Gemeinsamer Bundesausschuss

# Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

# und

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

## Vorgang: 2016-B-032 Pertuzumab

Stand: Mai 2016

| I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA | |
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| **Pertuzumab**<br>**[adjuvante Behandlung von HER2-positivem, frühem Brustkrebs]** | |
| **Kriterien gemäß 5. Kapitel § 6 VerfO** | |
| Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben. | *Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet".*<br>Der vorliegenden Fragestellung entsprechend, nur in Bezug auf die adjuvante (nicht: neoadjuvante) Behandlung von HER2-positivem, frühem Brustkrebs.<br>Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung zur Behandlung des Hormonrezeptor-positiven Mammakarzinoms bzw. als endokrine Therapie. |
| Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein. | Strahlentherapie |
| Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen | • Richtlinie des Gemeinsamen Bundesausschusses zur Regelung von Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V (DMP-Richtlinie), zuletzt geändert am 20. November 2014: Anforderungen an die Ausgestaltung von Strukturierten Behandlungsprogrammen für Patientinnen mit Brustkrebs<br>• Gemcitabin: Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie - Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten - (Stand: 26. Februar 2016): Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind: Gemcitabin in der Monotherapie beim Mammakarzinom der Frau |
| 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** | |
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| **Wirkstoff**<br>**ATC-Code**<br>**Handelsname** | **Anwendungsgebiet**<br>(Text aus Fachinformation) |
| Zu prüfendes Arzneimittel: | |
| Pertuzumab<br>L01XC13<br>Perjeta® | Geplantes Anwendungsgebiet:<br>Perjeta ist in Kombination mit Trastuzumab und Chemotherapie bei erwachsenen Patienten zur adjuvanten und neoadjuvanten Behandlung von HER2-positivem, frühem Brustkrebs indiziert.<br>*[Der vorliegenden Fragestellung entsprechend, in Bezug auf die adjuvante (nicht: neoadjuvante) Behandlung von HER2-positivem, frühem Brustkrebs.]* |
| **Zytotoxische Chemotherapien** | |
| Cyclophosphamid<br>L01AA01<br>Endoxan | Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt:<br>– Adjuvante Therapie des Mammakarzinoms nach Resektion des Tumors beziehungsweise Mastektomie<br>– Palliative Therapie des fortgeschrittenen Mammakarzinoms (Endoxan, April 2016) |
| Docetaxel<br>L01CD02<br>Taxotere® | Brustkrebs<br>Taxotere ist in Kombination mit Doxorubicin und Cyclophosphamid angezeigt für die adjuvante Therapie von Patientinnen mit:<br>– operablem, nodal positivem Brustkrebs,<br>– operablem, nodal negativem Brustkrebs.<br>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. (Taxotere®, April 2016) |
| Doxorubicin<br>L01DB01<br>Adrimedac® | Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist:<br>– Mammakarzinom<br>[…]<br>Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.<br>(Adrimedac®, April 2016) |
| Epirubicin<br>L01DB03<br>Farmorubicin® | Mammakarzinom<br>(Farmorubicin®, April 2016) |
| 5-Fluorouracil<br>L01BC02<br>Benda-5 FU® | – Fortgeschrittenes und/oder metastasiertes Mammakarzinom<br>– Adjuvante Therapie des primären invasiven Mammakarzinoms<br>(Benda-5 FU®, April 2016) |

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| Methotrexat<br>L01BA01<br>Methotrexat-GRY® | <u>Mammakarzinome</u><br>In Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.<br>(Methotrexat-GRY®, April 2016) |
| Paclitaxel<br>L01CD01<br>Paclitaxel Hospira | <u>Mammakarzinom</u><br>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.<br>(Paclitaxel Hospira, April 2016) |
| Vincristin<br>L01CA02<br>Vincristinsulfat-TEVA® | Vincristinsulfat-TEVA® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von:<br>– soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom, kleinzelligem Bronchialkarzinom<br>(Vincristinsulfat-TEVA®, April 2016) |
| **HER2-gerichtete Therapien** | |
| Trastuzumab<br>L01XC03<br>Herceptin® | <u>Brustkrebs im Frühstadium</u><br>Herceptin ist zur Behandlung von erwachsenen Patienten mit HER2-positivem Brustkrebs im Frühstadium (early breast cancer – EBC) indiziert:<br>– nach einer Operation, Chemotherapie (neoadjuvant oder adjuvant) und Strahlentherapie (soweit zutreffend).<br>– nach adjuvanter Chemotherapie mit Doxorubicin und Cyclophosphamid, in Kombination mit Paclitaxel oder Docetaxel.<br>– in Kombination mit adjuvanter Chemotherapie mit Docetaxel und Carboplatin.<br>– in Kombination mit neoadjuvanter Chemotherapie, gefolgt von adjuvanter Therapie mit Herceptin, bei lokal fortgeschrittenem (einschließlich entzündlichem) Brustkrebs oder Tumoren > 2 cm im Durchmesser.<br>(Herceptin®, April 2016) |

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

# Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT) nach § 35a SGB V

**Inhalt**



## Indikation für die Recherche bei Pertuzumab

Perjeta ist in Kombination mit Trastuzumab und Chemotherapie bei erwachsenen Patienten zur adjuvanten Behandlung von HER2-positivem, frühem Brustkrebs indiziert (siehe Abschnitt 5.1).

## Berücksichtigte Wirkstoffe/Therapien:

siehe Unterlage zur Beratung in AG: Übersicht zVT, Tabellen „I. Zweckmäßige Vergleichstherapie“ und „II. Zugelassene Arzneimittel im Anwendungsgebiet.“

## Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation Brustkrebs durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die

Recherche am 01.04.2016 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Aufgrund der onkologischen Indikation wurde zusätzlich in folgenden Datenbanken bzw. Internetseiten folgender Organisationen gesucht: CCO, ESMO, NCCN, NCI. 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 1161 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 14 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

| | |
|---|---|
| AI | Aromataseinhibitoren |
| AC | Doxorubicin + Cyclophosphamid |
| ACE | angiotensin converting enzyme |
| AWMF | Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften |
| CCO | Cancer Care Ontario |
| CI | Confidence Interval |
| CHF | congestive heart failure |
| CMF | cyclophosphamide, methotrexate, and 5-fluorouracil |
| CNS | zentrales Nervensystem |
| DAHTA | Deutsche Agentur für Health Technology Assessment |
| 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** |
| 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 |
| NCCN | National Comprehensive Cancer Network |

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| NCCP | National Cancer Control Programme |
| NCI | U.S. *National Cancer Institute* |
| NGC | National Guideline Clearinghouse |
| NICE | National Institute for Health and Care Excellence |
| NNH | Number needed to harm |
| OR | Odds Ratio |
| OS | Overall survival |
| PEBC | Program in Evidence-Based Care |
| PFS | Progresion free survival |
| PLD | pegylated liposomal doxorubicin |
| RR | Relatives Risiko |
| 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 |

**IQWiG Berichte/ G-BA Beschlüsse**

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| **IQWiG, 2014 [7].**<br>Systematische Leitlinien-recherche und -bewertung sowie Extraktion relevanter Empfehlungen für das DMP Brustkrebs IQWiG-Berichte – Nr. 224<br><br>*Siehe auch:*<br>**G-BA 2014 [5].**<br>Richtlinie DMP-Brustkrebs | **Fragestellung/Ziele:**<br>Ziel der vorliegenden Untersuchung war es, durch eine systematische Recherche nach neuen thematisch relevanten evidenzbasierten Leitlinien und durch die Synthese der Leitlinienempfehlungen einen potenziellen Aktualisierungs- bzw. Ergänzungsbedarf des bestehenden DMP Brustkrebs zu spezifizieren.<br><br>**Methodik**<br>• systematische Recherche nach Leitlinien über die Leitliniendatenbanken der Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), des Guidelines International Network (G-I-N), des National Guideline Clearinghouse (NGC) sowie aufseiten von fachübergreifenden und fachspezifischen Leitlinienanbietern durchgeführt. Zeitraum ab November 2007 bis November 2013.<br>• Leitlinien wurden mithilfe des Appraisal-of-Guidelines-for-Research-&-Evaluation(AGREE)-II-Instrumentes methodisch bewertet.<br>• Die für die Fragestellung relevanten Empfehlungen wurden extrahiert und den Versorgungsaspekten der Richtlinie des G-BA zur Regelung von Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen nach § 137f Abs. 2 SGB V vom 16.02.2012 (DMP-Richtlinie) zugeordnet.<br><br>**Ergebnis /Fazit:**<br>26 Leitlinien eingeschlossen, bewertet und ihre Empfehlungen extrahiert.<br><br>**<u>Versorgungsaspekt „Systemische adjuvante Therapie (endokrine Therapie, Chemotherapie und Antikörpertherapie“ (1.4.4 der DMP-Richtlinie)</u>**<br>Bei Patientinnen mit HER2/neu-positiven Tumoren (ab Stadium pT1c und / oder Lymphknotenbefall) soll eine Behandlung mit Trastuzumab erfolgen. (siehe auch G-BA 2014 [5])<br>*<u>Abgleich mit den Anforderungen der DMP-Richtlinie</u>*<br>Mehrere Leitlinien geben mit uneinheitlicher GoR- / LoE-Kategorie Empfehlungen zur Planung einer adjuvanten systemischen Therapie. Die Empfehlungen stimmen im Wesentlichen mit der DMP-Richtlinie überein, sind aber zum Teil ausführlicher. Es ergibt sich kein Aktualisierungs- bzw. Ergänzungsbedarf.<br><br>**adjuvanten Antikörpertherapie**<br>6 Leitlinien (DKG 2012, IKNL 2012, KCE 2013, NICE 2009 Ea, SIGN 2013 und NZGG 2009) geben Empfehlungen zur adjuvanten |

