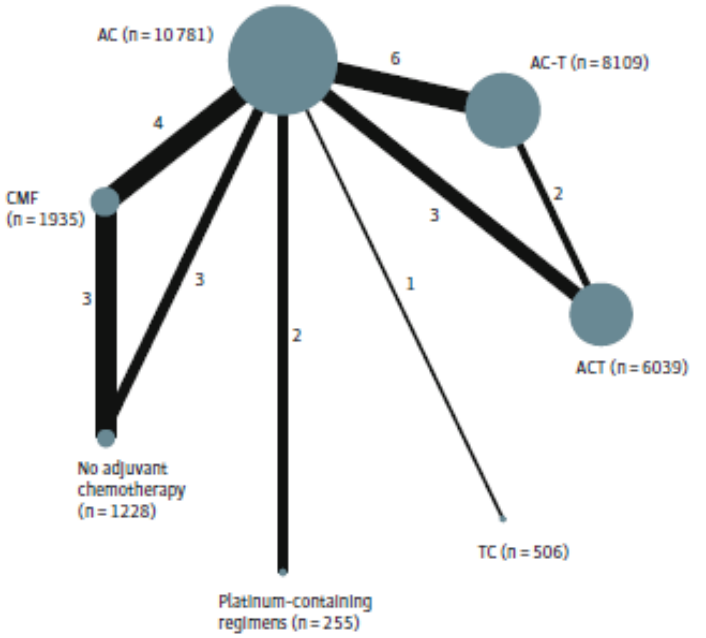
24 (n= 4324)

Charakteristika der Population:

eTable 3. Comparison of baseline patient and disease characteristics in each regimen

	Sequential AC-T	Concurrent ACT	AC	CMF	No adjuvant chemotherapy	Platinum-Containing Regimens	TC
Menopausal status							
Premenopause	3293 (50.7)	2921 (19.2)	4638 (55.1)	1397 (72.5)	437 (36.2)	N/A	N/A
Postmenopause	3204 (49.3)	3016 (50.8)	3777 (44.9)	530 (27.5)	770 (63.8)	N/A	N/A
Hormone receptor status							
Positive	5975 (75.8)	4532 (75.6)	6781 (67.9)	790 (51.5)	691 (67.4)	91 (63.6)	367 (72.8)
Negative	1905 (24.2)	1460 (24.4)	3207 (32.1)	745 (48.5)	334 (32.6)	52 (36.4)	137 (27.2)
Histology							
Ductal	1662 (85.6)	N/A	2761 (87.4)	660 (89.3)	193 (73.1)	N/A	446 (88.1)
Lobular	188 (9.7)	N/A	226 (7.2)	29 (3.9)	16 (6.1)	N/A	34 (6.7)
Others	91 (4.7)	N/A	173 (5.5)	50 (6.8)	55 (20.8)	N/A	26 (5.1)
Pathological T stage							
T1	3740 (47.3)	2513 (42.3)	4856 (49.6)	834 (45.2)	782 (66.3)	7 (9)	N/A
T2	3502 (44.3)	2977 (50.2)	4443 (45.4)	876 (47.5)	382 (32.4)	47 (60.3)	N/A
T3	668 (8.4)	444 (7.5)	484 (5.9)	134 (7.3)	16 (1.4)	24 (30.8)	N/A
Pathological N stage							
N0	951 (13.4)	956 (20.3)	2844 (30.6)	315 (16.6)	733 (60.5)	21 (8.4)	239 (47.2)
N1	3891 (54.9)	2540 (54)	4193 (45.1)	924 (48.7)	340 (28.1)	98 (39.4)	209 (41.3)
N2	1776 (25.1)	861 (18.3)	1996 (21.5)	597 (31.5)	138 (11.4)	76 (30.5)	58 (11.5)
N3	469 (6.6)	345 (7.3)	260 (2.8)	61 (3.2)	0 (0)	54 (21.7)	0 (0)
Nuclear Grade							
I/II	2704 (65.2)	1867 (55.2)	6586 (69.7)	289 (57.2)	449 (55.6)	N/A	N/A
III	1446 (34.8)	1516 (44.8)	2861 (30.3)	216 (42.7)	358 (44.4)	N/A	N/A

Figure 1. Network of Comparisons Included in the Network Meta-analysis



Node size is proportional to the total number of patients in the treatment group. Line width is proportional to the number of trials comparing the treatment groups connected by the line, which are represented by the numbers next to each line. A total of 24 trials were analyzed. AC indicates anthracycline-cyclophosphamide without taxane; AC-T, sequential anthracycline-cyclophosphamide and taxane; ACT, concurrent anthracycline-cyclophosphamide and taxane; CMF, cyclophosphamide, methotrexate, and fluorouracil; TC, docetaxel and cyclophosphamide.

Qualität der Studien:

eTable 1. Domain-based evaluation; assessment with Cochrane risk-of-bias tool

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Source of Bias
Clahsen 1995[15]	Yes	Yes	No	Yes	Yes	Yes
Coombes 1996[30]	Yes	Yes	No	Yes	Yes	Yes
Levine 1998[47]	Yes	Yes	No	No	Yes	Yes
Amadori 2000[17]	Yes	Yes	No	Yes	Yes	Yes
Icli 2001[21]	Unclear	Unclear	No	No	Yes	Yes
Paradiso 2001[44]	Yes	Yes	No	No	Yes	Yes
Piccart 2001[22]	Yes	Yes	No	No	Yes	Yes
Arriagada 2005[14]	Yes	Yes	No	Unclear	Yes	Yes
Mamounas 2005[19]	Yes	Yes	No	Yes	Yes	Yes
Martin 2005[32]	Unclear	Unclear	No	Yes	Yes	Yes
Hery 2006[36]	Unclear	Unclear	No	Unclear	Yes	Yes
Jones 2006[8]	Unclear	Yes	No	Yes	Yes	Yes
Roche 2006[45]	Yes	Yes	No	Yes	Yes	Yes
Ejlertsen 2007[18]	Yes	Yes	No	Yes	Yes	Lack of power
Goldstein 2008[16]	Yes	Unclear	No	Yes	Yes	Yes
Martin 2008[20]	Yes	Unclear	No	Yes	Yes	Yes
Kimura 2010[46]	Yes	Yes	No	Yes	Yes	Lack of power
Martin 2010[31]	Yes	Yes	No	Yes	Yes	Yes
Polyzos 2010[38]	Unclear	Yes	No	Yes	Yes	Yes
Sirohi 2010[43]	Yes	Yes	No	Yes	Yes	Lack of power
Eiermann 2011[42]	Unclear	Yes	No	Yes	Yes	Yes
Martin 2013[39]	Unclear	Yes	No	Yes	Yes	Yes
Sakr 2013[49]	Yes	Unclear	No	Yes	Yes	Yes
Swain 2013[35]	Yes	Unclear	No	Yes	Yes	Yes

eTable 11. Evaluation of the strength of evidence by using the AHRQ approach

Sequential AC-T vs Concurrent ACT

Domains pertaining to strength of evidence				
Risk of bias	**Consistency**	**Directness**	**Precision**	**Strength-of-evidence grade**
		Overall survival		
Low	Consistent	Direct	Imprecise	Moderate
		Event-free survival		
Low	Consistent	Direct	Imprecise	Moderate
		Adverse events		
Low	Consistent	Direct	Imprecise	Moderate

Sequential AC-T vs AC

Domains pertaining to strength of evidence				
Risk of bias	**Consistency**	**Directness**	**Precision**	**Strength-of-evidence grade**
		Overall survival		
Low	Consistent	Direct	Precise	High
		Event-free survival		
Low	Consistent	Direct	Precise	High
		Overall unacceptable adverse events		
Low	Consistent	Direct	Imprecise	Moderate

Sequential AC-T vs CMF

Domains pertaining to strength of evidence				
Risk of bias	**Consistency**	**Directness**	**Precision**	**Strength-of-evidence grade**
		Overall survival		
Low	Consistent	Indirect	Precise	Moderate
		Event-free survival		
Low	Consistent	Indirect	Precise	Moderate
		Overall unacceptable adverse events		
Low	Consistent	Indirect	Precise	Moderate

Sequential AC-T vs No adjuvant chemotherapy

Domains pertaining to strength of evidence				
Risk of bias	**Consistency**	**Directness**	**Precision**	**Strength-of-evidence grade**
		Overall survival		
Low	Consistent	Indirect	Precise	Moderate
		Event-free survival		
Low	Consistent	Indirect	Precise	Moderate
		Overall unacceptable adverse events		
Low	Consistent	Indirect	Imprecise	Low

Sequential AC-T vs Platinum-containing regimen

Domains pertaining to strength of evidence				
Risk of bias	**Consistency**	**Directness**	**Precision**	**Strength-of-evidence grade**
		Overall survival		
Low	Consistent	Indirect	Imprecise	Low
		Event-free survival		
Low	Consistent	Indirect	Imprecise	Low
		Overall unacceptable adverse events		
Low	Consistent	Indirect	Imprecise	Low

Sequential AC-T vs TC

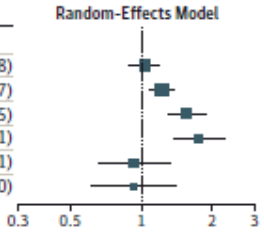
Domains pertaining to strength of evidence				
Risk of bias	**Consistency**	**Directness**	**Precision**	**Strength-of-evidence grade**
		Overall survival		
Low	Consistent	Indirect	Imprecise	Low
		Event-free survival		
Low	Consistent	Indirect	Imprecise	Low
		Overall unacceptable adverse events		
Low	Consistent	Indirect	Imprecise	Low

Studienergebnisse:

Figure 2. Survival Outcomes

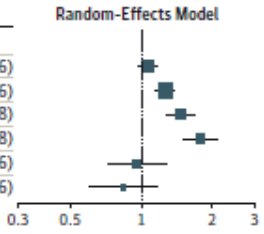
A Overall survival

Regimen	HR (95% CI)
AC-T	1.00
ACT	1.03 (0.90-1.18)
Anthracycline alone	1.22 (1.10-1.37)
CMF	1.56 (1.32-1.85)
No adjuvant chemotherapy	1.76 (1.40-2.21)
Platinum-containing regimens	0.93 (0.66-1.31)
TC	0.93 (0.62-1.40)



B Event-free survival

Regimen	HR (95% CI)
AC-T	1.00
ACT	1.06 (0.97-1.16)
Anthracycline alone	1.26 (1.16-1.36)
CMF	1.47 (1.28-1.68)
No adjuvant chemotherapy	1.78 (1.53-2.08)
Platinum-containing regimens	0.96 (0.73-1.26)
TC	0.84 (0.61-1.16)



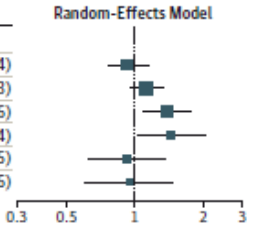
AC-T indicates sequential anthracycline-cyclophosphamide and taxane; ACT, concurrent anthracycline-cyclophosphamide and taxane; CMF, cyclophosphamide, methotrexate, and fluorouracil; TC, docetaxel and cyclophosphamide.

To test the effect of hormone receptor status on OS, we performed meta-regression analysis adjusting for the percentage of hormone receptor–positive patients in each study. Hazard ratios with this adjustment were similar to those without the adjustment, and the order of HRs remained unchanged (Figure 3A).

Figure 3. Meta-regression Analysis With Adjustment for Hormone Receptor Status for Survival Outcomes

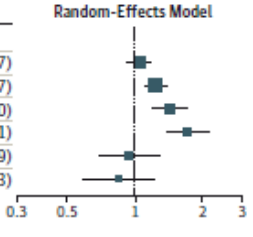
A Overall survival

Regimen	HR (95% CI)
AC-T	1.00
ACT	0.93 (0.77-1.14)
Anthracycline alone	1.13 (0.97-1.33)
CMF	1.39 (1.10-1.76)
No adjuvant chemotherapy	1.45 (1.03-2.04)
Platinum-containing regimens	0.93 (0.63-1.35)
TC	0.95 (0.60-1.46)



B Event-free survival

Regimen	HR (95% CI)
AC-T	1.00
ACT	1.05 (0.94-1.17)
Anthracycline alone	1.24 (1.12-1.37)
CMF	1.43 (1.20-1.70)
No adjuvant chemotherapy	1.71 (1.40-2.11)
Platinum-containing regimens	0.95 (0.70-1.29)
TC	0.86 (0.59-1.23)

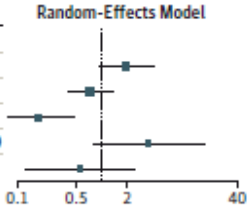


AC-T indicates sequential anthracycline-cyclophosphamide and taxane; ACT, concurrent anthracycline-cyclophosphamide and taxane; CMF, cyclophosphamide, methotrexate, and fluorouracil; TC, docetaxel and cyclophosphamide.

Figure 4. Adverse Events

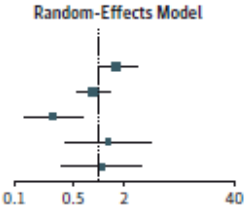
A Overall unacceptable AEs

Regimen	OR (95% CI)
AC-T	1.00
ACT	1.95 (0.97-3.93)
Anthracycline alone	0.73 (0.41-1.32)
CMF	0.18 (0.07-0.48)
Platinum-containing regimens	3.55 (0.80-15.71)
TC	0.56 (0.13-2.35)



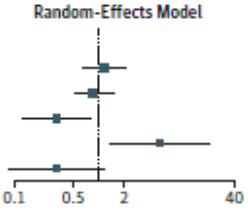
B Hematologic unacceptable AEs

Regimen	OR (95% CI)
AC-T	1.00
ACT	1.65 (0.99-2.74)
Anthracycline alone	0.88 (0.57-1.35)
CMF	0.29 (0.14-0.63)
Platinum-containing regimens	1.30 (0.42-4.07)
TC	1.08 (0.37-3.17)



C Nonhematologic unacceptable AEs

Regimen	OR (95% CI)
AC-T	1.00
ACT	1.17 (0.65-2.10)
Anthracycline alone	0.88 (0.53-1.46)
CMF	0.32 (0.13-0.78)
Platinum-containing regimens	5.17 (1.36-19.67)
TC	0.32 (0.09-1.12)



AC-T indicates sequential anthracycline-cyclophosphamide and taxane; ACT, concurrent anthracycline-cyclophosphamide and taxane; AE, adverse events; CMF, cyclophosphamide, methotrexate, and fluorouracil; TC, docetaxel and cyclophosphamid

Anmerkung/Fazit der Autoren

- Docetaxel and cyclophosphamide and platinum-containing regimens had overall survival benefit similar to that of sequential anthracycline-cyclophosphamide and taxane (AC-T).
- Patients treated with cyclophosphamide, methotrexate, and fluorouracil or anthracycline-cyclophosphamide without taxane had significantly worse overall survival than those treated with sequential AC-T.
- Platinum-containing regimens tended to be more toxic than sequential AC-T.
- The toxicity of docetaxel and cyclophosphamide was similar to or less than that of sequential AC-T.

Kommentare zum Review

Die methodische Güte der NMA ist nicht abschließend beurteilbar. Es handelt sich ohnehin um indirekte Vergleiche, die gegenüber direkten Vergleiche ein höheres Verzerrungspotezial aufweisen. Deshalb sind die Ergebnisse auch der direkten Vergleiche dargestellt.

Picot J et al., 2015 [39].

The INTRABEAM(R) Photon Radiotherapy System for the adjuvant treatment of early breast cancer: a systematic review and economic evaluation

Fragestellung

To assess the clinical effectiveness and cost-effectiveness of INTRABEAM for the adjuvant treatment of early breast cancer during surgical removal of the tumour.

Methodik

Population:

- people with early operable breast cancer; people with a local recurrence were excluded.
- For the systematic review of health-related quality of life (HRQoL), the population was not limited to early-stage breast cancer.

Intervention:

- The INTRABEAM patients received a typical dose of 20 Gy to the surface of the tumour bed (attenuating to 5–7 Gy at a 1 cm depth).

Komparator:

External beam radiotherapy patients received a typical dose of 40–56 Gy with/without an additional boost to the tumour bed of 10–16 Gy. Trial centres were allowed to stipulate local policy for the delivery of WB-EBRT and, therefore, there would have been some differences between WB-EBRT delivered at different centres. It is presumed that, in UK centres, 40 Gy in 15 fractions would have been the likely treatment schedule, whereas in some other centres local policy was an alternative schedule, for example 56 Gy in 28 fractions

Endpunkte:

- Local recurrance,
- OS,
- complications

Recherche/Suchzeitraum:

Electronic bibliographic databases, including MEDLINE, EMBASE and The Cochrane Library,

were searched from inception to March 2014 for English-language articles. Bibliographies of articles, systematic reviews, clinical guidelines and the manufacturer’s submission were also searched. The advisory group was contacted to identify additional evidence.

Qualitätsbewertung der Studien:

criteria devised by the Cochrane Collaboration

Ergebnisse

Anzahl eingeschlossener Studien:

One non-inferiority RCT, the TARGeted Intraoperative radioTherapy Alone (TARGIT-A) trial, which evaluated whether or not INTRABEAM treatment was no worse than WB-EBRT, met the inclusion criteria.

Charakteristika der Population:

Results were reported for the whole trial population (n = 3451) and separately for the pre-pathology stratum (n = 2298 randomisation to INTRABEAM or WB-EBRT prior to WLE of the primary tumour) and the post-pathology stratum (n = 1153 randomisation after initial surgery to either INTRABEAM as a second procedure or WB-EBRT). Median follow-up was 2 years 5 months, with 35% of participants achieving median follow-up of 5 years.

Qualität der Studien:

low risk of bias

Studienergebnisse:

- Local recurrence

  Local recurrence in the conserved breast (primary outcome) for the whole trial population was higher in the INTRABEAM group than in the WB-EBRT group (3.3% vs. 1.3%); however, the absolute difference in 5-year risk of local recurrence did not exceed the 2.5% non-inferiority margin. A similar result was observed for the pre-pathology stratum. In the post-pathology stratum, the non-inferiority margin was exceeded and non-inferiority was not established.

- Overall survival

  Overall survival (secondary outcome) for the whole trial population did not differ statistically significantly between INTRABEAM and WB-EBRT arms (3.9%vs. 5.3%; p = 0.099). Rates of breast cancer deaths were similar but there were significantly fewer non-breast cancer deaths in the INTRABEAM group than in the WB-EBRT group. In the pre-pathology stratum, lower overall mortality was observed in the INTRABEAM group because there were significantly fewer non-breast cancer deaths. In the post-pathology stratum, overall mortality, breast cancer mortality and non-breast cancer mortality were similar between treatment groups.

- Complications

  Wound seroma requiring more than three aspirations occurred more frequently in the INTRABEAM group (2.1% vs. 0.8%; p = 0.012), whereas a Radiation Therapy Oncology Group toxicity score of grade 3 or 4 was less frequent in the INTRABEAM group (0.5% vs. 2.1%; p = 0.002). These were the only statistically significant differences in complications.

  Health-related quality-of-life substudy

  One small single-centre substudy (n = 88) did not identify any statistically significant differences in QoL measures between the study arms.

Anmerkung/Fazit der Autoren

A significant investment in INTRABEAM equipment and staff training (clinical and non-clinical) would be required to make this technology available across the NHS. Longer-term follow-up data from the TARGIT-A trial and analysis of registry data are required as results are currently based on a small number of events and economic modelling results are uncertain

Limitations: The base-case result from the model is subject to uncertainty because the disease progression parameters are largely drawn from the single available RCT. The RCT median follow-up of 2 years 5 months may be inadequate, particularly as the number of participants with local recurrence is low. The model is particularly sensitive to this parameter.

Hicks M et al., 2015 [30].

Neoadjuvant Dual HER2-Targeted TherapyWith Lapatinib and Trastuzumab Improves Pathologic CompleteResponse in Patients With Early Stage HER2-Positive Breast Cancer: AMeta-Analysis of Randomized Prospective Clinical Trials

Fragestellung

Randomized clinical trials (RCT) that evaluated the addition of lapatinib to trastuzumab plus neoadjuvant chemotherapy (NAC) in patients with HER2-positive, operable breast cancer revealed a questionable improvement in pathologic complete response (pCR) rate. We performed a metaanalysis of prospective RCTs that examined the effect of adding lapatinib to trastuzumab and NAC on pCR rate.

Methodik

Population:

HER2+ operable breast cancer

Intervention:

NAC (neoadjuvant chemotherapy NAC) with trastuzumab

Komparator:

NAC with trastuzumab and lapatinib

Endpunkte:

- The primary objective of our study was to compare the rates of pCR following NAC plus trastuzumab with or without lapatinib. Treatment with lapatinib alone was excluded from the analysis because of toxicities and sufficient evidence that single-agent lapatinib plus NAC has inferior efficacy compared with NAC with trastuzumab or with trastuzumab and lapatinib [4–6].
- The definition of pCR varied among studies. Some studies defined pCR as no invasive disease in breast alone, whereas others defined pCR as no residual invasive disease in both breast and axillary lymph nodes. For the purpose of our analysis, we used pCRin the breast and lymphnodesas our primary endpoint and the definition of no invasive breast cancer in the breast as a secondary endpoint. As a subgroup analysis, we examined the difference in pCR rates for patients with HR1versus HR2 breast cancer.

Recherche/Suchzeitraum:

- PubMed citationswere reviewed from January 1998 to January 2014.
- Abstracts from the San Antonio Breast Cancer Symposium and the American SocietyofClinicalOncology annualmeetings between 2009 and 2014 were also queried. Subsequently, studies were reviewed for eligibility

Qualitätsbewertung der Studien:

Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

5 (n=1017)

Charakteristika der Population:

A total of 767 patients (n 5 384 in the lapatinib plus trastuzumab arm and n5383 in the trastuzumab arm) from 4 studies [4, 6, 24, 25] were analyzed for the effect of adding lapatinib to trastuzumab plus NAC on pCR rate in both breast and axillary lymph nodes.

Table 1. Characteristics of the randomized controlled trials included in the meta-analysis

Trial	Phase	Chemotherapy backbone	Duration (weeks)	Anthracycline containing	Arm	Participants enrolled (*n*)	Participants for analysis (*n*)	Quality of study[a]
Carey et al., 2013 [5] (CALGB 40601)[b]	III	P (80 mg/m^2)	16	No	Trastuzumab, 4 mg/kg loading, then 2 mg/kg	120	120	1
					Lapatinib plus trastuzumab, 750 mg/day	118	118	
					Lapatinib, 1,500 mg/day	67	67	
Robidoux et al., 2013 [6] (NSABP B-41)	III	AC (60 mg/m^2, 600 mg/m^2); P (80 mg/m^2)	4 cycles chemotherapy, then 4 cycles P and AHT	Yes	Trastuzumab, 4 mg/kg loading, then 2 mg/kg	181	177[c]	3
					Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day[d]	174	171	
					Lapatinib, 1,500 mg/day, then 1,250 mg/day	174	171	
Guarneri et al., 2008 [25] (CHERLOB)[e]	II	P (80 mg/m^2), then FEC (600 mg/m^2, 75 mg/m^2, and 600 mg/m^2)	12 weeks, then 4 courses	Yes	Trastuzumab, 4 mg/kg loading, then 2 mg/kg	36	36[f]	2
					Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day	46	45	
					Lapatinib, 1,500 mg/day, then 1,250 mg/day	39	38	
Baselga et al., 2012 [4] (NeoALTTO)[g]	III	P (80 mg/m^2)	6-week run-in, then 12 weeks AHT and P	No	Trastuzumab, 4 mg/kg loading, then 2 mg/kg	149	149	3
					Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day	152	152	
					Lapatinib, 1,500 mg/day	154	154	
Holmes et al., 2013[h] [24]	II	FEC75 (500 mg/m^2, 75 mg/m^2, 500 mg/m^2), then P (80 mg/m^2)	AHT 2-week run-in, then with 4 courses, then P 12 courses	Yes	Trastuzumab, 4 mg/kg loading, then 2 mg/kg	33	26[i]	3
					Lapatinib plus trastuzumab, 1,000 mg/day, then 750 mg/day	33	23	
					Lapatinib, 1,500 mg/day, then 1,250 mg/day	34	29	

[a]Study quality was assessed on the 7-item Jadad score, with a score range of 0–5 [9].
[b]The lapatinib arm was closed when negative efficacy and toxicity data emerged from preliminary analysis of ALTTO.
[c]Patients analyzed differed from intent to treat because they either withdrew consent from the study or did not have surgery.
[d]On June 10, 2008, the starting dose of lapatinib was reduced to 1,250 mg in the lapatinib group and 750 mg in the combination group because of the excessive diarrhea reported in other trials using the initial doses.
[e]Lapatinib doses were reduced because of the occurrence of grade 2 diarrhea in 20% of patients in the lapatinib-alone group and 41% of patients in the combination group.
[f]Patients analyzed differed from intent to treat because of protocol violations or they withdrew consent.
[g]Lapatinib dose was reduced from 1,000 to 750 mg when P was added to reduce the occurrence of diarrhea.
[h]Lapatinib dose was reduced to reduce diarrhea after a safety review of the first 45 patients enrolled.
[i]Patients analyzed differed from the intention-to-treat population because of selection of patients who received surgery and >75% chemotherapy.
Abbreviations: AC, doxorubicin and cyclophosphamide; AHT, anti-HER2 therapy; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide; P, weekly paclitaxel.

Qualität der Studien:

- Siehe Tab. 1, Charakteristik der Studie
- All trials included in this meta-analysis were randomized, multicenter, open-label, phase II/III trials.

Studienergebnisse:

- pCR

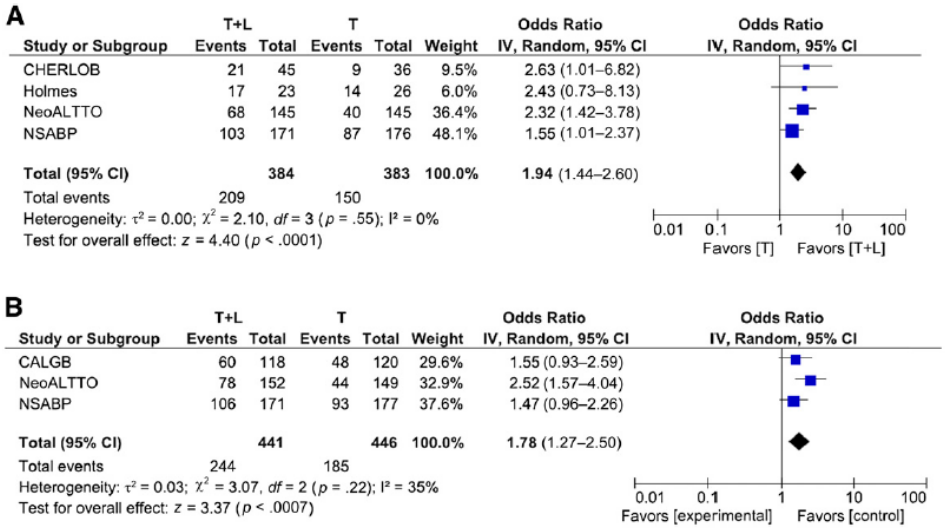


Figure 2. Forest plots for pooled odds ratio and the corresponding 95% CIs of incidence of pathologic complete response rates defined as no invasive disease in the breast and lymph nodes (A) or no invasive disease in the breast only (B).

Abbreviations: CI, confidence interval; IV, inverse variance; L, lapatinib; T, trastuzumab; T1L, trastuzumab plus lapatinib.

Table 2. Incidence and odds ratios of pCR stratified by definition of pCR and hormonal status

		Dual therapy (lapatinib and trastuzumab plus chemotherapy)				Control arm (trastuzumab plus chemotherapy)				Overall	
Treatment	Number of trials	Patients achieved pCR (*n*)	Total patients (*N*)	pCR (%)	95% CI	Patients achieved pCR (*n*)	Total patients (*N*)	pCR (%)	95% CI	OR	95% CI
Definition of pCR[a]											
Breast and lymph nodes	4 [4, 6, 24, 25]	209	384	55.76	45.19–66.33	150	383	38.36	23.85–52.88	1.94	1.44–2.60
Breast only	3 [4–6]	244	441	55.01	47.55–62.46	185	446	40.70	26.87–54.53	1.78	1.27–2.50
Hormonal status											
Hormone receptor positive	2[b] [4, 6]	92	185	48.87	35.16–62.57	74	197	34.76	11.18–58.33	1.76	1.06–2.93
Hormone receptor negative	2[b] [4, 6]	92	138	67.19	55.74–78.64	63	129	50.80	22.42–79.19	2.06	1.08–3.91

The *p* value for the OR and heterogeneity tests are as follows: breast and lymph nodes, $p \leq .001$ ($p = .55$; $I^2 = 0\%$); breast only, $p = .0007$ ($p = .22$; $I^2 = 35\%$); hormone receptor-positive subgroup, $p = .03$ ($p = .23$: $I^2 = 29\%$); hormone receptor-negative subgroup, $p = .03$ ($p = .21$: $I^2 = 37\%$). There was no difference of effect of the dual therapy between hormone receptor-positive and -negative subgroups ($p = .71$).

[a]One study [5] reported breast-only pCR, two studies [24, 25] reported only breast and lymph node pCR, and two studies [4, 6] reported both breast-only and breast and lymph node pCR rate.

[b]Hormone receptor status was subcategorized in the breast-only definition of pCR. *Breast only* indicates no invasive disease remaining in the breast. *Breast and lymph nodes* indicates no remaining invasive disease in breast or lymph nodes.

Abbreviations: CI, confidence interval; OR, odds ratio; pCR, pathologic complete response.

Anmerkung/Fazit der Autoren

Patients with early stage HER21 breast cancer have a statistically significant increase in the odds of achieving pCRwith the addition of lapatinib to trastuzumab and NAC. This result is

clinically relevant as the oncology community continues to learn more about the impact of pCR on recurrence and breast cancer-related death. Although lapatinib combined with trastuzumab may be an important treatment strategy, the increase in toxicity [26] should be weighed against the potential overall benefit. Long-term breast cancer recurrence data from these large randomized studies will be crucial to understanding the impact of this combination on breast cancer-related mortality

Kommentare zum Review

Die Suche nach Primärstudien fand (nahezu) allein in PubMed statt.

Sun J et al., 2015 [43].

Lapatinib combined with neoadjuvant paclitaxel‐trastuzumab‐based chemotherapy in patients with human epidermal growth factor receptor 2‐positive breast cancer: A meta‐analysis of randomized controlled trials

Fragestellung

The purpose of the present study was to quantify the cumulative randomized evidence for the efficacy and safety of lapatinib combined with neoadjuvant therapy in human epidermal growth factor receptor (HER) 2‐positive breast cancer.

Methodik

Population:

(HER) 2‐positive breast cancer

Intervention:

trastuzumab‐based chemotherapy

Komparator:

- neoadjuvant chemotherapy using a combination of agents including lapatinib
- All cytotoxic chemotherapy regimens were considered eligible for the present meta‐analysis if the same chemotherapy agents were administered at the same dose in all treatment arms and that the arms differed systematically only in the anti‐HER2 therapy administered.

Endpunkte:

- pathological complete response (pCR) rate,
- breast‐conserving surgery (BCS) rate
- occurrence of adverse events

Recherche/Suchzeitraum:

Three electronic databases, MEDLINE, Embase and Cochrane Central Register of Controlled Trials, and the abstracts of major international conferences between inception and 15 December 2013 were searched.

Qualitätsbewertung der Studien:

- Cochrane's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

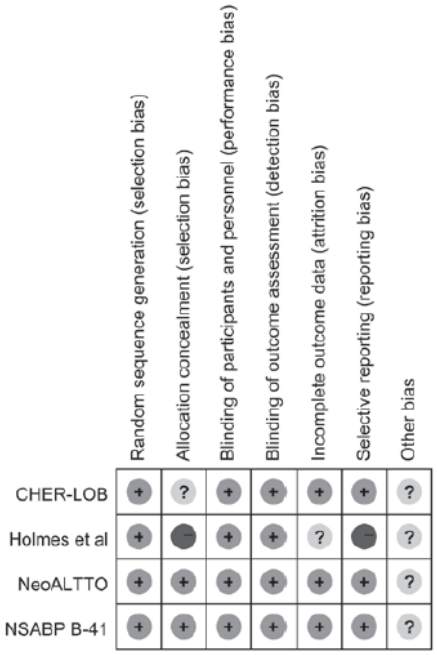
4 (n=779)

Table I. Characteristics of eligible trials.