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| | Antikörpertherapie.<br>4 Leitlinien empfehlen bei Patientinnen mit HER2-positiven Tumoren (≥ 1 cm) eine Behandlung mit Trastuzumab über einen Zeitraum von 1 Jahr (DKG 2012 [GoR-Kategorie A, LoE-Kategorie Ib]; KCE 2013 [GoR-Kategorie A, LoE-Kategorie Ia-IV]; NICE 2009 Ea [keine Angaben zu GoR, LoE n. z.]; NZGG 2009 [GoR-Kategorie A]). Eine Leitlinie führt eine genaue Definition für HER2-Positivität als Voraussetzung für die Trastuzumab-Therapie an (DKG 2012 [GoR-Kategorie A, LoE-Kategorie IIb]).<br>Die Leitlinie DKG 2012 empfiehlt zudem die zusätzliche Gabe von Trastuzumab, wenn die Indikation für eine Chemotherapie bei Tumoren < 10 mm vorliegt (GoR-Kategorie B). Laut der Leitlinie SIGN 2013 sollte grundsätzlich bei allen Patientinnen mit HER2-positiven Tumoren, die eine Chemotherapie erhalten, zusätzlich eine Therapie mit Trastuzumab in Betracht gezogen werden (keine Angaben zu GoR, LoE n. z.). Trastuzumab kann entweder mit Taxanen bei einer Anthrazyklin-basierten Chemotherapie oder mit einer nicht Anthrazyklin-basierten Chemotherapie kombiniert werden (KCE 2013 [GoR-Kategorie 0; LoE-Kategorie Ia-IV]). Ein simultaner Start der Behandlung mit der Taxan-Phase der adjuvanten Chemotherapie (DKG 2012 [GoR-Kategorie B, LoE-Kategorie IIa]; SIGN 2013 [keine Angaben zu GoR, LoE n. z.]) oder alternativ eine sequenzielle Verabreichung (SIGN 2013 [keine Angaben zu GoR, LoE n. z.]) wird empfohlen. Von einer gleichzeitigen Gabe von Trastuzumab während einer Therapie mit Anthrazyklinen wird jedoch abgeraten (SIGN 2013 [keine Angaben zu GoR, LoE n. z.]). Die Leitlinie IKNL 2012 gibt spezifische Angaben für die Dosierung von Taxanen in Kombination mit Trastuzumab und empfiehlt nach Beendigung der Chemotherapie eine weiterführende Therapie mit Trastuzumab über einen Zeitraum von 1 Jahr (keine Angaben zu GoR, LoE n. z.).<br>Vor der Behandlung mit Trastuzumab und in regelmäßigen Abständen während der Therapie sollte die Herzfunktion überprüft werden (IKNL 2012 [keine Angaben zu GoR, LoE n. z.];KCE 2013 [GoR-Kategorie A, LoE-Kategorie Ia-IV]; NICE 2009 Ea [keine Angaben zu GoR, LoE n. z.]; SIGN 2013 [keine Angaben zu GoR, LoE n. z.]; NZGG 2009 [GoR-Kategorie B]). Der Nutzen einer Therapie mit Trastuzumab bei Patientinnen mit signifikanten kardialen Komorbiditäten sollte eingehend geprüft werden (IKNL 2012 [keine Angaben zu GoR, LoE n. z.]; SIGN 2013 [keine Angaben zu GoR, LoE n. z.]). Laut der Leitlinie NZGG 2009 kann es bei Patientinnen mit eingeschränkter linksventrikulärer Auswurffraktion sinnvoll sein, die Behandlung mit Trastuzumab erst nach Beendigung der Chemotherapie zu beginnen (GoR-Kategorie 0). |

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| | *<u>Abgleich mit den Anforderungen der DMP-Richtlinie</u>*<br>Mehrere Leitlinien geben mit überwiegend hoher GoR-Kategorie Empfehlungen für eine adjuvante Therapie mit Trastuzumab bei HER2-positiven Tumoren. Die Empfehlungen stimmen im Wesentlichen mit der DMP-Richtlinie überein, sind aber ausführlicher. Es ergibt sich kein Aktualisierungs- bzw. Ergänzungsbedarf.<br>Mehrere Leitlinien geben mit uneinheitlicher GoR-Kategorie Empfehlungen für eine regelmäßige Überprüfung der Herzfunktion während einer Behandlung mit Trastuzumab. Hierbei handelt es sich im Vergleich zur DMP-Richtlinie um eine zusätzliche Empfehlung. Ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf kann diskutiert werden.<br><br>**adjuvanten Chemotherapie**<br>Bei Patientinnen mit hormonrezeptornegativem Brustkrebs empfehlen 2 Leitlinien grundsätzlich die Durchführung einer adjuvanten Chemotherapie (DKG 2012 [GoR-Kategorie A, LoE-Kategorie Ia]; NZGG 2009 [GoR-Kategorie A]). Die Leitlinie SIGN 2013 empfiehlt grundsätzlich bei allen Patientinnen mit Brustkrebs, nach Nutzen-Risiko-Abwägung eine adjuvante Chemotherapie in Betracht zu ziehen (keine Angaben zu GoR, LoE n. z.). Laut der Leitlinie NZGG 2009 sollte bei prämenopausalen Frauen mit hormonrezeptorpositiven Tumoren eine Kombination von Chemotherapie und endokriner Therapie in Erwägung gezogen werden; bei postmenopausalen Patientinnen sind Nutzen und Risiken abzuwägen (2 x GoR-Kategorie A). Dabei wird empfohlen, zuerst die Chemotherapie und danach die endokrine Therapie durchzuführen (NZGG 2009 [GoR-Kategorie 0]).<br>Weitere Indikationen sind laut der Leitlinie DKG 2012 (GoR-Kategorie B, LoE-Kategorie Ia):<br>• positiver HER2-Status,<br>• endokrin nicht sensitive Tumoren,<br>• nodal positive Tumoren oder nodal-negative Tumoren mit hohem Rezidivrisiko,<br>• Grading 37 und<br>• Patientinnen unter 35 Jahren.<br><br>Die Patientin sollte unter Berücksichtigung des individuellen Risikoprofils über Nutzen und Schaden von Taxanen aufgeklärt werden (NBOCC 2008 taxane [2 x LoE-Kategorie Ia]; NZGG 2009 [GoR-Kategorie 0]). Dabei sollte auch auf das erhöhte Risiko einer febrilen Neutropenie durch eine Taxan-haltige Chemotherapie hingewiesen werden (NBOCC 2008 taxane [keine Angaben zu GoR / LoE]). Laut der Leitlinie KCE 2013 sollten Patientinnen regelmäßig hinsichtlich des Auftretens febriler Neutropenien überprüft werden (GoR-Kategorie A). Bei einem Risiko der febrilen Neutropenie von |

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| | über 20 % sollte der prophylaktische Einsatz eines Granulozyten-Kolonie stimulierenden Faktors in Erwägung gezogen werden (KCE 2013 [GoR-Kategorie A]; SIGN 2013 [keine Angaben zu GoR, LoE n. z.]). Die Dosierungen von Taxanen sollten individuell abgestimmt werden (NBOCC 2008 taxane [keine Angaben zu GoR / LoE]).<br><br>*Abgleich mit den Anforderungen der DMP-Richtlinie*<br>Mehrere Leitlinien geben mit überwiegend hoher GoR-Kategorie Empfehlungen zur Indikation für eine adjuvante Chemotherapie. Die Empfehlungen stimmen im Wesentlichen mit der DMP-Richtlinie überein. Es ergibt sich kein Aktualisierungs- bzw. Ergänzungsbedarf.<br>Mehrere Leitlinien geben mit überwiegend hoher GoR- / LoE-Kategorie Empfehlungen für eine Chemotherapie. Die Leitlinien nennen ausdrücklich Taxan-haltige und / oder Anthrazyklin-basierte Regime. Hierbei handelt es sich im Vergleich zur DMP-Richtlinie um zusätzliche Empfehlungen. Es besteht ein potenzieller Aktualisierungs- bzw. Ergänzungsbedarf. |
| **G-BA, 2010 [6]**<br>Anlage VI – Off-Label-Use Gemcitabin in der Mono-therapie beim Mammakarzinom der Frau I | **Fazit:**<br><br>Die Anlage VI wird im Teil B wie folgt ergänzt: „IV. Gemcitabin in der Monotherapie beim Mammakarzinom der Frau“<br><br>Teil B: Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-<br>Label-Use) nicht verordnungsfähig sind |

**Cochrane Reviews**

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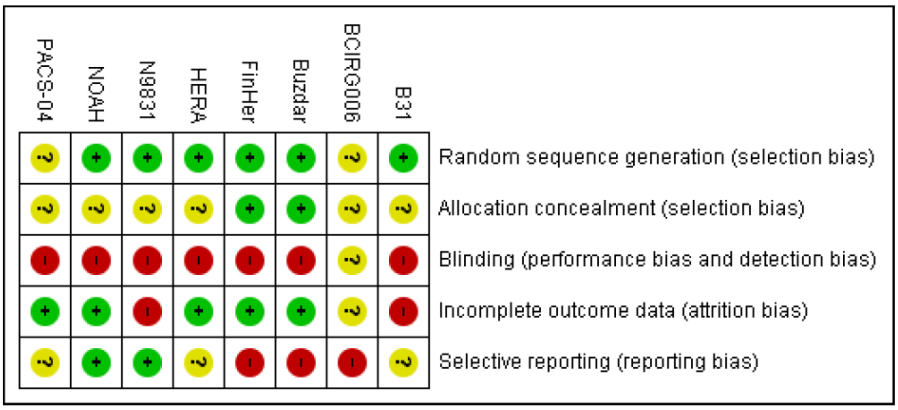
| **Moja L. et al., 2012 [11].**<br>Trastuzumab containing regimens for early breast cancer (Review) | 1. Fragestellung<br>To assess the evidence on the efficacy and safety of therapy with trastuzumab, overall and in relation to its duration, concurrent or sequential administration with the standard chemotherapy regimen in patients with HER2-positive early breast cancer. |
| | 2. Methodik<br><br>Population: Women with HER2-positive breast cancer (early or locally advanced) of any age,menopausal status, nodal or hormone-receptorstatus.<br><br>Intervention: trastuzumab given following or in combination with standard chemotherapy regimen.<br><br>Komparator: the same chemotherapy regimen used in the intervention group without trastuzumab.<br><br>Endpunkte<br><br><u>Primary outcomes</u><br><br>• Overall survival (OS)<br>• Disease-free survival (DFS).<br><br><u>Secondary outcomes</u><br><br>• Cardiac toxicity<br>• Tumour recurrences<br>• Other toxicities<br>• Brain metastases as first site of relapse.<br>• Treatment-related deaths.<br>• Quality of life (QoL).<br><br>Suchzeitraum (Aktualität der Recherche): 01/1996-02/2010<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 8 Studien, davon für 2 Studien relevant (FinHer, NOAH)<br><br>Qualitätsbewertung der Studien:*Cochrane Risk of Bias Tool* |
| | 3. Ergebnisdarstellung<br><br>**Relevante Studien:**<br><br>• FinHer: N=1010 davon 232 HER2 positiv;<br>Arm A (N = 58): docetaxel (100 mg/sm, every three weeks, three cycles) followed by FEC [fluorouracile, epirubicin and cyclophosphamide (600 mg/sm, 60 mg/sm, 600 mg/sm every three weeks, three cycles)]<br><u>Arm B (N = 54):</u> docetaxel (100 mg/sm, every three weeks, three |

cycles) plus trastuzumab (4 mg/kg loading dose and 2 mg/kg following, weekly, nine cycles) followed by FEC [fluorouracile, epirubicin and cyclophosphamide (600 mg/sm, 60 mg/sm, 600 mg/sm every three weeks, three cycles)]. The first trastuzumab infusion was given on day 1 of the first docetaxel cycle
Arm C und D nicht im AWG zugelassen

- NOAH: N=235 Women,
  Group 1 (randomised N = 117) doxorubicin 60 mg/sm plus paclitaxel 150 mg/ sm, every three weeks for three cycles, followed by paclitaxel 175 mg/sm administered every three weeks for four cycles followed by cyclophosphamide (600 mg/sm), methotrexate (40 mg/sm), and fluorouracil (600 mg/sm) given on days 1 and 8 every four weeks for three cycles
  Group 2 (randomised N = 118): the same chemotherapy of the first group plus trastuzumab loading dose of 8 mg per kg, followed by ten cycles of 6 mg/kg every three weeks alongside chemotherapy Trastuzumab could be given every 4 weeks during cyclophosphamide, methotrexate, and fluorouracil chemotherapy. After surgery (see below), additional cycles of trastuzumab were given, starting before or during radiotherapy (at the investigator's discretion), to complete one year of trastuzumab treatment [Anmerkung FBMed: Unterscheidung zw. adjuvanter und neoadjuvanter Therapie nicht eindeutig möglich!]

**Risk of Bias:**




**Overall Survival (OS)**

- FinHer: HR=0,55 (95% CI 0,27-1,11) zugunsten Trastuzumab
- NOAH: HR=0,62 (95% CI 0,34-1,11) zugunsten Trastuzumab

**Disease free survival**

FinHer: HR=0,42 (95% CI 0,21-0,83)

NOAH: HR=0,59 (95% CI 0,38-0,91)

**Sicherheit:**

Congestive heart failure (CHF):

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| | FinHer: HR=0,50 (95% CI 0,07-3,74)<br><br>NOAH: HR=4,91 (95% CI 0,39-62,24)<br><br><u>Decline in left ventricular ejection fraction</u><br><br>Nur gepoolte Ergebnisse für (BCIRG006;Buzdar; FinHer; HERA; NOAH; N9831; PACS-04): trastuzumab significantly increased the risk of LVEF decline (RR 1.83; 90% CI 1.36 to 2.47, P = 0.0008). substantial heterogeneity ($I^2$ = 71%).<br><br><u>Neutropenic fever</u><br><br>Keine statistisch sign. Assoziation gepoolt für (BCIRG006; Buzdar; FinHer; NOAH)<br><br><u>Anaemia</u><br><br>Gepoolte Ergebnisse für: (BCIRG006; FinHer): nicht stat. signifikant<br><br><u>Neutropenia</u><br><br>Four trials (BCIRG006; Buzdar; FinHer; NOAH) nicht statistisch signifikant<br><br><u>Brain metastases as the site of first relapse</u><br><br>Five trials (B31; FinHer; HERA; N9831; PACS-04) geppolte Ergebnisse: significantly higher in patients receiving trastuzumab (RR 1.75; 90% CI 1.29 to 2.38, P = 0.002). |
| | 4. Anmerkungen/Fazit der Autoren<br><br>Trastuzumab significantly improves OS and DFS in HER2-positive women with early and locally advanced breast cancer, although it also significantly increases the risk of CHF and LVEF decline. |

**Systematische Reviews**

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| **Mantarro S. et al., 2016 [9].**<br>Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer | 1. Fragestellung<br>In this systematic review and meta-analysis of clinical trials and cohort studies, we aimed to assess the frequency of severe cardiovascular events after trastuzumab treatment in women with HER2-positive breast cancer |
| | 2. Methodik<br>Population: Frauen mit HER2+ Brustkrebs<br>Intervention: trastuzumab als single-agent, in combination with chemotherapy, hormonal therapy, or radiotherapy<br>Komparator k.A.<br>Endpunkt severe cardiac events (Primärer E.), mild or asymptomatic cardiac events (Sekundärer E.)<br>Suchzeitraum (Aktualität der Recherche): bis 01/2014 (in MEDLINE, EMBASE, The Cochrane Library, American Society of Clinical Oncology und San Antonio Breast Cancer Symposium annual meetings<br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 58 Studien<br>Studies included in quantitative synthesis (meta-analysis) (n = 58)<br>• 19 randomized controlled trials<br>• 6 uncontrolled clinical trials<br>• 32 observational studies<br>• 1 open-label extension study<br>– studies that administered trastuzumab to treat EBC or MBC (including locally advanced/recurrent disease), or both EBC and MBC, defined as mixed studies.<br>– excluded studies using lapatinib or pertuzumab in association with trastuzumab<br>Qualitätsbewertung der Studien: ja, anhand folgender Kriterien:<br>– representativeness of the exposed cohort (lack of generalizability bias)<br>– retrospective or prospective analysis and source of data (record bias)<br>– withdrawals and dropouts (attrition bias)<br>– length of period of observation (detection bias)<br>– relevance and definition of measured outcome for cardiotoxicity (reporting bias).<br>→ maximal zu erreichende Punkte = 10); 7-10 Punkte = hohe |

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| | Qualität, 5-6 = medium Qualität, 1-4 = geringe Qualität<br>• The quality of studies ranged from 2 to 10 stars (23 Studien = high quality; 28 Studien = medium quality; 7 Studien low quality)<br>→ As a sensitivity analysis, the pooling process was repeated after excluding studies with a low-quality score. |
| | 3. Ergebnisdarstellung<br>35 Studien berücksichtigen ausschließlich Patienten mit EBC (early breast cancer); N= 23,383 Patienten; median age was 50 (range 20–99)<br>→ davon **5 Studien relevant** (17, 18, 45, 48, 50)<br>**(17) Perez EA et al. (2008):** Cardiac Safety Analysis of Doxorubicin and Cyclophosphamide Followed by Paclitaxel With or Without Trastuzumab in the North Central Cancer Treatment Group N9831 Adjuvant Breast Cancer Trial (Jaded Score=7)<br>– doxorubicin plus cyclophosphamide (AC) followed by either weekly paclitaxel (arm A); paclitaxel then trastuzumab (arm B); or paclitaxel plus trastuzumab then trastuzumab alone (arm C)<br>– Cardiac events (congestive heart failure [CHF] or cardiac death [CD]): arm A, n = 3 (2 CHF, 1 CD); arm B, n = 19 (18 CHF, 1 CD); arm C, n = 19 (all CHF); 3-year cumulative incidence: 0.3%, 2.8%, and 3.3%, respectively.<br>– Factors associated with increased risk of a cardiac event in arms B and C: older age (*P* < .003), prior/current antihypertensive agents (*P* = .005), and lower registration LVEF (*P* = .033).<br>**(18) Tan-Chiu E et al. (2005):** Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol 23(31):7811–7819.<br>– Regimens consisted of either doxorubicin (60 mg/m2) and cyclophosphamide (600 mg/m2) every 21 days for four cycles followed by paclitaxel (175 mg/m2) every 3 weeks for four cycles (arm 1) or the same chemotherapy plus weekly trastuzumab starting with the first dose of paclitaxel at a loa)ding dose of 4 mg/kg followed by 2 mg/kg for 51 weeks (arm 2).<br>– The difference in cumulative incidence at 3 years was 3.3% (4.1% for trastuzumab-treated patients minus 0.8% for control patients; 95% CI, 1.7% to 4.9%). Twenty-seven of the 31 patients in the trastuzumab arm have been followed for ≥ 6 months after diagnosis of a CE; 26 were asymptomatic at last assessment, and 18 remained on cardiac medication. CHFs were more frequent in older patients and patients with marginal post-AC LVEF |