Clinical trial (reference)	Total number of patients, n	HER2 status assessment	Number of patients analyzed, n	Treatment arm	Number of patients per arm, n	HR-positive tumors, n (%)	Neoadjuvant chemotherapy	Neoadjuvant anti-HER2 therapy	Duration of anti-HER2 therapy, weeks
CHER-LOB (9)	121	IHC3+ or FISH amplification	82	No Lap	36	21 (58)	P weekly → 4 x FEC	T 4→2 mg/kg weekly	26
				Lap	46	28 (62)	P weekly → 4 x FEC	Lap 1000 mg daily + T 2 mg/kg weekly	26
Holmes *et al* (10)	100	IHC3+ or FISH ratio >2.2	66	No Lap	33	15 (45)	4 x FEC → P weekly	T 4→2 mg/kg weekly	26
				Lap	33	20 (61)	4 x FEC → P weekly	Lap 750 mg daily + T 2 mg/kg weekly	26
NeoALTTO (11)	455	IHC3+ or FISH amplification	301	No Lap	149	75 (50)	P weekly	T 4→2 mg/kg weekly	18
				Lap	152	77 (51)	P weekly	Lap 1000 mg daily + T 2 mg/kg weekly	18
NSABP B-41 (12)	529	IHC3+, FISH or CISH amplification	355	No Lap	181	122 (67)	4 x AC → P weekly	T 4→2 mg/kg weekly	16
				Lap	174	108 (62)	4 x AC → P weekly	Lap 750 mg daily + T 2 mg/kg weekly	16

CHER-LOB, chemotherapy, Herceptin and lapatinib in operable breast cancer; NeoALTTO, Neo-adjuvant Lapatinib and/or Trastuzumab Treatment Organisation; NSABP, National Surgical Adjuvant Breast and Bowel Project. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescent *in situ* hybridization; CISH, chromogenic *in situ* hybridisation; HR, hormone receptor; P, paclitaxel; Lap, lapatinib; T, trastuzumab; FEC, fluorouracil-epirubicine-cyclophosphamide; AC, adriamycin-cyclophosphamide; 4 x, four cycles; →, followed.

Qualität der Studien:

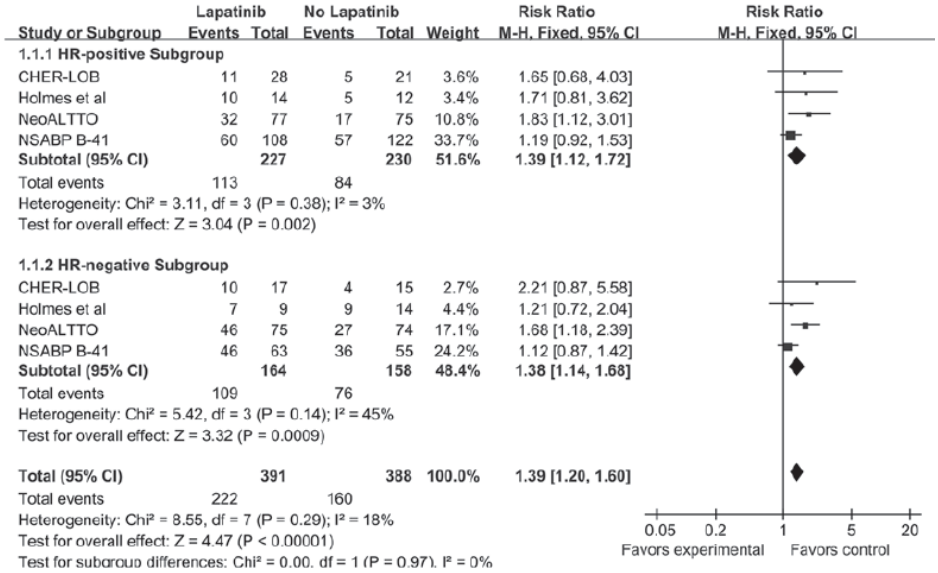


Studienergebnisse:

- pCR

  Compared with the patients who did not receive lapatinib, the pCR rate was higher in the hormone receptor (HR)‑positive [risk ratio (RR), 1.39; 95% confidence interval (CI), 1.12‑1.72; P=0.002) and HR‑negative (RR, 1.38; 95% CI, 1.14‑1.68; P=0.0009) patients that received lapatinib.

  Figure 5. Forest plot of pathological complete response. The pathological complete response rate was significantly higher in the lapatinib group compared with the no lapatinib group for HR‑positive and -negative patients. M‑H, Mantel‑Haenszel; CI, confidence interval; HR, hormone receptor; CHER‑LOB, chemotherapy, Herceptin and lapatinib in operable breast cancer; NeoALTTO, Neo‑adjuvant Lapatinib and/or Trastuzumab Treatment Organisation; NSABP, National Surgical Adjuvant Breast and Bowel Project.



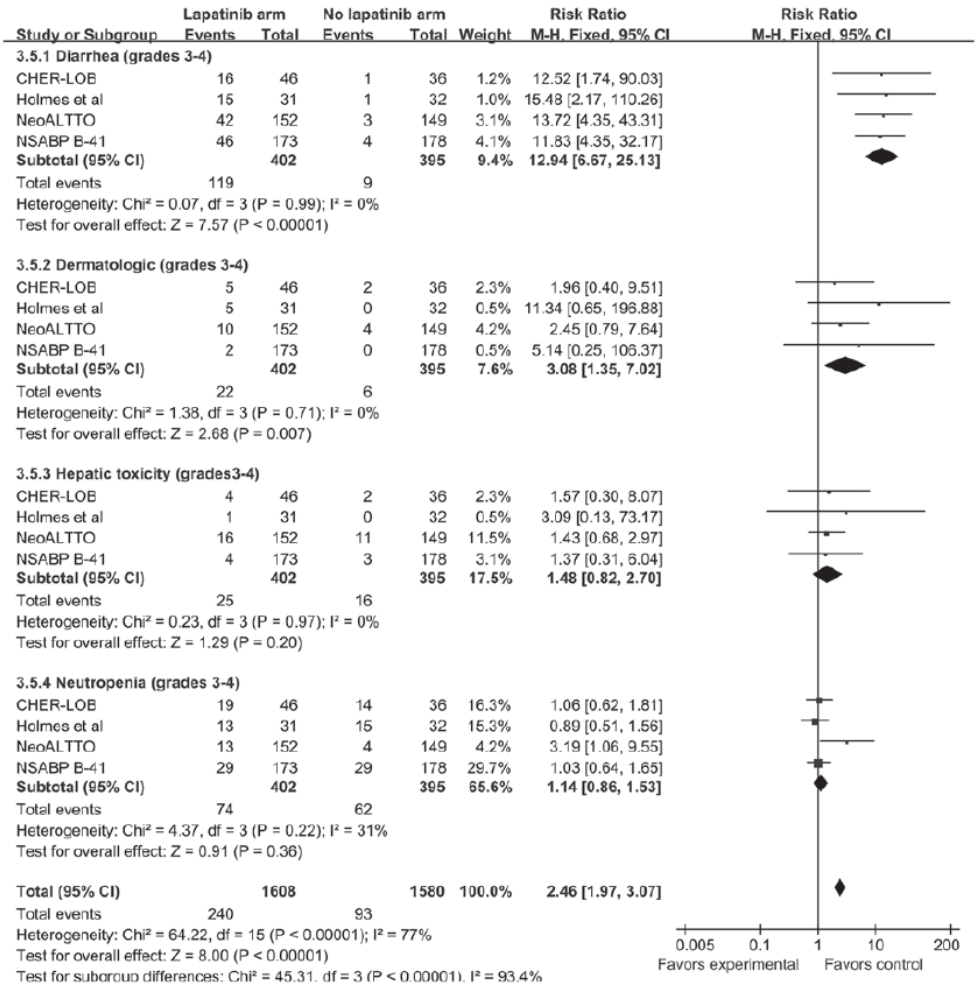
- No significant difference between the BCS rate of the two treatment arms was observed in two trials (n=382; RR, 1.14; 95% CI, 0.89‑1.47; P=0.31). The primary adverse events, including diarrhea, dermatological toxicity, hepatic toxicity and neutropenia, were statistically more frequent in patients that received lapatinib (RR, 2.46; 95% CI, 1.97‑3.07; P<0.00001).
- AE

Table II. Pooled analysis of other adverse events.

Adverse event	Number of trials	Events, n/total number of patients		RR	95% CI	P-value	I^2, %
		L arm	No L arm				
Vomiting, grades 3-4	3	17/250	6/246	2.56	1.06-6.15	0.04	0
Fatigue, grades 3-4	3	14/250	12/246	1.12	0.54-2.36	0.76	0
Sensory neuropathy, grades 3-4	3	11/250	6/246	1.82	0.71-4.67	0.21	0
Mucositis, grades 3-4	2	3/219	2/214	1.31	0.27-6.24	0.74	31
Febrile neutropenia	3	14/250	11/246	1.28	0.60-2.75	0.52	0
Dyspnoea	2	17/204	18/210	0.97	0.52-1.83	0.93	40
Nausea, grades 3-4	2	9/204	2/210	3.91	0.99-15.53	0.05	0
Dehydration	2	10/204	6/210	1.66	0.64-4.34	0.30	0
CHF	3	2/341	7/326	0.50	0.03-9.48	0.65	59
LVEF decline[a]	3	1/341	2/326	0.53	0.07-3.85	0.53	0

[a]LVEF <50% or decline >10% from baseline. L, lapatinib; RR, risk ratio; CI, confidence interval; CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

Figure 6. Forest plot of primary adverse events (grades 3‑4). The primary adverse were statistically more frequent in patients that received lapatinib. M‑H, Mantel‑Haenszel; CI, confidence interval; HR, hormone receptor; CHER‑LOB, chemotherapy, Herceptin and lapatinib in operable breast cancer; NeoALTTO, Neo‑adjuvant Lapatinib and/or Trastuzumab Treatment Organisation; NSABP, National Surgical Adjuvant Breast and Bowel Project



Anmerkung/Fazit der Autoren

The present analysis revealed that the addition of lapatinib to neoadjuvant chemotherapy for HER2‑ positive breast cancer improves the probability of achieving a higher pCR rate, but the use of lapatinib is associated with a higher risk of adverse events.

Kommentare zum Review

Die Vergleichsarme schlossen unterschiedliche Wirkstoffe bzw. Wirkstoffkombinationen ein. (administration of trastuzumab with the administration of lapatinib or a combination of the two for neoadjuvant chemotherapy, with all regimens including paclitaxel in the regimen.

Kong L et al, 2014 [32].

Efficacy and Safety of Accelerated Partial Breast Irradiation after Breast-conserving Surgery: A Meta-analysis of Published Comparative Studies

Fragestellung

To compare the treatment outcomes between accelerated partial breast irradiation (APBI) and conventional whole-breast irradiation (WBI) and to explore the efficacy and safety of APBI as an adjuvant treatment for early stage breast cancer who received breast-conserving therapy.

Methodik

Population:

- early stage breast cancer who received breast-conserving therapy

Intervention:

partial breast irradiation (APBI)

Komparator:

conventional whole-breast irradiation (WBI)

Endpunkte:

- The primary outcome of interest was LR, which was defined as a recurrence of tumor within the treated area or new tumor occurring outside the treated area in the same breast.
- Secondary outcomes were axillary failure (AF), supraclavicular failure (SF), distant metastasis (DM), overall survival (OS), and disease-free survival (DFS). AF and SF were, respectively, defined as the failure within the axillary and supraclavicular lymphatics; DM was determined by a combination of clinical, radiographic, and pathologic factors; OS was defined as time from the start of radiotherapy to death from any cause; DFS was defined as survival without a LR, regional failure, or DM.

Recherche/Suchzeitraum:

Eligible studies were identified on Medline, Embase, and the Cochrane Library updated to July 10, 2012.

Qualitätsbewertung der Studien:

Cochrane handbook 5.0.2.

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 (n= 7097)

Charakteristika der Population:

Table 1. Study Characteristics

Study (year)	Follow-up (year)	Design	Group	No	Irradiation technique	Irradiation dose and fraction	Study quality	Age	Tumor size >2 (%)	Margins negative (%)
Ribeiro et al. (1993)	7	RCT	APBI	353	Limited field irradiation	40–42.5 Gy/8 f	Randomization; Allocation concealment; Described reasons for withdrawal	53	35.6	Unclear
			WBI	355	Wide field irradiation	40 Gy/15 f				
King et al. (2000)	6.25	Retrospective cohort	APBI	51	MIB	LDR: 45 Gy/4 days; HDR: 32 Gy/4 days	8*	59	13.1	100
			WBI	94	External beam radiation	Not mentioned				
Polgar et al. (2004)	7	Prospective cohort	APBI	45	MIB	30.3 or 36.4 Gy/7f	7*	57	0	100
			WBI	80	External beam radiation	Whole breast: 50 Gy/25f; boost: 10–16 Gy electrons or 14.25 Gy/3f HDR-BT				
Dodwell et al. (2005)	8	RCT	APBI	84	A variety of techniques	55 Gy/20f	Unclear	52	Unclear	100
			WBI	90	External beam radiation	Whole breast: 40 Gy/15f; boost: 15 Gy/5f				
Polgar et al. (2007)	5	RCT	APBI	128	MIB	HDR (n = 88): 36.4 Gy/7f; electron beam irradiation (n = 40): 50 Gy/25f	Randomization; Allocation concealment; Described reasons for withdrawal	59	0	100
			WBI	130	External beam radiation	Telecobalt (n = 29) or 6–9-MV photon (n = 100) beams: 50 Gy/25f				
Ko et al. (2010)	1.4	Retrospective cohort	APBI	100	MammoSite	34 Gy/10f bid	5*	64	10	100
			WBI	100	External beam radiation	Whole: 42.4/16f, 45–50.4 Gy/25f; boost: 60–66 Gy				
Vaidya et al. (2010)	4	RCT	APBI	1113	Argeted intraoperative radiotherapy	Surface of the tumor bed: 20 Gy; 1 cm depth: 5–7 Gy	Randomization; Allocation concealment; Described reasons for withdrawal	63	13.4	86.8
			WBI	1119	External beam radiation	Whole breast: 40–56 Gy; boost: 10–16 Gy				
Zauls et al. (2012)	4	Prospective cohort	APBI	183	MammoSite	34 Gy	6*	62	12.4	>90, <100
			WBI	276	External beam radiation	Whole breast: 50 Gy/25f; boost: 10 Gy				
Shah et al. (2011)	12	Matched-pair	APBI	199	MIB	Low-dose rate (LDR): 50 Gy/96 hours; HDR: 32 Gy/8f bid or 34 Gy/10f bid	7*	64	10.55	98.5
			WBI	199	Not mentioned	Not mentioned				
Shah et al. (2012)	>5	Matched-pair	APBI	1051	MammoSite	34 Gy/10f bid	6*	65	<10	100
			WBI	1051	External beam radiation	Not mentioned				
Ferraro et al. (2012)	5	Prospective cohort	APBI	202	MIB	34 Gy/10f bid	7*	58	Unclear	100
			WBI	94	External beam radiation	Whole: 42.56/16f, 50.4 Gy/28f; boost: 60 Gy				

RCT, randomized controlled trial; APBI, accelerated partial breast irradiation; WBI, whole-breast irradiation; MIB, multicatheter interstitial brachytherapy; HDR, high-dose rate.
*Judged using the Newcastle–Ottawa Scale (NOS).

Qualität der Studien:

k.A.

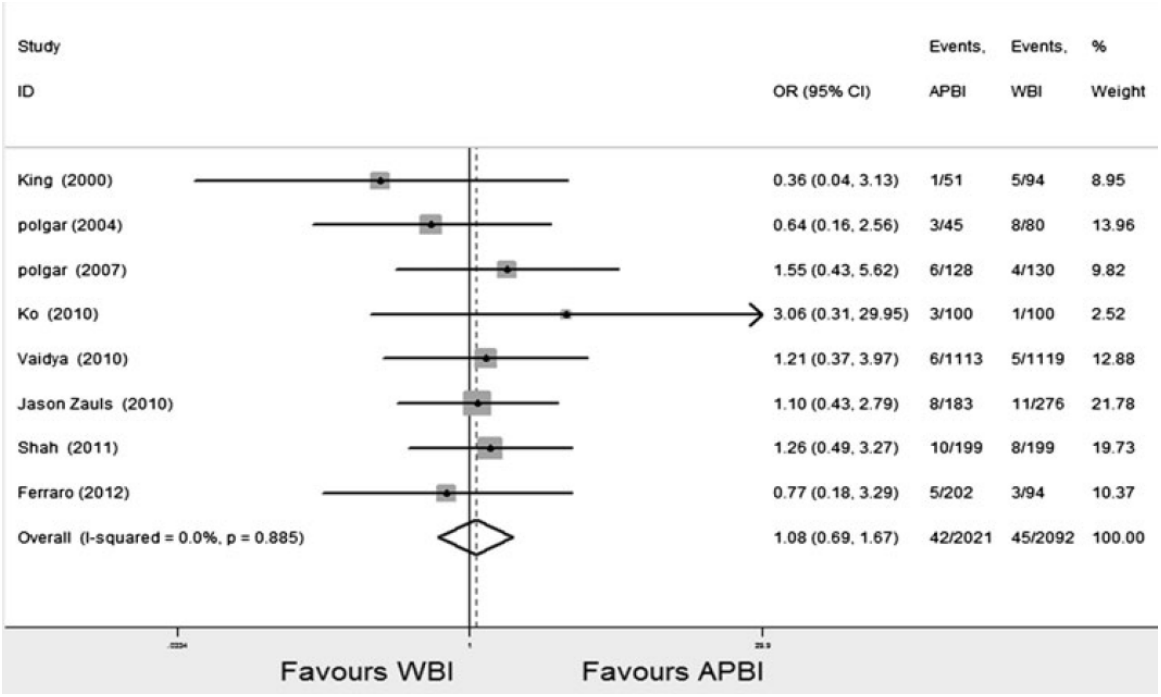
Studienergebnisse:

Table 2. Primary Analysis

	No. of studies	Tests of Homogeneity		Pooled estimate (95% CI)	p-value
		I^2 (%)	p-value		
LR	10	0	0.565	1.54(1.15–2.06)	0.004
AF	5	0	0.878	2.52(1.72–3.68)	0.000
SF	2	0	0.504	1.06(0.55–2.04)	0.853
DM	6	0	0.570	0.70(0.45–1.08)	0.104
OS	8	0	0.509	0.88(0.73–1.06)	0.177
DFS	6	0	0.450	1.10(0.81–1.51)	0.539

LR, local recurrence; AF, axillary failure; SF, supraclavicular failure; DM, distant metastases; OS, overall survival; DFS, disease-free survival.

Figure 4. Forest plot of odds ratios (OR) comparing local recurrence rate for patients who received accelerated partial breast irradiation using the four the four principal techniques with those who received conventional whole-breast irradiation. OR for each trial are represented by the squares, the size of the square represents the weight of the trial in the meta-analysis, and the horizontal line crossing the square represents the 95% confidence interval (CI). The diamonds represent the estimated overall effect based on the meta-analysis fixed effect of all trials.



Anmerkung/Fazit der Autoren

APBI is a safe treatment modality and could become a potential option for the delivery of adjuvant radiation therapy in patients receiving breast-conserving therapy, especially for the suitable group that was classified by the American Society of Radiation Oncology Consensus Panel.

Kommentare zum Review

Of the 11 studies, four studies were RCT, two studies were retrospective cohort study, and five studies were prospective cohort study.

Ye X-P et al., 2013 [48].

Accelerated Partial Breast Irradiation for Breast Cancer: A Meta-Analysis

Fragestellung

To evaluate the long-term effect of breast conservation with accelerated partial breast irradiation (APBI) for early-stage breast cancer

Methodik

Population:

early-stage breast cancer

Intervention:

accelerated partial breast irradiation (APBI)

Komparator:

whole-breast radiotherapy (WBRT)

Planned conventional radiotherapy was 40 to 60 Gy for 5 to 6 weeks.

Endpunkte:

Primary outcomes were response rate of excellent/good cosmetic results, the 5- and 8-year overall survival, the 10-year overall survival, the 5-year LR-free survival, cancer-specific survival, disease-free survival, LR, the rate of contralateral breast cancer and distant metastasis.

Recherche/Suchzeitraum:

PubMed (1966-June 2013), Cochrane Library (Issue 3, 2008), EMBASE (1974-June 2013), Web of Science (1974-June 2013), Chinese Biomedical Literature Database (1978-June 2013), Chinese Scientific Journals Full-text Database (1989-June 2013), and China Journal Full-text Database (1997-June 2013)

Manual searches were done by reviewing articles and abstracts cited in the reference lists of identified RCTs.

Qualitätsbewertung der Studien:

using the following Quality Assess Criteria of RCT: 1) randomized method, 2) allocation concealment, 3) blindness to whether it was adapted, and 4) with or without lost follow-up (if it has been lost to follow-up, whether with analysis in intention to treat)

Ergebnisse

Anzahl eingeschlossener Studien:

4 (n= 919)

Charakteristika der Population:

APBI modalities varied between the trials in terms of study, sample, outcome indexes, as well as quality assessment. Thus, there were no significant differences in main characteristics between groups.

Qualität der Studien:

Table 2. Quality Assessment of Randomized Controlled Trials Included in this Meta-Analysis.

Study (year)	Randomization	Allocated Concealment	Blinding	Loss of Follow-up	Selective Outcome Reporting	Other Potential Threats to Validity
Dodwell DJ et al. (2005)	Unclear	Unclear	Unclear	No	Unclear	Unclear
Polgár C et al. (2007)	Compute	Adequate	Single-blind	No	Unclear	Unclear
Antonucci JV et al. (2009)	Unclear	Unclear	Unclear	No	Unclear	Unclear
Major T. et al. (2004)	Unclear	Unclear	Unclear	No	Unclear	Unclear

Studienergebnisse:

- Overall survival.

  Three trials [17,19,20] reported the 5-, 8-, and 10-year overall survival rate. There were no differences statistically between APBI and WBRT in 5-year overall survival rate [odds ratio (OR) = 1.76 (95% CI = 0.67-4.62), P = .25] and 8-year overall survival rate [OR = 0.86 (95% CI = 0.44-1.66), P = .65], but there was statistical difference in 10-year overall survival rate [OR = 0.56 (95% CI = 0.35-0.91), P = .02].

- LR-free survival.

  Two trials [17,18] reported the 5- and 7-year LR-free survival rate. There were no differences between APBI and WBRT in 5-year LR-free survival rate [OR = 0.65 (95% CI = 0.18-2.34), P = .51] and 7-year LR-free survival rate [OR = 1.33 (95% CI = 0.49-3.62), P = .57].

- Cancer-specific survival.

  Three trials [17–19] reported the 5-, 7-, and 10-year cancer-specific survival rate. There were no differences between APBI and WBRT in 5-year cancer-specific survival rate [OR = 1.67 (95% CI = 0.39-7.12), P = .49], 7-year cancer-specific survival rate [OR = 1.40 (95% CI = 0.29-6.65), P = .67], and 10-year cancer-specific survival rate [OR = 1.43 (95% CI = 0.62-3.30), P = .40].

- Disease-free survival.

  Two trials [17,19] reported the 5- and 10-year disease-free survival rate. There were no differences between APBI and WBRT in 5-year disease-free survival rate [OR = 0.84 (95% CI = 0.38-1.84), P = .66], but there was difference in 10-year disease-free survival rate [OR = 0.63 (95% CI = 0.41-0.99), P = .04].

- The rate of excellent/good cosmetic results.

  Two trials [17,18] reported the 5- and 7-year excellent/good cosmetic rate. There were differences between APBI and WBRT in 5-year excellent/good cosmetic rate [OR = 2.09 (95% CI = 1.21-3.62), P = .009] and 7-year excellent/good cosmetic rate [OR = 3.42 (95% CI = 1.25-9.38), P = .02].

- LR rate.

Two trials [17,18] reported the 5-year LR rate. There were no differences between APBI and WBRT in 5-year LR rate [OR = 1.36 (95% CI = 0.46-3.99), P = .58]. Tests for heterogeneity in the analysis were not statistically significant (P = .70). Two trials [19,20] reported the 8- and 10-year LR rate. There were no differences between APBI and WBRT in 8-year LR rate [OR = 2.91 (95% CI = 0.87-9.65), P = .08] and in 10-year LR rate [OR = 1.26 (95% CI = 0.49-3.27), P = .63].

- The contralateral breast cancer rate.

  Three trials [17–19] reported the 5-, 7-, and 10-year contralateral breast cancer rate. There were no differences between APBI and WBRT in 5-year contralateral breast cancer rate [OR = 2.82 (95% CI = 0.73-10.89), P = .13], in 7-year contralateral breast cancer rate [OR = 0.19 (95% CI = 0.01-4.00), P = .28], and in 10-year contralateral breast cancer rate [OR = 0.48 (95% CI = 0.20-1.15), P = .10].

- Distant metastasis rate.

  Two trials [17,19] reported the 5- and 10-year distant metastasis rate. There were no differences between APBI and WBRT in 5-year distant metastasis rate [OR = 0.71 (95% CI = 0.22-2.31), P = .57] and in 10-year distant metastasis rate [OR = 0.53 (95% CI = 0.24-1.18), P = .12].

- The grade 2 or worse late radiation side effects.

  One trial [18] reported the 7-year grade 2 or worse late radiation side effects. There were no differences between APBI and WBRT in 7-year grade 2 or worse late radiation side effects [OR = 0.47 (95% CI = 0.08-2.68), P = .39] and in 7-year incidence of grades 2 to 3 fibrosis rate [OR = 3.42 (95% CI = 0.86-13.60), P = .08].

[17] Polgár C, Fodor J, Major T, Németh G, Lövey K, Orosz Z, Sulyok Z, Takácsi-Nagy Z, and Kásler M (2007). Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma–5-year results of a randomized trial. Int J Radiat Oncol Biol Phys 69(3), 694–702.

[18] Polgár C, Major T, Fodor J, Németh G, Orosz Z, Sulyok Z, Udvarhelyi N, Somogyi A, Takácsi-Nagy Z, Lövey K, et al. (2004). High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: seven-year results of a comparative study. Int J Radiat Oncol Biol Phys 60(4), 1173–1181.

[19] Antonucci JV, Wallace M, Goldstein NS, Kestin L, Chen P, Benitez P, Dekhne N, Martinez A, and Vicini F (2009). Differences in patterns of failure in patients treated with accelerated partial breast irradiation versus whole-breast irradiation: a matched-pair analysis with 10-year follow-up. Int J Radiat Oncol Biol Phys 74(2), 447–452.

[20] Dodwell DJ, Dyker K, Brown J, Hawkins K, Cohen D, Stead M, and Ash D (2005). A randomised study of whole-breast vs tumour-bed irradiation after local excision and axillary dissection for early breast cancer. Clin Oncol (R Coll Radiol) 17(8), 618–622.

Anmerkung/Fazit der Autoren

APBI significantly improved the rate of excellent/good cosmetic results anywhere in the breast, shortened the treatment time, alleviated the pain, and improved the quality of life. Future large-scale, high-quality, and double-blind trials are needed.

Valachis A et al., 2013 [44].

Cardiac toxicity in breast cancer patients treated with dual HER2 blockade

Fragestellung

Although dual HER2 blockade shows promising results in patients with HER2-positive breast cancer it is unclear whether this treatment strategy increases the risk for cardiac adverse

events. We conducted a meta-analysis of randomized trials to investigate the risk of cardiac adverse events when a combination of anti-HER2 therapies compared to anti-HER2 monotherapy.

Methodik

Population:

Breast cancer

Intervention:

anti-HER2 monotherapy (lapatinib or trastuzumab or pertuzumab)

Komparator:

anti-HER2 combination therapy with or without chemotherapy

Endpunkte:

The following adverse outcomes were considered as cardiac adverse events and were included in the analyses: left ventricular ejection fraction (LVEF) decline less than 50% or a decrease of more than 10% from baseline and congestive heart failure (CHF) grade 3 or higher according to the National Cancer Institute Common Toxicity Criteria (NCICTC version 3).

Recherche/Suchzeitraum:

Our systematic review entailed computer-based searches of Medline, and the Cochrane Library without year and language restrictions, by using algorithms including the following keywords: trastuzumab, pertuzumab, lapatinib, breast cancer. The last search was updated in July 2012.

Qualitätsbewertung der Studien:

Cochrane's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6

Charakteristika der Population:

Table 1. Baseline characteristics of the trials included in the analysis

Trial (ref)	Treatment setting	Treatment arms	Dose of anti-HER2 treatment	Chemotherapy concomitant with anti-HER2 treatment	Duration of anti-Her2 treatment	No of patients (safety analysis)
Blackwell et al.[9]	Metastatic	Lapatinib	1	No	Until progression or unacceptable toxicity	146
		Lapatinib plus trastuzumab	1	No	Until progression or unacceptable toxicity	149
CHER-LOB[10]	Neoadjuvant	Trastuzumab	2 mg/kg weekly (loading 4 mg/kg)	Weekly Pacl => FEC	26 weeks	36
		Lapatinib	1,500 mg daily	Weekly Pacl => FEC	26 weeks	39
		Lapatinib plus trastuzumab	1,000 mg daily + 2 mg/kg weekly (loading 4 mg/kg)	Weekly Pacl => FEC	26 weeks	46
CLEOPATRA[13]	Metastatic	Trastuzumab	6 mg/kg q3w (loading 8 mg/kg)	Docetaxel q3w	Until progression or unacceptable toxicity	397
		Trastuzumab + pertuzumab	6 mg/kg q3w (loading 8 mg/kg) +	Docetaxel q3w	Until progression or unacceptable toxicity	407
NeoALTTO[11]	Neoadjuvant	Trastuzumab	2 mg/kg weekly (loading 4 mg/kg)	Weekly pacl	18 weeks	149
		Lapatinib	1,500 mg daily	Weekly pacl	18 weeks	154
			1,000 mg daily + 2 mg/kg weekly (loading 4 mg/kg)	Weekly pacl	18 weeks	152
NeoSphere[14]	Neoadjuvant	Trastuzumab	6 mg/kg q3w (loading 8 mg/kg)	Docetaxel	12 weeks	107
		Trastuzumab + pertuzumab	6 mg/kg q3w (loading 8 mg/kg) +	Docetaxel	12 weeks	107
		Trastuzumab + pertuzumab	420 mg/kg q3w (loading 840 mg/kg)	No	12 weeks	108
			6 mg/kg q3w (loading 8 mg/kg) +	Docetaxel	12 weeks	94
			420 mg/kg q3w (loading 840 mg/kg)			
			420 mg/kg q3w (loading 840 mg/kg)			
NSABP B-41[12]	Neoadjuvant	Trastuzumab	2 mg/kg weekly (loading 4 mg/kg)	Weekly pacl	12 weeks	178
		Lapatinib	1,250 mg daily	Weekly pacl	12 weeks	173
		Lapatinib plus trastuzumab	750 mg daily + 2 mg/kg weekly (loading 4 mg/kg)	Weekly pacl	12 weeks	173

Abbreviations: ref, reference; No, number; mg, milligram; kg, kilogram; Pacl, Paclitaxel; FEC, Fluorouracil (5FU), epirubicin and cyclophosphamide; q3w, three-weekly.

Qualität der Studien:

One trial has only been presented in abstract form to date, but we had access to all presentation slides from the ASCO Annual Meeting.12 Thus, we were not able to assess the methodological quality of this trial. Among the remaining five trials, four reported an adequate randomization mode and allocation concealment,10,11,13,14 while two clearly reported blinding of outcome assessment.11,13 In addition, only one trial reported that it was designed as a double-blind

trial.13

Studienergebnisse:

Overall incidence results for CHF in the combined anti-HER2 therapy and the anti-HER2 monotherapy were 0.88% (95% CI: 0.47–1.64%) and 1.49% (95% CI: 0.98–2.23%). The incidence of LVEF decline was 3.1% (95% CI: 2.2–4.4%) and 2.9% (95% CI: 2.1–4.1%), respectively. The OR of CHF between anti-HER2 combination and monotherapy was 0.58 (95% CI: 0.26–1.27, p-value5 0.17) while the OR of LVEF decline was 0.88 (95% CI: 0.53–1.48, p-value5 0.64).