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| | **(45) Rayson D et al. (2012)** Cardiac safety of adjuvant pegylated liposomal doxorubicin with concurrent trastuzumab: a randomized phase II trial. Ann Oncol 23(7):1780–1788.<br>– 1 : 2 ratio (doxorubicin : PLD) and were stratified by age (<55 and ≥55 years).<br>– The incidence of cardiac toxicity or inability to administer trastuzumab due to cardiotoxicity was 18.6% [n = 11; 95% confidence interval (CI) 9.7% to 30.9%] with A + C → T + H and 4.2% (n = 5; 95% CI 1.4% to 9.5%) with PLD + C + H → T +H (P = 0.0036).<br>**(48) Spielmann M et al. (2009): Trastuzumab** for patients with axillary-node positive breast cancer: results of the FNCLCC-PACS 04 trial. J Clin Oncol 27(36):6129–6134.<br>– evaluate the incidence of cardiac dysfunction, characterize its natural history, and identify the degree of reversibility using cardiac MRI<br>– The incidence of trastuzumab discontinuation due to cardiac disorders was low (4.3%). The incidence of cardiac end points was higher in the trastuzumab group compared with observation (severe congestive heart failure [CHF], 0.60% *v* 0.00%; symptomatic CHF, 2.15% *v* 0.12%; confirmed significant LVEF drops, 3.04% *v* 0.53%).<br>**(50) Suter TM et al. (2007)** Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol 25(25):3859–3865.<br>– Herceptin Adjuvant (HERA) trial<br>– The incidence of cardiac end points was higher in the trastuzumab group compared with observation (severe congestive heart failure [CHF], 0.60% *v* 0.00%; symptomatic CHF, 2.15% *v* 0.12%; confirmed significant LVEF drops, 3.04% *v* 0.53%). |
| | 4. Anmerkungen/Fazit der Autoren<br>Clinicians should consider carefully the trade-offs of trastuzumab, without misleading their patients by emphasizing the benefits and omitting information on major harms.<br>5. Hinweise durch FB Med<br>Nur 5 Studien für das vorliegende Indikationsgebiet relevant, Studienqualität mittel bis hoch, im Fokus kardiologische Ereignisse |
| **Olson EM et al., 2013 [13].** | 1. Fragestellung<br>We investigate the incidence and risk of CNS metastases detected at the time of first recurrence in an up-to-date, comprehensive meta-analysis of |

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| Incidence and risk of central nervous system metastases as site of first recurrence in patients with HER2-positive breast cancer treated with adjuvant trastuzumab | randomized, controlled trials of adjuvant trastuzumab administered for 1 year in patients with HER2- amplified breast cancer. |
| | 2. Methodik<br><br>Population: Frauen mit HER2+ Brustkrebs<br><br>Intervention: trastuzumab (Herceptin)<br><br>Komparator k.A.<br><br>Endpunkt recurrence events and CNS metastases as a site of first relapse events, OS und DFS<br><br>Suchzeitraum (Aktualität der Recherche): zwischen 01/2009 und 12/2011 (Syst. Recherche in PubMed + American Society of Clinical Oncology und San Antonio Breast Cancer Symposium)<br><br>Anzahl eingeschlossene Studien/Patienten (Gesamt): 4 Studien (n= 9,020 Patienten)<br><br>Qualitätsbewertung der Studien: ausschließlich narrativ berichtet, dass es sich im peer-reviewed multicenter, open-label, phase-III studien handelt; patients with HER2-positive breast cancer by Egger (P = 0.5774) or Begg's test (P = 0.3337). |
| | 3. Ergebnisdarstellung<br><br>Eingeschlossene Studien (Baseline-Charakteristik siehe Anhang S. 33) :<br><br>1. Perez EA et al. (2011): Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 2011; 29: 3366–3373.<br><br>2. Perez EA et al. (2011) Sequential versus concurrent trastuzumab in adjuvant chemotherapy for breast cancer. J Clin Oncol 2011; 29: 4491–4497.<br><br>3. Gianni L et al. (2011): Dafni U, Gelber RD et al Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. Lancet Oncol 2011; 12: 236–244.<br><br>4. Spielmann M et al. (2009): Trastuzumab for patients with axillarynode– positive breast cancer: results of the FNCLCC-PACS 04 Trial. J Clin Oncol 2009; 27: 6129–6134.<br><br>**Inzidenz von CNS-Metastasen:**<br><br>– The incidence of CNS metastases as the first site of distant relapse was 2.56% (95% CI 2.07% to 3.01%).<br>– there is an overall increase of 76% in risk of the detection of a CNS lesion at diagnosis of first relapse in trastuzumab-treated patients compared with controls. |

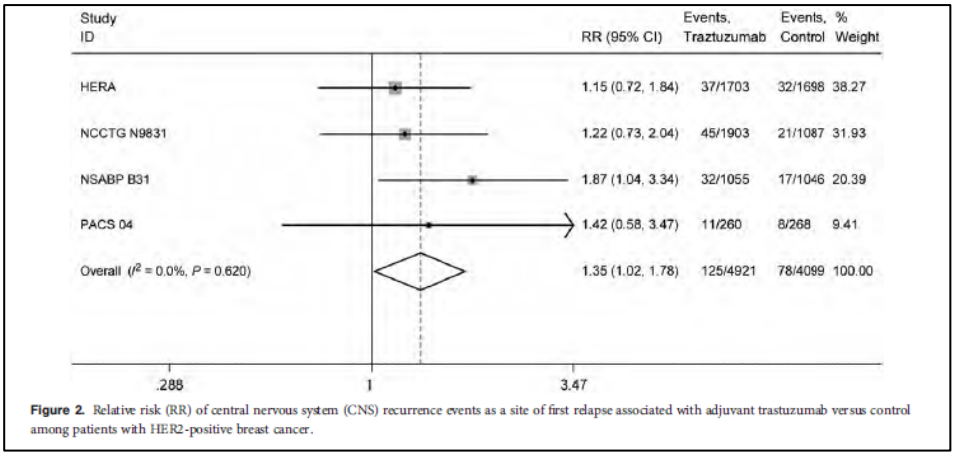


**Figure 2.** Relative risk (RR) of central nervous system (CNS) recurrence events as a site of first relapse associated with adjuvant trastuzumab versus control among patients with HER2-positive breast cancer.

- The overall RR of developing CNS metastases as the first site of recurrence with 1 year of adjuvant trastuzumab was 1.35 (95% CI 1.02–1.78, P = 0.038) compared with patient who did not receive trastuzumab therapy.

**influence of concurrent versus sequential trastuzumab**

- The incidence of CNS metastases as a site of first recurrence was 2.94% (95% CI 2.26% to 3.72%) and 2.31% (95% CI 1.80% to 2.89%) for concurrent and sequential trastuzumab → no differences were found between concurrent versus sequential trastuzumab administration

**influence of weekly versus every 3-week trastuzumab**

- The incidence of CNS metastases as a site of first recurrence were 2.63% (95% CI 2.08% to 3.23%) and 2.45% (95% CI 1.81% to 3.18%) in the weekly versus every 3-week dosing → no differences were noted between weekly versus every 3-week administration of trastuzumab.

4. Anmerkungen/Fazit der Autoren

In conclusion, the use of adjuvant trastuzumab may fail to prevent CNS metastases at time of first recurrence in patients with HER2-amplified breast cancer. Although the overall incidence remains low, the RR is significant with a doubling in the proportion of relapsed patients with brain metastases after trastuzumab compared with control arms.

5. Hinweise durch FB Med

- Qualitätsbewertung der Studien ausschließlich narrativ berichtet

**Leitlinien**

| | |
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| **NCCN, 2016 [12].**<br>Breast Cancer<br>Version 1.2016 | NCCN Clinical Practice Guidelines in Oncology<br>Fragestellung: nicht spezifiziert |
| | **Methodik**<br>→ Update der Version 2.2015<br>Grundlage der Leitlinie: Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Repräsentativität der Gremien unklar - ob formalisierte Konsensusverfahren angewendet werden ist unklar - Diskussion der Literatur und Empfehlungen im Expertenpanel - eigenes Graduierungssystem (siehe unten) - industriefinanziert<br>Literatursuche (Update): in PubMed zwischen 06/2013 und 06/2014<br>GoR, LoE: Alle Empfehlungen entsprechen der Kategorie 2A, sofern nicht explizit anders spezifiziert.<br>**NCCN Categories of Evidence and Consensus**<br>**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.<br>**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.<br>**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.<br>**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.<br>**All recommendations are category 2A unless otherwise noted.**<br>Sonstige methodische Hinweise<br>• *„discussion update in progress“* |

**Freitext/Empfehlungen/Hinweise**

**1. Trastuzumab für HER2-positiv Tumore > 1cm (Category 1)**

The B-31 and NCCTG N9831 trials have been jointly analyzed with the merged control arms for both trials compared with the merged arms using trastuzumab begun concurrently with paclitaxel. There were 4045 patients included in the joint analysis performed at 3.9 years median follow-up. A 48% reduction in the risk of recurrence (HR, 0.52; 95% CI, 0.45–0.60; *P* < .001) and a 39% reduction in the risk of death (HR, 0.61; 95% CI, 0.50–0.75; log-rank *P* = .001) were documented.[351] Similar significant effects on DFS were observed when results of the NSABP B-31 and NCCTG N9831 trials were analyzed separately. Cardiac toxicity was increased in patients treated with trastuzumab.[226,353,354] In the adjuvant trastuzumab trials, the rates of grade III/IV congestive heart failure (CHF) or cardiac-related death in patients receiving treatment regimens containing trastuzumab ranged from 0% (FinHer trial) to 4.1% (NSABP B-31 trial).[223,224,226,228,353,354] The frequency of cardiac dysfunction appears to be related to both age and baseline left ventricular ejection fraction. An analysis of data from N9831 showed the 3-year cumulative incidence of CHF or cardiac death to be 0.3%, 2.8%, and 3.3% in the arms of the trial without trastuzumab, with trastuzumab following chemotherapy, and with trastuzumab initially combined with paclitaxel, respectively.[353] The acceptable rate of significant cardiac

[351] Perez EA et al. (2011): Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31.