Table 3. Subgroup analyses of risk for CHF and LVEF decline from dual anti-HER2 treatment

		Dual anti-HER2 treatment		Monotherapy		
Subgroup	No of trials	CHF	Total	CHF	Total	OR (95% CI), p-value
Treatment setting						
Neoadjuvant	4	2	478	14	930	0.74 (0.02–29.54)
Metastatic	2	7	556	8	543	0.85 (0.31–2.37)
Type of anti-HER2 therapy						
Trastuzumab *vs.* trastuzumab + lapatinib	3	2	371	7	363	0.33 (0.08–1.41)
Lapatinib *vs.* trastuzumab + lapatinib	4	5	520	8	509	0.64 (0.22–1.88)
		LVEF decline	Total	LVEF decline	Total	
Treatment setting						
Neoadjuvant	4	4	305	5	579	1.52 (0.44–5.32)
Metastatic	2	23	556	28	543	1.11 (0.24–5.02)
Type of anti-HER2 therapy						
Trastuzumab *vs.* trastuzumab + lapatinib	2	1	198	2	185	0.53 (0.07–3.98)
Lapatinib *vs.* trastuzumab + lapatinib	3	9	347	4	339	2.27 (0.69–7.49)
Trastuzumab *vs.* trastuzumab + pertuzumab	2	18	514	26	504	0.66 (0.36–1.23)

Abbreviations: CHF, Congestive Heart Failure; LVEF, Left ventricular ejection fraction; No, number; OR, Odds Ratio; CI, Confidence Interval

Anmerkung/Fazit der Autoren

This meta-analysis provides evidence supporting comparable cardiac toxicity between anti-HER2 combination therapy and anti-HER2 monotherapy.

3.4 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften), Deutschen Krebsgesellschaft e.V. (DKG) und Deutschen Krebshilfe (DKH), 2018 [33].

Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 4.3

Leitlinienorganisation/Fragestellung

Langversion 4.1 – September 2018 AWMF-Registernummer: 032-045OL

Die Ziele der S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms wurden aus der Ur-sprungsversion und den ersten beiden Aktualisierungen beibehalten und für die 3. Neuauflage ergänzt bzw. konkretisiert

Methodik

Grundlage der Leitlinie

Die methodische Vorgehensweise bei der Erstellung der Leitlinie ist im Leitlinienreport dargelegt. Dieser ist im Internet z. B. auf den Seiten des Leitlinienprogramms Onkolo-gie (http://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/) und den Seiten der AWMF (http://www.awmf.org/) frei verfügbar.

Recherche/Suchzeitraum:

Unterschiedliche Zeitpunkte für verschiedene Themen/Empfehlungen, da Leitlinien-Update

LoE

Tabelle 5: Schema der Evidenzgraduierung nach Oxford (Version März 2009)

Level	Therapy / Prevention, Aetiology / Harm	Prognosis	Diagnosis	Differential diagnosis / symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity) of RCTs	SR (with homogeneity) inception cohort studies; CDR validated in different populations	SR (with homogeneity) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity) of prospective cohort studies	SR (with homogeneity) of Level 1economic studies
1b	Individual RCT (with narrow Confidence Interval)	Individual inception cohort study with > 80% follow-up; CDR validated in a single population	Validating cohort study with good reference standards; or CDR tested within one clinical centre	Prospective cohort study with good follow-up	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
2a	SR (with homogeneity) of cohort studies	SR (with homogeneity) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity) of Level >2 diagnostic studies	SR (with homogeneity) of Level 2b and better studies	SR (with homogeneity) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR or validated on split-sample	Exploratory cohort study with good reference standards; CDR after derivation, or validated only on split-sample or da-	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses

		only	tabases		
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity) of case-control studies		SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies	SR (with homogeneity) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study; or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations
4	Case-series (and poor quality cohort and case-control studies)	Case-series (and poor quality prognostic cohort studies)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

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Tabelle 6: Schema der Empfehlungsgraduierung

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll/soll nicht
B	Empfehlung	sollte/ sollte nicht
0	Empfehlung offen	kann/kann verzichtet werden

Tabelle 7: Konsensusstärke

Konsenstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	> 75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	> 50 – 75% der Stimmberechtigten
Dissens	< 50% der Stimmberechtigten

Empfehlungen

Indikationen für eine adjuvante Chemotherapie sind:

• bei HER2-positiven Tumoren ist die simultane Anti-HER2-Therapie mit Trastu-zumab über die Dauer von 1 Jahr in Kombination mit einer (neo)adjuvanten Chemotherapie Standard

• bei endokrin nicht sensitiven Tumoren (ER- und PgR-negativ)

• bei fraglich endokrin sensitiven Tumoren

• bei nodal-positiven Tumoren (innerhalb von Studien wird derzeit evaluiert, ob bei Patientinnen mit niedrigem Nodalbefall (1–3 befallene LK) und günstiger Tumorbiologie (Luminal A) auf eine adjuvante Chemotherapie verzichtet werden kann)

• G 3

• junges Erkrankungsalter (< 35 Jahre)

Endokrine Therapie

4.50.	Evidenzbasierte Empfehlungen
	Indikationen für eine endokrine Therapie
Empfehlungsgrad A	a.) Patientinnen mit östrogen- und/oder progesteronrezeptor-positiven (*) invasiven Tumoren sollen eine endokrine Therapie erhalten. * (>/=10% progesteronrezeptor-positive Tumorzellkerne)
Level of Evidence 1a	Quellen: [29, 726-729]
	Starker Konsens
Empfehlungsgrad A	b.) Diese soll erst nach Abschluss der Chemotherapie begonnen werden, kann aber parallel zur Strahlentherapie erfolgen.
Level of Evidence 1a	Quellen: [580, 726-728] [29, 729]
	Starker Konsens

Adjuvante endokrine Therapien wie Tamoxifen und Aromatasehemmer reduzieren sig-nifikant die Wahrscheinlichkeit eines Rezidivs um relativ ca. 40% und die Wahrschein-lichkeit des Versterbens um relativ ca. 30% [227, 363, 727, 730].

Diese relative Risikoreduktion ist unabhängig vom Alter der Patientin, dem Tumorsta-dium und der Vortherapie wie einer adjuvanten Chemotherapie, bezieht sich allerdings immer auf Frauen mit einem Hormonrezeptor-positiven Mammakarzinom.

Diese günstigen Effekte der endokrinen Therapie werden nur bei ausreichender Thera-pieadhärenz realisiert. Aber nur etwa die Hälfte der Frauen mit Brustkrebs führt diese Behandlung über die empfohlenen 5 Jahre durch. Dieser Mangel an Compliance ist mit einem signifikant erhöhten Sterberisiko verbunden. Es ist wichtig, die Patientinnen von der Notwendigkeit der Therapie zu überzeugen, durch sorgfältige Anamnese das Be-wusstsein für Nebenwirkungen und für therapieunabhängig auftretende Beschwerden zu schärfen und diese adäquat zu behandeln. Bei schweren Nebenwirkungen, die die Therapieadhärenz gefährden, kann bei postmenopausalen Patientinnen der Wechsel von einem Aromatasehemmer auf Tamoxifen und umgekehrt oder zwischen den Aro-matasehemmern (steroidal vs. non-steroidal) erwogen werden. Gelingt es, durch diese Maßnahmen die Therapietreue zu erhöhen, rettet dies möglicherweise mehr Leben als eine zusätzliche Chemotherapie.

Die Gruppe der Patientinnen mit einem schwach ER-positiven Mammakarzinom (1-9% gefärbte Tumorzellkerne) verhält sich in einigen Analysen ([474] N=251) prognostisch eher wie rezeptornegative Patientinnen und weist (an kleineren Patientinnenzahlen un-tersucht, N=26) ähnliche molekulare Eigenschaften wie triple-negative Mammakarzi-nome auf [470, 471]. In einer

Untersuchung an 314 Patientinnen wiesen die mit einer geringen ER-Färbung (1-9%) eine ähnliche Häufigkeit von BRCA-1-Mutationen auf wie ER-negative Patientinnen [473].

Da sich diese Patientinnengruppe (1-9% positive ER) prognostisch offensichtlich anders als die mit einer ER-Positivität von > 10% verhält [731], sollte bei ihnen eine zusätzliche adjuvante oder neoadjuvante Chemotherapie erwogen werden.

Karzinome mit einer schwachen PR-Färbung (<10%) und negativen ER-Färbung könnten molekular dem triple-negativen Mammakarzinom entsprechen [732, 733]. Diese Daten werden unterstützt durch die EBCTCG-Analyse von 2008 “Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer”, in der nachgewiesen wurde, dass Tamoxifen nur einen geringen Effekt auf die Rezidivrate und das Überleben bei Patientinnen mit einer schwachen Östrogenrezeptor-Expression hatte und einen nur geringen zusätzli-chen Effekt zur adjuvanten Chemotherapie.

Daten einiger Studien (wie Tam-02, [734, 735]) weisen darauf hin, dass ein späterer Beginn (bis zu 5 Jahre nach abgeschlossener Lokaltherapie und/oder Chemotherapie) mit einer adjuvanten endokrinen Therapie besser ist, als ganz auf diese endokrine Therapie zu verzichten. Auch dieser spätere Beginn der endokrinen Therapie verlänger-te das DFS und das OS bzw. DDFS. Die MA.17-Studie [736], die auch ein längeres the-rapiefreies Intervall zwischen Tamoxifen und Letrozol zuließ, zeigte ähnliche Ergebnis-se. Das sind Hinweise darauf, dass bei Nebenwirkungen eine Therapiepause einem ge-nerellen Abbruch vorzuziehen ist.

4.51.	Evidenzbasierte Empfehlung
	Endokrine Therapie
Empfehlungsgrad A/B	Nach 5 Jahren Tamoxifen soll für jede Patientin mit einem ER+-Mammakarzinom die Indikation zu einer erweiterten endokrinen Therapie geprüft werden. Die Indikationsstellung sollte in der Abwägung des Rückfallrisikos und den thera-pieassoziierten Nebenwirkungen (Toxizität, verminderte Adhärenz) erfolgen. Bei der Wahl der endokrinen Therapie soll der aktuelle Menopausenstatus der Pati-entin berücksichtigt werden.
Level of Evidence LL-Adapt.	Leitlinienadaptation: [737]
	Starker Konsens

Die endokrine adjuvante Behandlung des frühen Mammakarzinoms gehört zu den ef-fektivsten Therapiemöglichkeiten. Aktuelle Publikationen belegen dies für ein Zeitin-tervall von bis zu 15 Jahren. Dabei unterschied man die initiale adjuvante Therapie (I-AT, Jahr 0-5) und die erweiterte adjuvante Therapie (EAT: Jahr 6-10).

Die therapieassoziierte Nebenwirkungsrate dieser kontinuierlichen Therapien reduziert die Therapieadhärenz und führt zu einem Effektivitätsverlust. Daher wäre in Studien zu prüfen, ob eine intermittierende adjuvante endokrine Therapie ebenso wirksam wie die EAT sein könnte.

Derzeit fehlen verlässliche diagnostische Instrumente, um das Risiko einer späten Me-tastasierung (nach Jahr 5) verlässlich für eine solche Intervention vorherzusagen. Dazu könnten in Studien z.B. Multi-Gene-Assays prospektiv evaluiert werden.

Nach 5 Jahren Tamoxifen reduzieren weitere 5 Jahre adjuvant Tamoxifen bei Patientin-nen mit Hormonrezeptor-positiven Mammakarzinomen die Rezidivrate (absolut -2,8% in der ATLAS-Studie) und verlängern das Gesamtüberleben (absolut -2,48% in der AT-LAS-Studie, [738-740]) unabhängig vom Menopausenstatus (allerdings waren nur 9% der Patientinnen in der ATLAS-Studie prämenopausal). Die Häufigkeit einer Lungenem-bolie und eines Endometriumkarzinoms waren nach 10 Jahren Tamoxifen signifikant erhöht im Vergleich zu 5 Jahren Tamoxifen ohne Einfluss auf die Mortalität. Eine is-chämische Herzkrankheit und Herzinfarkte waren nach 10 Jahren signifikant seltener als nach 5 Jahren Tamoxifen.

Wurden die Patientinnen nach 5 Jahren adjuvant Tamoxifen postmenopausal, verbes-serte die nachfolgende Gabe von Letrozol für 5 Jahre adjuvant das DFS und das OS, be-sonders bei Frauen, die vor dem Letrozol prämenopausal waren oder Lymphknotenme-tastasen hatten [736]. Zugelassen für diese EAT in Deutschland nach 5 Jahren Tamoxi-fen sind Tamoxifen und Letrozol.

4.52.	**Evidenzbasierte Empfehlung**
	Therapie bei prämenopausalen Patientinnen
Empfehlungsgrad **A**	Bei prämenopausalen Patientinnen soll eine Tamoxifentherapie für mindestens 5 Jahre durchgeführt werden. Die antiöstrogene Therapie mit Tamoxifen 20 mg pro Tag soll in Abhängigkeit des Rezidivrisikos über eine Zeitdauer von 5 – 10 Jahren bzw. bis zum Rezidiv erfolgen. Die Indikation der erweiterten Therapie ist vom Rezidivrisiko und Wunsch der Pati-entin abhängig.
Level of Evidence **1a**	Quellen: [726, 727][738, 739, 741]
	Starker Konsens

Wenn die Gabe des Tamoxifens von 5 auf 10 Jahre verlängert wird, werden die ipsi- und kontralateralen Rezidivhäufigkeiten reduziert und in der ATLAS-Studie das Ge-samtüberleben verlängert. Allerdings sind die Raten an Lungenembolien und Endomet-riumkarzinomen erhöht, ohne Einfluss auf die Mortalität [738-740]. Die risikoadaptierte Dauer der Tamoxifen-Gabe (längere Gabe bei erhöhtem Rezidivrisiko) wird von der ASCO empfohlen [737].

4.53.	Evidenz- /konsensbasierte Empfehlungen
	Endokrine Therapie
EK	a.) Für Patientinnen mit einem ER+-Mammakarzinom und erhöhtem Risiko, die nach abgeschlossener Chemotherapie noch prämenopausal sind, kann unter Ausschaltung der Ovarfunktion ein Aromatasehemmer eingesetzt werden.
	Konsens
Level of Evidence **1b**	b.) Die alleinige Ovarialsuppression kann entweder durch Gabe eines GnRHa oder durch eine bilaterale Ovarektomie für prämenopausale Frauen mit einem ER+-Mammakarzinom erwogen werden, die kein Tamoxifen erhalten können oder wollen.
	Leitlinienadaptation: [730]
	Starker Konsens
Empfehlungsgrad **A**	c.) Die Ovarialsuppression (GnRHa oder bilaterale Ovarektomie) zusätzlich zu Tamoxifen oder einem Aromatasehemmer soll nur bei hohem Rezidivrisiko und prämenopausaler Situation nach adjuvanter Chemotherapie erwogen werden. Bei Einsatz eines Aromatasehemmers soll eine Ovarialsuppression obligat erfolgen.
Level of Evidence **1b**	Leitlinienadaptation: [730]
	Starker Konsens

In verschiedenen Studien (z.B. SOFT, TEXT, [742]) wurde der Effekt der Unterdrückung der Ovarialfunktion von bis zu 5 Jahren zusammen mit der Gabe von Exemestan oder zusammen mit Tamoxifen vs. der alleinigen Tamoxifen-Gabe in der adjuvanten Therapie von Frauen mit einem Hormonrezeptor-positiven Mammakarzinom untersucht, die prämenopausal waren oder innerhalb von 8 Monaten nach Abschluss der adjuvanten Chemotherapie wieder prämenopausal wurden. Nach der Einzelanalyse jeder dieser Studien und nach der kombinierten Analyse von zwei dieser Studien (SOFT, TEXT) zeigte sich eine erhöhte Effektivität der zusätzlichen Ausschaltung der Ovarialfunktion nur in der Gruppe der unter 35-jährigen Patientinnen, die ein hohes Rezidivrisiko hatten (und deshalb eine Chemotherapie erhielten). In einer Metaanalyse aller dieser Studien [743] zeigten sich eine höhere Wirksamkeit in Bezug auf das DFS, aber eine erhöhte Nebenwirkungsrate bis hin zu mehr Todesfällen für die Kombination der Unterdrückung der Ovarialfunktion mit einem Aromatasehemmer als für die Kombination der Unterdrückung der Ovarialfunktion zusammen mit Tamoxifen. Die höhere Nebenwirkungsrate bedingt ein Risiko für eine verminderte Therapieadhärenz.

Die Gabe eines GnRH-Analogons ist entsprechend der Ergebnisse verschiedener Studien (z.B. ZIPP-Studie, [744]) und Metaanalysen der alleinigen Tamoxifengabe äquivalent, allerdings mit einer erhöhten Nebenwirkungsrate und damit Abbruchrate im Vergleich mit Tamoxifen verbunden. Obgleich verlässliche Daten fehlen, kann ebenfalls mit einer erhöhten Spättoxizität (z.B. Koronarerkrankungen, Osteoporose, Demenz) gerechnet werden.

4.54.	Evidenzbasierte Empfehlung
	Therapie bei postmenopausalen Patientinnen
Empfehlungsgrad B	Die adjuvante endokrine Therapie für postmenopausale Patientinnen mit einem ER+ Mammakarzinom sollte einen Aromatasehemmer enthalten.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

In den Metaanalysen [363, 726, 727, 745] zeigen sich in Bezug auf das OS und das DFS eine Überlegenheit der adjuvanten Aromatasegabe (AI) allein oder in Sequenz mit Tamoxifen im Vergleich zum Tamoxifen allein bei postmenopausalen Patientinnen mit einem Hormonrezeptor-positiven Mammakarzinom. In der EBCTCG-Metaanalyse wur-den 2 Kohorten gebildet:

Kohorte 1 als Vergleich zwischen 5 Jahren AI vs. 5 Jahren Tamoxifen und Kohorte 2 mit der Gaben AI nach 2-3 Jahren Tamoxifen für insgesamt 5 Jahre. Die Gaben von 5 Jahren AI nach 5 Jahren Tamoxifen wurden nicht in diese Metaanalyse einbezogen. Da die Analyse nur Daten bis 2006 einschloss, wurden die Studien ABCSG 12 und die Switch-Arme der BIG 1-98 Studie nicht in diese Metaanalyse eingeschlossen. In Kohorte 1 wur-de die signifikante Überlegenheit der AI-Gabe gegenüber Tamoxifen in Bezug auf das DFS, aber nicht in Bezug auf die Mortalität nachgewiesen. In Kohorte 2 zeigte sich der signifikante Vorteil der zusätzlichen AI-Gabe in Bezug auf DFS und Überleben im Ver-gleich zur alleinigen Tamoxifen-Gabe.

Die alleinige Gabe des Aromatasehemmers über 5 Jahre reduziert die Rezidivrate be-sonders wirksam bei High-risk Mammakarzinomen und/oder lobulären invasiven Mammakarzinomen.

Wenn nach 5 Jahren Tamoxifen die Patientin postmenopausal geworden ist und ein er-höhtes Rezidivrisiko hat, wird entsprechend der MA.17-Studie die Gabe von Letrozol für weitere 5 Jahre empfohlen [736]. Dieses Vorgehen wird auch von der ASCO [746] nach ihrer Metaanalyse aller bis 2013 abgeschlossenen Studien empfohlen.

Auf dem SABCS 2016 wurden weitere Studien zur verlängerten (EAT) Gabe eines Aro-matasehemmers nach bereits 5 Jahren vorgestellt, z.B. NSABP B-42 (10 vs. 5 Jahre AI, [747]) oder IDEAL trial (5 Jahre AI nach 5 Jahren einer adjuvanten endokrinen Therapie mit Tamoxifen und/oder AI) [748]. In keiner dieser Studien konnte eine signifikante Verlängerung des Überlebens oder eine signifikante Reduktion der Mortalität durch diese verlängerte AI-Gabe gezeigt werden, allenfalls eine Reduktion der ipislateralen und kontralateralen Rezidivrate (Zusammenfassung durch Gnant 2016). Zu gleichen Ergebnissen kam auch die MA.17R-Studie, die bereits publiziert ist [749]. Mit jüngeren postmenopausalen Patientinnen, die bereits eine endokrine Therapie mit einem AI in den ersten 5 Jahren erhalten und gut vertragen hatten, kann eine erweiterte endokrine Therapie mit einem AI unter bestimmten Umständen (erhöhtes Rezidivrisiko z.B. bei positivem Nodalstatus, keine Osteopenie/Osteoporose) diskutiert werden [750].

- Adjuvante Chemotherapie

4.55.	Evidenzbasierte Empfehlungen
	Indikationen für eine adjuvante Chemotherapie
Empfehlungsgrad **B**	a.) Eine Indikation für eine adjuvante Chemotherapie sollte gestellt werden bei: • HER2-positiven Tumoren (ab pT1b, N0; pT1a, N0 wenn weiteres Risiko: G3, ER/PR neg., Ki67 hoch) • Triple-negativen Tumoren (ER- und PgR-negativ, HER2-negativ) • Luminal-B-Tumoren mit hohem Rezidivrisiko (Ki-67 hoch, G 3, high risk multigen assay, junges Erkrankungsalter, Lymphknotenbefall)
Level of Evidence **1a**	Quellen: [180, 363, 751-754]
	Starker Konsens
Empfehlungsgrad **A**	b.) Eine Chemotherapie soll in den empfohlenen Dosierungen verabreicht werden. Bei Unterdosierung oder Reduktion der Zyklen droht ein Effektivitätsverlust.
Level of Evidence **1a**	Quellen: [753, 755-759]
	Starker Konsens

4.56.	Evidenzbasierte Empfehlung
	Verabreichung der Zytostatika
Empfehlungsgrad **B**	Zytostatika können zeitlich simultan oder sequenziell verabreicht werden (entsprechend evidenzbasierter Protokolle). Bei hohem tumorbedingtem Mortalitätsrisiko und dafür geeigneten Patientinnen sollten dosisdichte Therapien eingesetzt werden.
Level of Evidence **1b**	Quellen: [760-762] [763-765]
	Starker Konsens

4.57.	Evidenzbasierte Empfehlung
	Anthrazyklin/Taxanhaltige adjuvante Standard-Chemotherapie
Empfehlungsgrad **B**	Die adjuvante Chemotherapie sollte ein Taxan und ein Anthrazyklin enthalten.
	Starker Konsens
Empfehlungsgrad **O**	6 Zyklen TC (Docetaxel/Cyclophosphamid) können bei einem mittleren klinischen Risiko (≤ 3 befallene Lymphknoten) eine Alternative darstellen.
	Konsens
Empfehlungsgrad **A**	Eine adjuvante Standard-Chemotherapie soll 18–24 Wochen dauern.
	Konsens
Level of Evidence **1a**	Quellen: [751, 761, 766-774]

Die durch Daten des Oxford Overviews (EBCTCG) nachgewiesenen positiven Effekte ei-ner adjuvanten Chemotherapie auf die Rezidiv- und Sterberisiken sind am stärksten bei Frauen unter 50 Jahren ausgeprägt. Ein Nutzen ist auch für postmenopausale Frauen gegeben [753].

Die Datenlage zur adjuvanten Chemotherapie mit Taxanen wird durch aktuelle Studienergebnisse untermauert. Vor allem Frauen mit Lymphknotenbefall bzw. mit nodalnegativen Karzinomen und zusätzlichen Risikokriterien (z. B. G2/3, ER- und PgR-negativ, pT > 2 cm, Alter < 35 Jahre [775]) profitieren vom Einsatz der Taxane in der adjuvanten Therapie [752, 763, 766-769, 771, 775-778].

Mehrere effektive Regime stehen zur Verfügung. Gegen einen adäquaten Anthrazylin-Standard wurden getestet: FEC x 3 → Doc x 3 (PACS-01), 3 x FEC → 8 x Pac weekly sowie DocAC („TAC“, BCIRG 006) [771, 775, 778, 779]. 6 x DocAC und 4 x AC → 4 x Doc sind äquieffektiv, unterscheiden sich aber in ihrem Nebenwirkungsspektrum.

In der Sequenz nach 4 x AC sind 4 x Docetaxel alle 3 Wochen (100 mg/m2) und 12 x Paclitaxel wöchentlich (80 mg/m2) als gleichwertig anzusehen [752, 780]. Die Se-quenz 4 Zyklen AC – 4 x Paclitaxel q21 („Henderson-like“) ist 6 x CEF unterlegen (MA-21 [781]).

Die Zweifachkombination 4 x DocC (TC) ist hinsichtlich DFS und OS dem alten Standard 4 x AC überlegen und vermeidet anthrazyklinassoziierte Toxizitäten [613, 782].

Generell scheint die Gabe einer längeren adjuvanten Chemotherapie vorteilhaft, wie der Vergleich von 4 Zyklen vs. 8 Zyklen gezeigt hat [759, 769]. Mehrere Studien zei-gen, dass 6 Zyklen TC für bestimmte Patientengruppen genauso wirksam sind wie eine Anthrazyklin-taxanhaltige Sequenztherapie. Ob diese aktuellen Wirksamkeitsdaten für 6 Zyklen TC auch für 4 Zyklen TC zutreffen, kann derzeit anhand der vorliegenden Da-tenlage nicht entschieden werden. Eine entsprechende Verkürzung der Zyklenzahl soll-te daher nur bei nicht tolerablen Toxizitäten erfolgen.

In der dänischen DBCG-07-READ Studie bei TOPO2A-normalem frühen Mammakarzi-nom zeigte sich kein Unterschied bei DFS und OS für 6x TC vs. 3x EC – 3x DOC [773]. Die WSG-PlanB-Studie zeigte ebenfalls keinen Unterschied zwischen 6x TC und 4x EC – 4x Docetaxel beim HER2-negativen frühen Mammakarzinom [774]. Die gepoolte Analy-se von 3 US-Studien (ABC Trials) konnte formal die non-inferiority zwischen 6x TC und einer anthrazyklin-taxanhaltigen Sequenztherapie nicht bestätigen (iDFS HR 1.202; 95% KI 0,97-1,49 bei einem vordefinierten Grenzwert von 1,18). Der absolute Unterscheid zwischen beiden Armen war jedoch gering (Differenz 4-Jahres iDFS 2,5%) und Sub-gruppenanalysen zeigten, dass der größte Nutzen zugunsten der einer anthrazyklin-taxanhaltigen Sequenztherapie bei einem hohen klinischen Risiko (z.B. > 3 befallene Lymphknoten) zu finden war [772].

Der Stellenwert von neuen Substanzen in der adjuvanten Therapie (z. B. Gemcitabine, Capecitabine) als vierte Substanz zusätzlich zu Anthrazyklinen, Taxanen und Cyclophosphamid kann noch nicht abschließend beurteilt werden. Während die Hinzunahme von Gemcitabine nicht mit einem Vorteil verbunden ist [783], lassen einige Daten für Capecitabine einen Trend hinsichtlich einer weiteren Verbesserung von DFS bzw. OS erkennen [784, 785]. Diese Verbesserung war jedoch mit einer erhöhten Toxizität ver-bunden [784, 785]. In der FinXX-Studie war die Verbesserung von DFS und OS nach 5 Jahren im Gesamtkollektiv nicht mehr signifikant, nur noch bei Risikopatientinnen (trip-le-negativ, > 3 LK), Cave: Standardarm [786].

In neueren Studien konnte eine höhere Wirksamkeit der dosisdichten (q2w) [761, 765] bzw. der dosisintensivierten dosisdichten Chemotherapie [764, 787] im Vergleich zu einer konventionellen Chemotherapie (q3w) gezeigt werden. Insbesondere für Patien-tinnen mit

hohem Risiko (≥ 4 befallene LK) ist die dosisintensivierte dosisdichte Che-motherapie (ETC) ein Standardregime. Patientinnen mit niedrigen oder moderaten Re-zidivrisiko hingegen profitieren nicht von einer dosisdichten Therapie im Vergleich zu einer Standardchemotherapie [788, 789].

Myeloablative Hochdosis-Chemotherapien haben derzeit keinen Stellenwert in unselek-tierten Hochrisikokollektiven: Sie zeigen verglichen mit konventioneller Chemotherapie ein besseres ereignisfreies Überleben, das Gesamtüberleben bleibt jedoch unbeein-flusst [790, 791]. Therapieassoziierte Sterblichkeit und Nebenwirkungen sind signifi-kant erhöht [791, 792].

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772. Blum, J.L., et al., Anthracyclines in Early Breast Cancer: The ABC Trials-USOR 06-090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J Clin Oncol, 2017: p. Jco2016714147.

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778. Martin, M., et al., Adjuvant docetaxel for node-positive breast cancer. N Engl J Med, 2005. 352(22): p. 2302-13.

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786. Joensuu, H., et al., Adjuvant capecitabine, docetaxel, cyclophosphamide, and epirubicin for early breast cancer: final analysis of the randomized FinXX trial. J Clin Oncol, 2012. 30(1): p. 11-8.

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789. Cameron, D., et al., Abstract S3-3: The UK TACT2 Trial: comparison of standard vs accelerated epirubicin in patients requiring chemotherapy for early breast cancer (EBC)(CRUK/05/019). 2012, AACR.

790. Berry, D.A., et al., High-dose chemotherapy with autologous stem-cell support as adjuvant therapy in breast cancer: overview of 15 randomized trials. J Clin Oncol, 2011. 29(24): p. 3214-23.

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792. Farquhar, C., et al., High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. Cochrane Database Syst Rev, 2005(3): p. Cd003142.

- Neoadjuvante Therapie

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

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

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

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

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

Zahlreiche Studien haben gezeigt, dass bezüglich des Langzeitüberlebens keinerlei Unterschiede zwischen neoadjuvantem und adjuvantem Einsatz einer Chemotherapie be-stehen, wenn die gleichen Therapeutika eingesetzt werden und die gleiche Dosis und Zyklenzahl appliziert werden. In einigen Studien scheint das Lokalrezidivrisiko bei neo-adjuvanter Therapie erhöht zu sein, wobei hier zum Teil unterlegene bzw. heute nicht mehr dem Standard entsprechende Chemotherapieregime und operative Strategien Anwendung fanden [796, 797].

796. Mieog, J.S., J.A. van der Hage, and C.J. van de Velde, Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev, 2007(2): p. Cd005002.

797. Mauri, D., N. Pavlidis, and J.P. Ioannidis, Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst, 2005. 97(3): p. 188-94.

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 Rah-men der post neoadjuvanten Studien schneller individuelle Therapieansätze zu entwi-ckeln [793]. Bei Patientinnen mit HER2-positiver/Hormonrezeptor-negativer oder triple-negativer Erkrankung kann im Falle einer pathologischen Komplettremission (pCR) von einer sehr günstigen Langzeitprognose ausgegangen werden [558, 560].

793. Kaufmann, M., et al., Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol, 2006. 24(12): p. 1940-9.

558. von Minckwitz, G., et al., Impact of treatment characteristics on response of different breast cancer phenotypes: pooled analysis of the German neo-adjuvant chemotherapy trials. Breast Cancer Res Treat, 2011. 125(1): p. 145-56.

560. Cortazar, P., et al., Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet, 2014. 384(9938): p. 164-72.

Die NACT sollte ein Anthrazyklin und ein Taxan enthalten und über mindestens 6 Zyk-len, sämtlich vor der Operation, durchgeführt werden. Bei Patientinnen mit HER2-überexprimierendem Tumor kann die präoperative Gabe von Trastuzumab sowie Trastuzumab und Pertuzumab simultan zur Chemotherapie die pCR-Rate signifikant erhöhen [798-803]. Die Trastuzumab-Therapie sollte postoperativ auf die Dauer von einem Jahr komplettiert werden.

798. Buzdar, A.U., et al., Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol, 2005. 23(16): p. 3676-85.

799. Gianni, L., et al., Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. Lancet, 2010. 375(9712): p. 377-84.

800. Untch, M., et al., Pathologic complete response after neoadjuvant chemotherapy plus trastuzumab predicts favorable survival in human epidermal growth factor receptor 2-overexpressing breast cancer: results from the TECHNO trial of the AGO and GBG study groups. J Clin Oncol, 2011. 29(25): p. 3351-7.

801. Gianni, L., et al., Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol, 2012. 13(1): p. 25-32.

802. Gianni, L., et al., 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol, 2016. 17(6): p. 791-800.

803. Schneeweiss, A., et al., Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals of oncology, 2013. 24(9): p. 2278-2284

Die histopathologische Komplettremission (pCR), definiert als kein invasiver Tumor-zellnachweis in der Brust und der Axilla nach Durchführung der NACT, hat in Studien eine deutliche Korrelation mit dem Langzeitüberleben gezeigt, d. h. Patientinnen, die auf eine NACT bis zur Operation oder schon nach den ersten Chemotherapiezyklen nicht ansprechen, haben eine ungünstigere Prognose als solche, die auf die Therapie ansprechen [560, 794, 795]. Trotz dieses beobachteten Zusammenhangs innerhalb der Studien gibt es bisher keine belastbaren Daten, die zeigen, dass Unterschiede bezüg-lich der pCR-Rate in Studienarmen Unterschiede hinsichtlich des ereignisfreien Überle-bens bzw. des Gesamtüberlebens zuverlässig vorhersagen [560, 804, 805]. Somit stellt die pCR-Rate derzeit keinen validen Surrogatendpunkt für die Beurteilung der Wirk-samkeit einer neoadjuvanten Therapie hinsichtlich patientenrelevanter Endpunkte dar.

560. Cortazar, P., et al., Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet, 2014. 384(9938): p. 164-72

794. Bear, H.D., et al., Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer:National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol, 2006. 24(13): p. 2019-27.

795. von Minckwitz, G., et al., In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. Ann Oncol, 2005. 16(1): p. 56-63.

804. Korn, E.L., M.C. Sachs, and L.M. McShane, Statistical controversies in clinical research: assessing pathologic complete response as a trial-level surrogate end point for early-stage breast cancer. Ann Oncol, 2016. 27(1): p. 10-5.

805. Bazzola, L., et al., Combination of letrozole, metronomic cyclophosphamide and sorafenib is well-tolerated and shows activity in patients with primary breast cancer. British Journal of Cancer, 2015. 112(1): p. 52-60.

Der wichtigste prädiktive Marker für das Ansprechen eines Taxan-anthrazyklinhaltigen Regimes ist der Hormonrezeptorstatus. Bei Patientinnen mit negativem Hormonrezep-torstatus kann eine pCR Rate von bis zu 70-80 % erzielt werden. Prädiktoren für das Ansprechen sind: Jüngeres Erkrankungsalter, Patientinnen mit cT1- oder cT2-Karzinomen, Nodalnegativität, G3, negativer Hormonrezeptorstatus, triple-negatives Mammakarzinom.

Bei postmenopausalen Patientinnen mit endokrin sensitivem Mammakarzinom kann, wenn eine Operation und eine Chemotherapie nicht möglich sind, eine neoadjuvante endokrine Therapie durchgeführt werden. In dieser Indikation werden Aromatasehem-mer der dritten Generation empfohlen [806-808].

806. Ellis, M.J., et al., Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. J Clin Oncol, 2001. 19(18): p. 3808-16.

807. Smith, I.E., et al., Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol, 2005. 23(22): p. 5108-16.

808. Spring, L.M., et al., Neoadjuvant Endocrine Therapy for Estrogen Receptor-Positive Breast Cancer: A Systematic Review and Meta-analysis. JAMA Oncol, 2016. 2(11): p. 1477-1486.

Nach Abschluss der NACT sollte die Patientin eine operative Therapie, wie oben beschrieben, erhalten. Der Exzisionsumfang sollte den erzielten Effekt der neoadjuvanten Therapie ausnutzen und kann in den neuen Tumorgrenzen erfolgen. Da bei Erreichen einer pCR die Identifizierung des ursprünglichen Tumorherdes erschwert sein kann, empfiehlt sich die Lokalisation des Tumorbettes mithilfe eines Clips bereits bei der prätherapeutischen Stanzbiopsie. Bei radiologisch kompletter Remission unter primärer systemischer Therapie soll dementsprechend eine Exzision der ehemaligen Tumorlokalisation zur Abklärung, ob noch vitale Tumorzellen im Tumorbett vorhanden sind, durchgeführt werden. Die Indikationen zur postoperativen Radiotherapie entsprechen denen, die für die adjuvante Situation beschrieben wurden, und orientieren sich am prätherapeutischen Ausgangsbefund [793]. Die Deeskalation der lokoregionalen Strahlentherapie wird im Rahmen prospektiver Studien geklärt (NSABP B 51).

793. Kaufmann, M., et al., Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. J Clin Oncol, 2006. 24(12): p. 1940-9.

Zur Operation bzw. axillären Intervention vor und nach der adjvuanten Chemotherapie siehe Operatives Kapitel 4.4

Burstein HJ et al., 2018 [4].

American Society of Clinical Oncology (ASCO)

Adjuvant Endocrine Therapy for Women With Hormone Receptor–Positive Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Leitlinienorganisation/Fragestellung

To update the ASCO clinical practice guideline on adjuvant endocrine therapy based on emerging data about the optimal duration of aromatase inhibitor (AI) treatment.

Target Population: Postmenopausal women with stages I to III hormone receptor–positive breast cancer.

Methodik

Grundlage der Leitlinie

ASCO conducted a systematic review of randomized clinical trials from 2012 to 2018. Guideline recommendations were based on the Panel's review of the evidence from six trials.

Recherche/Suchzeitraum:

- 2012-2018

LoE/ GoR

- K.A. (Die Empfehlungen wurde in einem SR erarbeitet.)

Sonstige methodische Hinweise

Study quality was formally assessed for the six included studies. Design aspects related to the individual study quality were assessed by one reviewer and independently audited by another for factors such as blinding, allocation concealment, placebo control, intention to treat, and funding sources. The risk of bias was assessed as low to intermediate for the included trials.

Empfehlungen

The six included studies of AI treatment beyond 5 years of therapy demonstrated that extension of AI treatment was not associated with an overall survival advantage but was significantly associated with lower risks of breast cancer recurrence and contralateral breast cancer compared with placebo. Bone-related toxic effects were more common with extended AI treatment.

Does extended adjuvant AI therapy after 5 years of sequential endocrine therapy improve clinically meaningful outcomes (DFS, OS, quality of life, and toxicity) in postmenopausal women with hormone receptor–positive early breast cancer? If so, which patients should be advised to receive such therapy, and how should treatment optimally be administered?

Focused Update Recommendations

Recommendation 1.

Many women with node-negative breast cancer are potential candidates for and may be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment based on considerations of recurrence risk using established prognostic factors. However, as the recurrence risk is lower, the benefits are likely narrower for such patients. Women with low-risk node-negative tumors should not routinely be offered extended therapy.

Recommendation 2.

Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment.

Recommendation 3.

Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment.

Recommendation 4.

As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment.

Recommendation 5.

Extended therapy carries ongoing risks and side effects, which should be weighed against the potential absolute benefits of longer treatment in a shared decision-making process between the clinical team and the patient.

Qualifying statement.

To date, none of the studies have shown improvement in overall survival with longer-duration AI therapy. As such, the recommendations on extended adjuvant AI therapy are based on benefits that include prevention of distant recurrence and prevention of second breast cancers.

Literature review and analysis. This section summarizes the results of the six trials included in the 2018 updated systematic review.

Hinweis:

Das Review ist Bestandteil der Publikation, wird aber aus Platzgründen hier nicht extrahiert.

National Institute for Health and Care Excellence (NICE), 2018 [38].

Early and locally advanced breast cancer: diagnosis and treatment

Leitlinienorganisation/Fragestellung

This guideline covers diagnosing and managing early and locally advanced breast cancer. It aims to help healthcare professionals offer the right treatments to people, taking into account the person's individual preferences. NICE has also produced guidelines on advanced breast cancer, familial breast cancer and suspected cancer recognition and referral.

Methodik

Grundlage der Leitlinie

Leitlinien-Update (per Review geänderte Abschnitte sind genannt)

> These recommendations are marked [2009, amended 2018].
>
> Recommendations marked [2009] last had an evidence review in 2009. In some cases, minor changes have been made to the wording to bring the language and style up to date, without changing the meaning.

Who is it for?

- Healthcare professionals
- Commissioners and providers of breast cancer services
- People with early and locally advanced breast cancer, their families and carers

You can see everything NICE says on early and locally advanced breast cancer in our interactive

flowchart on early and locally advanced breast cancer. To find out what NICE has said on topics related to this guideline, see our web page on breast cancer.

For full details of the evidence and the guideline committee's discussions, see the evidence reviews. You can also find information about how the guideline was developed, including details of the committee.

https://www.nice.org.uk/guidance/NG101/history

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting NICE guidelines into practice, see resources to help you put guidance into practice.

Recherche/Suchzeitraum:

- Unterschiedlich für erschiedene Leitlinienbaschnitte (z.B. adjuvante Chemotherapie: September 2017)

LoE/ GoR:

- Siehe oben: Grundlagen

Sonstige methodische Hinweise

- Es existieren umfassende SRs zu einzelnen Teilen der Leitlinie, die hier nicht dargestellt werden, und die unter der o.g. Internetadresse abrufbar sind.

Empfehlungen

Endocrine therapy for ductal carcinoma in situ

1.7.10 Offer endocrine therapy after breast-conserving surgery for women with ER-positive DCIS if radiotherapy is recommended but not received. [2018]

1.7.11 Consider endocrine therapy after breast-conserving surgery for women with ER-positive DCIS if radiotherapy is not recommended. [2018]

1.7.12 Discuss the benefits and risks of endocrine therapy after breast-conserving surgery for women with ER-positive DCIS. Topics to discuss include those in table 3. [2018]

Table 3 Effects of endocrine therapy after breast-conserving surgery for women with ER-positive DCIS

	Endocrine therapy after breast-conserving surgery for women with ER-positive DCIS
Definition	Tamoxifen or an aromatase inhibitor for 5 years. Taken as a once-daily tablet.
Effect on survival and disease recurrence *NOTE: The benefit for an individual person will depend on the risk of their cancer returning. For people with low risk of recurrence, the benefits may not outweigh the risks or side effects.* *Risk can be estimated using a range of standardised tools and clinical expertise.*	No effect on how many women are alive 5 and 10 years after diagnosis. Lower rate of recurrence of DCIS and lower rate of invasive breast cancer, compared with women who did not receive endocrine therapy or radiotherapy after surgery.
Side effects	All endocrine therapies: menopausal symptoms such as hot flushes. For tamoxifen: increased risk of thrombosis, endometrial cancer and possibly bone density loss in premenopausal women. For aromatase inhibitors: joint and muscle pain, urogenital symptoms and bone density loss.
Fertility and family planning	Effects on fertility and family planning as women should not become pregnant while taking tamoxifen, or within 2 months of stopping, because it may have adverse effects on the baby.

1.8 Adjuvant chemotherapy for invasive breast cancer

1.8.1 For people with breast cancer of sufficient risk that chemotherapy is indicated,

offer a regimen that contains both a taxane[6] and an anthracycline[7]. [2018]

1.8.2 Discuss with people the benefits and risks of adding a taxane[6] to anthracycline[7]-containing regimens. Topics to discuss include those in table 4 and:

the benefits of reduced cardiac toxicity and reduced nausea the risks of additional side effects, including neuropathy, neutropenia and hypersensitivity the different side effects and dosing frequencies of different docetaxel and paclitaxel regimens, and the additional clinic visits that may be needed that absolute benefit is proportional to absolute risk of recurrence. [2018]

Table 4 Benefits and risks of adding a taxane to anthracycline-containing regimens and comparison of different taxane regimens

	Effect of adding a taxane to an anthracycline containing regimen	
	3-weekly docetaxel	Weekly or fortnightly paclitaxel
Effect on survival *NOTE: The benefit for an individual person will depend on the risk of their cancer returning. For people with low risk of recurrence, the benefits may not outweigh the risks or side effects.* *Risk can be estimated using a range of standardised tools and clinical expertise.*	Some evidence for improved outcomes including reducing the risk of breast cancer returning and increasing the chance of surviving.	
Benefits	Smaller doses of anthracyclines can be used, which can reduce the risk of side effects such as nausea and vomiting. Smaller cumulative doses of individual drugs may reduce long-term side effects, for example, cardiac toxicity and risk of second malignancies.	
Side effects	Additional side effects may include joint and muscle pain, nerve damage, higher rates of febrile neutropenia and hypersensitivity reactions. Some people have long-term hair loss (alopecia) after treatment with taxanes.	Additional side effects may include nerve damage and hypersensitivity reactions but febrile neutropenia is less likely than with 3-weekly docetaxel. Some people have long-term hair loss (alopecia) after treatment with taxanes. Weekly paclitaxel is tolerated best, but even fortnightly is better tolerated than 3-weekly docetaxel.
Administration	Visits to hospital every 3 weeks.	Visits to hospital every week or every 2 weeks.
Length of course	9 to 12 weeks (3 to 4 cycles).	9 to 12 weeks (9 to 12 doses)

1.8.3 Weekly and fortnightly paclitaxel should be available locally because these regimens are tolerated better than 3-weekly docetaxel, particularly in people with comorbidities. [2018]

Biological therapy

1.8.4 Offer adjuvant trastuzumab for people with T1c and above HER2-positive invasive breast cancer, given at 3-week intervals for 1 year in combination with surgery, chemotherapy and radiotherapy as appropriate. [2009, amended 2018]

1.8.5 Consider adjuvant trastuzumab for people with T1a/T1b HER2-positive invasive breast cancer, taking into account any comorbidities, prognostic features and possible toxicity of chemotherapy. [2018]

1.8.6 Assess cardiac function before starting treatment with trastuzumab. [2009]

1.8.7 Use trastuzumab with caution in people with HER2-positive invasive breast cancer who have any of the following:

a baseline left ventricular ejection fraction (LVEF) of 55% or less a history of, or current, congestive heart failure a history of myocardial infarction angina pectoris needing medication

cardiomyopathy cardiac arrhythmias needing medical treatment clinically significant valvular heart disease haemodynamic effective pericardial effusion poorly controlled hypertension. [2009, amended 2018]

1.8.8 Repeat cardiac function assessments every 3 months during trastuzumab treatment. If the LVEF drops by 10 percentage (ejection) points or more from baseline and to below 50%, suspend trastuzumab treatment. Restart trastuzumab only after reassessing cardiac function and discussing the possible benefits and risks. Cardiac function assessments should also be repeated every 6 months following discontinuation of treatment until 24 months from the last administration of trastuzumab. [2009, amended 2018]

1.9 *Bisphosphonate* therapy

Adjuvant bisphosphonate therapy

1.9.1 Offer bisphosphonates (zoledronic acid or sodium clodronate)[8] as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer.[2018]

1.9.2 Consider bisphosphonates (zoledronic acid or sodium clodronate)[8] as adjuvant therapy for postmenopausal women with node-negative invasive breast cancer and a high risk[1] of recurrence. [2018]

1.9.3 Discuss the benefits and risks of bisphosphonate treatment with women, particularly the risk of osteonecrosis of the jaw, atypical femoral fractures and osteonecrosis of the external auditory canal. Follow the Medicines and Healthcare products Regulatory Agency/Commission on Human Medicines (MHRA/CHM) advice on bisphosphonates. [2018]

Radiotherapy *after* breast-conserving surgery

1.10.3 Offer whole-breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins. [2018]

1.10.4 Consider partial breast radiotherapy (as an alternative to whole-breast radiotherapy) for women who have had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins and who:

have a low absolute risk of local recurrence (defined as women aged 50 and over with tumours that are 3 cm or less, N0, ER-positive, HER2-negative and grade 1 to 2) and

have been advised to have adjuvant endocrine therapy for a minimum of 5 years. [2018]

1.10.5 When considering partial breast radiotherapy (see recommendation 1.10.4), discuss the benefits and risks, and explain that:

- local recurrence with partial breast radiotherapy at 5 years is equivalent to that with whole-breast radiotherapy
- the risk of local recurrence beyond 5 years is not yet known
- there is a potential reduction in late adverse effects. [2018]

1.10.6 When delivering partial breast radiotherapy, use external beam radiotherapy. [2018]

1.10.7 Consider omitting radiotherapy for women who:

have had breast-conserving surgery for invasive breast cancer with clear margins and

have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) and are willing to take adjuvant endocrine therapy for a minimum of 5 years. [2018]

1.10.8 When considering omitting radiotherapy for the population in recommendation

1.10.7, discuss the benefits and risks, including those in table 5, and explain that:

- without radiotherapy, local recurrence occurs in about 50 women per 1,000 at 5 years, and with radiotherapy, occurs in about 10 women per 1,000 at 5 years
- overall survival at 10 years is the same with or without radiotherapy
- there is no increase in serious late effects if radiotherapy is given (for example, congestive cardiac failure, myocardial infarction or secondary cancer). [2018]

Table 5 Benefits and risks of radiotherapy compared with no radiotherapy in the group of women at low risk described in recommendation 1.10.7

	Radiotherapy	No radiotherapy
Effect on local recurrence	On average, in 1,000 women, over 5 years local recurrence occurs in about 10 women, and does not occur in about 990 women.	On average, in 1,000 women, over 5 years local recurrence occurs in about 50 women, and does not occur in about 950 women.
Effect on survival	No difference in overall survival at 10 years.	No difference in overall survival at 10 years.
Risks	Possibility of short- and long-term adverse effects on the breast, and resulting cosmetic changes (such as skin soreness, changes to colour of skin, radiation fibrosis or stiffening of the breast tissue).	No short- or long-term adverse effects on the breast, or cosmetic changes.
Side effects	In this group of women at low risk, there is no increase in serious late side effects of radiotherapy (such as congestive cardiac failure, myocardial infarction or secondary cancer).	No side effects of radiotherapy will occur.
Administration	Given at the treatment centre 5 days a week for 3 weeks after surgery.	No need to attend the treatment centre for radiotherapy sessions.

1.10.9 Consider adjuvant radiotherapy for women with DCIS following breast-conserving surgery with clear margins, and discuss with them the possible benefits and risks of radiotherapy (also see surgery to the breast). [2009, amended 2018]

<u>Radiotherapy after mastectomy</u>

1.10.10 Offer adjuvant postmastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins. [2018]

1.10.11 Consider adjuvant postmastectomy radiotherapy for people with node-negative T3 or T4 invasive breast cancer. [2018]

1.10.12 Do not offer radiotherapy following mastectomy to people with invasive breast cancer who are at low risk[1] of local recurrence (for example, most people who have lymph node-negative breast cancer). [2018]

Dose fractionation

1.10.13 Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for women with invasive breast cancer after breast-conserving surgery or mastectomy. [2009]

Breast boost following breast-conserving surgery

1.10.14 Offer an external beam boost to the tumour bed for women with invasive breast cancer and a high risk[1] of local recurrence, following whole-breast radiotherapy. [2009, amended 2018]

1.10.15 Inform women of the risk of side effects associated with an external beam boost to the tumour bed following whole-breast radiotherapy. [2009, amended 2018]

1.11 Primary systemic therapy

Neoadjuvant chemotherapy

1.11.1 Offer neoadjuvant chemotherapy to people with ER-negative invasive breast cancer as an option to reduce tumour size. [2018]

1.11.2 Offer neoadjuvant chemotherapy to people with HER2-positive invasive breast cancer in line with the NICE technology appraisal on pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer. [2018]

1.11.3 Consider neoadjuvant chemotherapy for people with ER-positive invasive breast cancer as an option to reduce tumour size if chemotherapy is indicated. [2018]

Neoadjuvant chemotherapy regimens

1.11.4 For people with triple-negative invasive breast cancer, consider a neoadjuvant chemotherapy regimen that contains both a platinum[10] and an anthracycline. [2018]

1.11.5 Discuss the benefits and risks of adding a platinum[12] to an anthracycline-containing neoadjuvant chemotherapy regimen. Topics to discuss include those in table 6, and particularly the risk of increased toxicity. [2018]

Table 6 Benefits and risks of adding a platinum to anthracycline-containing neoadjuvant chemotherapy for triple-negative invasive breast cancer

	Effect of adding a platinum to anthracycline-containing (with or without taxane) neoadjuvant chemotherapy
Effect on breast conservation rate	Adding a platinum improves response rates compared with anthracycline-based (with or without taxane) chemotherapy. This may mean that some women who would otherwise need a mastectomy can be offered breast-conserving surgery.
Effect on pathological complete response rate (no residual cancer found at surgery)	Adding a platinum improves the chances of all signs of cancer disappearing in both the breast and lymph nodes in the armpit, compared with anthracycline-based (with or without taxane) neoadjuvant chemotherapy.
Effect on survival	No increase in overall survival with platinum-based chemotherapy.
Side effects *NOTE: Platinum-based therapy is only suitable for fit patients with no significant comorbidities.*	Adding a platinum may mean that side effects are more severe. Anaemia, thrombocytopenia, neutropenia and febrile neutropenia are seen more frequently with platinum-based chemotherapy. On average, if 1,000 women with triple-negative breast cancer receive platinum-containing neoadjuvant chemotherapy, about 70 additional women would experience severe or life-threatening side effects compared with non-platinum neoadjuvant chemotherapy. Bone marrow suppression and renal problems are likely in older people.
Licensed status	At the time of publication (July 2018), platinums did not have UK marketing authorisation for this indication.

Neoadjuvant endocrine therapy

1.11.6 Consider neoadjuvant endocrine therapy for postmenopausal women with

ER-positive invasive breast cancer as an option to reduce tumour size if there is

no definite indication for chemotherapy. [2018]

1.11.7 Advise premenopausal women that neoadjuvant chemotherapy may be more likely to produce a clinical response than neoadjuvant endocrine therapy, but that some tumours do respond to neoadjuvant endocrine therapy. [2018]

1.11.8 Discuss with women the benefits and risks of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy. Topics to discuss include those in table 7. [2018]

Table 7 Benefits and risks of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy

	Neoadjuvant endocrine therapy	Neoadjuvant chemotherapy

Definition	Tamoxifen or an aromatase inhibitor started before surgery. Only an option for women with ER-positive breast cancer.	Chemotherapy given before surgery. Only an option for people who would be recommended adjuvant (after surgery) chemotherapy.
Administration	Tablet taken once a day at home.	Intravenous administration in hospital, as an outpatient.
Effectiveness	**For postmenopausal women:** may be as effective as neoadjuvant chemotherapy in terms of breast conservation rates and shrinking the tumour. **For premenopausal women:** less effective than neoadjuvant chemotherapy at shrinking the tumour (but some tumours may respond so may be effective in some women).	**For postmenopausal women:** effective at improving breast conservation rates and shrinking the tumour. **For premenopausal women:** more effective than endocrine therapy at shrinking the tumour.
Potential disadvantages	If neoadjuvant endocrine therapy is not effective, then women may proceed to surgery earlier or may still need to have chemotherapy, either before or after surgery.	

Side effects	All endocrine therapies: menopausal symptoms such as hot flushes. For tamoxifen: increased risk of thrombosis and endometrial cancer. For aromatase inhibitors: joint and muscle pain, urogenital symptoms, bone density loss (may also occur with tamoxifen in premenopausal women). Side effects are usually reversible. May allow women to avoid the additional side effects of chemotherapy (although women may still need adjuvant chemotherapy after surgery).	Side effects may include nausea and vomiting, risk of infections that may be life threatening, fatigue, neuropathy, cardiac toxicity, diarrhoea, constipation, sore mouth, skin and nail changes, risk of blood clots, risk of second malignancies, fluid retention, allergic reactions and hair loss. Side effects may persist long term.
Fertility and family planning	Women should not become pregnant while taking tamoxifen, or within 2 months of stopping, because it may have adverse effects on the baby.	Often causes temporary infertility. May cause permanent infertility.
Length of course	May take longer than chemotherapy to shrink the tumour enough for breast-conserving surgery.	The duration of neoadjuvant chemotherapy is shorter than neoadjuvant endocrine therapy.

National Comprehensive Cancer Network (NCCN), 2018 [37].

Breast Cancer; Version 3.2018

Leitlinienorganisation/Fragestellung

National Comprehensive Cancer Network (NCCN); k.A.

Methodik

Grundlage der Leitlinie

Leitlinien-Update der Version 2.2018

Recherche/Suchzeitraum:

k.A.

LoE/ GoR

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

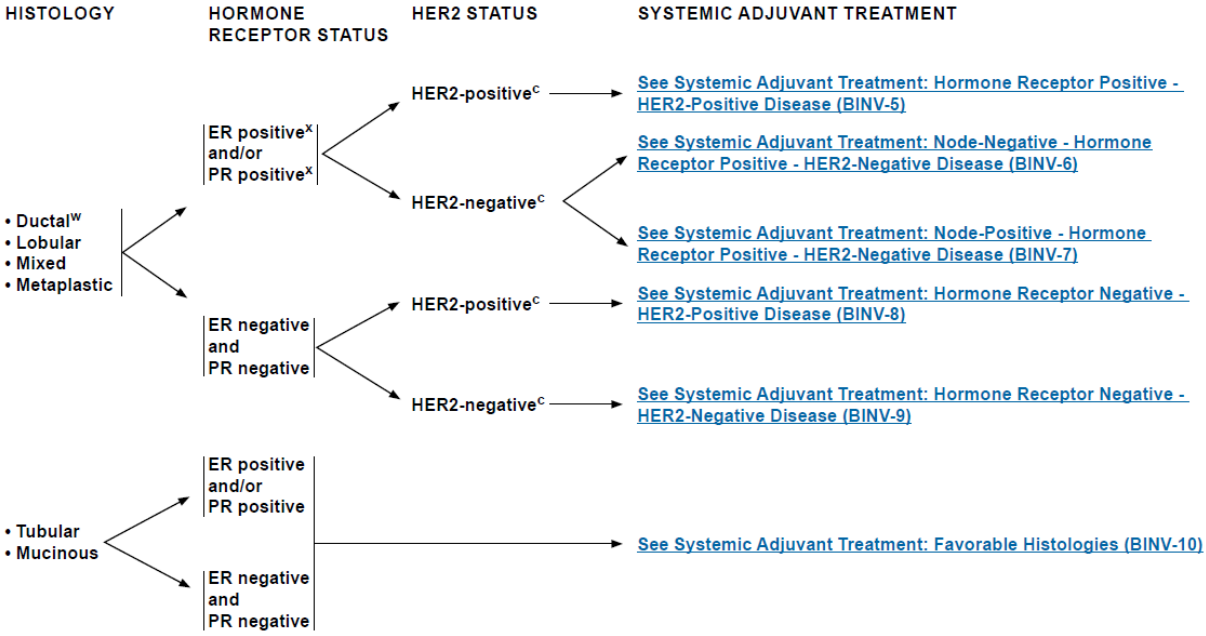
NCCN Categories of Preference:
All recommendations are considered appropriate.

See NCCN Categories of Preference.

Sonstige methodische Hinweise

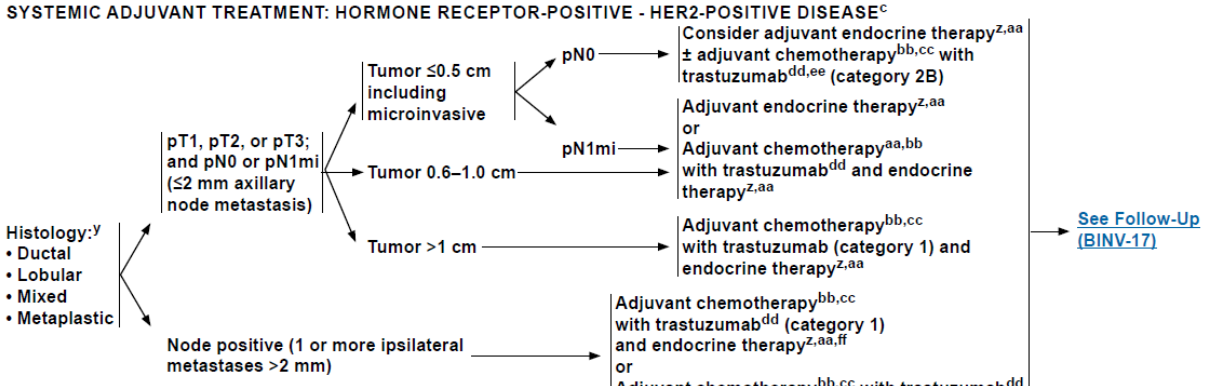
Die Leitlinie entspricht hinsichtlich ihrer methodischen Qualität nicht einer S-3 Leitlinie, wird aber aufgrund ihrer Aktualität und Verbreitung an dieser Stelle ergänzend dargestellt.

Empfehlungen



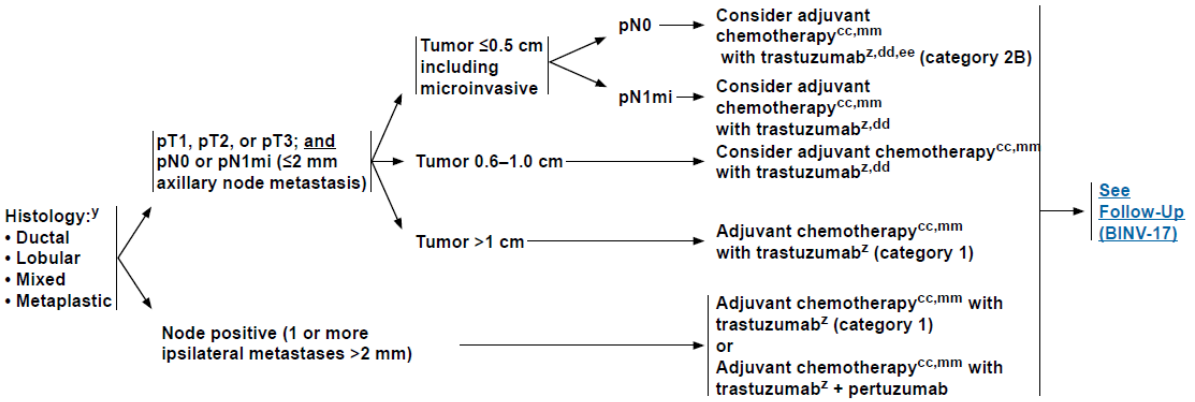
[c]See Principles of HER2 Testing (BINV-A).
[w]This includes medullary and micropapillary subtypes.
[x]The expression of ER and PR in breast cancer can range from low (1%–10%) to high levels. The biologic behavior of ER/PR low-expressing tumors may be more similar to ER/PR-negative cancers and this should be considererd in decision-making for adjuvant therapy.

SYSTEMIC ADJUVANT TREATMENT: HORMONE RECEPTOR-POSITIVE - HER2-POSITIVE DISEASE[c]



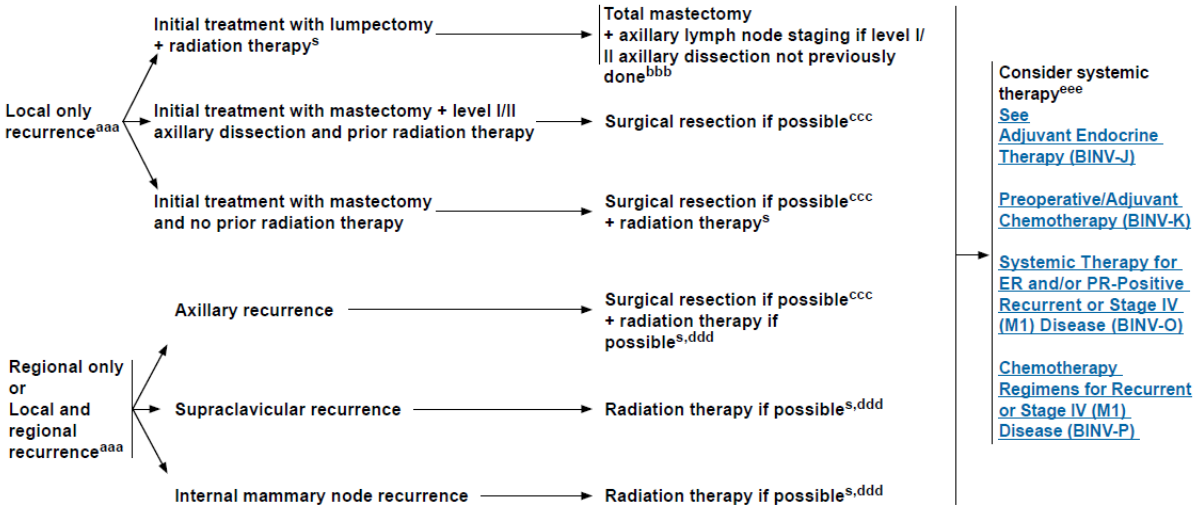
[c]See Principles of HER2 Testing (BINV-A).
[y]Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.
[z]Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.
[aa]Evidence supports that the magnitude of benefit from surgical or radiation ovarian ablation in premenopausal women with hormone receptor-positive breast cancer is similar to that achieved with CMF alone. See Adjuvant Endocrine Therapy (BINV-J).
[bb]Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy. Available data suggest that sequential or concurrent endocrine therapy with radiation therapy is acceptable. See Adjuvant Endocrine Therapy (BINV-J) and Preoperative/Adjuvant Therapy Regimens (BINV-K).
[cc]There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.
[dd]The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.
[ee]Adjuvant chemotherapy with weekly paclitaxel and trastuzumab (Tolaney et al. NEJM 2015) can be considered for T1,N0,M0, HER2-positive cancers, particularly if the primary cancer is ER negative. The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with ER-positive cancers and tumor size bordering on T1mic (<1 mm), when the estimated recurrence risk is less than 5% and endocrine therapy remains a viable option for systemic treatment.
[ff]Consider extended adjuvant neratinib following adjuvant trastuzumab-containing therapy for patients with HR-positive, HER2-positive disease with a perceived high risk of recurrence. The benefit or toxicities associated with extended neratinib in patients who have received pertuzumab is unknown.