[353] Perez EA et al. (2008): Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial.

[354] Tan-Chiu E et al. (2005): Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31.

[226] Ramond EH et al. (2005): Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer.

[224] Piccart-Gebhart MJ et al. (2005): Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.

[228] Slamon D et al. (2011): Adjuvant trastuzumab in HER2-positive breast cancer.

A third trial (HERA) (N = 5081) tested trastuzumab for 1 or 2 years compared to none following all local therapy and a variety of standard chemotherapy regimens in patients with node-positive disease or node-negative disease with tumor greater than or equal to 1 cm.[224] At a median follow-up of one year, a 46% reduction in the risk of recurrence was reported in those who received trastuzumab compared with those who did not (HR, 0.54; 95% CI, 0.43–0.67; *P* < .0001), there was no difference in OS, and acceptable cardiac toxicity was reported. The 2-year data indicate that 1 year of trastuzumab therapy is associated with an OS benefit when compared with observation (HR for risk of death = 0.66; 95% CI, 0.47–0.91; *P* = .0115).[357] After this initial analysis, patients randomized to chemotherapy alone were allowed to cross over to receive trastuzumab. Intent-to-treat analysis including a crossover patient was reported at 4-year median follow-up.[352] The primary endpoint of DFS continued to be significantly higher in the trastuzumab-treated group (78.6%) versus the observation group (72.2; HR, 0.76; 95% CI, 0.66–0.87; *P* < .0001). At a median follow-up of 8 years, the study reported no significant difference in DFS, a secondary endpoint, in patients treated with trastuzumab for 2 years compared with 1 year.[225] Therefore, 1 year of adjuvant trastuzumab remains the current standard of treatment.

[224] Piccart-Gebhart MJ et al. (2005): Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.

[357] Smitz I et al. (2007): 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial.

[352] Gianni L et al. (2011): Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial.

[225] Goldhirsch A et al. (2012): 2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial.

The BCIRG 006 study randomized 3222 women with HER2-positive, node-positive, or high-risk node-negative breast cancer to AC followed by docetaxel; AC followed by docetaxel plus trastuzumab for one year; or carboplatin, docetaxel, and trastuzumab for one year.[228] At 65-month follow-up, patients receiving AC followed by docetaxel with trastuzumab (AC-TH) had an HR for DFS of 0.64 (*P* < .001) when compared with the group of patients in the control arm receiving the same chemotherapy regimen without trastuzumab (AC-T). The HR for DFS was 0.75 (*P* = .04) when patients in the carboplatin/docetaxel/ trastuzumab

[228] Slamon D et al. (2011): Adjuvant trastuzumab in HER2-positive breast cancer.

(TCH)-containing arm were compared to patients in the control arm. No statistically significant difference in the HR for DFS was observed between the two trastuzumab-containing arms. An OS advantage was reported for patients in both trastuzumab-containing arms relative to the control arm (HR for AC-TH vs. AC-T = 0.63; *P* = .001; HR for TCH vs. AC-T = 0.77; *P* = .04). Cardiac toxicity was significantly lower in the TCH arm (9.4% patients with >10% relative decline in left ventricular ejection fraction) compared with the AC-TH arm (18.6%; *P* < .0001). CHF was also more frequent with AC-TH than TCH (2% vs. 0.4%; *P* < .001). Analysis of this trial by critical clinical event revealed more distant breast cancer recurrences with TCH (144 vs. 124) but fewer cardiac events with TCH compared with AC-TH (4 vs. 21).[228] In the FinHer trial, 1010 women were randomized to 9 weeks of vinorelbine followed by 3 cycles of FEC chemotherapy versus docetaxel for 3 cycles followed by 3 cycles of FEC chemotherapy.[223] Patients (n = 232) with HER2-positive cancers that were either node-positive or node-negative and greater than or equal to 2 cm and PR-negative were further randomized to receive or not receive trastuzumab for 9 weeks during the vinorelbine or docetaxel portions of the chemotherapy only. With a median follow-up of 3 years, the addition of trastuzumab was associated with a reduction in risk of recurrence (HR, 0.42; 95% CI, 0.21–0.83; *P* = .01). No statistically significant differences in OS (HR, 0.41; 95% CI, 0.16–1.08; *P* = .07) or cardiac toxicity were observed with the addition of trastuzumab.[223] At 5-year follow-up, a comparison of the two arms (ie, chemotherapy with and without trastuzumab) demonstrated that the HRs for distant DFS (HR, 0.65; 95% CI, 0.38–1.12; *P* = .12) and OS (HR, 0.55; 95% CI, 0.27–1.11; *P* = .094) were higher relative to those reported at 3 years.[350]

[228] Slamon D et al. (2011): Adjuvant trastuzumab in HER2-positive breast cancer.

* Vinorelbine nur zugelassen für lokal fortgeschrittenes oder metastasierendes Mammakarzinom

A recent single-arm, multicenter trial studied the benefit of trastuzumab-based chemotherapy in patients with HER2-positive, node-negative tumors less than or equal to 3 cm. All patients received trastuzumab and weekly paclitaxel for 12 weeks, followed by completion of a year of trastuzumab monotherapy.[365] Fifty percent of patients enrolled had tumors less than or equal to 1.0 cm and 9% of patients had tumors that were between 2 and 3 cm. The endpoint of the study was DFS. The

365. Tolaney S, Barry W, Dang C, et al. A phase II study of adjuvant paclitaxel (T) and trastuzumab (H) (APT trial) for node-negative, HER2-positive breast cancer (BC) [abstract]. San Antonio Breast Symposium Meeting Abstract 2013:Abstract S 1-04 (Oral Presentation). Available at:

results presented at the 2013 Annual San Antonio Breast Cancer Symposium demonstrated that the 3-year DFS rate in the overall population was 98.7% (95% CI, 97.6–99.8; *P* < .0001).

The NCCN Panel suggests trastuzumab and chemotherapy be used for women with HER2-positive, node-negative tumors measuring 0.6 to 1.0 cm (ie, T1b) and for smaller tumors that have less than or equal to 2 mm axillary node metastases (pN1mi). Some support for this recommendation comes from studies showing a higher risk of recurrence for patients with HER2-positive, node-negative tumors less than or equal to 1 cm compared to those with HER2-negative tumors of the same size.[361] Ten-year breast cancer-specific survival and 10-year recurrence-free survival were 85% and 75%, respectively, in women with tumors characterized as HER2-positive, ER-positive tumors, and

[361] Chia S et al. (2008): Human epidermal growth factor receptor 2 overexpression as a prognostic factor in a large tissue microarray series of node-negative breast cancers.

**2. Doxorubicin und Cyclophosphamid gefolgt von Paclitaxel mit Trastuzumab für 1 Jahr beginnend mit der ersten Dosis von Paclitaxel als präferiertes HER2-targeted therapy (Category 2A)**

*NCCN Recommended HER-Targeted Regimens*
The panel recommends AC followed by paclitaxel with trastuzumab for 1 year commencing with the first dose of paclitaxel as a preferred HER2 targeting adjuvant regimen. The TCH regimen is also a preferred regimen, especially for those with risk factors for cardiac toxicity, given the results of the BCIRG 006 study that demonstrated superior DFS in patients receiving TCH or AC followed by docetaxel plus trastuzumab compared with AC followed by docetaxel alone.

Other trastuzumab-containing regimens included in the NCCN Guidelines are: AC followed by docetaxel and trastuzumab,[228] and docetaxel plus trastuzumab followed by FEC[223] (see *Neoadjuvant/Adjuvant Chemotherapy* in the algorithm for a complete list of regimens).

The NCCN Panel has included paclitaxel and trastuzumab as an option for patients with low-risk, HER2-positive, stage 1 tumors. This is based on a trial that studied this combination in 406 patients with small, node-negative, HER2-positive tumors. The results showed that the 3-year rate of disease-free survival was 98.7% (95% CI, 97.6–99.8) and the risk of serious toxic effects with this regimen was low (incidence of heart failure reported was 0.5%).[376]

[376] Tolaney SM et al. (2015): Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer.