SYSTEMIC ADJUVANT TREATMENT: HORMONE RECEPTOR-NEGATIVE - HER2-POSITIVE DISEASE[c]



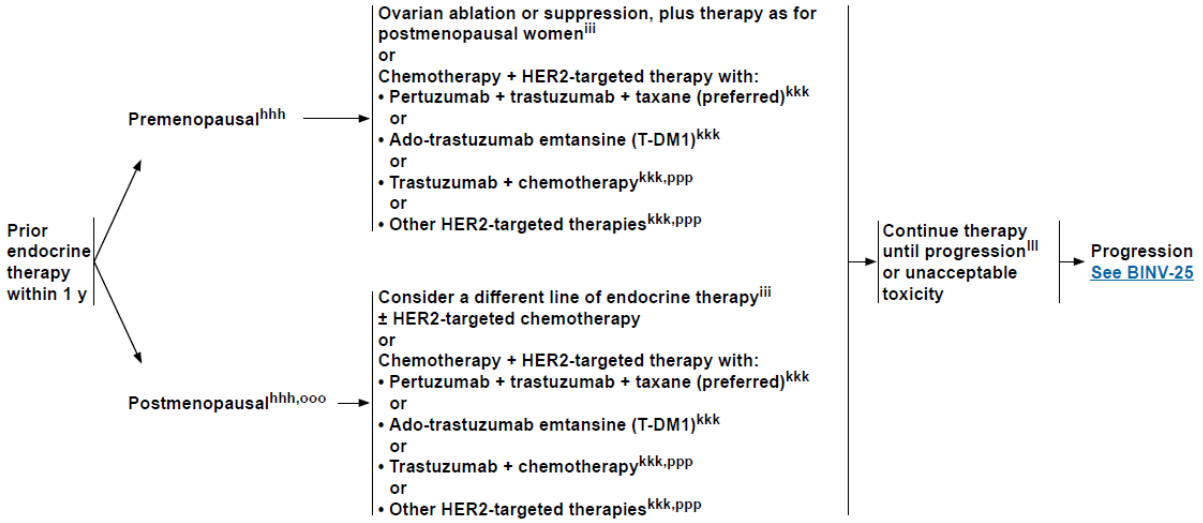
[c] See Principles of HER2 Testing (BINV-A).
[y] Mixed lobular and ductal carcinoma should be graded based on the ductal component and treated based on this grading. For metaplastic carcinoma, the prognostic value of the histologic grading is uncertain. However, when a specific histologic subtype of metaplastic carcinoma is present and accounts for more than 10% of the tumor, the subtype is an independent prognostic variable.
[z] Consider adjuvant bisphosphonate therapy in postmenopausal (natural or induced) patients receiving adjuvant therapy.
[cc] There are limited data to make chemotherapy recommendations for those >70 y of age. See NCCN Clinical Practice Guidelines for Older Adult Oncology.
[dd] The prognosis of patients with T1a and T1b tumors that are node negative is uncertain even when HER2 is amplified or overexpressed. This is a population of breast cancer patients that was not studied in the available randomized trials. The decision for use of trastuzumab therapy in this cohort of patients must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain, absolute benefits that may exist with trastuzumab therapy.
[ee] Adjuvant chemotherapy with weekly paclitaxel and trastuzumab (Tolaney et al. NEJM 2015) can be considered for T1,N0,M0, HER2-positive cancers, particularly if the primary cancer is ER negative. The absolute benefit of HER2-based systemic chemotherapy is likely negligible in patients with ER-positive cancers and tumor size bordering on T1mic (<1 mm), when the estimated recurrence risk is less than 5% and endocrine therapy remains a viable option for systemic treatment.
[mm] See Preoperative/Adjuvant Therapy Regimens (BINV-K).

TREATMENT OF LOCAL AND REGIONAL RECURRENCE



[s] See Principles of Radiation Therapy (BINV-I).
[aaa] Multidisciplinary approach is especially important in the management of breast cancer recurrence to consider all potential treatment options for optimal outcomes.
[bbb] In women with a local breast recurrence after breast-conserving surgery who had a prior sentinel node biopsy (SNB), a repeat SNB may be technically possible. The accuracy of repeat SNB is unproven, and the prognostic significance of repeat SNB after mastectomy is unknown and its use is discouraged.
[ccc] If not technically resectable, consider systemic therapy to best response, then resect if possible.
[ddd] The decision to use radiation therapy to treat locoregional recurrence must factor in any prior radiation to the area and the risk of late normal tissue toxicity from the sum of the prior and planned radiation courses.
[eee] For additional information see the Discussion section.

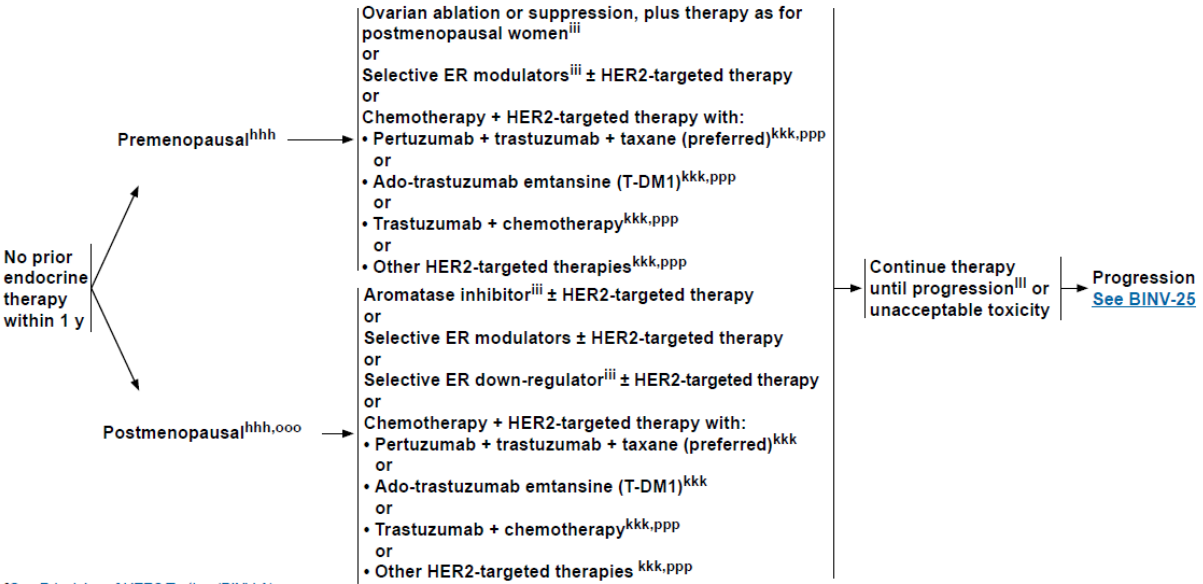
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER and/or PR POSITIVE; HER2 POSITIVE[c]



[c] See Principles of HER2 Testing (BINV-A).
[hhh] See Definition of Menopause (BINV-N).
[iii] See Systemic Therapy for ER and/or PR Positive Recurrent or Stage IV (M1) Disease (BINV-O).
[kkk] See Chemotherapy Regimens for Recurrentor Stage IV (M1) Disease (BINV-P).
[lll] See Principles of Monitoring Metastatic Disease (BINV-Q).

[ooo] Limited studies document a progression-free survival advantage of adding trastuzumab or lapatinib to aromatase inhibitor in postmenopausal patients with ER-positive, HER2-positive disease. However, no overall survival advantage has been demonstrated.
[ppp] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER AND/OR PR POSITIVE; HER2 POSITIVE[c]



[c] See Principles of HER2 Testing (BINV-A).
[hhh] See Definition of Menopause (BINV-N).
[iii] See Systemic Therapy for ER and/or PR Positive Recurrent or Stage IV (M1) Disease (BINV-O).
[kkk] See Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-P).
[lll] See Principles of Monitoring Metastatic Disease (BINV-Q).

[ooo] Limited studies document a progression-free survival advantage of adding trastuzumab or lapatinib to aromatase inhibitor in postmenopausal patients with ER-positive, HER2-positive disease. However, no overall survival advantage has been demonstrated.
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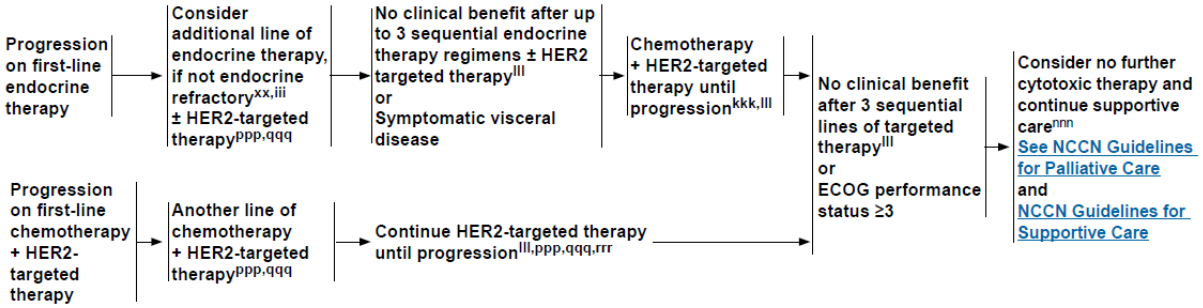
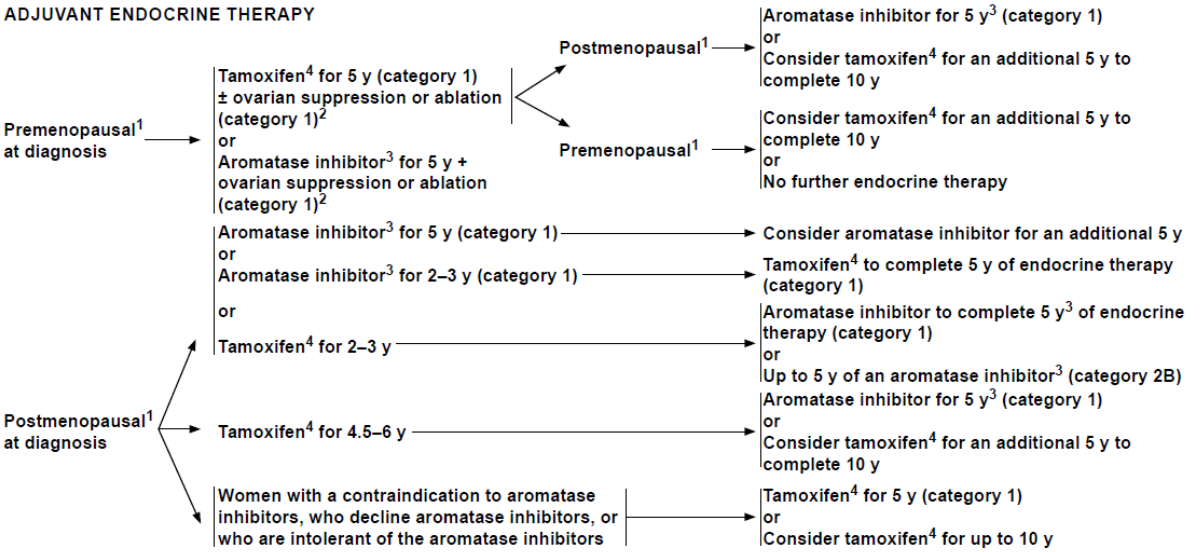
SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER and/or PR POSITIVE; HER2 POSITIVE[c]



[c] See Principles of HER2 Testing (BINV-A).
[xx] False-negative ER and/or PR determinations occur, and there may be discordance between the ER and/or PR determination between the primary and metastatic tumor(s). Therefore, endocrine therapy with its low attendant toxicity may be considered in patients with non-visceral or asymptomatic visceral tumors, especially in patients with clinical characteristics predicting for a hormone receptor-positive tumor (eg, long disease-free interval, limited sites of recurrence, indolent disease, older age).
[iii] See Systemic Therapy for ER and/or PR Positive Recurrent or Stage IV (M1) Disease (BINV-O).
[kkk] See Chemotherapy Regimens for Recurrent or Stage IV (M1) Disease (BINV-P).
[lll] See Principles of Monitoring Metastatic Disease (BINV-Q).
[nnn] The potential side effects of additional chemotherapy may outweigh any clinical benefit in a patient who has a compromised performance status.
[ppp] Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[qqq] Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
[rrr] Continue HER2-targeted therapy following progression on first-line HER2-targeted chemotherapy for metastatic breast cancer. The optimal duration of trastuzumab in patients with long-term control of disease is unknown.

ADJUVANT ENDOCRINE THERAPY



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

PREOPERATIVE/ADJUVANT THERAPY REGIMENS[1,2,3,4,5]

HER2-Negative[6]

- **Preferred regimens:**
  - Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks[7]
  - Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel[7]
  - TC (docetaxel and cyclophosphamide)
- **Useful in certain circumstances:**
  - Dose-dense AC (doxorubicin/cyclophosphamide)
  - AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)
  - CMF (cyclophosphamide/methotrexate/fluorouracil)
  - AC followed by weekly paclitaxel
- **Other recommended regimens:**
  - AC followed by docetaxel every 3 weeks
  - EC (epirubicin/cyclophosphamide)
  - TAC (docetaxel/doxorubicin/cyclophosphamide)

HER2-Positive

- **Preferred regimens:**
  - AC followed by T + trastuzumab[8] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab, various schedules)
  - AC followed by T + trastuzumab + pertuzumab[8] (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab plus pertuzumab)
  - Paclitaxel + trastuzumab[9]
  - TCH (docetaxel/carboplatin/trastuzumab)
  - TCH (docetaxel/carboplatin/trastuzumab) + pertuzumab
- **Useful in certain circumstances:**
  - Docetaxel + cyclophosphamide + trastuzumab
- **Other recommended regimens:**
  - AC followed by docetaxel + trastuzumab[8] (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab)
  - AC followed by docetaxel + trastuzumab + pertuzumab[8] (doxorubicin/cyclophosphamide followed by docetaxel plus trastuzumab plus pertuzumab)

[1]Retrospective evidence suggests that anthracycline-based chemotherapy regimens may be superior to non-anthracycline-based regimens in patients with HER2-positive tumors.
[2]Randomized clinical trials demonstrate that the addition of a taxane to anthracycline-based chemotherapy provides an improved outcome.
[3]CMF and radiation therapy may be given concurrently, or the CMF may be given first. All other chemotherapy regimens should be given prior to radiotherapy.
[4]Chemotherapy and endocrine therapy used as adjuvant therapy should be given sequentially with endocrine therapy following chemotherapy.
[5]Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m^2.
[6]The regimens listed for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.
[7]It would be acceptable to change the administration sequence to paclitaxel followed by dose-dense AC.
[8]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[9]Paclitaxel + trastuzumab may be considered for patients with low-risk T1,N0,M0, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.

CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[1]

HER2-Negative
Single agent[2]
Preferred regimens:

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- PARP inhibitors (options for patients with HER2-negative tumors and germline *BRCA1/2*- mutation)[3]
  - Olaparib[3] (category 1)
  - Talazoparib[3] (category 1)

Other recommended regimens:

- Cyclophosphamide
- Carboplatin
- Docetaxel
- Albumin-bound paclitaxel
- Cisplatin
- Epirubicin
- Ixabepilone

HER2-Negative
Combination regimens[2]
Preferred regimens:

- None[2]

Useful in certain circumstances[2]:

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[4]

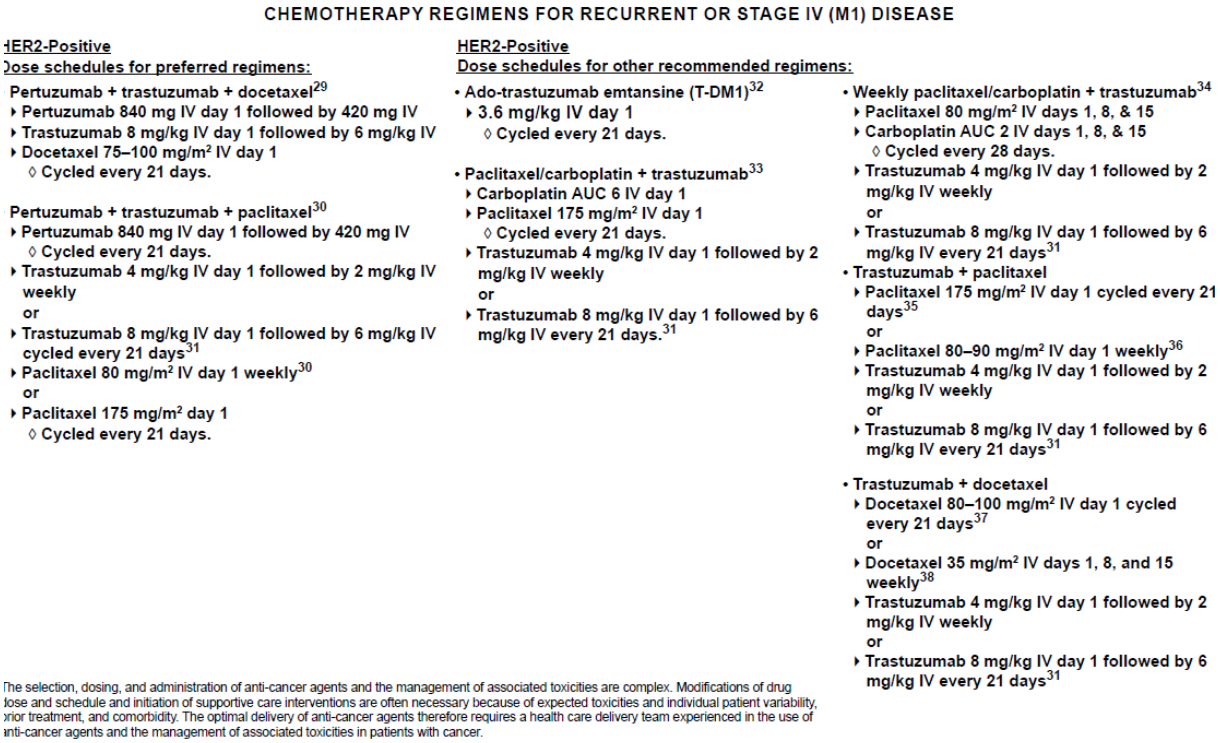
HER2-Positive
Preferred regimens:

- Pertuzumab + trastuzumab + docetaxel (category 1)[5]
- Pertuzumab + trastuzumab + paclitaxel[5]

Other recommended regimens:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel[5] ± carboplatin
- Trastuzumab + docetaxel[5]
- Trastuzumab + vinorelbine[5]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[5,6,7]

[1]Nab-paclitaxel may be substituted for paclitaxel or docetaxel due to medical necessity (ie, hypersensitivity reaction). If substituted for weekly paclitaxel or docetaxel, then the weekly dose of nab-paclitaxel should not exceed 125 mg/m^2.
[2]Sequential single agents are preferred, but chemotherapy combinations may be used in select patients with high tumor burden, rapidly progressing disease, and visceral crisis.
[3]Patients with HER2-negative disease eligible for single-agent therapy, strongly consider for germline *BRCA 1/2* testing.
[4]Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.
[5]Patients previously treated with chemotherapy plus trastuzumab in the absence of pertuzumab in the metastatic setting may be considered for one line of therapy including both trastuzumab plus pertuzumab in combination with or without cytotoxic therapy (such as vinorelbine or taxane). Further research is needed to determine the ideal sequencing strategy for anti-HER2 therapy.
[6]Trastuzumab given in combination with an anthracycline is associated with significant cardiac toxicity. Concurrent use of trastuzumab and pertuzumab with an anthracycline should be avoided.
[7]Trastuzumab may be safely combined with all non-anthracycline containing preferred and other single agents listed above for recurrent or metastatic breast cancer.



CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE

HER2-Positive
Dose schedules for preferred regimens:

Pertuzumab + trastuzumab + docetaxel[29]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV
- Docetaxel 75–100 mg/m² IV day 1
  - ◊ Cycled every 21 days.

Pertuzumab + trastuzumab + paclitaxel[30]
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV
  - ◊ Cycled every 21 days.
- Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  or
- Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV cycled every 21 days[31]
- Paclitaxel 80 mg/m² IV day 1 weekly[30]
  or
- Paclitaxel 175 mg/m² day 1
  - ◊ Cycled every 21 days.

HER2-Positive
Dose schedules for other recommended regimens:

- Ado-trastuzumab emtansine (T-DM1)[32]
  - 3.6 mg/kg IV day 1
    - ◊ Cycled every 21 days.
- Paclitaxel/carboplatin + trastuzumab[33]
  - Carboplatin AUC 6 IV day 1
  - Paclitaxel 175 mg/m² IV day 1
    - ◊ Cycled every 21 days.
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days.[31]
- Weekly paclitaxel/carboplatin + trastuzumab[34]
  - Paclitaxel 80 mg/m² IV days 1, 8, & 15
  - Carboplatin AUC 2 IV days 1, 8, & 15
    - ◊ Cycled every 28 days.
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[31]
- Trastuzumab + paclitaxel
  - Paclitaxel 175 mg/m² IV day 1 cycled every 21 days[35]
    or
  - Paclitaxel 80–90 mg/m² IV day 1 weekly[36]
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[31]
- Trastuzumab + docetaxel
  - Docetaxel 80–100 mg/m² IV day 1 cycled every 21 days[37]
    or
  - Docetaxel 35 mg/m² IV days 1, 8, and 15 weekly[38]
  - Trastuzumab 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    or
  - Trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days[31]

The selection, dosing, and administration of anti-cancer agents and the management of associated toxicities are complex. Modifications of drug dose and schedule and initiation of supportive care interventions are often necessary because of expected toxicities and individual patient variability, prior treatment, and comorbidity. The optimal delivery of anti-cancer agents therefore requires a health care delivery team experienced in the use of anti-cancer agents and the management of associated toxicities in patients with cancer.

Denduluri N et al., 2018 [13].

American Society of Clinical Oncology (ASCO)

Selection of Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer: ASCO Clinical Practice Guideline Focused Update

Hinweis: siehe auch: **Burstein 2014 HJ et al. [5].**

Leitlinienorganisation/Fragestellung

To update key recommendations of the ASCO guideline adaptation of the Cancer Care Ontario guideline on the selection of optimal adjuvant chemotherapy regimens for early breast cancer and adjuvant targeted therapy for breast cancer.

Questions Addressed in Focused Update

- Should adjuvant capecitabine be given following completion of standard preoperative anthracycline- and taxane-based combination chemotherapy in patients with early-stageHER2-negative breast cancer with residual invasive disease at surgery?
- Should 1 year of adjuvant pertuzumab be added to trastuzumab-based combination chemotherapy in patients with early stage HER2-positive breast cancer?
- Should neratinib be offered as extended adjuvant therapy for patients after combination chemotherapy and trastuzumabbased adjuvant therapy with early-stage, HER2-positive breast cancer?

Target Population

Patients who are being considered for, or who are receiving, systemic therapy following definitive surgery for early-stage invasive breast cancer, defined largely as invasive cancer anatomic stages I to IIIC

Target Audience

Medical oncologists, pathologists, surgeons, oncology nurses, patients, and caregivers.

Methodik

Grundlage der Leitlinie

An Expert Panel conducted targeted systematic literature reviews guided by a signals approach to identify new, potentially practice-changing data that might translate to revised practice recommendations.

Recherche/Suchzeitraum:

- PubMed; July 2015 to December of 2017

LoE

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

GoR

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

Sonstige methodische Hinweise

Guide for Types of Recommendations

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

Hinweis: Bei diesem Update wurde lediglich in PubMed gesucht.

Empfehlungen

The Expert Panel reviewed phase III trials that evaluated adjuvant capecitabine after completion of standard preoperative anthracycline- and taxane-based combination chemotherapy by patients with early-stage breast cancer HER2-negative breast cancer with residual invasive disease at surgery; the addition of 1 year of adjuvant pertuzumab to combination chemotherapy and trastuzumab for patients with early-stage, HER2-positive breast cancer; and the use of neratinib as extended adjuvant therapy for patients after combination chemotherapy and trastuzumab-based adjuvant therapy with early-stage, HER2-positive breast cancer.

Focused Update Recommendations

(1) Patients with early-stage HER2-negative breast cancer with pathologic invasive residual disease at surgery following standard anthracycline- and taxane-based preoperative therapy may be offered up to six to eight cycles of adjuvant capecitabine. (Type: evidence-based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate.)

Qualifying statements. If clinicians decide to use capecitabine, then the Expert Panel preferentially supports the use of adjuvant capecitabine in the subgroup of patients with hormone receptor–negative, HER2-negative disease. The capecitabine dosage used in the CREATE-X study (1,250 mg/m2 twice daily) is associated with higher toxicity in patients <= 65 years old.

Quality Assessment for Randomized Controlled Trial of Adjuvant Capecitabine for HER2-Negative Breast Cancer After Neoadjuvant Chemotherapy

Author	Adequate Random-ization	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intent-to-treat Analysis	Insignificant Conflicts of Interest	OVERALL RISK OF BIAS
Masuda et al 2017 **CREATE-X**	Yes	With the recruitment period set at 5 years, the follow-up period at a maximum of 5 years, the beta level at 0.2, and the alpha level at 0.05 (two-sided), the authors calculated that the trial would need to include 427 patients in each group. They thus planned to enroll 900 patients (450 patients per group).	Yes (see Table 1 of article)	No	Yes	Yes	Yes	Yes (Funders and sponsors had no role in the trial design, data collection and analysis, or the interpretation of the results.)	Low to intermediate

(2) Clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy in patients with high-risk, earlystage, HER2-positive breast cancer. (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate.)

Qualifying statements. The Expert Panel preferentially supports pertuzumab in patients with node-positive, HER2-positive breast cancer in view of the clinically insignificant absolute benefit observed among node-negative patients. After a median follow-up of 3.8 years, pertuzumab offered a modest disease-free survival (DFS) benefit. The first planned interim analysis did not show an overall survival (OS) benefit in the trial population. There are no data to guide the duration of pertuzumab in patients who received neoadjuvant pertuzumab and achieved a pathologic complete response.

Quality Assessment for Randomized Controlled Trial of Adjuvant Pertuzumab After Trastuzumab-based Combination Chemotherapy in Early-stage HER2-positive Breast Cancer

Author	Adequate Random-ization	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intent-to-treat Analysis	Insignificant Conflicts of Interest	OVERALL RISK OF BIAS
Von Minckwitz et al 2017 APHINITY	Yes	The trial was designed to have 80% power to detect a hazard ratio of 0.75 at a 5%, two-sided significance level.	Yes	Yes	Yes	Authors discuss that might be too short for assessment of effect size, especially in the cohorts of patients with hormone-receptor–positive or node-negative disease. Subsequent analyses are planned.	Yes	Yes (Funded by F. Hoffmann–La Roche/Genentech but sponsor had no access to the full database before the release of the results by the steering committee.)	Low to intermediate

(3) Clinicians may use extended adjuvant therapy with neratinib to follow trastuzumab in patients with early-stage, HER2-positive breast cancer. (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate.) Neratinib causes substantial diarrhea, and diarrhea prophylaxis must be used.

Qualifying statements. The Expert Panel preferentially favors use of neratinib in patients with HER2-positive, hormone receptor–positive, and node-positive disease. At a median follow-up of 5.2 years, no OS benefit has been observed. Patients who began neratinib within 1 year of trastuzumab completion appeared to derive the greatest benefit.

Quality Assessment for Randomized Controlled Trial of Neratinib After Trastuzumab-based Adjuvant Therapy in HER2-positive Breast Cancer

Author	Adequate Random-ization	Sufficient Sample Size	Similar Groups	Blinded	Validated and Reliable Measures	Adequate Follow-up	Intent-to-treat Analysis	Insignificant Conflicts of Interest	OVERALL RISK OF BIAS
Chan et al 2016; Martin et al 2017 ExteNET	Yes	Designed to enroll 3850 patients with 90% power to detect a hazard ratio (HR) of 0·7 for invasive disease-free survival. Later, power was projected to be 88%, assuming an HR of 0·667.	Yes	Yes	Yes	Yes 5-year data reported in Martin et al 2017	Yes	No Funders of the study designed the trial and were responsible for data collection, data integrity and analyses, and data interpretation Funders provided review of and input on manuscript	Low to intermediate

There are no data on the added benefit of neratinib in patients who also received pertuzumab in the neoadjuvant or adjuvant setting.

Smith DB et al., 2018 [42].

Radiation Therapy for the Whole Breast: an American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline

Leitlinienorganisation/Fragestellung

This guideline is endorsed by the Royal Australian and New Zealand College of Radiologists and the Society of Surgical Oncology.

Methodik

Grundlage der Leitlinie

In June 2015, the ASTRO Guidelines Subcommittee convened a work group to review new evidence published after completion of the systematic review for the prior ASTRO WBI guideline and to recommend whether the guideline should be withdrawn completely, updated, replaced, or reaffirmed. The group comprised one co-lead of the original guideline, two guidelines subcommittee members, and two additional topic experts (one not involved in the original guideline). After review of new literature, the work group recommended development of a new guideline that would replace the prior ASTRO WBI guideline and address a broader array of issues related to whole breast radiation. The work group also specifically recommended that discussion of regional nodal treatment not be included in this work product as this topic was felt to merit its own guideline. The proposal was approved by the ASTRO Board of Directors in October 2015. A task force of radiation oncologists specializing in breast cancer was recruited, as well as a medical physicist and a patient representative. The members were drawn from academic settings, community practice, and residency.

Through calls and emails, the task force formulated recommendation statements and narratives based on the literature review. The draft manuscript was reviewed by six expert reviewers (see Acknowledgments) and ASTRO legal counsel. The update was posted online for public comment in May and June 2017. The Board of Directors approved the final document in November 2017. Going forward, the ASTRO Guidelines Subcommittee will monitor this guideline beginning at two years after publication and initiate updates according to ASTRO policies.

Recherche/Suchzeitraum:

- A systematic literature review formed the basis of the guideline. An analytic framework incorporating the population, interventions, comparators, and outcomes (PICO) was used to develop search strategies in MEDLINE PubMed for each key question (KQ).
- The searches identified English-language studies between January 2009 and January 2016 for KQs 1-3 and between January 2000 and May 2016 for KQs 4-5. The included trials evaluated adults with invasive or in situ breast cancer receiving breast conserving surgery and WBI with or without a tumor bed boost.

LoE

The quality of evidence underlying each recommendation statement was categorized as either high, moderate, or low. These quality levels indicated:

- • “High: We are very confident that the true effect lies close to that of the estimate of the effect.

- • Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- • Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

GoR

- Guideline recommendation statements were developed based on the current literature using a modified GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology. GRADE is an explicit, systematic approach to defining the recommendation strength and quality of evidence. When available high-quality data formed the basis of the statements in accordance with the National Academies of Science, Engineering, and Medicine's Health and Medicine Division (formerly Institute of Medicine) standards. When necessary, expert opinion supplemented the evidence.
- Recommendations were classified as "strong" or "conditional." A strong recommendation indicated the task force was confident the benefits of the intervention clearly outweighed the harms, or vice-versa, and "all or almost all informed people would make the recommended choice for or against an intervention." Conditional recommendations were made when the balance between risks and benefits was more even or was uncertain. In these cases, the task force believed "most informed people would choose the recommended course of action, but a substantial number would not" and, therefore, "clinicians and other health care providers need to devote more time to the process of shared decision-making by which they ensure that the informed choice reflects individual values and preferences."

Sonstige methodische Hinweise

Consensus within the task force on the recommendation statements was evaluated through a modified Delphi approach adapted from the American Society of Clinical Oncology (ASCO) process.18 Task force members (except the patient representative) completed an online survey to rate their agreement with the recommendations on a five-point Likert scale, ranging from strongly disagree to strongly agree. The medical physics representative abstained from rating some clinically-focused recommendations, which are designated by an asterisk beside the consensus percentage. A pre-specified threshold of ≥75% of raters selecting "agree" or "strongly agree" indicated when consensus was achieved. If a recommendation statement did not meet this threshold, it was modified and re-surveyed or excluded from the guideline.

Empfehlungen

Empfehlung 1

Key Question 1: For patients receiving WBI without additional fields to cover the regional lymph nodes, what is/are the preferred dose-fractionation scheme(s) and how should these vary as a function of:

• Grade

• Margins

• ER/PR/HER2-neu status and other assessments of tumor biology

• Normal tissue exposure

• Systemic therapy receipt (including prior chemotherapy, concurrent endocrine, or targeted therapies)
• Age
• Stage (including DCIS versus invasive disease)
• Histology
• Breast size and dose homogeneity
• Collagen vascular disease and other relative contraindications to radiation
• Intent to cover the low axilla

Grade, margins, ER/PR/HER2 status and biology

Statement KQ1B: The decision to offer HF-WBI should be independent of tumor grade.
• Recommendation strength: Strong
• Quality of evidence: High
• Consensus: 100%

Statement KQ1C: The decision to offer HF-WBI may be independent of hormone receptor status, HER2 receptor status, and margin status.
• Recommendation strength: Conditional
• Quality of evidence: Moderate
• Consensus: 100%

There is no evidence indicating differential local control rates for HF-WBI compared to CF-WBI for patients with low to intermediate grade tumors. For patients with high grade tumors, the most current evidence also suggests that long-term local control is similar among patients treated with either HF-WBI or CF-WBI. Initially, an unplanned subgroup analysis of the OCOG trial indicated a higher risk of local failure with HF-WBI compared to CF-WBI among patients with high grade tumors, HR=3.08 (1.22–7.76, p=0.01).19 However, an update with a central pathologic review of 989 of 1234 patients enrolled failed to confirm this finding.24 In addition, a meta-analysis of 1272 patients participating in the START pilot, A, and B trials also showed no difference in the local-regional relapse by grade, with a hazard ratio of 0.86 (0.59–1.25).8 Population-based studies have also demonstrated similar long-term local control in grade 3 cancer treated with HF-WBI compared to CF-WBI.25 In light of the totality of this evidence, the task force felt that the decision to recommend HF-WBI versus CF-WBI should be independent of histologic grade.

In the OCOG trial, breast cancer subtype (luminal A, luminal B, HER2 enriched and basal) measured using immunohistochemistry and fluorescence in situ hybridization (FISH) was associated with risk of local recurrence, with higher risks noted in the luminal B and HER2 groups compared to luminal A. However, risk of local recurrence did not differ significantly by treatment arm when stratified by molecular subtype (for luminal A, HR=0.56, 95% CI 0.24-1.33; for luminal B, HR=0.89, 95% CI 0.68-2.12; for HER2, HR=0.91, 95% CI 0.22-3.81; and for basal, HR=1.27, 95% CI 0.21-7.58; HR<1 favors the 4250 cGy arm and HR>1 favors 5000 cGy arm; for overall comparison, interaction P-value = 0.73). Still, given the small subgroups with, for example, basal (n=125) or HER2 positive (n=39) breast cancer, power to detect an interaction between subtype and treatment arm was limited. Further, local control by molecular

subtype was not reported by the START investigators. As a result, it should be emphasized that the available evidence, while not conclusively demonstrating differences in local recurrence risk between HF-WBI and CF-WBI for any particular molecular subtype, does not necessarily rule out clinically meaningful differences in local recurrence risks for basal or HER2 positive patients by selected WBI dose-fractionation, as both of these subtypes were underrepresented in the OCOG trial. The task force felt that additional research in this area could be helpful. Regarding margins of resection, our systematic literature review did not identify any evidence evaluating whether width of margin negativity interacted with dose-fractionation of WBI; we would refer the reader to the recently published guidelines on these topics for further elaboration.26,27

Collagen vascular disease and other relative contraindications to radiation

Statement KQ1J: In patients with breast augmentation, either HF-WBI or CF-WBI may be used.

• Recommendation strength: Conditional

• Quality of evidence: Low

• Consensus: 85%*

Statement KQ1K: In patients with collagen vascular disease, if the patient and her physician opt for WBI, then either HF-WBI or CF-WBI may be used.

• Recommendation strength: Conditional

• Quality of evidence: Low

• Consensus: 85%*

The task force suggests that hypofractionation may be considered for women with collagen vascular disease or breast augmentation in cases where conventional fractionation would be considered. Such patients were not excluded from the original trials of hypofractionation and there are no specific data that women with these risk factors for increased radiation late effects have different outcomes when treated with hypofractionation of 4000-4250 cGy in 3 weeks or 5000 cGy in 5 weeks. Given the limited data in this setting, CF-WBI is also reasonable.47-49 Although choice of fractionation should always reflect individualized incorporation of the patient's values and preferences in a model of shared decision-making, this may be particularly important in cases like this where the evidence does not exist.

<u>Empfehlung 2</u>

Key Question 2: When should patients receive a tumor bed boost in conjunction with WBI and how should this vary as a function of:

• Stage/histology (including DCIS versus invasive disease)

• Age

• Grade

• Margins

• ER/PR/HER2-neu status and other assessments of tumor biology

• Dose-fractionation used for WBI

• Ability to limit dose to critical normal tissues, including heart and whole breast volume?

Age, grade, margins, and biology for invasive disease

Statement KQ2A: A tumor bed boost is recommended for patients with invasive breast cancer who meet any of the following criteria: age ≤50 years with any grade, age 51 to 70 years with high grade, or a positive margin.

• Recommendation strength: Strong

• Quality of evidence: Moderate

• Consensus: 100%

Statement KQ2B: Omitting a tumor bed boost is suggested in patients with invasive breast cancer who meet the following criteria: age >70 years with hormone receptor-positive tumors of low or intermediate grade resected with widely negative (≥2 mm) margins.

• Recommendation strength: Conditional

• Quality of evidence: Moderate

Consensus: 100%

Statement KQ2C: For patients with invasive breast cancer not meeting criteria articulated in KQ2A or KQ2B, individualized decision-making is suggested, as the decision in these cases is highly sensitive to patient preferences and values regarding the modest expected disease control benefit and the modest increase in treatment-related burden and toxicity associated with boost RT.

• Recommendation strength: Conditional

• Quality of evidence: Moderate

• Consensus: 100%

Age, grade, and margins for DCIS

Statement KQ2D: A tumor bed boost may be used for patients with DCIS who meet any of the following criteria: age ≤50 years, high grade, or close (<2 mm) or positive margins.

• Recommendation strength: Conditional

• Quality of evidence: Moderate

Consensus: 92%*

Statement KQ2E: A tumor bed boost may be omitted in patients with DCIS who, if age >50 years, meet the following criteria: screen detected, total size ≤2.5 cm, low to intermediate nuclear grade, and widely negative surgical margins (≥3 mm).

• Recommendation strength: Conditional

• Quality of evidence: Moderate

• Consensus: 100%*

Dose-fractionation used for WBI

Statement KQ2G: The decision to use a tumor bed boost is recommended to be based on the clinical indications for a boost and be independent of the whole breast fractionation scheme.

• Recommendation strength: Strong

• Quality of evidence: High

• Consensus: 100%

Narrative

Among task force members, there was general agreement that indications for a tumor bed boost are likely to be similar regardless of the WBI fractionation scheme. The task force agreed HF-WBI alone (without a boost) is not sufficient when a boost is indicated.

There is evidence from prospective trials to define the toxicity and efficacy of a tumor bed boost in patients treated with HF-WBI. In the Canadian hypofractionation trial, none of the 1234 patients received a boost, but the risk of IBTR at 10 years was only 6.5%, suggesting that potential benefit of a boost is likely to be small.19 However, a recent subset analysis performed on patients with available paraffin blocks did demonstrate a higher local relapse rate of 16.9% at 10 years in the subset of patients with Her2 enriched tumors, independent of the fractionation scheme. Whether the use of anti-Her2 therapy or a boost would have an impact on the relapse rate cannot be determined from these data.24

Sixty-one percent of patients in the prospective randomized START A hypofractionation trial and 43% of those in the START B trial undergoing breast-conserving surgery received the optional tumor bed boost of 1000 cGy in 5 fractions.5,6 Entry into the START trials was stratified by intention to give a boost. Boosts were equally distributed between the treatment arms. In a recent update of those trials, Haviland et al. reported in a post-hoc subgroup analysis of combined hypofractionation arms compared to the control arms that with respect to local control, the treatment effect was not significantly different, irrespective of the use of a boost. Notably, whether or not a boost was employed, normal tissue effects appeared to favor the hypofractionation approach.8 Given these observations, task force members agreed that the use of a boost in conjunction with HF-WBI appears reasonable.

One final caveat relevant to this topic pertains to use of CF-WBI when a boost is omitted. Typically, the standard CF-WBI dose in the setting of boost omission is 5000 cGy in 25 fractions or 5040 cGy in 28 fractions. Lower doses of CF-WBI such as 4600 cGy in 23 fractions or 4500 cGy in 25 fractions are not typically used when a boost is omitted.

Empfehlung 3

Key Question 3: What is/are preferred dose-fractionation scheme(s) for a tumor bed boost and how should this vary as a function of:

- Stage/histology (including DCIS versus invasive disease)
- Age
- Grade
- Margins
- ER/PR/HER2-neu status and other assessments of tumor biology

Dose-fractionation used for WBI?

Statement KQ3A: In the absence of strong risk factors for local recurrence such as those enumerated in KQ3B, 1000 cGy in 4 to 5 fractions is suggested as the standard tumor bed boost dose-fractionation, regardless of whole breast dose-fractionation, stage, or histology.

- Recommendation strength: Conditional
- Quality of evidence: Moderate
- Consensus: 100%

Statement KQ3B: Particularly in the presence of strong risk factor(s) for local recurrence, such as the single risk factor of positive margins or a combination of risk factors such as young age and close margins, a higher radiation boost dose of 1400 to 1600 cGy in 7 to 8 fractions or 1250 cGy in 5 fractions may also be used.

• Recommendation strength: Conditional

• Quality of evidence: Low

• Consensus: 85%*

Department of Health, 2015 [14].

Diagnosis, staging and treatment of patients with breast cancer.

National Clinical Guideline No. 7.

Leitlinienorganisation/Fragestellung

The National Clinical Guideline on the diagnosis, staging and treatment of patients with breast cancer in Ireland was developed by the National Cancer Control Programme (NCCP), in collaboration with clinicians, librarians and stakeholder groups.

In 2006, the second national cancer strategy, A Strategy for Cancer Control in Ireland (DoHC, 2006), advocated a comprehensive cancer control programme. It was recommended that national site-specific multidisciplinary groups be convened to develop national evidence-based clinical guidelines for cancer care. The principal objective of developing these guidelines is to improve the quality of care received by patients. Other objectives include:

• Improvements in the quality of clinical decisions,

• Improvement in patient outcomes,

• Potential for reduction in morbidity and mortality and improvement in quality of life,

• Promotion of interventions of proven benefit and discouragement of ineffective ones, and

• Improvements in the consistency and standard of care.

Patients that are covered by this guideline are: Adults (18 years or older) with newly diagnosed early and locally advanced breast cancer.

Methodik

Grundlage der Leitlinie

The methodology for the development of the guideline was designed by a research methodologist and is based on the principles of Evidence-Based Practice (EBP) (Sackett et al., 2000). The methodology is described in detail in the NCCP Methodology Manual for guideline development.

Recherche/Suchzeitraum:

- The following bibliographic databases were searched in the order specified below using keywords implicit in the PICO(T) question and any identified subject headings:
  - Cochrane Library
  - Point-of-Care Reference Tools
  - Medline

• Embase (where available)

• Other bibliographic databases such as PsycINFO, CINAHL, as appropriate.

The literature was searched based on the hierarchy of evidence. All literature searches were updated prior to publication and are current up to September 2014. A full set of literature search strategies is available on the NCCP and NCEC websites.

LoE/ GoR

International guidelines were appraised using the international, validated tool; the AGREE II instrument (Brouwers et al., 2010). Primary papers were appraised using validated checklists developed by the Scottish Intercollegiate Guideline Network (SIGN). There were three main points considered when appraising all the research evidence:

• Are the results valid? (internal validity)

• What are the results? (statistical and clinical significance)

• Are the results applicable/generalisable to the patient/population of the guideline?

(external validity).

Table 9 Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

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+

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

Sonstige methodische Hinweise

- Laut Angaben der Autoren ist diese Leitlinie möglicherweise bereits veraltet:

  „This guideline was published in June 2015 and will be considered for review by the NCCP in three years."

Empfehlungen

Medical oncology

2.4.1.1 Adjuvant chemotherapy should be considered for all patients with breast cancer whose disease is at moderate/high risk of recurrence. (A)

2.4.1.2 Adjuvant trastuzumab should be considered in all patients with HER2 positive breast cancer who receive adjuvant chemotherapy. (A)

2.4.1.3 The standard duration of treatment with adjuvant trastuzumab is one year. (A)

2.4.1.4 Adjuvant trastuzumab should preferably be given concurrently with taxane based regimens. It should not be given concurrently with anthracyclines. (A)

2.4.2.1 Premenopausal women with hormone receptor positive breast cancer should be treated with tamoxifen. (A)

2.4.2.2 The standard duration of treatment with tamoxifen for premenopausal women with hormone receptor positive breast cancer is at least five years, but there is evidence to support up to 10 years of use. (A)

2.4.2.3 Currently, the routine use of adjuvant ovarian ablation/suppression is not considered standard practice. (B)

2.4.3.1 Postmenopausal women with hormone receptor positive breast cancer should be treated with hormonal therapy for at least five years. The options include:

- Tamoxifen for five years followed by five years of an aromatase inhibitor. (A)
- An aromatase inhibitor as initial adjuvant therapy for five years. (A)
- Tamoxifen for two to three years followed by an aromatase inhibitor to complete five years of adjuvant endocrine therapy or tamoxifen for two to three years followed by five years of adjuvant endocrine therapy. (A)

2.4.3.2 In postmenopausal women, the use of tamoxifen alone for five years can be considered for those who decline, have a contraindication to, or are intolerant of aromatase inhibitors. (A)

2.4.4.1 Any patient who is a candidate for adjuvant systemic therapy can be considered for neoadjuvant systemic therapy. (A)

2.4.4.2 Neoadjuvant chemotherapy can be considered as part of a multimodal treatment approach for patients with stage IIa, IIb, and III breast cancer. (A)

2.4.4.3 For patients with locally advanced or inflammatory breast cancer preoperative chemotherapy is the preferred option. (A)

2.4.4.4 Patients with HER2 positive breast cancer, receiving neoadjuvant chemotherapy, should receive trastuzumab. (A)

HER2 positive

Trastuzumab should be incorporated in the treatment plan for women with HER2 positive breast cancer. The addition of neoadjuvant trastuzumab to chemotherapy leads to improved disease free survival (HR 0.60, 95% CI 0.50 to 0.71, P<0.00001) and overall survival (HR 0.66, 95% CI 0.57 to 0.77, P<0.00001) (Moja et al., 2012). 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) (Valachis et al., 2011). 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% versus 13%) (Semiglazov et al., 2011). (SIGN, 2013)

In women with HER2 positive tumours treated with neoadjuvant chemotherapy, the addition of neoadjuvant trastuzumab to paclitaxel followed by chemotherapy with FEC (fluorouracil/epirubicin/ cyclophosphamide) was associated with an increase in the pathologic complete response rate from 26% to 65.2% (P=0.016) (Buzdar et al., 2005). (NCCN, 2014).

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SEMIGLAZOV, V., EIERMANN, W., ZAMBETTI, M., MANIKHAS, A., BOZHOK, A., LLUCH, A., TJULANDIN, S., SABADELL, M. D., CABALLERO, A., VALAGUSSA, P., BASELGA, J. & GIANNI, L. 2011. Surgery following neoadjuvant therapy in patients with HER2-positive locally advanced or inflammatory breast cancer participating in the NeOAdjuvant Herceptin (NOAH) study. Eur J Surg Oncol, 37, 856-63.

SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN). 2013. Treatment of primary breast cancer – a national clinical guideline. Edinburgh: SIGN; 2013. (SIGN publication no. 134). [cited 01 Nov 2014]. Available: www.sign.ac.uk

BUZDAR, A., IBRAHIM, N., FRANCIS, D., BOOSER, D., THOMAS, E., THERIAULT, R., PUSZTAI, L., GREEN, M., ARUN, B., GIORDANO, S., CRISTOFANILLI, M., FRYE, D., SMITH, T., HUNT, K., SINGLETARY, S., SAHIN, A., EWER, M., BUCHHOLZ, T., BERRY, D. & HORTOBAGYI, G. 2005. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: Results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. Journal of Clinical Oncology, 23, 3676-3685.

NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN) 2014. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2014. © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [July 21, 2014]. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

2.4.4.5 Neoadjuvant endocrine therapy is an option for patients with oestrogen-receptor positive breast cancer considered unsuitable for neoadjuvant chemotherapy or primary surgery. (C)

Radiation onkology

2.5.1.1 Postmastectomy radiotherapy should be recommended in patients with lymph node positive breast cancer if they have high risk of recurrence (≥4 positive lymph nodes and/or T3/T4 primary tumour). (A)

2.5.1.2 Postmastectomy radiotherapy should be considered in patients with intermediate risk of recurrence (1-3 nodes) and individual patients should be discussed at multidisciplinary team meeting. (B)

2.5.2.1 All patients with ductal carcinoma in situ having breast conserving surgery should be considered for adjuvant radiotherapy. (A)

2.5.3.1 Radiotherapy is recommended for all patients undergoing breast conserving surgery for early breast cancer. (A)

2.5.3.2 Hypofractionation schedules are recommended for patients with early breast cancer. (A)

2.5.4.1 In patients who have undergone breast conserving surgery for early breast cancer, adjuvant radiotherapy shows a benefit in all subpopulations. (A)

2.5.5.1 In patients who have breast conserving surgery, radiotherapy boost is recommended for patients aged 50 or under at diagnosis. (A)

2.5.5.2 Radiotherapy boost should be considered in patients >50 who have risk factors (e.g. high grade invasive cancers). (A)

2.5.6.1 Women who have undergone surgery for breast cancer should receive local breast irradiation as soon as possible following wound healing. A safe interval between surgery and the start of radiotherapy is unknown, but it is reasonable to start breast irradiation within 12 weeks of definitive surgery. (C)

2.5.7.1 Recommend adjuvant radiation to the supraclavicular fossa in patients with four or more positive axillary nodes. (C)

2.5.7.2 Consider adjuvant radiation to the supraclavicular fossa in selected patients with 1-3 positive axillary nodes. (C)

2.5.7.3 Consider irradiation to the internal mammary chain in patients with positive axillary nodes and/or inner quadrant tumours. (B)

2.5.7.4 Consider adjuvant radiation to the axilla in patients with positive axillary nodes who have not had an axillary dissection. (B)

Cancer Australia, 2015 [6].

Hypofractionated radiotherapy for early (operable) breast cancer

Leitlinienorganisation/Fragestellung

Cancer Australia

This guideline includes statements, recommendations and practice points based on available, high-level evidence about the use of hypofractionated radiotherapy for the treatment of women with early (operable) breast cancer. The guideline aims to provide all health professionals within a multi-disciplinary team with information to assist in making management recommendations for improved patient outcomes.

Methodik

Grundlage der Leitlinie

This guideline was first published in November 2011 and has been updated to incorporate new evidence.

The Statements and Recommendations on the use of hypofractionated radiotherapy for early (operable) breast cancer are based on two Cancer Australia systematic reviews:

1. Cancer Australia systematic review of RCTs which included available evidence published from January 2001 to March 2010,19 that informed the clinical practice guidelines on the use of hypofractionated radiotherapy for early (operable) breast cancer published by Cancer Australia in November 2011.

2. Updated Cancer Australia systematic review of RCTs to identify new and updated evidence published from January 2010 to November 2013.20

Recherche/Suchzeitraum:

- Siehe Grundlage der Leitlinie

LoE/ GoR

The Recommendations are based on Statements of Evidence on the use of hypofractionated radiotherapy for the treatment of early (operable) breast cancer. Practice points are also provided to help guide clinical decisions for the use of hypofractionated radiotherapy for the treatment of early (operable) breast cancer.

Practice points are based on expert opinion when the evidence to make a recommendation is insufficient or where the evidence is outside the scope of the systematic review.

All Recommendations have been graded using the National Health and Medical Research Council (NHMRC) FORM methodology.8,9 The NHMRC grades (A-D) assigned to the recommendation given are intended to indicate the strength of the body of evidence underpinning the recommendation (refer to Table 1).

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Sonstige methodische Hinweise

Es ist unklar, was genau im Leitlinien-Update von 2015 gegenüber der Version von 2011 geändert wurde.

Empfehlungen

The total body of evidence on hypofractionated radiotherapy for early (operable) breast cancer from these two systematic reviews includes:

Six primary Randomised Controlled Trials (RCTs): START A trial, START B trial, a trial by Spooner et al, the UK FAST trial, the Canadian trial and the United Kingdom Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) trial Three RCTs published as conference abstracts only.

Of the six primary RCTs, all but one (UK FAST) were included in the evidence base for the 2011 Cancer Australia Guidelines. Thus, the evidence base for the current guideline includes the most current data from these five trials together with data from the UK FAST trial.

Patients

Recommendations		Grade	References
1	In selected patients* with early breast cancer who require post-operative whole breast radiotherapy, hypofractionated radiotherapy is a suitable alternative to conventionally fractionated radiotherapy, and should be offered where appropriate. *Patients: • Women aged 50 years or older • with pathological stage T1-2, node-negative (N0), non-metastatic (M0) disease • who have undergone breast conserving surgery, with clear surgical margins	A	Haviland 2013[10] (START A and B) Spooner 2012[11] UK FAST trial 2011[12] Whelan 2010[6] (Canadian trial) Owen 2006[7] (RMH/GOC trial)
2	For women outside the above criteria with early breast cancer who require post-operative whole breast radiotherapy, hypofractionated radiotherapy could be considered as an alternative to conventionally fractionated radiotherapy. Note: there is insufficient evidence to make a recommendation for or against the use of hypofractionated radiotherapy for men with breast cancer.	C	Haviland 2013[10] (START A and B) Spooner 2012[11] UK FAST trial 2011[12] Whelan 2010[6] (Canadian trial) Owen 2006[7] (RMH/GOC trial)
Practice point			
a	Recent evidence indicates that tumour grade does not need to be		Whelan 2010[6]

	taken into account when considering the use of hypofractionated radiotherapy	Bane 2014[14] Haviland 2013[10] Herbert 2012[15]

Optimal Schedules

Recommendation		Grade	References
3	For women not receiving a tumour bed boost, recommended hypofractionated schedules for whole breast radiotherapy based on current evidence are: • 40 Gy in 15 fractions given at the rate of one fraction per day, 5 fractions per week over 21 days; or • 42.5 Gy in 16 fractions given at the rate of one fraction per day, 5 fractions per week over 22 days	A	Haviland 2013[10] (START B) Canadian[6,13] Spooner 2012[11]
Practice point			
b	For women in whom a tumour bed boost is indicated, specific evidence-based dose-fractionation schedules for use with tumour bed boost have not been defined, but the following boost doses are considered acceptable: • 10 Gy in 5 fractions		[10] Haviland 2013 (START B)

Adverse Events And Toxicity

Recommendation		Grade	References
4	When selecting an appropriate radiotherapy schedule consideration should be given to the possibility of adverse events including acute reactions and late effects, noting that cosmetic outcomes are equivalent with the recommended optimal schedules for hypofractionated radiotherapy versus a conventionally fractionated radiotherapy schedule.	B	Haviland 2013[10] (START A and B) Spooner 2012[11] UK FAST trial 2011[12] Whelan 2010[6] (Canadian trial) Owen 2006[7] (RMH/GOC trial)

Practice Point		
c	As cardiac effects from radiation therapy may take up to 20 years to develop, heart sparing protocols should be adopted irrespective of the dose fractionation regimen used. Particular consideration should be given to these effects when prescribing hypofractionated radiation therapy to the left breast, especially in women with pre-existing heart disease..	Haviland 2013[10] (START A and B)

Alberta Provincial Breast Tumour Team, 2015 [1].

Adjuvant radiation therapy for ductal carcinoma in situ

Leitlinienorganisation/Fragestellung

- What is the optimal RT treatment after surgery (BCS or mastectomy) for patients with DCIS? For patients with DCIS, how should a close radial margin of excision be handled following BCS?

  (Ductal carcinoma in situ (DCIS); breast-conserving surgery (BCS))

Methodik

Grundlage der Leitlinie

The recommendations contained in this guideline were developed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical, radiation and surgical oncologists, as well as nurses, pathologists and pharmacists. Evidence in support of the guidelines was selected and reviewed by a working group from the Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during guideline development can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in June 2008. This guideline was revised in April 2012, and June 2015.

Target population: These recommendations apply to adult patients with DCIS who have had BCS or a mastectomy.

Recherche/Suchzeitraum:

- Bis Juni 2015

LoE/ GoR

Evidence Tables. Evidence tables generally document the following information: authors, year of publication, patient group/stage of disease, study methods, and main outcomes of interest. Existing guidelines on the topic will be assessed by the KMS using portions of the AGREE-II instrument (http://www.agreetrust.org/agree-ii/). Guidelines meeting the minimum requirements will be included in the evidence document.2,3 Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge the quality of the studies.

Sonstige methodische Hinweise

- Obwohl allgemeine methodische Standards der Leitlinienerstellung genannt sind, bleibt im konkreten Fall unklar, wie diese Leitlinie zustande kam, wie und in welchem Ausmaß Konsens gefunden wurde und wie stark die Empfehlungen sind.

Empfehlungen

For breast cancer patients with DCIS, recommendations are presented in Table 1 for the standard of care for adjuvant RT following surgery.

Table 1 Adjuvant RT for Patients with DCIS

Type of Surgery	
BCS	**Mastectomy**
• Adjuvant whole breast radiotherapy (WBRT) recommended • Partial breast RT investigational as part of clinical trial if available • For positive margins (ink on margin), re-excision recommended (close margin at fascia is an exception) • Pathologic/radiologic correlation required with margin width less than 2 mm; re-excision may be considered if there is discordance and based on individual case details • For close margins not treated with re-excision, the role of RT boost is not well defined	• No adjuvant RT recommended, even if resection margins close. Adjuvant RT can be considered when margin positive but benefit not defined

Dose/Fractionation Schedule and Acute Toxicity

The three randomized trials in DCIS used the same dose, fractionation schedule, and 5000 cGy in 25 fractions in five weeks.5-9,11 Whereas the Ontario Clinical Oncology Group (OCOG) trial randomized 1,234 women with invasive disease treated with BCS to a course of 5000 cGy in 25 fractions over five weeks or a course of 4250 cGy in 16 fractions over three weeks.12,13 At a median follow-up of 69 months, the five-year local recurrence-free survival was 97.2% in the long arm (absolute difference, 0.4%; 95% CI = -1.5%-2.4%). No difference was detected between arms in terms of disease-free or overall survival rates. The 16 fraction arm had better cosmetic outcome compared to the 25 fraction schedule (76.8% vs. 77.4%, absolute difference, 0.6%; 95% CI, -6.5%-5.5%). However, skin toxicity (Grade II or III) had a non-statistically significant higher incidence in the 16 fraction arm compared to the 25 fraction arm (absolute difference, 6%; 95% CI, -0.3%-10%), but there was no significant difference in the incidence of radiation pneumonitis. Only rib fracture in the 25 fraction arm was reported. This information suggests that the risk of toxicity from the 4250 cGy in 16 fractions protocol has a similar toxicity rate to the 5000cGy in 25 fractions protocol. There is no randomized data using the shorter fraction schedule in DCIS, but the OCOG data has been extrapolated to the DCIS population.

Side effects of radiotherapy

The side effects of modern breast RT are modest including altered pigmentation,14 breast discomfort, and firmness. 15,16 The risk of cardiac disease is generally low with modern RT techniques.13,16,17 Several studies report an association between RT and cardiovascular morbidity, including myocardial infraction and congestive heart failure. 18,19 In addition, a few studies have shown an increased risk of cardiovascular disease in patients who were treated with left-sided breast irradiation after breast-conserving therapy.20,21

There is a higher risk of some malignancies in women receiving RT versus women not receiving RT. Increased RR was reported for lung cancer at 10-14 years and 15 or more years after initial breast cancer diagnosis (RR 1.62, 95% CI; 1.05-2.54 and RR 1.49, 95% CI; 1.05-2.14, respectively), for second breast cancer at 5-10 years (RR 1.34; 95% CI, 1.10-1.63) and 15 + years (RR 1.26; 95% CI, 1.00-1.59) and oesophageal cancer at 15 or more years (RR 2.19; 95% CI, 1.10-4.62).22 However given the protracted interval between treatment and the development of another neoplasm in the irradiated field, many of these studies are old. The risk of a second malignancy related to breast cancer RT treatment is currently estimated to be approximately one per thousand women receiving RT.

Alberta Provincial Breast Tumour Team, 2015 [2].

Adjuvant radiation therapy for invasive breast cancer

Leitlinienorganisation/Fragestellung

- For patients with T1, T2, T3, T4 invasive breast cancer, what is the optimal RT treatment after surgery (BCS or mastectomy) according to lymph node status (positive or negative)?
- How should a positive margin be handled for patients treated with BCS?
- For patients with invasive breast cancer treated with neoadjuvant chemotherapy, what is the optimal radiotherapy treatment after surgery (BCS or mastectomy)?
- For left-sided breast cancer patients, can cardiac irradiation be minimized?

Methodik

Grundlage der Leitlinie

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in June 2008. This guideline was revised in April 2012, March 2013, June 2014, and June 2015.

Target pupulation: These recommendations apply to adult patients with invasive breast cancer who have had BCS or a mastectomy.

Recherche/Suchzeitraum:

k.A.

LoE/ GoR

Evidence Tables. Evidence tables generally document the following information: authors, year of publication, patient group/stage of disease, study methods, and main outcomes of interest. Existing guidelines on the topic will be assessed by the KMS using portions of the AGREE-II instrument (http://www.agreetrust.org/agree-ii/). Guidelines meeting the minimum requirements will be included in the evidence document.2,3 Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge the quality of the studies.

Sonstige methodische Hinweise

Obwohl allgemeine methodische Standards der Leitlinienerstellung genannt sind, bleibt im konkreten Fall unklar, wie diese Leitlinie zustande kam, wie und in welchem Ausmaß Konsens gefunden wurde und wie stark die Empfehlungen sind.

Empfehlungen

Recommendations about the optimal use of RT following BCS for patients with invasive breast cancer are presented in Table 1.

Table 1 Radiotherapy Recommendations for Invasive Breast Cancer Following Surgery

Type of Breast Cancer	Surgery	
	Breast-conserving*	**Mastectomy**
T1/T2 and node negative	• Adjuvant whole breast radiation therapy (WBRT) alone (no regional nodal radiation therapy [RT]) is recommended • Partial breast radiotherapy investigational as part of clinical trial if available, or in very select patients	• No adjuvant radiotherapy recommended, if negative margins are achieved. Adjuvant RT can be considered when margin positive, but benefit not defined

T1/T2 and node positive	Adjuvant WBRT recommended in all cases
	
	Regarding regional nodal irradiation (RNI):
	• Isolated tumour cells in nodes (N0 as per TNM staging):
	  ○ RNI not recommended
	• Sentinel lymph node biopsy (SLNB) positive micromets:
	  ○ RNI individualized based on risk assessment
	  ○ Warrant a discussion with a radiation oncologist:
	• Macrometastatic nodal disease:
	  ○ RNI recommended
		• Isolated tumour cells in nodes (N0 as per TNM staging):
		  ○ No adjuvant RT recommended
		• SLNB positive micromets warrant a discussion with a radiation oncologist:
		  ○ Chest wall with RNI individualized, based on risk assessment
		• Macrometastatic nodal disease:
		  ○ Chest wall and RNI recommended

T3/T4 and node negative or node positive	• Radiotherapy to breast and RNI recommended	• Radiotherapy to chest wall and RNI recommended

Treated with neoadjuvant chemotherapy	• Radiotherapy to breast recommended regardless of final pathology
	
	Regarding RNI:
	• Clinical stage T1/T2N0:
	  ○ No RNI recommended
	• Clinical stage II (T1/T2N1 or T3N0):
	  ○ RNI based on consultation with radiation oncologist and degree of pathologic response
	• Clinical stage III/Locally advanced breast cancer (T1-T4N2-3, T3N1):
	  ○ RNI recommended
		• Clinical stage T1/T2N0:
		  ○ No adjuvant radiotherapy recommended
		• Clinical stage II (T1/T2N1 or T3N0):
		  ○ Adjuvant radiotherapy individualized based on consultation with radiation oncologist and degree of pathologic response
		• Clinical stage III/Locally advanced breast cancer (T1-T4N2-3, T3N1):
		  ○ Chest wall and RNI recommended

Left-sided breast cancer	Deep inspiration breath hold (DIBH) during adjuvant radiation therapy should be an available treatment option to minimize cardiac dose.	