<table>
<tr><td></td><td><u>Zusammenfasung:</u><br><br><u>Regimens for HER2-positive disease</u>[6,7,8]<br><u>Preferred regimens</u>:<br>• AC followed by T + trastuzumab ± pertuzumab[9]<br>(doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab ± pertuzumab, various schedules)<br>• TCH (docetaxel/carboplatin/trastuzumab) ± pertuzumab<br><br><u>Other regimens</u>:<br>• AC followed by docetaxel + trastuzumab ± pertuzumab[9]<br>• Docetaxel + cyclophosphamide + trastuzumab<br>• FEC followed by docetaxel + trastuzumab + pertuzumab[9]<br>• FEC followed by paclitaxel + trastuzumab + pertuzumab[9]<br>• Paclitaxel + trastuzumab[10]<br>• Pertuzumab + trastuzumab + docetaxel followed by FEC[9]<br>• Pertuzumab + trastuzumab + paclitaxel followed by FEC[9]<br><br>[6]In patients with HER2-positive and axillary node-positive breast cancer, trastuzumab should be incorporated into the adjuvant therapy (category 1). Trastuzumab should also be considered for patients with HER2-positive node-negative tumors ≥1 cm (category 1).<br>[7]Trastuzumab should optimally be given concurrently with paclitaxel as part of the AC followed by paclitaxel regimen, and should be given for one year total duration.<br>[8]A pertuzumab-containing regimen can be administered to patients with ≥T2 or ≥N1, HER2-positive, early-stage breast cancer preoperatively. Patients who have not received a pertuzumab-containing regimen can receive adjuvant pertuzumab.<br>[9]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.<br>[10]Paclitaxel + trastuzumab may be considered for patients with low-risk stage I, HER2-positive disease, particularly those not eligible for other standard adjuvant regimens due to comorbidities.</td></tr>
<tr><td rowspan="2">National Cancer Control Programme (NCCP), 2015 [1].<br><br>Diagnosis, staging and treatment of patients with breast cancer</td><td>National Clinical Guideline<br><br>Relevante Fragestellungen aus der Guideline (2.4.1)<br><br>In patients with breast cancer:<br><br>a) What is the evidence that adjuvant chemotherapy is effective?<br><br>b) What is the optimal chemotherapy regimen?</td></tr>
<tr><td><u>Methodik</u><br><br><u>Grundlage der Leitlinie:</u> Leitlinienprozess basiert auf 4 wesentlichen Entwicklungsschritten:<br><br>• Entwicklung klinischer Fragestellungen entsprechend dem PICO-Schema<br>• Syst. Evidenzrecherche<br>• Beurteilung der Evidenz hinsichtlich Validität und Anwendbarkeit → 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).<br>• Empfehlungen formulieren und einstufen (Grade nach SIGN für</td></tr>
</table>

Interventionsstudien)

Literatursuche: in Medline, Embase, Cochrane, Point of care reference tools, PsycINFO, CINAHL etc. bis einschließlich 2014

GoR, LoE:

**Table 8** Levels of evidence for interventional studies (SIGN grading system 1999-2012)

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| 1++ | High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. |
| 1+ | Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias. |
| 1- | Meta-analyses, systematic reviews, or RCTs with a high risk of bias. |
| 2++ | High quality systematic reviews of case control or cohort studies.<br>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 (e.g. case reports, case series). |
| 4 | Expert opinion. |

**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<br>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<br>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<br>Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4; or<br>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:

- The guideline was commissioned and funded by the NCCP; however, the guideline content was not influenced by the NCCP or any other funding body. This process is fully independent of lobbying powers. All recommendations were based on the best research evidence integrated with clinical expertise.

Freitext/Empfehlungen/Hinweise

| **Recommendation 2.4.1.2** | **Grade** |
|---|---|
| Adjuvant trastuzumab should be considered in all patients with HER2 positive breast cancer who receive adjuvant chemotherapy. | **A** |

| **Recommendation 2.4.1.3** | **Grade** |
|---|---|
| The standard duration of treatment with adjuvant trastuzumab is one year. | **A** |

| **Recommendation 2.4.1.4** | **Grade** |
|---|---|
| Adjuvant trastuzumab should preferably be given concurrently with taxane based regimens. It should **not** be given concurrently with anthracyclines. | **A** |

**Good practice point**
Cardiac function should be monitored in patients being treated with anthracyclines or trastuzumab.

Empfehlungen basieren auf dem Cochrane Review von Moja et al. (2012) → dieses ist ebenfalls in der Eviednzsynopse unter CR

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| | dargestellt.<br><br>The Early Breast Cancer Trialists' Collaborative Group (Peto et al., 2012) meta-analysis of greater than 100,000 patients have shown that the use of adjuvant chemotherapy has led to a significant reduction in breast cancer recurrence and improvement in overall survival. This meta-analysis compared adjuvant chemotherapy using an anthracycline-based regimen or cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) to no treatment and found that both regimens were associated with significant improvement in the risk of recurrence and a reduction in both breast cancer mortality and overall mortality at 10 years.<br><br>In treating HER2 positive breast cancer, trastuzumab administered for 12 months in the adjuvant setting was associated with an improvement in overall survival (HR 0.67, 95% CI 0.57-0.80). (Burstein, 2014a)<br><br>BURSTEIN, H. 2014a. Adjuvant medical therapy for HER2-positive breast cancer. In: UpToDate, Post TW (Ed), UpToDate, Waltham, MA. (Accessed on July 16, 2014)<br><br>Commonly used regimens for HER2 positive breast cancer include:<br><br>– AC-TH (doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab) |
| **Scottish Intercollegiate Guidelines Network (SIGN), 2013 [14].**<br><br>Treatment of primary breast cancer | This guideline provides recommendations based on current evidence for best practice in the treatment of patients with operable early breast cancer. |
| | Methodik<br><br><u>Grundlage der Leitlinie:</u> 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. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.<br><br><u>Literatursuche</u>: Medline, Embase, Cinahl, PsycINFO und Cochrane zwischen 2003 und 2011<br><br><u>Eingeschlossene Publikationen:</u> RCTs, SR, Beobachtungsstudien, Diagnostische und Ökonomische Studien.<br><br>– Methodische bewertung der eingschlossenen Publikationen anhand von Checklisten (SR = SIGN Tool, RCTs = AMSTAR) |

GoR, LoE:

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

| 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<br>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:

*This guideline was issued in 2013 and will be considered for review in three years.*

Freitext/Empfehlungen/Hinweise

- 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.
- Cardiac function should be monitored in patients being treated with anthracyclines and/or trastuzumab.
- Trastuzumab should be used with caution in patients with significant cardiac comorbidity. The benefits of adjuvant chemotherapy with or without trastuzumab may be outweighed by the potential harms in these patients, and treatment should only be recommended after careful consideration.
- A consensus statement for the assessment and management of cardiac function in patients receiving trastuzumab highlights that (LoE4):
    - cardiac assessment, including LVEF measurement, should be performed before any chemotherapy
    - heart function measurement should be referenced to the local normal range for the modality used.
    - management of cardiac risk factors including hypertension should occur before the first cycle of chemotherapy.
    - reassessment of LVEF should occur after

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| | completing chemotherapy and before starting trastuzumab.<br>o repeat measurements should be performed after four and eight months of trastuzumab treatment.<br><br>The consensus statement also makes recommendations on interrupting and restarting trastuzumab treatment, gives clear advice on initiating an angiotensin converting enzyme (ACE) inhibitor and when to consult a cardiologist.<br><br>Dahabreh IJ, Linardou H, Siannis F, Fountzilas G, Murray S. Trastuzumab in the adjuvant treatment of early-stage breast cancer: a systematic review and meta-analysis of randomized controlled trials. Oncologist 2008;13(6):620-30.<br><br>Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database of Systematic Reviews 2012, Issue 4.<br><br>Jin W, Jiang Y, Shen Z, Shao Z, Lu J. Trastuzumab in the adjuvant treatment of HER2-positive early breast cancer patients: a metaanalysis of published randomized controlled trials. PLoS One 2011;6(6):e21030.<br><br>Goldhirsch A, Piccart-Gebhart MJ, Procter M, de Azambuja E, Weber HA, Untch M, et al. HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up. Cancer Res;72(24 Suppl 3):S5-2. |
| **Leitlinienprogramm Onkologie der AWMF, 2012 [8].**<br><br>Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms | S3-Leitlinie (evidenz- und konsensusbasiert) |
| | Methodik (siehe Leitlinienreport)<br><br><u>Grundlage der Leitlinie:</u> methodische Vorgehensweise bei der Aktualisierung der Leitlinie ist im Leitlinienreport dargelegt<br><br>– systematische Leitlinienrecherche,- auswahl und -adaptation sowie de Novo-Recherchen durchgeführt<br>– Systematische Literaturrecherche nach Primär- und/oder Sekundärliteratur systematische Recherche in der bibliographischen Datenbank Medline (PubMed) und in den Leitlinien-Datenbanken des National Guideline Clearinghouse (NGC), des Guideline International Network (G-I-N) und des NHS Guidelinesfinder → Auswahl nach zuvor festgelegten Ein- und Ausschlusskriterien<br>– gültig bis 30.06.2017<br><br><u>Literatursuche</u>: am 21. Juli 2010 (Aktualisierung: 18.11.2010) → eingeschlossen wurden Publikation zwischen 01.01.2006 und 18.11.2010<br><br><u>GoR, LoE:</u> In der Leitlinie werden alle evidenzbasierten Kernaussagen und Empfehlungen hinsichtlich der Evidenzstärke und Empfehlungen zusätzlich mit dem Grad der Empfehlung ausgewiesen. In der Regel bestimmt die Evidenzstärke die Stärke der Empfehlung, Abweichungen des Evidenzgrades und des |