* For positive margins, re-excision is recommended (positive margins at fascia is an exception); radiotherapy boost recommended in all women <40 yrs regardless of margin; in women >40 yrs, boost individualized based on risk assessment

Dose/Fractionation schedule

The majority of trials examining WBRT delivered doses of 40-50 Gy to the whole breast, and a boost to the primary site when indicated.12,22,24-28 In the NSABP B-06 trial, a dose of 50 Gy was delivered to the entire breast without a boost in patients with histologically negative margins.

None of these trials with follow-up times of up to 20 years found any significant differences in overall or disease-free survival when comparing the different fractionation schedules.

Choosing Wisely Canada, a campaign to help physicians and patients engage in conversation about tests, treatments, and procedures, recommend that WBRT in 25 fractions as part of breast conservation therapy not be initiated in women who are 50 years of age or older with early stage invasive breast cancer without considering shorter treatment schedules.29 While the radiation oncologists involved in publishing this guideline agree with Choosing Widely Canada, in some cases a hyperfractionated schedule is more favorable (e.g. immediate reconstruction, postoperative infections, unfavourable body habitus, etc.).

Side effects of radiotherapy

The side effects of modern breast RT are modest, including altered pigmentation,30 breast discomfort, and firmness.11,31 The risk of cardiac disease is generally low with modern radiotherapy techniques. 11,32,33 Several studies report as association between RT and cardiovascular morbidity, including myocardial infarction and congestive heart failure.34,35 In addition, a few studies have shown an increased risk ofcardiovascular disease in patients who were treated with left-sided breast irradiation after breast conserving therapy.36,37

There is a higher risk of some malignancies in women receiving RT versus women not receiving RT. Increased relative risks (RR) was reported for lung cancer at 10-14 years and 15 or more years after initial breast cancer diagnosis (RR 1.62, 95% confidence interval [CI] 1.05-2.54 and RR 1.49, 95% CI 1.05-2.14, respectively), for second breast cancer at 5-10 years and 15 or more years (RR 1.34, 95% CI 1.10-1.63 and RR 1.26, 95% CI 1.00-1.59, respectively), and oesophageal cancer at 15 or more years (RR 2.19, 95% CI 1.10-4.62).37 However given the protracted interval between treatment and the development of

another neoplasm in the irradiated field, many of these studies are old. The risk of a second malignancy related to breast cancer RT is currently estimated to be approximately one per thousand women receiving RT.38

If nodal RT is delivered, the volume of skin irradiated is increased as is the potential volume of lung (and heart for left-sided tumours). The post-operative risk of lymphedema is approximately doubled if the entire axilla is included. Risk of clinically significant pneumonitis is approximately one percent. DIBH has been shown effective in reducing cardiac doses for patients receiving adjuvant left breast radiotherapy, and available data suggest that these reductions likely result in reduced long-term cardiac morbidity and mortality.39 Therefore, DIBH should be an available treatment option for patients being treated with adjuvant radiation therapy for left-sided breast cancers.

Eisen A et al., 2014 [15].

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Optimal Systemic Therapy for Early Female Breast Cancer

Hinweis: Folgende SRs wurden hier verwendet: **Eisen A et al, 2015 [16]; Ghandi S et at., 2015 [19]; Freedman OC et al. [17], 2015; Mates M et al., 2015 [34]**

Leitlinienorganisation/Fragestellung

What is the optimal adjuvant[1] systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered?

1 Several of the systemic therapies discussed in this guideline can be considered in the neoadjuvant setting. However, this guideline makes recommendations specifically for adjuvant therapy for the following reasons: a) there is significant variability within the patient population for whom neoadjuvant therapy may be considered (from early, operable breast cancer, to locally advanced breast cancer, which may have unique treatment needs) and b) our systematic review of the evidence focused on trials with disease-free survival (DFS) and overall survival (OS) as endpoints, and thus excluded several trials that used pathologically complete response (pCR) as a primary endpoint. Therefore, our recommendations represent only some of the data that may be relevant to neoadjuvant patients.

Target population: This guideline deals with female patients who are being considered for or are receiving systemic therapy for early-stage invasive breast cancer. The preferred definition of early breast cancer in this guideline is invasive cancers Stage I−IIA (T1N0−1, T2N0). Studies with cancer described as operable (no other description of stage) and some studies with both Stage I−IIA and operable Stage IIB−IIIA (sometimes considered locally advanced) are included.

Methodik

Grundlage der Leitlinie

An assessment conducted in December 2017 deferred the review of Evidencebased Series (EBS) 1-21. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

- A systematic review was conducted based on a literature search of MEDLINE and EMBASE for the period 2008 to March 2012. Guidelines were also identified from the SAGE Directory of Cancer Guidelines. Identified systematic reviews, meta-analyses, and practice guidelines were used to identify earlier studies or as the full evidence base when there were no more recent studies. Relevant abstracts presented at large academic meetings were used to update included trials or identify ongoing trials. The Working Group summarized the evidence and drafted recommendations that were then circulated to members of the consensus group. The consensus group (including the Working Group members) consisted of medical oncologists from Ontario who either were members of the Breast Cancer DSG or were invited to ensure representation from all regional cancer centres and programs in Ontario.
- A consensus panel process among the participants was used as the method to review and provide feedback on the draft recommendations. In doing so, the large amount of evidence and wide scope of the document could be managed, the current use of several chemotherapy regimens that do not have direct randomized controlled trial (RCT) comparisons and that may have differential benefits in specific subpopulations of patients could be debated and judged, differences in practice patterns among different centres and regions of Ontario could be taken into account, and gaps in evidence for certain practices could be more easily identified. The consensus process was envisioned as a way to engage the larger clinical community, promote greater standardization of practice, raise awareness of some of the challenging issues surrounding treatment decisions, and reveal practices that are not according to best evidence.
- The draft recommendations were circulated to all consensus group members and voted on prior to the consensus meeting of November 23, 2012 using a 5−point Likert scale (strongly disagree, disagree, undecided, agree, strongly agree). Consensus was defined as at least 80% agreement (agree or strongly agree) and no strong disagreement. Recommendations without consensus from the initial questionnaire were presented, discussed, revised, and voted on at the consensus meeting.

- Meta-analyses performed in other publications are cited but no meta-analysis was conducted in the preparation of this guideline.

Recherche/Suchzeitraum:

- MEDLINE and EMBASE; update of May 2014 resulted in 5350 RCT/trial publications and 1714 systematic reviews or guidelines
- 2017

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- Five of the guidelines by the PEBC and four others have been summarized or referred to in this evidentiary review. AGREE II ratings of the non-PEBC guidelines are provided
- systematic reviews and non-systematic reviews. Quality assessment of the systematic reviews and meta-analyses using the AMSTAR tool
- Trials were only included in the literature search with ≥100 patients, with patients randomized to at least one systemic agent, and with survival rate data available as one of the primary or secondary outcomes. Most of the RTCs found in the literature search were already included and assessed in the reviews, guidelines, or meta-analyses discussed in this subsection, and there was therefore no additional quality assessment of these studies.
- Because assessment of study quality is based primarily on design of the study, quality assessment is done per trial and therefore updates were not assessed for trial quality. A summary of study/trial design and quality characteristics is provided in Appendix G for new RCTs (i.e., RCTs not included in the cited guidelines, reviews, or meta-analyses).

GoR

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Sonstige methodische Hinweise

- Nachfolgend extrahiert wurden lediglich die Empfehlungen und Evidenz für HER2+.

Empfehlungen

R4.	**In those patients in whom chemotherapy would likely be tolerated and is acceptable to the patient, adjuvant chemotherapy should be considered for patients with the following tumour characteristics (in no particular order):** • **Lymph node positive: one or more lymph nodes with a macro-metastatic deposit (>2 mm)** • **ER− with T size >5mm** • **HER2+ tumours** • **High-risk lymph node negative tumours with T size >5 mm and another high-risk feature (see next recommendation, R5)** • **Adjuvant! Online 10−year risk of death from breast cancer >10%**

Qualifying Statements

- The consideration of disease factors for selecting patients to receive chemotherapy was based on review of existing guidelines and models of risk stratification, as outlined in the introduction. The Adjuvant! Online 10−year risk of death was considered by the panel at two cut-offs: 10% and 15%. There was strong consensus for 15%, and less robust consensus for using a 10% cut-off. Therefore, either a 10% or 15% 10−year risk of death according to the Adjuvant! Online model is a reasonable threshold for considering chemotherapy.

R5.	When considering lymph node negative tumours with T>5mm, the following should be considered high-risk features (thus considered candidates for chemotherapy): • Grade 3 • Triple negative (ER−, PR−, and HER2−) • LVI positive • An Oncotype DX recurrence score (RS) that is associated with an estimated distant relapse risk of 15% or more at 10 years • HER2+

Qualifying Statements

- The panel reached consensus for considering all these features as high risk; therefore, patients with tumours possessing these characteristics should be considered for adjuvant chemotherapy. As previously noted, these features were derived from review of existing guidelines and models of risk stratification.

RECOMMENDATIONS 26−34. ADJUVANT TARGETED THERAPY (HER2+ CANCERS)

R26.	Only patients with HER2+ breast cancer (IHC 3+, ISH ratio ≥2, or 6+ HER2 gene copies per cell nucleus) should be offered adjuvant trastuzumab.

Key Evidence and Qualifying Statements

- Trastuzumab is the targeted therapy for HER2+ early-stage breast cancer that has been most fully evaluated in completed RCTs (69-73). The TEACH trial (see Table 15) compared lapatinib to placebo and found benefit in DFS but not OS rates. The effect was greater in patients with hormone receptor negative cancer, although adverse effects (diarrhea, rash, hepatobilliary effects) were also higher with lapatinib. The ALTTO trial compared lapatinib, trastuzumab, and their combinations but the lapatinib arm was discontinued for futility. The other arms detected no significant differences, although lapatinib had more adverse effects. Follow-up is ongoing. Although lapatinib and pertuzumab have been investigated in the setting of locally advanced and metastatic disease (74,75), no recommendation for these agents can be made at this time. The role of dual blockade with trastuzumab and pertuzumab is currently being evaluated in the ongoing APHINITY trial (http://clinicaltrials.gov/ct2/show/NCT01358877).
- The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) (76,77) define a positive HER2 result as IHC staining of 3+ (uniform, intense membrane staining of >10% of invasive tumour cells); an in situ hybridization (e.g., FISH, SISH or CISH) ratio (HER2 gene signals to chromosome 17 signals) of ≥2.0; or HER2 gene polysomy of ≥6.0 HER2 gene copies per nucleus. Equivocal results, defined as IHC 2+ or ISH equivocal based on single-probe ISH average HER2 copy number ≥4.0 and <6.0 signals/cell or based on dual-probe HER2/CEP17 ratio <2.0 with an average HER2 copy number ≥4.0 and <6.0 signals/cells, should be reported as equivocal and reassessed using a reflex test (same specimen using the alternative test) or new test (new specimen, if available, using same or alternative test).

R27.	Trastuzumab plus chemotherapy is recommended for all patients with HER2+ node positive breast cancer and for patients with for HER2+ node negative breast cancer greater than 1 cm in size.

Key Evidence and Qualifying Statements

- Phase III clinical studies have demonstrated improved DFS and OS with the addition of trastuzumab to chemotherapy compared with chemotherapy alone in HER2+ early breast cancer (see Table 14 in Evidentiary Base).
- The majority of adjuvant trastuzumab trials included patients with lymph node positive

breast cancer, or lymph node negative disease with one of the following high-risk features: ER−, grade 2 or 3, T ≥1cm, or age <35 years. Trastuzumab may still be considered in patients with HER2+ disease outside these features. Although most studies excluded patients with tumours <1 cm, the benefit of trastuzumab was equivalent in both node negative and node positive tumours in the HERA trial which included small N0 tumours (1 cm was the formal inclusion criteria, although 60 patients with tumours <1 cm were also enrolled). The BCIRG 006 trial (71,72) analysis by tumour size found benefit in tumours <1 cm, <2 cm, and ≥2 cm, but not for tumours 1−2 cm in size; however, interpretation is limited because of the small number of patients in each category. The review by Petrelli and Barni (78) concluded that patients with HER2+ tumours have a higher rate of recurrence and poorer survival rate than patients with HER2− cancer of the same size/stage, confirming that HER2 positivity itself is a risk factor. There does not appear to be a threshold according to tumour size, and size alone should not be the deciding factor in whether to administer trastuzumab to patients with tumours <1 cm. In Ontario, tumours <1 cm can be treated under the Evidence Building Program (EBP).

- The meta-analysis by Moja et al (Cochrane Collaboration) (79) found that the hazard ratio for trastuzumab-containing regimens vs chemotherapy alone was 0.66 for OS and 0.60 for DFS ($p<0.00001$ for both). The risk of congestive heart failure and left ventricular ejection decline were higher with trastuzumab (RR=5.11, $p<0.00001$ and RR=1.83, $p<0.0008$, respectively). In patients at high risk of recurrence without cardiac problems, there is clear survival rate benefit for trastuzumab.
- The benefit of adjuvant trastuzumab in the absence of cytotoxic chemotherapy is unknown because it has not been evaluated in clinical trials. Trastuzumab monotherapy vs trastuzumab + chemotherapy is being evaluated in elderly patients in the SAS BC07 (RESPECT) study (80).

R28.	**Trastuzumab therapy can be considered in small (≤1 cm) tumours as part of clinical studies or evidence-building programs (such as the one currently available in Ontario).**

Key Evidence and Qualifying Statements

- Evidence for trastuzumab use is included in the Evidence Summary (Section 2, Subsection 4.4).
- Because most major phase III trials that confirmed the benefit of adjuvant trastuzumab did not include small (≤1 cm diameter) node negative breast cancer, there is little evidence from RCTs evaluating the effect of trastuzumab in tumours ≤1cm. HERA and BCIRG 006 as discussed in R27 are exceptions.
- Several retrospective case series of HER2 positive $pT_{1a/b}N_0M_0$ carcinoma seem to demonstrate that they have a higher risk of relapse compared with the HER2 negative counterpart (79).
- In the HERA trial (81), the subgroup of 510 patients with node negative disease and tumours ranging from 1.1 to 2.0 cm in diameter had similar three-year DFS rate benefit with trastuzumab as in the overall cohort (trastuzumab vs observation HR=0.53, 95% CI 0.26−1.07; all patients HR=0.64, 95% CI 0.54−0.76).
- The American trials found a similar trend with benefit in $pT_1N_0M_0$ tumours smaller than 2 cm. Although there has not been a confirmatory trial, there is no reason to think that high-risk $pT_{1a/b}N_0M_0$ breast cancer cannot benefit from trastuzumab in the same way as more advanced stages of the disease. There does not appear to be a threshold according to tumour size, and size alone should not be the deciding factor in whether to administer trastuzumab to patients with tumours ≤1 cm. In Ontario, tumours ≤1 cm can be treated under the Evidence Building Program.

R29. **Trastuzumab can be adm regimen.**

Key Evidence and Qualifying Stat

- Evidence on use of trastuzuma Evidentiary Base. The majo regimens.
- Three large RCTs (>1000 pa [AC→paclitaxel in NSABP B31 BCIRG 006 (71,72)], whereas containing arm [docetaxel + significant survival rate benefit
- The HERA trial (81) gave trast (neoadjuvant, adjuvant, or bo chemotherapy: 68% received anthracycline. When results we unblinding, there was persiste benefit of trastuzumab in comb issue of which chemotherapy is
- PEBC Guideline #1-17 (86) reco instead of CMF.
- Because anthracyclines are kn even more cardiotoxic, non-ar patients. The BCIRG 006 t (AC→TH) and docetaxel/carbop the AC→T control. TCH and significant difference in OS or seemed to have a stronger effe cardiotoxicity and leukemia. W the trial was not designed to containing regimens.

R30. **The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended because of the potential of increased cardiotoxicity.**

Key Evidence and Qualifying Statements

- Anthracyclines are known to be cardiotoxic and anthracycline followed by#trastuzumab even more cardiotoxic. Anthracyclines administered concurrently with trastuzumab in patients with metastatic breast cancer resulted in high rates (25%) of congestive heart failure. Concurrent use of trastuzumab + anthracycline has been explored in several small trials in the neoadjuvant setting without significant cardiotoxicity. Long-term results of these trials have yet to be reported; therefore, this approach should not be considered outside the context of a clinical trial.

R33. **Phase III evidence for the addition of trastuzumab to some chemotherapy regimens such as TC (docetaxel/cyclophosphamide) does not exist. However, these regimens may be in use and are reasonable options, particularly to mitigate cardiotoxicity in certain patients.**

Key Evidence and Qualifying Statements

- HERA (73,81,88,89) was a large phase III international RCT that randomized patients with HER2+ early breast cancer to one year vs two years vs no trastuzumab after completion of adjuvant systemic therapy (as per investigator choice). Patients experienced significant clinical benefit with the addition of trastuzumab to chemotherapy, regardless of the chemotherapy backbone. TC has not been formally evaluated with trastuzumab in the context of an RCT; however, given the results of the HERA trial (systemic therapy as per investigator choice), TC could be considered a reasonable systemic option in combination with trastuzumab, particularly in patients for whom there is a concern with regards to cardiotoxicity.

R34.	**Patients should be offered one year total of adjuvant trastuzumab, with regular cardiac functional assessments during this period.**

Key Evidence and Qualifying Statements

- Current evidence suggests that the optimal duration of adjuvant trastuzumab is one year (see Subsection 4.4.2 of Section 2: Evidentiary Base). Data for shorter durations of trastuzumab are being evaluated.
- Trastuzumab therapy for one year total continues to be the standard of care for patients with early-stage HER2+ disease. Studies with regular cardiac monitoring discontinued trastuzumab if there was cardiotoxicity.
- Trastuzumab can be administered concurrently with [see NSABP B-31 and NCCTG N9831 (69,83,85,90)] or sequential to radiotherapy [HERA (73,88,89)].
- The recent HERA update (73) on one- vs two-year trastuzumab subgroups found no DFS or OS rate benefits for the longer treatment duration, but increased cardiotoxicity (based on the secondary cardiac endpoint).
- The PHARE trial is a phase III RCT comparing 6 vs 12 months of adjuvant trastuzumab. Results presented at ESMO 2012 (91,92) were inconclusive as to whether 6 months of trastuzumab was non-inferior to 12 months with a nonsignificant trend favouring 12 months. Further results after 3.5 years follow-up (93) also concluded that they failed to show that 6 months trastuzumab was non-inferior to 12 months trastuzumab, although there were significantly more cardiac events in the 12 month group (5.7% vs 1.9%).
- Two small trials [FinHER, 9 weeks trastuzumab (94,95); E-2198, 12 vs 52 weeks trastuzumab (96)] suggest trastuzumab may be beneficial when administered for shorter durations resulting in less cardiotoxicity than longer treatment. Results need to be confirmed in larger trials that are ongoing. The Short-HER and SOLD studies are looking at one year vs nine weeks trastuzumab and the Hellenic Group and PERSEPHONE trials are looking at one year vs six months trastuzumab. Based on the completed trials plus neoadjuvant trials that found trastuzumab + chemotherapy increased the pathologically

  complete response (pCR) rate compared with chemotherapy alone, some have suggested that shorter trastuzumab therapy (even if not optimal for preventing recurrence) may be acceptable, particularly for those patients who cannot tolerate trastuzumab for one year.
- The NICE guideline (97) recommends that patients receiving trastuzumab should have cardiac functional assessments every three months during trastuzumab treatment, and trastuzumab should not be offered to patients with any of the following:
  - A left ventricular ejection fraction LVEF of <55%
  - A history of documented congestive heart failure
  - High-risk uncontrolled arrhythmias
  - Angina pectoris requiring medication
  - Clinically significant valvular disease
  - Evidence of transmural infarction on electrocardiograph (ECG)
  - Poorly controlled hypertension.

  Most of the clinical trials evaluating trastuzumab excluded these patients. Patients who develop cardiotoxicity during administration of trastuzumab should be treated and monitored closely by a knowledgeable multidisciplinary team (oncologists and cardiologists).

Brackstone M et al., 2014 [3].

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Locoregional Therapy of Locally Advanced Breast Cancer (LABC)

Leitlinienorganisation/Fragestellung

1. In female patients with locally advanced breast cancer with good response to neoadjuvant therapy, what is the role of breast-conserving surgery (BCS) compared with mastectomy?

2a. In female patients with locally advanced breast cancer who have had a mastectomy is radiotherapy indicated?

2b. In female patients with locally advanced breast cancer does locoregional irradiation result in higher survival and lower recurrence rates compared with breast/chest wall irradiation alone?

2c. In female patients with locally advanced breast cancer and pathologically complete response to neoadjuvant therapy is radiotherapy indicated?

3. In female patients with locally advanced breast cancer who receive neoadjuvant chemotherapy is sentinel lymph node biopsy (SLNB) or axillary dissection the most appropriate axillary staging procedure? Is SLNB indicated before neoadjuvant chemotherapy rather than at the time of surgery?

4. How should female patients with locally advanced breast cancer who do not respond to initial neoadjuvant therapy be treated?

Target population:

This guideline is pertinent to female patients with locally advanced breast cancer (LABC). For purposes of this guideline, LABC includes Stages IIB and IIIABC and inflammatory cancer, as defined in the AJCC Cancer Staging Manual, 6th edition (1). Most studies in the evidentiary base (see Section 2) included heterogeneous populations spanning Stages IIB – IIIC and sometimes included inflammatory breast cancer. Very few studies dealt only with Stage III or specific subgroups such as patients with T3N0 cancer. As most of the major studies did not report results separately for patients with Stage IIB and Stage III cancers, the evidence did not support recommendations based on a narrower definition of LABC or subdivided by stage. Although some people do not consider Stage IIB to be locally advanced, there is an increasing trend to treat less bulky disease (Stage IIB) in a similar manner, including neoadjuvant therapy; therefore, the recommendations may also be applicable to this group.

Methodik

Grundlage der Leitlinie

This Working Group consisted of one surgeon, two medical oncologists, one radiation oncologist, one pathologist, and one health research methodologist. The Working Group and DSG also formed LABC guideline development group. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (56,213). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

Recherche/Suchzeitraum:

Using the research questions described previously, a search for RCTs, meta-analyses, and existing systematic reviews was conducted using the MEDLINE and EMBASE databases (1996 to December 2013) and the Cochrane Library, as described in Section 2 of this EBS.

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Sonstige methodische Hinweise

Die methodischen Schritte und Ergebnisse der Recherche und Evidenzbewertung auch durch externe Reviews sind in einem gesonderten Dokument detailliert beschrieben, das der Leitlinie beigefügt ist:

Brackstone et al., 2014: Locoregional Therapy of Locally Advanced Breast Cancer (LABC): Development Methods, Recommendations Development and External Review Process

Empfehlungen

- Question 1. In female patients with locally advanced breast cancer (LABC) with good response to neoadjuvant therapy, what is the role of breast-conserving surgery (BCS) compared with mastectomy?

Recommendation 1

For most patients with LABC, mastectomy should be considered to be the standard of care. [See Question 2b and 3 for issues on axillary management and staging.]

BCS may be considered for some patients with non-inflammatory LABC on a case-by-case basis when the surgeon deems the disease can be fully resected and there is strong patient preference for breast preservation.

Key Evidence (go to Results in Section 2)

☐ No randomized controlled trials (RCTs) that directly compared BCS with mastectomy in patients with LABC were found in the literature review (see Section 2).

☐ Evidence in early breast cancer is that BCS plus radiation is equivalent to mastectomy alone (8,9). There is a continuum in breast cancer stage, as opposed to a sharp cut-off between early and locally advanced (see Target Population). The Cancer Care Ontario/Program in Evidence-Based Care (CCO/PEBC) guideline (9) included all of Stage I and II, although the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) defined early as "breast cancer in which all clinically apparent disease can be removed surgically" (10). Therefore, at least some cancers defined as LABC in the current guideline (e.g., Stage IIB) are covered in the recommendations of these other guidelines.

Guidelines by the American College of Radiology (ACR) (11), National Comprehensive Cancer Network (NCCN) (12), and the Consensus Conference on Neoadjuvant Chemotherapy in Carcinoma of the Breast (13) indicate BCS is appropriate for some patients with LABC after NACT. This may include small N2/N3 tumours with nodal response, or large (T3N0 or T3N1) tumours with good response. NCCN recommends patients initially Stage IIIABC (except T3N1) with good response be treated with mastectomy or consider lumpectomy (plus ALND plus RT). We endorse the criteria for BCS as outlined in the ACR (11) and Consensus Conference guidelines (13) and The International Expert Panel on Inflammatory Breast Cancer (14).

Qualifying Statements

☐ Patients should be informed that for LABC as a whole the data are insufficient to recommend BCS as a rule; however, there may be some exceptions that can be considered on a case-by-case basis.

☐ The extent of surgery, including BCS, should be determined after full discussion between the patient and the treating oncologist, taking into consideration the patient's values and the lack of direct evidence regarding the relative benefit of BCS vs mastectomy in this particular situation. Treatment of the axilla is discussed in Recommendations 2 and 3.

☐ When considering between mastectomy and BCS (for those meeting selection criteria), benefits and harms must be weighed. BCS is considered to have generally better cosmetic effects, and for some female patients may have less impact on body image, self-esteem and sexuality than complete breast removal by mastectomy. With BCS there is usually no need for additional reconstructive surgery and the operation may be less complex. In some cases of BCS, there may be positive margins requiring re-excision. In cases of recurrence after BCS, further surgical procedure may be needed, and some patients may wish to reduce this possibility by having mastectomy as initial treatment.

☐ Wide excision of the remaining tumour in the region of the original pre-neoadjuvant treatment tumour bed plus RT is recommended for patients with LABC who strongly desire BCS. The volume of tissue to excise will be decreased if there is response to neoadjuvant therapy. Surgical clips marking the original (pretreatment) tumour location should be inserted before administration of neoadjuvant therapy (see Preamble).

☐ BCS is not advised in inflammatory breast cancer because the extent of tumour involvement cannot be reliably ascertained.

☐ There is continuing evolution in the type of surgical procedures offered (e.g., skin-sparing mastectomy with immediate reconstruction), but these are beyond the scope of this guideline.

- Question 2a. In female patients with locally advanced breast cancer who have had a mastectomy is radiotherapy indicated?

Recommendation 2a

Radiotherapy following mastectomy is recommended for patients with LABC.

Key Evidence (go to Results in Section 2)

☐ The EBCTCG meta-analyses (15,16) (see Section 2 Table 1) found postmastectomy radiotherapy (PMRT) significantly reduced 5-year and 10-year recurrence risk in patients with positive nodes (including subgroups with 1-3 positive nodes or with ≥4 positive nodes) or who received systemic therapy (primarily cyclophosphamide + methotrexate +fluorouracil [CMF] and/or tamoxifen; >85% of patients with positive nodes received systemic therapy). This recurrence risk reduction applied to patients who had mastectomy plus ALND, mastectomy plus axillary sampling, or mastectomy only.

☐ In the EBCTCG meta-analyses PMRT significantly improved 20-year breast cancer mortality (including all subgroups). PMRT also significantly improved 20-year overall mortality for node positive patients with ALND (overall or with ≥4 positive nodes) or with axillary sampling.

☐ The benefit of RT in reducing breast cancer recurrence and mortality rates appears to be offset by adverse effects in older trials (primarily cardiovascular and lung adverse effects) especially in female patients with lower risk of recurrence. The ratio of breast cancer mortality rate to other mortality rates was strongly affected by nodal status, age, and decade of follow-up. The absolute benefit still favoured RT overall, but not necessarily in subgroups with particularly low risk of recurrence. More recent reviews found that the effectiveness of RT is increased and cardiopulmonary adverse effects are greatly reduced

with modern RT planning and technique; therefore, the non-cancer mortality rate data in the EBCTCG meta-analyses may not be relevant to current practice.

Qualifying Statements

☐ The use of three-dimensional (3D) treatment planning is important to minimize the dose to the lung and heart to ensure improvements in breast-cancer-specific survival rates are not offset by non-breast cancer mortality rates. Treatments provided should conform to accepted standards with respect to tissue coverage and dose. Techniques such as gated RT or active breath-hold are used in some centres to reduce cardiotoxicity, although these were not evaluated in this guideline series.

☐ Radiotherapy after BCS was not part of this review, however guidelines for early breast cancer recommend radiation following BCS (8,9) and this is the current standard of care. In the absence of RCTs to the contrary, it is logical that radiation be used following BCS for LABC as well. Radiotherapy following BCS for LABC is the current standard of care.

☐ The EBCTCG meta-analyses found RT improved recurrence and survival rates in the subgroup of patients with systemic treatment. Several of the studies used older regimens such as CMF. Whelan et al (17) also found RT reduced mortality in patients with node-positive breast cancer who received systemic treatment. Figure 1 of Section 2 indicates RT significantly improved the local recurrence rate in patients receiving anthracycline-based chemotherapy but there was no effect on survival rate. No studies were included in the systematic review (Section 2) using taxane-based chemotherapy. Newer chemotherapies and targeted therapies may reduce the absolute benefit of RT for some patients, although in the absence of RCTs, RT is still recommended.

☐ Patients should be informed that improvements in recurrence and disease-specific survival rates have not necessarily translated into advantages in OS, possibly related to radiation-induced adverse effects in older studies. This applies especially in patients at lower risk of recurrence; however, most LABC patients who receive NACT would not be considered at low risk. Of patients with LABC, those with T3N0 confirmed by SLNB as N0 prior to chemotherapy are of lower risk than N+ patients. RT reduced the recurrence rates in all groups reported, but the absolute benefit in patients with very low risk of recurrence due to disease characteristics and systemic therapy may be small, and some may consider the incremental benefit of RT, although statistically significant, to be clinically unimportant.

☐ Lymphedema is more likely when surgical procedures include ALND or/and when RT includes the nodal areas (see Section 2). Decreased shoulder mobility, decreased strength, arm weakness, and paresthesia/hypesthesia have also been reported. The German Breast-Cancer Study Group trial (also referred to as the Bundesministerium für Forschung und Technologie [BMFT] 03 study) (18) found that 25% of RT patients had acute skin reactions, and 28% had long-term skin alterations (1-2 years after RT). Radiation pneumonitis in the MA.20 trial was reported in 1.3% of patients receiving RT and 0.2% without. In some older RT regimens there was a significant increase in contralateral breast cancer and non-cancer mortality rates, primarily from heart disease and lung cancer (15,19). Careful treatment planning is likely to reduce (but not eliminate) risks other than lymphedema and skin effects.

☐ The benefit of PMRT in patients with node-negative LABC (T3-4N0) is less clear because they have not been reported separately from smaller (T2N0) cancers. Additionally, in patients clinically T3N0 the rate of pathological node positivity exceeds 50% and these patients may be considered T3Nx unless deemed N0 by SLNB before NACT or by ALND. The EBCTCG fifth cycle analysis (16) found that patients with node-negative cancer (primarily early cancer)

treated with mastectomy + ALND + RT had no difference in recurrence risk (3.0% RT vs 1.6%, p>0.1)due to RT but significantly higher overall mortality rate (47.6% vs 41.6%, p=0.03). Control patients (no RT) with node negative cancer in studies using mastectomy + axillary sampling had higher recurrence than in studies with ALND (17.8% vs 1.6%); RT in patients treated with axillary sampling resulted in significantly lower recurrence risk (3.7% vs 17.8%) and no difference in 20-year mortality (46.1% vs 49.9%, RR=1.0, p>0.1). Patients with T3N0 cancer remain a group with limited data and should be discussed individually with regards to risks and benefits.

- Question 2b. In female patients with locally advanced breast cancer does locoregional irradiation result in higher survival and lower recurrence rates compared with breast/chest wall irradiation alone?

Recommendation 2b

It is recommended that patients with LABC receive locoregional radiation encompassing the breast/chest wall and local node-bearing areas following breast-conserving surgery or mastectomy.

Key Evidence (go to Results in Section 2)

☐ The recommendation for breast/chest wall irradiation is based on several RCTs as summarized in the EBCTCG meta-analyses (10,15,20-23) and is discussed in Question 2a.

☐ A prospective nonrandomized study (24) in high-risk patients with Stage II-III breast cancer found improved disease-free survival (DFS) rates at median 77 months follow-up (73% with internal mammary (IM) node RT vs 52% without, p=0.02), whereas OS was 78% vs 64%, p=0.08. Subgroups at higher risk of recurrence may have greater benefit, as has been reported for patients with positive nodes.