Empfehlungsgrades aufgrund der klinischen Beurteilung der Aussagefähigkeit und Anwendbarkeit der Evidenz, im engl. considered adjudgement genannt, werden entsprechend begründet

| Empfehlungsgrad | Beschreibung | Syntax |
|---|---|---|
| A | Starke Empfehlung | soll |
| B | Empfehlung | sollte |
| 0 | Empfehlung offen | kann |

| Level of Evidence (LOE) | | Studien zu Therapie, Prävention, Ätiologie | Studien zur Güte diagnostischer Testverfahren |
|---|---|---|---|
| 1 | 1a | Qualitativ hochwertiger Systematischer Review (SR) von randomisiert-kontrollierten Studien (RCT) mit geringem Risiko für Verzerrungen | Qualitativ hochwertiger Systematischer Review (SR) von Validierungs-Kohortenstudien mit geringem Risiko für Verzerrungen |
| | 1b | Einzelne RCT mit geringem Risiko für Verzerrungen | Einzelne Validierungs-Kohortenstudie mit geringem Risiko für Verzerrungen |
| | 1c | „Alle oder Keiner"-Prinzip* | Absolute SpPins und SnNouts ** |
| 2 | 2a | SR von Kohortenstudien mit geringem Risiko für Verzerrungen | SR von explorativen Kohortenstudien |
| | 2b | Einzelne Kohortenstudie mit geringem Risiko für Verzerrungen | Explorative Kohortenstudie |
| | 2c | Ergebnisforschung; ökologische Studien | - |
| 3 | 3a | SR von Fallkontrollstudien | SR von 3b und besseren Studien |
| | 3b | Einzelne Fallkontrollstudie | Kohortenstudie Studie mit Risiko für Verzerrungen (z.B. nicht-konsekutiv oder ohne Konsistenz der angewendeten Referenz-standards) |
| 4 | | Fallserie | Diagnostische Fallkontrollstudie |
| 5 | | Expertenmeinung oder basierend auf pathophysiologischen Modellen oder experimenteller Grundlagenforschung oder „Grundprinzipien" | |

Sonstige methodische Hinweise:

- *LL gefördert durch Deutsche Krebshilfe im Rahmen des onkologischen Rahmenprogramms*
- *Interessenkonflikterklärungen durch die AWMF geprüft*
- *Die Deutsche Krebshilfe stellte über das Leitlinienprogramm Onkologie die finanziellen Mittel zur Verfügung. ... Die Erarbeitung der Leitlinie erfolgte in redaktioneller Unabhängigkeit von der finanzierenden Organisation.*
- *Alle Mitglieder der Leitliniengruppe legten eine schriftliche Erklärung zu eventuell bestehenden Interessenkonflikten*

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| | *vor* |
| | Freitext/Empfehlungen/Hinweise<br><table><tr><td>Adj-2</td><td>Medikamentöse Behandlung der Primärerkrankung</td></tr><tr><td>Empfehlungsgrad<br>A</td><td>Die medikamentöse Behandlung der Primärerkrankung wird in Form einer Chemotherapie, einer endokrinen Therapie, einer Anti-HER2-Antikörpertherapie oder in einer Kombination bzw. Sequenz dieser Therapieformen vor oder nach der Operation durchgeführt.</td></tr><tr><td>Level of Evidence<br>1a</td><td>(EBCTCG 2005; NCCN 2006)</td></tr></table> |
| **Eisen A et al., 2014 [2].**<br>**Cancer Care Ontario (CCO)**<br>Optimal Systemic Therapy for Early Female Breast Cancer<br><br>*Siehe auch:*<br>**Ghandi S et al., 2015 [4].**<br>**Eisen A et al., 2015 [3].**<br>**Mates M et al., 2014 [10].** | Fragestellung<br>What is the optimal adjuvant systemic therapy for female patients with early-stage operable breast cancer, when patient and disease factors are considered? |
| | Methodik<br>Grundlage der Leitlinie: developed by the Program in Evidence-Based Care (PEBC)/Cancer Care Ontario (CCO) use the methods of the Practice Guidelines Development Cycle<br>• body of evidence in this review is primarily mature RCT data<br>• basis of the recommendations developed by the Early Breast Cancer Systemic Therapy Consensus Panel<br>• Auswahl & Bewwertung der Literatur nach vordefinieren Ein- und Ausschlusskriterien<br>Literatursuche: Medline & Embase zwischen 2008 und 2012 (Update 2014)<br>Eingeschlossene Publikationen: RCTs, Leitlinien, SR, Meta-Analysen<br>GoR, LoE: k.A.<br>Sonstige methodische Hinweise:<br>– *The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.* |
| | Freitext/Empfehlungen/Hinweise<br>(1) Only patients with HER2+ breast cancer (IHC 3+, ISH ratio ≥2, or 6+ HER2 gene copies per cell nucleus) should be offered adjuvant trastuzumab<br>→ Empfehlung beruht auf 4 RCTs<br>Perez EA, Romond EH, Suman VJ, Jeong J-H, Davidson NE, Geyer CE, Jr., et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: |

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| | joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol. 2011;29(25):3366-73.<br><br>Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE, Jr., Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673-84.<br><br>Slamon D, Crown J, Pienkowski T. BCIRG 006. 2nd analysis presented at SABCS 2006 [Internet]. 2006 [cited 2011 Oct 27].<br><br>Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.<br><br>Goldhirsch A, Piccart M, Procter M, De Azambuja E, Weber H, Untch M, et al. HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up [abstract]. Ann Oncol. 2012;23(Suppl 9. Abstract Book of the 37th ESMO Congress Vienna, Austria, 28 September – 2 October 2012)<br><br>**(2)<u>Trastuzumab</u> 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.**<br><br>→ Phase 3 clinical studies have demonstrated improved DFS and OS with the addition of trastuzumab to chemotherapy compared to chemotherapy alone in HER2 positive early breast cancer<br><br>→ 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).<br><br>→ The benefit of adjuvant trastuzumab in the absence of cytotoxic chemotherapy is unknown because it has not been evaluated in clinical trials.<br><br>Slamon D, Crown J, Pienkowski T. BCIRG 006. 2nd analysis presented at SABCS 2006 [Internet]. 2006 [cited 2011 Oct 27]. http://www.cirg.org/html/images/BCIRG006+2nd+Interim+Analysis.pdf<br><br>Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273-83.<br><br>Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. 2012 Apr 18 [cited 2012 May 22]. Cochrane Database Syst Rev<br><br>Sawaki M, Tokudome N, Mizuno T, Nakayama T, Taira N, Bando H, et al. Evaluation of trastuzumab without chemotherapy as a post-operative adjuvant therapy in HER2-positive elderly breast cancer patients: randomized controlled trial [RESPECT (N-SAS BC07)]. Jpn J Clin Oncol. 2011;41(5):709-12.<br><br>**(3)<u>Trastuzumab</u> 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).** |

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| | → 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.<br><br>→ Several retrospective case series of HER2 positive pT1a/bN0M0 carcinoma seem to demonstrate that they have a higher risk of relapse compared with the HER2 negative counterpart<br><br>→ In the HERA trial, 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).<br><br>Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V, et al. Trastuzumab containing regimens for early breast cancer. 2012 Apr 18 [cited 2012 May 22]. Cochrane Database Syst Rev<br><br>Untch M, Gelber RD, Jackisch C, Procter M, Baselga J, Bell R, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol. 2008;19(6):1090-6.<br><br>**(4) <u>Trastuzumab</u> can be administered with any acceptable adjuvant chemotherapy regimen.**<br><br>→ Three large RCTs → Trastuzumab had a significant survival rate benefit in all these trials (NSABP B31, NCCTG N9831, BCIRG 006)<br><br>→ The HERA trial (81): 68% received anthracycline, 26% anthracycline + taxane, and 6% no anthracycline → DFS and OS rate benefit. This trial suggests there is benefit of trastuzumab in combination with any chemotherapy, but it did not address the issue of which chemotherapy is optimal.<br><br>→ PEBC Guideline #1−17 (86) recommended that trastuzumab be used with an anthracycline instead of CMF.<br><br>→ BCIRG 006: no significant difference in OS or DFS rates among trastuzumab regimens, although AC→TH seemed to have a stronger effect in some subgroups. TCH had a much lower incidence of cardiotoxicity and leukemia. Whether TCH is equivalent to AC→TH was not established as the trial was not designed to test for non-inferiority between the two trastuzumab-containing regimens.<br><br>**(5) <u>The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is generally not recommended because of the potential of increased cardiotoxicity.</u>** |

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| | → 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.<br><br>**(6) Adjuvant trastuzumab can be initiated either concurrently or sequentially with the taxane portion of a chemotherapy regimen.**<br><br>→Meta-analysis of 11,631 patients in six studies found taxanes superior to non-taxane-based regimens for DFS in both HER2+ and HER2− disease. There was no evidence of interaction between HER2 status and taxane efficacy (459).<br><br>**(7) TCH (docetaxel/carboplatin/trastuzumab) is less cardiotoxic than AC TH (doxorubicin/cyclophosphamide-docetaxel/trastuzumab) and is recommended for patients at higher risk for cardiotoxicity.**<br><br>**(8) 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.**<br><br>→ 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.<br><br>Goldhirsch A, Piccart M, Procter M, De Azambuja E, Weber H, Untch M, et al. HERA TRIAL: 2 years versus 1 year of trastuzumab after adjuvant chemotherapy in women with HER2-positive early breast cancer at 8 years of median follow up [abstract]. Ann Oncol. 2012;23(Suppl 9. Abstract Book of the 37th ESMO Congress Vienna, Austria, 28 September – 2 October 2012) |

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|---|---|
| | Untch M, Gelber RD, Jackisch C, Procter M, Baselga J, Bell R, et al. Estimating the magnitude of trastuzumab effects within patient subgroups in the HERA trial. Ann Oncol. 2008;19(6):1090-6. 82. Perez EA, Jenkins RB, Dueck<br><br>Procter M, Suter TM, de Azambuja E, Dafni U, van Dooren V, Muehlbauer S, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. J Clin Oncol. 2010;28(21):3422-8.<br><br>Dowsett M, Procter M, McCaskill-Stevens W, de Azambuja E, Dafni U, Rueschoff J, et al. Disease-free survival according to degree of HER2 amplification for patients treated with adjuvant chemotherapy with or without 1 year of trastuzumab: the HERA Trial. J Clin Oncol. 2009;27(18):2962-9.<br><br>**(9) <u>Patients should be offered one year total of adjuvant trastuzumab, with regular cardiac functional assessments during this period.</u>**<br><br>→ 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%).<br><br>– European Society for Medical Oncology (ESMO). PHARE trial results comparing 6 to 12 months of adjuvant trastuzumab in early breast cancer. 2012 Oct 1 [cited 2012 Oct 11]. ESMO 2012 News<br>– Pivot X, Romieu G, Bonnefoi H, Pierga J-Y, Kerbrat P, Gaustalla J-P, et al. PHARE trial results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer. Ann Oncol. 2012;23(Suppl 9. Abstract Book of the 37th ESMO Congress Vienna, Austria, 28 September – 2 October 2012):ixe2. Abstract no. LBA5_PR. |