☐ A meta-analysis of the role of RT to regional nodes included three trials (two abstracts and one full publication) in patients with early/LABC (25) and concluded that regional RT to IM and medial supraclavicular (MS) nodes improves DFS, OS, and distant metastasis-free survival (DMFS) in Stage I-III breast cancer. This analysis did not meet our inclusion criteria because only approximately 36% of patients had LABC; therefore, the results need to be confirmed when the trials are fully published including subgroup data.

☐ The recommendation to include local node-bearing areas is consistent with current practice and other clinical practice guidelines. The NCCN guideline (12) recommends that if IM lymph nodes are clinically or pathologically positive, RT should be administered to the IM nodes; otherwise, treatment to the IM nodes should be strongly considered in patients with node-positive and T3N0 cancer. NCCN also states that RT to the infraclavicular region and supraclavicular area is recommended for patients with ≥4 positive nodes and should be strongly considered if 1-3 nodes are positive, and considered for patients with T3N0 cancer (especially if inadequate axillary evaluation or extensive lymphovascular invasion).

☐ The ACR (26) recommends PMRT for T1-2N2+ and T3-4N+, usually including ipsilateral supraclavicular fossa for patients with positive nodes. There is more variation for IM nodes, but IM RT is considered for patients at risk of IM involvement such as those with medial or centrally located tumours and positive axillary lymph nodes. PMRT treatment of T1-2N1 and T3NO is controversial and should be individualized.

Qualifying Statements

☐ Locoregional treatment (compared with breast/chest wall alone) increases the risk for cardiovascular/pulmonary adverse effects. The additional fields are more technically complex

to administer. The use of 3D treatment planning is important to minimize the dose to the lung and heart to ensure improvements in breast-cancer-specific survival are not offset by non-breast cancer mortality.

☐ The risk of long-term adverse effects from locoregional radiation should be weighed against the potential benefits in patients with lower-risk disease, particularly those with left-sided tumours. Ideally, such patients should be discussed in a multidisciplinary setting.

☐ In light of incomplete data, any recommendations regarding the role of regional radiation to specific nodal groups (e.g., IMC, MS, apical axilla, full axilla) in LABC are significantly limited. Although some studies attempted to isolate the role of irradiation to the IM nodes (27,28), others included additional radiation to the MS nodes (29-31) or all locoregional nodes (32,33).

☐ The additional benefit of regional nodal RT is small, but significant for the overall patient groups studied in RCTs (early cancers plus LABC combined).

☐ The incidence and/or severity of lymphedema is higher with locoregional RT. Especially in patients with lower-risk disease, the risk of long-term adverse effects from locoregional radiation should be weighed against the potential benefit of reduced recurrence rates and increased survival rates.

☐ Patients with T3N0 cancer (verified to be node negative [N0] pre- and post-neoadjuvant therapy) remain a heterogeneous group with limited data and should be discussed individually with regards to risks and benefits. In patients clinically T3N0 the rate of pathological node positivity exceeds 50% and these patients may be considered T3Nx unless deemed N0 by SLNB before NACT or by ALND. In the latter case, they may be similar to T2N0 patients and less RT to the chest wall may be considered.

- Question 2c. In female patients with locally advanced breast cancer and pathologically complete response to neoadjuvant therapy is radiotherapy indicated?

Recommendation 2c

It is recommended that postoperative radiotherapy remains the standard of care for patients with LABC who have pathologically complete response to neoadjuvant therapy.

Qualifying Statements (go to Results in Section 2)

☐ No prospective randomized studies were found in the literature review (see Section 2) that compared treatment with vs without RT in female patients with pathologically complete response (pCR) to neoadjuvant therapy. The consensus of the authors is that postoperative RT should therefore remain the standard of care.

☐ When examining the evidence, it is important for the clinician to be aware of the various definitions for pCR that have been used in clinical studies. These range from no microscopic evidence of viable tumour cells, only residual necrotic or nonviable tumour cells, or only residual intraductal tumour cells in the resected specimen. The MD Anderson Cancer Center requires the added disappearance of axillary lymph node metastasis for a pCR.

☐ Randomized trials such as those planned by the Athena Breast Cancer Network (34,35) and the NSABP B51/RTOG 1304 trial may provide data to re-evaluate the recommendation for specific subgroups in the future.

- Question 3. In female patients with locally advanced breast cancer who receive neoadjuvant chemotherapy is sentinel lymph node biopsy (SLNB) or axillary dissection the most appropriate axillary staging procedure? Is SLNB indicated before neoadjuvant chemotherapy rather than at the time of surgery?

Recommendation 3-1

It is recommended that axillary dissection remain the standard of care for axillary staging in LABC, with the judicious use of SLNB in patients who are advised of the limitations of current data.

Key Evidence (go to Results in Section 2)

☐ The median sentinel lymph node (SLN) identification rates (SLN ID rates) for the trials in Section 2 were 88% overall, 93% in patients with cN0 cancer and 85% in patients with clinically positive nodes. SLN ID rates depend on the experience of surgeons and the techniques used (see Section 2 for details).

☐ The ACOSOG Z1071 trial (36,37) conducted with patients with positive nodes (>85% LABC) is one of the largest and most recent studies. It found a 93% SLN ID rate for cN1 cancer and 89% for cN2 cancer. This study found detection with radiolabeled colloid much better than blue dye alone (94% colloid + dye, 91% colloid, 79% dye).

☐ For the studies in Section 2, median false negative (FN) rates were 10% overall, 7% cN0, and 13% clinically node positive. The SN FNAC study (38,39) found the FN rate decreased with the number of sentinel nodes removed (FN rate 19% for 1 SN, 7% for 2+ SN) and is consistent with the SENTINA trial findings. Using radiolabelled tracer plus blue dye and removing at least 2-3 SLNs, the best teams achieved FN rates of 5-7%. The FN rate is not dissimilar to the FN rates of 5-10% for early breast cancer surgery (40-42).

☐ Although the studies indicate that SLNB is technically feasible in both early and locally advanced breast cancer, a small percentage of patients will be understaged using SLNB alone. This risk needs to be weighed against the increased adverse effects of ALND.

☐ This recommendation is based on the authors' valuing potentially increased survival rates with use of ALND over increased postoperative complications. Given the results of the Z0011 and EBCTCG studies for early or operable cancers, some patients may decide that for less advanced LABC (e.g, Stages 2b-3a) the adverse effects of ALND are greater than the benefits.

Qualifying Statements

☐ Although the SLNB technique in patients (mostly with LABC) receiving NACT is comparable to that in early breast cancer, the clinical implications of a FN SLNB is not known in these patients (see Discussion in Section 2).

☐ The benefit of ALND is that more nodes are removed and examined, giving more accurate staging for some patients. Provided that locoregional RT is to be administered in all patients, as recommended in Questions 2a and 2b, the staging may have no impact on treatment. However, some patients may value the additional prognostic information. If a patient is not going to receive locoregional RT, then ALND is recommended. Trials in patients with LABC are ongoing.

☐ More than 80% of female patients undergoing ALND have at least one postoperative complication in the arm and psychological distress is common (43). In the Z0011 trial (44,45) ALND added to SLNB resulted in more wound infections, axillary seromas, paresthesias, and subjective reports of lymphedema than SLNB alone.

☐ The NCCN guideline (12) (not specifically on NACT) indicates "in the absence of definitive data demonstrating superior survival [with axillary lymph node staging], the performance of ALND may be considered optional in patients who have particularly favourable tumours, patients for whom the selection of adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with serious comorbid conditions". They recommend that cN0 plus SLN negative (including T3N0) need no further ALND. However, the authors of the current

guideline note that most patients with LABC are pathologically node positive before neoadjuvant therapy, even those considered clinically negative; therefore, a high portion may still be pathologically node positive after neoadjuvant therapy.

☐ None of the studies included inflammatory breast cancer; therefore, these findings cannot be extrapolated to that cohort of patients.

Recommendation 3-2

Although SLNB before or after NACT is technically feasible, there is insufficient data to make any recommendation regarding the optimal timing of SLNB with respect to NACT. Limited data suggests higher SLN ID rates and lower FN rates when SLNB is conducted before NACT; however, this must be balanced against the requirement for two operations if SLNB is not performed at the time of resection of the main tumour.

Key Evidence (go to Results in Section 2)

☐ Only three of the studies in Table 6 of the evidence summary (46-48) compared timing of SLNB (before or after NACT) and one additional study (abstract only) performed SLNB before neoadjuvant therapy (49). The rest of the studies performed SLNB and ALND after completion of NACT. Before NACT the SLN ID rate was 98-99%, whereas after NACT it was a median of 93% in patients with clinically node-negative cancer and 88% overall. The studies also suggest FN rates are lower when SLNB is conducted before NACT.

☐ The SENTINA study (46) did not conduct ALND if the SLNB before NACT was negative so FN rates could not be determined for this subgroup. Arm B of the SENTINA trial included patients initially cN0 with a positive SLN (pN1SN) before NACT and conducted a second SLNB plus ALND after NACT. SLN ID rate was 76% in the second SLNB and the FN rate based on the second SLNB was 61% compared with a SLN ID rate of 99% in patients with cN0 cancer when SLNB was performed before NACT. This suggests that SLNB should not be performed both before and after NACT.

Qualifying Statements

☐ It is often considered that adjuvant treatment should be based on the initial stage as determined before any treatment, although the extent of surgery depends on the size/extent of the tumour immediately before the surgical procedure (i.e., after any neoadjuvant treatment). Some studies suggest NACT often eliminates cancer from the SLN but not all the other nodes. For these reasons, there is theoretical justification for performing SLN biopsy before NACT. The very limited data would support this, but is considered insufficient at this time to make a strong recommendation due to the trade-off required in risk and inconvenience of needing to perform two separate operations (one for SLNB and one to remove the main tumour) compared with the normal procedure of removing the tumour and SLN (or ALND) in one operation.

- Question 4. How should female patients with locally advanced breast cancer who do not respond to initial neoadjuvant therapy be treated?

Recommendation 4-1

It is recommended that patients receiving neoadjuvant anthracycline-taxane-based therapy (or other sequential regimens) whose tumours do not respond to the initial agent(s) or where there is disease progression be expedited to the next agent(s) of the regimen.

Recommendation 4-2

For patients who, in the opinion of the treating physician, fail to respond or who progress on first-line NACT, there are several therapeutic options to consider including second-line

chemotherapy, hormonal therapy (if appropriate), radiotherapy, or immediate surgery (if technically feasible). Treatment should be individualized through discussion at a multidisciplinary case conference, considering tumour characteristics, patient factors and preferences, and risk of adverse effects.

Key Evidence (Recommendations 4-1 and 4-2) (go to Results in Section 2)

☐ Anthracycline-taxane is a standard therapy, with the taxane administered either concurrently or consecutively. The NSABP B-27 trial (50-52) found AC followed by docetaxel gave significantly improved clinical and pathological response and lower rates of local recurrence compared with neoadjuvant AC alone. Because most patients were not LABC and patients were not randomized based on response, the trial is not included in the evidence review of Section 2.

☐ The GeparTrio study (53) and a trial by Qi et al (54) evaluated early switching to second-line chemotherapy after nonresponse to two cycles of first-line chemotherapy and demonstrated conflicting findings: the GeparTrio demonstrated no improved response to treatment but better tolerability and DFS; the other trial demonstrated some improved response but worse adverse effects and treatment delays. There is therefore insufficient evidence to switch chemotherapy mid-treatment.

☐ The recommendations are based on current practice and are consistent with the guidelines by NCCN (12), Health Canada (55), and the Consensus Panel for Neoadjuvant Chemotherapy (13).

Qualifying Statements (Recommendation 4-2)

☐ There is a body of literature including patients with locally advanced and metastatic disease (mostly single-arm case series, small pilot studies, or retrospective studies) that supports a variety of second-line single agent and multi-agent NACT and/or RT regimens to improve response (including pCR) and, thus, operability or survival. Although the data are limited and not within the rigorous inclusion criteria of the literature review, Table 8 of Section 2 lists some of these studies as examples of regimens in the medical literature that have been tried in this clinical scenario. These data are not systematically reviewed nor of quality sufficient to make a recommendation as to preferred regimens. It is advised that oncologists individualize the choice of therapy based on the patient and risk of adverse effects.

Wildiers H et al., 2013 [45].

Belgian Health Care Knowledge Centre (KCE)

Breast cancer in women: diagnosis, treatment and follow-up

Leitlinienorganisation/Fragestellung

- Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of breast cancer women.
- This guideline replaces the 2nd version of the KCE report 143 2, published in 2010. It adds the evidence for the four abovementioned research questions to the main part of the KCE report 143. Updated conclusions and recommendations are added to their respective sections with a special indication. This guideline provides recommendations based on current scientific evidence both for the diagnosis, treatment, follow-up and supportive care

of women with an early, invasive or metastatic breast cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences.

The CPG addresses the following clinical questions:

1. What diagnostic tests are the most effective to confirm the diagnosis
   - of breast cancer?
   - Triple test approach: clinical examination / mammography / pathology
   - MRI
   - MIBI scintimammography
2. What diagnostic tests are necessary to investigate the extent of the
   - breast cancer?
   - • Sentinel biopsy
   - Chest X-ray
   - Ultrasonography of the liver
   - Bone scintigraphy
   - Biochemical and tumour markers; hormonal receptors
   - CT scan of the thorax
   - PET scan
3. What is the most effective treatment strategy for:
   - Non-invasive breast cancer (ductal carcinoma in situ, Paget's disease)
   - Early-stage invasive breast cancer
   - Locally-advanced invasive breast cancer
   - Metastatic breast cancer
   - Locoregional recurrence of breast cancer
4. What is the place of supportive treatment of breast cancer, including erythropoesis stimulating proteins, bisphosphonates, physiotherapy, physical training, psychological support and hormonal substitution?
- 5. What is the place of reconstructive surgery in the treatment of breast cancer?
- 6. What is the most effective strategy for the follow-up of patients with breast cancer?

Methodik

Grundlage der Leitlinie

The KCE guideline is drawn up according to highly codified principles, based on scientific information regularly updated from the international literature. KCE analyses clinical practices in current use on the basis of existing recommendations. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

This guideline was developed owing a collaboration between multidisciplinary groups of practising clinicians and KCE experts. The composition of the Guideline Development Group

is documented in Appendix 1. Guideline development and literature review expertise, support and facilitation were provided by the KCE Expert Team.

Recherche/Suchzeitraum:

- A broad search of electronic databases (Medline, PreMedline, EMBASE), specific guideline websites and websites of organisations in oncology was conducted.
- Both national and international CPGs on breast cancer were searched. A language (English, Dutch, French) and date restriction (2006 – 2009) were used. CPGs without references were excluded, as were CPGs without clear recommendations.
- Guideline update (2013): Systematic reviews were searched from January 2010 onwards (the search date of the Guideline version 2010) for all research questions in OVID Medline, PreMedline, Embase, and The Cochrane Library (Cochrane Database of Systematic Reviews, DARE, HTA database). In addition, the protocols and reviews of the Cochrane Breast Cancer Group were browsed.

LoE/ GoR

Table 3 – A summary of the GRADE approach to grading the quality of evidence for each outcome.[12]

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Table 4 - Levels of evidence according to the GRADE system.

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

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

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

Table 10 - Interpretation of strong and conditional (weak)* recommendations.[13, 14]

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** the terms "conditional" and "weak" can be used synonymously*

Sonstige methodische Hinweise

Aus der Leitlinie wurden lediglich diejenigen Informationen extrahiert, die sich auf die Therapie von HER2+ Patienten beziehen.

Empfehlungen

Recommendation

- **The choice of the adjuvant systemic treatment for invasive breast cancer should be driven by the hormonal sensitivity, risk profile of the tumour, age, menopausal status and comorbidities of the patient (1A evidence).**

Recommendations

- **For patients with Stage I-III breast cancer, preferred regimens are standard anthracycline-based regimens with or without a taxane (1A evidence).**
- **For patients with lymph node-positive breast cancer, preferred regimens are standard anthracycline and taxane-based regimens (2A evidence).**
- **For patients with HER-2 positive breast cancer who receive trastuzumab, a sequential regimen of anthracyclines and taxanes is recommended to decrease the total dose of anthracyclines and hence reduce the cardiotoxicity (expert opinion).**
- **Women receiving an adjuvant anthracycline–taxane regimen should be closely monitored for febrile neutropenia.**
- **Primary prophylactic G-CSF (granulocyte colony-stimulating factor) is recommended if risk of febrile neutropenia is 20% or higher (1A evidence).**
- **Secondary prophylaxis with CSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (1A evidence).**
- **In patients with breast cancer, high-dose chemotherapy with stem-cell transplantation cannot be recommended (1A evidence).**
- **For women of childbearing age, fertility issues should always be discussed before the induction of breast cancer therapy (1C evidence).**
- **Chemotherapy during pregnancy is not contraindicated after 14 weeks of gestation (2C evidence).**

Recommendations

- **Premenopausal women with hormone-receptor positive breast cancer should receive adjuvant endocrine treatment with tamoxifen for 5 years, with or without an LHRH analogue (1A evidence).**
- **Premenopausal women with stage I or II breast cancer who cannot take tamoxifen, should receive a LHRH analogue (1A evidence).**
- **Postmenopausal women with hormone-receptor positive breast cancer should receive adjuvant endocrine treatment with either (1A evidence):**
  - **tamoxifen (for 5 years),**
  - **anastrozole (for 5 years) or letrozole (for 5 years),**
  - **or tamoxifen (for 2 - 3 years) followed by an aromatase inhibitor (up to a total of five years of hormone therapy),**
  - **or an aromatase inhibitor (for 2 years) followed by tamoxifen (up to a total of 5 years).**
- **Postmenopausal women with hormone receptor-positive tumours who have completed five years of adjuvant tamoxifen therapy should be considered for extended treatment with an aromatase inhibitor (for up to 5 years) if they were node-positive or high-risk node-negative (pT2 or grade III) (1A evidence).**

Update 2013

Conclusions

Among breast cancer patients with HER-2 positive invasive (non-metastatic) breast cancer in the adjuvant setting, treated with trastuzumab with adjuvant non-anthracycline chemotherapy versus trastuzumab with adjuvant anthracycline–taxane chemotherapy:

- A difference in overall survival after 5 years (median follow-up 65 months) could neither be demonstrated nor refuted (Slamon 2011; low level of evidence).
- A difference in disease free survival after 5 years (median follow-up 65 months) could neither be demonstrated nor refuted (Slamon 2011; low level of evidence).
- There are indications that trastuzumab plus adjuvant non-anthracycline chemotherapy leads to less congestive heart failure (New York Heart Association grade 3 or 4) than trastuzumab with adjuvant anthracycline–taxane chemotherapy (Slamon 2011; low level of evidence).

- There are indications that trastuzumab plus adjuvant non-anthracycline chemotherapy leads to less >10% relative reduction in left ventricular ejection fraction than trastuzumab with adjuvant anthracycline–taxane chemotherapy (Slamon 2011; low level of evidence).

Recommendations 2013

- A one-year course of trastuzumab is indicated for women with HER2-positive, node-positive or high-risk node-negative breast cancer (tumour size > 1 cm) who received chemotherapy, and with a left ventricular ejection fraction of ≥ 55% and no important cardiovascular risk factors (strong recommendation).
- Trastuzumab can be combined either with a taxane in an anthracycline containing regimen or with a non-anthracycline regimen (TCH) (weak recommendation).
- In patients under trastuzumab, cardiac function should be monitored during treatment (e.g. every 3 months) and during follow-up (strong recommendation).
- Benefits and risks of each treatment have to be discussed with the patient (strong recommendation).

Recommendations

- Metastatic lesions should be biopsied whenever accessible and ER, PgR and HER2 should be reassessed (1B evidence).
- In both pre- and postmenopausal women, HER2 status should be used to identify patients most likely to benefit from Trastuzumab (1B evidence).

Scottish Intercollegiate Guidelines Network (SIGN), 2013 [40].

Treatment of primary breast cancer. A national clinical guideline

Leitlinienorganisation/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

Grundlage der Leitlinie

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as ‘off label’ use.

SIGN guidelines are produced using a standard methodology that has been equality impact assessed to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can SIGN guidelines are produced using a standard methodology that has been equality impact assessed to ensure that these equality aims are addressed in every guideline. This methodology is set out in the current version of SIGN 50, our guideline manual, which can be found at www.sign.ac.uk/guidelines/fulltext/50/index.html.be found at www.sign.ac.uk/guidelines/fulltext/50/index.html.

Recherche/Suchzeitraum:

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2003-2011. Internet

searches were carried out on various websites including the US National Guidelines Clearinghouse.

LoE/GoR

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
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 of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding 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

Sonstige methodische Hinweise

Die Leitlinie ist möglicherweise veraltet; ein geplantes Update der Leitlinienherausgeber fand nicht statt. Hinweise der Leitlinienherausgeber auf der SIGN-Internetseite zu dieser Leitlinie:

- This guideline was issued in 2013 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the review report.
- Current 3-7 years: Some recommendations may be out of date, declaration of interests governance may not be in line with current policy.

Empfehlungen

Key recommendations

2.1 SURGERY

✓ The choice of surgery must be tailored to the individual patient, who should be fully informed of the options and made aware that breast irradiation is required following conservation, and that further surgery may be required if the margins are not clear of tumour.

R **If there is proven axillary lymph node disease preoperatively axillary lymph node clearance should be undertaken; if there is no proven disease the optimal axillary procedure is a sentinel lymph node biopsy** (or if not available axillary node sample is an alternative).

2.2 RADIOTHERAPY

R **Postoperative external beam radiotherapy to the conserved breast should be considered for all patients undergoing conservation surgery for early breast cancer.**

Post-mastectomy radiotherapy should be considered in patients with lymph node-positive breast cancer if they have high risk of recurrence (≥4 positive lymph nodes and T3/4 tumours).

Post-mastectomy radiotherapy may be considered in patients with intermediate risk of recurrence (high-risk node negative tumours or one to three positive axillary lymph nodes).

All patients with ductal carcinoma in situ should be considered for breast radiotherapy following breast conservation surgery.

2.3 ADJUVANT SYSTEMIC THERAPY

R **Adjuvant chemotherapy should be considered for all patients with breast cancer where benefit outweighs risk.**

Adjuvant anthracycline-taxane combination chemotherapy should be considered for all patients with breast cancer where the additional benefit outweighs the risk.

Primary prophylaxis with granulocyte colony stimulating factors should be considered where the risk of febrile neutropenia exceeds 20%.

Adjuvant trastuzumab should be considered in all patients with HER-2 positive breast cancer who receive adjuvant chemotherapy.

Adjuvant trastuzumab should not be given concurrently with anthracyclines but may be given either concurrently with taxane based regimens or sequentially.

2.4 ADJUVANT ENDOCRINE THERAPY

R **Pre-menopausal women with ER positive invasive breast cancer should be treated with tamoxifen for at least five years, to a total of ten years, unless there are contraindications or side effects.**

Postmenopausal women with ER positive early breast cancer should be considered for treatment with aromatase inhibitors as an alternative to tamoxifen, either:

- **as an upfront aromatase inhibitor for five years, or**
- **by switching to an aromatase inhibitor after two to three years of tamoxifen for a total of five years.**

2.5 NEOADJUVANT SYSTEMIC THERAPY

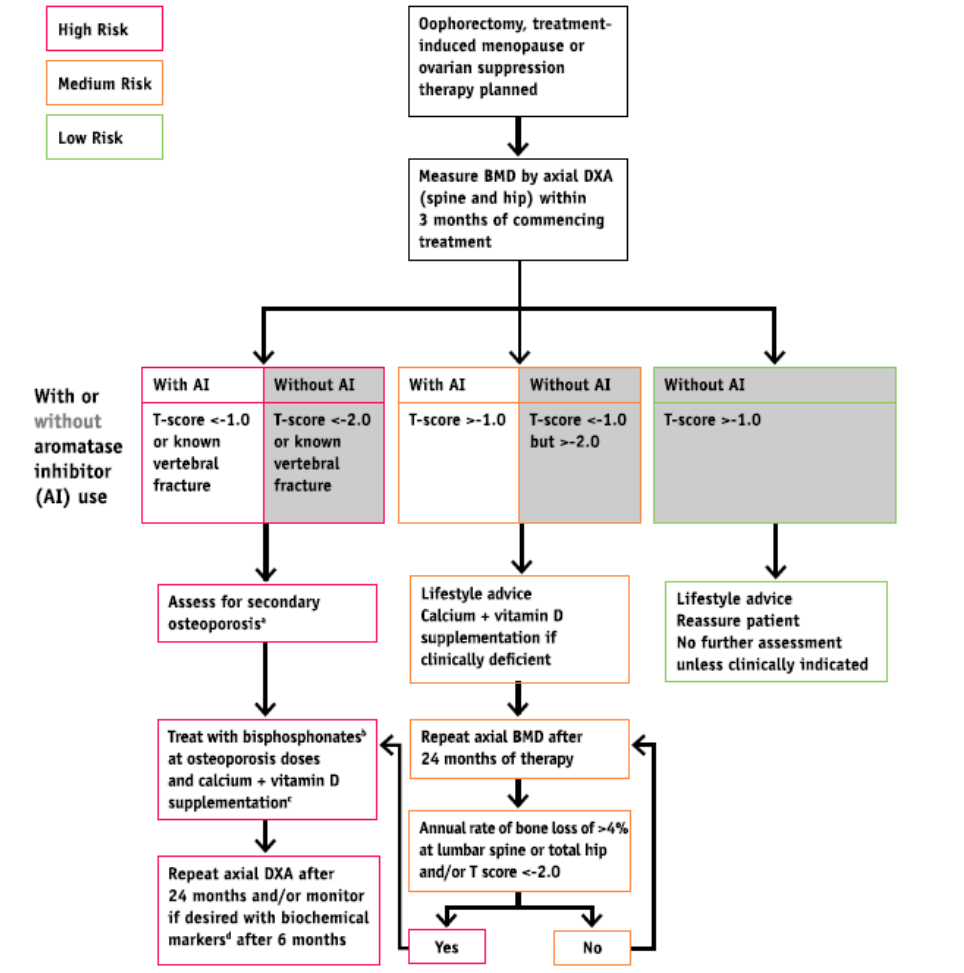
R **Neoadjuvant chemotherapy should be considered for all patients with breast cancer whose disease is either:**

- **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.**

2.6 NEOADJUVANT ENDOCRINE THERAPY

R **Aromatase inhibitor is recommended for ER positive postmenopausal women receiving neoadjuvant endocrine therapy.**

Algorithm 1: Adjuvant treatment associated with ovarian suppression/failure with or without concomitant aromatase inhibitor use in women who experience premature menopause



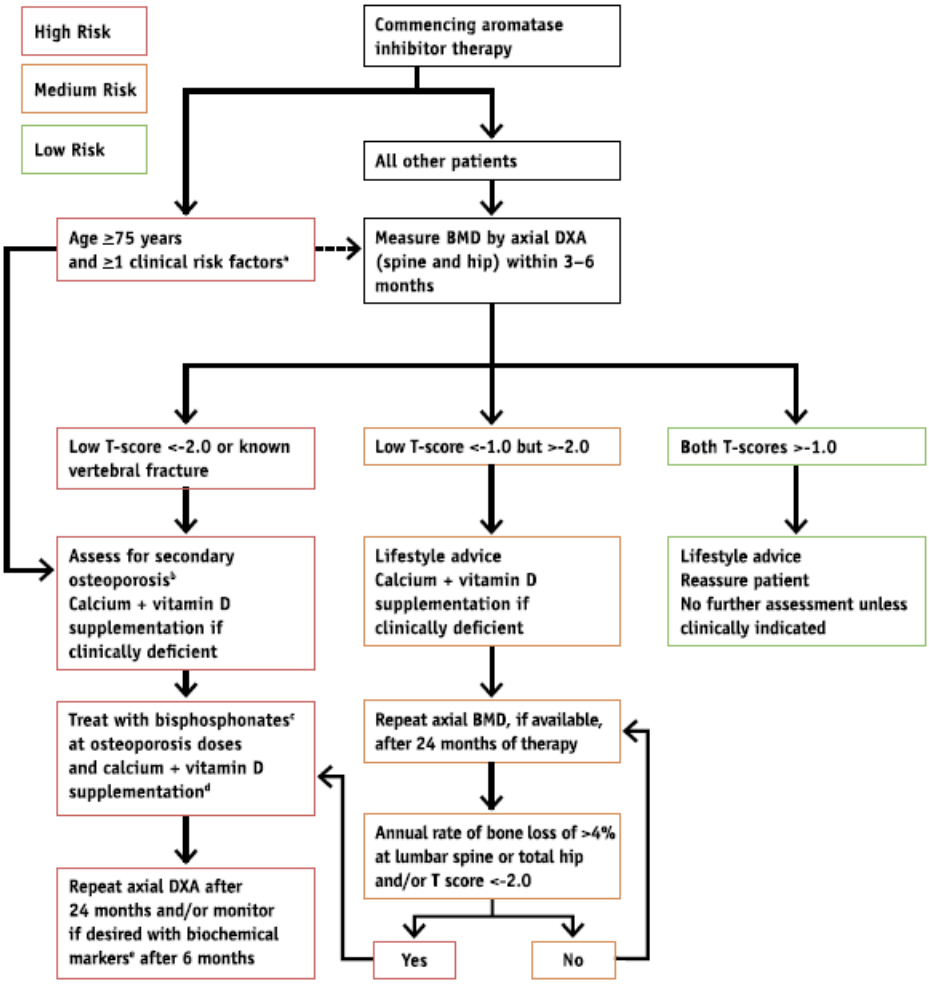
a ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST / ALT), serum creatinine, endomysial antibodies, serum thyroid stimulating hormone

b Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

c To be given as ≥1 g of calcium + ≥800 IU of vitamin D

d Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

Algorithm 2: Postmenopausal adjuvant treatment with aromatase inhibitors



a Previous low-trauma fracture after age 50, parental history of hip fracture, alcohol intake of ≥4 units/day, diseases associated with secondary osteoporosis, prior corticosteroids for >6 months, low BMI (<22)

b ESR, FBC, bone and liver function (calcium, phosphate, alkaline phosphatase, albumin, AST /γGT), serum creatinine, endomysial antibodies, serum thyroid stimulating hormone

c Alendronate 70 mg per week, risedronate 35 mg per week, ibandronate (150 mg po monthly or 3 mg iv 3-monthly), zoledronic acid 4 mg iv 6-monthly

d To be given as ≥1 g of calcium + ≥800 IU of vitamin D

e Biochemical markers such as serum C-terminal telopeptide of type I collagen or urinary N-telopeptide of type I collagen

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 11 of 12, November 2018) am 09.11.2018

#	Suchfrage
1	[mh "Breast Neoplasms"]
2	(breast or mamma*):ti,ab,kw
3	(cancer* or tum*r* or carcinoma* or neoplas* or lesions* or malignan*):ti,ab,kw
4	#1 or (#2 and #3)
5	#4 with Cochrane Library publication date from Nov 2013 to Nov 2018

Systematic Reviews in Medline (PubMed) am 09.11.2018

#	Suchfrage
1	breast neoplasms/therapy[majr]
2	(breast[ti]) OR mamma*[ti]
3	(cancer*[ti] OR tumour*[ti] OR tumor[ti] OR tumors[ti] OR carcinom*[ti] OR neoplas*[ti] OR malignan*[ti])
4	treatment*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR treating[tiab] OR treated[tiab] OR management[tiab] OR drug*[tiab] OR chemotherap*[tiab]
5	#2 AND #3 AND #4
6	#1 OR #5
7	(#6) AND (HER2*[tiab] OR (human epidermal growth factor receptor*[tiab] AND 2[tiab]) OR erbB2*[tiab] OR primar*[tiab] OR (earl*[tiab] AND (stag*[tiab] OR phase*[tiab])))
	((HER2*[tiab] OR (human epidermal growth factor receptor*[tiab] AND 2[tiab]) OR erbB2*[tiab] OR hormone receptor-positive[tiab] OR HR+*[tiab] primar*[tiab] OR (earl*[tiab] AND (stag*[tiab] OR phase*[tiab]))))
8	(#7) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
9	((#8) AND ("2013/11/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 09.11.2018

#	Suchfrage
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	cancer*[ti] OR tumour*[ti] OR tumor[ti] OR tumors[ti] OR carcinom*[ti] OR neoplas*[ti] OR malignan*[ti]

4	#2 AND #3
5	#1 OR #4
6	(#5) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))
7	(((#6) AND ("2013/11/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))

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