## Anhang

**Baseline characteristics of the patients on the trials included in the meta-analysis (Olson et al. 2013)**

| Study and treatment arm | Phase | Crossover allowed | Total number of patients enrolled on study regardless of HER2 status | Median follow-up (months) | HR of OS (95% CI) | HR of DFS (95% CI) | No. of patients for analysis | No. of CNS events[a] | No. recurrence events[b] |
|---|---|---|---|---|---|---|---|---|---|
| NSABP B31 [1][c] | III | Yes | 2101 | 46.8[d] | 0.59 (0.48–0.73)[e] | 0.51 (0.44–0.59)[e] | | | |
| AC followed by paclitaxel | | | | | | | 1046 | 17 | 243 |
| AC followed by paclitaxel and concurrent trastuzumab | | | | | | | 1055 | 32 | 137 |
| NCCTG N9831 [2][c] | III | Yes | 3505 | 72 | 0.88 (0.67–1.15)[f] | 0.67 (0.54–0.81)[f] | | | |
| AC followed by paclitaxel | | | | | | | 1087 | 21 | 225 |
| AC followed by paclitaxel and sequential trastuzumab | | | | | | | 954 | 19 | 174 |
| AC followed by paclitaxel and concurrent trastuzumab | | | | | | | 949 | 26 | 139 |
| HERA [3][g] | III | Yes | 5102 | 48.4 | 0.85 (0.701–1.04) | 0.76 (0.66–0.87) | | | |
| Observation | | | | | | | 1698 | 32 | 458 |
| One year of trastuzumab | | | | | | | 1703 | 37 | 369 |
| Two years of trastuzumab | | | | | | | NR | NR | NR |
| PACS 04 [4][h] | III | No | 3010 | 47 | 1.27 (0.68–2.38) | 0.86 (0.61–1.22) | | | |
| FEC versus ED followed by observation | | | | | | | 268 | 8 | 52 |
| FEC versus ED followed by 1 year of trastuzumab | | | | | | | 260 | 11 | 44 |

All trials evaluated patients with localized HER2-positive breast cancer. Crossover indicates that patients were allowed to receive trastuzumab after the initial efficacy results were made public.
[a]Number of CNS events reported as first site of recurrent disease.
[b]Total number of patients with a recurrence event.
[d]Median follow-up for combined analysis of NSABP B31 and NCCTG N9831. Follow-up for NSABP B31 alone NR.
[c]Dosing for NSABP B31 [1] and NCCTG N9831 [2]: doxorubicin 60 mg/m$^2$ and cyclophosphamide 600 mg/m$^2$ every 3 weeks for four cycles followed by paclitaxel 175 mg/m$^2$ every 3 weeks for four cycles or paclitaxel 80 mg/m$^2$ every week for 12 weeks. Patients randomized to trastuzumab received an initial loading dose of 4 mg/kg followed by 2 mg/kg given once a week for a total of 52 weeks.
[e]HR reported in the combined analysis of NSABP B31 and the concurrent arm of NCCTG N9831.
[f]HR reported for sequential trastuzumab compared with chemotherapy alone. The concurrent trastuzumab outcome data are combined with the NSABP B31 data above.
[g]Dosing for HERA [3] Patients must have received at least four cycles of chemotherapy, choice of agent was at the discretion of the treating physician. Patients randomized to trastuzumab was administered at a loading dose of 8 mg/kg (day 1 of first cycle) with subsequent doses administered at 6 mg/kg every 3 weeks for a total course of 1 or 2 years. Outcome data for the 2-year arm have not yet been reported.
[h]Dosing for PACS04 [4] Patients were randomized initially to either six courses of FEC or ED regimen. FEC regimen included fluorouracil 500 mg/m$^2$, epirubicin 100 mg/m$^2$, and cyclophosphamide 500 mg/m$^2$ every 3weeks. ED regimen included epirubicin 75 mg/m$^2$ and docetaxel 75 mg/m$^2$. Patients were subsequently randomized to trastuzumab was administered at a loading dose of 8 mg/kg (day 1 of first cycle) with subsequent doses administered at 6 mg/kg every 3 weeks for a total course of 1 year.
NSABP, National Surgical Adjuvant Breast and Bowel Project (NSABP); AC, doxorubicin and cyclophosphamide; NCCTG, North Central Cancer Treatment Group; HERA, herceptin adjuvant; HER2, human epidermal growth factor receptor 2; FEC, fluorouracil, epirubicin, and cyclophosphamide; ED, epirubicin and docetaxel; HR, hazard ratio; DFS, disease-free survival; OS, overall survival; NR, not recorded.

### Detaillierte Darstellung der Recherchestrategie:

**Cochrane Library** (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) am 01.04.2016

| Suchschritt | Suchfrage |
|---|---|
| 1 | MeSH descriptor: [Breast Neoplasms] explode all trees |
| 2 | "breast":ti,ab,kw or mamma*:ti,ab,kw (Word variations have been searched) |
| 3 | (cancer*):ti,ab,kw or (tumor*):ti,ab,kw or (tumour*):ti,ab,kw or (carcinom*):ti,ab,kw or (adenocarcinom*):ti,ab,kw or (neoplas*):ti,ab,kw (Word variations have been searched) |
| 4 | #2 and #3 |
| 5 | #1 or #4 |
| 6 | #5 Publication Year from 2011 to 2016, in Cochrane Reviews (Reviews only) |

| Suchschritt | Suchfrage |
|---|---|

| | |
|---|---|
| 1 | MeSH descriptor: [Breast Neoplasms] explode all trees |
| 2 | "breast":ti,ab,kw or mamma*:ti,ab,kw (Word variations have been searched) |
| 3 | (cancer*):ti,ab,kw or (tumor*):ti,ab,kw or (tumour*):ti,ab,kw or (carcinom*):ti,ab,kw or (adenocarcinom*):ti,ab,kw or (neoplas*):ti,ab,kw (Word variations have been searched) |
| 4 | #2 and #3 |
| 5 | #1 or #4 |
| 6 | HER2*:ti,ab,kw or erbB2*:ti,ab,kw or human epidermal growth factor receptor 2:ti,ab,kw (Word variations have been searched) |
| 7 | (early):ti,ab,kw or (locally next advanced):ti,ab,kw or (LABC):ti,ab,kw or (IBC):ti,ab,kw or (inflammatory):ti,ab,kw (Word variations have been searched) |
| 8 | (primary next breast next cancer):ti,ab,kw (Word variations have been searched) |
| 9 | #6 or #7 |
| 10 | #5 and #9 |
| 11 | #10 or #8 |
| 12 | #11 Publication Year from 2011 to 2016 |
| 13 | (#11) Publication Year from 2011 to 2016, in Other Reviews and Technology Assessments |

**SR, HTAs in Medline (PubMed) am 01.04.2016**

| Suchschritt | Suchfrage |
|---|---|
| 1 | "breast neoplasms"[MeSH Major Topic] |
| 2 | (breast[Title]) OR mamma*[Title] |
| 3 | (((((cancer*[Title]) OR tumour*[Title]) OR tumor*[Title]) OR carcinom*[Title]) OR adenocarcinom*[Title]) OR neoplas*[Title] |
| 4 | (#2) AND #3 |
| 5 | (#1) OR #4 |
| 6 | ((((((((((((treatment*[Title/Abstract]) OR therapy[Title/Abstract]) OR therapies[Title/Abstract]) OR therapeutic[Title/Abstract]) OR monotherap*[Title/Abstract]) OR polytherap*[Title/Abstract]) OR pharmacotherap*[Title/Abstract]) OR effect*[Title/Abstract]) OR efficacy[Title/Abstract]) OR treating[Title/Abstract]) OR treated[Title/Abstract]) OR management[Title/Abstract]) OR drug*[Title/Abstract]) |
| 7 | (#5) AND #6 |
| 8 | "breast neoplasms/therapy"[MeSH Major Topic] |
| 9 | (#7) OR #8 |
| 10 | ((HER2*[Title/Abstract]) OR human epidermal growth factor receptor 2[Title/Abstract]) OR erbB2*[Title/Abstract] |
| 11 | (#9) AND #10 |
| 12 | (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) |
| 13 | (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract])))) |
| 14 | (#12) OR #13 |
| 17 | (#11) AND #14 |
| 19 | (#18) AND ("2011/04/01"[PDAT] : "2016/04/01"[PDAT]) |

**Leitlinien in Medline (PubMed) am 31.03.2016**

| Suchschritt | Suchfrage |
|---|---|
| 1 | "breast neoplasms"[MeSH Major Topic] |
| 2 | (breast[Title]) OR mamma*[Title] |
| 3 | (((((cancer*[Title]) OR tumour*[Title]) OR tumor*[Title]) OR carcinom*[Title]) OR adenocarcinom*[Title]) OR neoplas*[Title] |
| 4 | (#2) AND #3 |
| 5 | (#1) OR #4 |
| 6 | (((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title] |
| 7 | (#5) AND #6 |
| 8 | (#7) AND ("2011/03/01"[PDAT] : "2016/03/31"[PDAT]) |

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