Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-035 Pertuzumab/Trastuzumab

Stand: April 2020

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

Pertuzumab/Trastuzumab
[zur adjuvanten Behandlung von HER2-positivem, frühem Brustkrebs mit hohem Rezidivrisiko]

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 zur Behandlung des Hormonrezeptor-positiven Mammakarzinoms bzw. endokrinen 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	**Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** - Pertuzumab (Beschluss vom 20. Dezember 2018) **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie** – Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind; Stand 17. Oktober 2019: - Gemcitabin in der Monotherapie beim Mammakarzinom der Frau **Richtlinie Methoden Krankenhausbehandlung** - § 4 Ausgeschlossene Methoden, in Kraft getreten am 19. Dezember 2019: - Protonentherapie beim Mammakarzinom
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pertuzumab/ Trastuzumab n.d. n.d.	<u>Geplantes Anwendungsgebiet laut Beratungsanforderung:</u> Pertuzumab/Trastuzumab ist zur Anwendung in Kombination mit Chemotherapie indiziert zur adjuvanten Behandlung von erwachsenen Patienten mit HER2-positivem frühem Brustkrebs mit hohem Rezidivrisiko.
Zytotoxische Chemotherapien	
Cyclophosphamid L01AA01 Endoxan®	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Adjuvante Therapie des Mammakarzinoms nach Resektion des Tumors beziehungsweise Mastektomie
Docetaxel L01CD02 Taxotere®	<u>Brustkrebs</u> Taxotere 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 Adrimedac®	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: - Mammakarzinom […] Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Epirubicin L01DB03 Farmorubicin®	Mammakarzinom
Fluorouracil L01BC02 Benda-5 FU®	Adjuvante Therapie des primären invasiven Mammakarzinoms

Methotrexat L01BA01 Methotrexat-GRY®	<u>Mammakarzinome</u> In Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.
Paclitaxel L01CD01 Paclitaxel onkovis®	<u>Mammakarzinom</u> Paclitaxel onkovis ist indiziert zur adjuvanten Therapie von Patientinnen mit nodalpositivem Mammakarzinom im Anschluss an eine Anthracyclin-/Cyclophosphamid-Therapie (AC). Die adjuvante Therapie mit Paclitaxel onkovis sollte als Alternative zu einer verlängerten AC-Therapie angesehen werden.
Vincristin L01CA02 Vincristinsulfat-TEVA®	Vincristinsulfat-TEVA® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom, kleinzelligem Bronchialkarzinom
HER2-gerichtete Therapien	
Pertuzumab L01XC13 Perjeta®	<u>Brustkrebs im Frühstadium (early breast cancer – EBC)</u> Perjeta ist zur Anwendung in Kombination mit Trastuzumab und Chemotherapie indiziert zur: - adjuvanten Behandlung von erwachsenen Patienten mit HER2-positivem frühem Brustkrebs mit hohem Rezidivrisiko
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.
Trastuzumab Emtansin L01XC14 Kadcyla®	<u>Brustkrebs im Frühstadium (EBC – Early Breast Cancer)</u> 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.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-035 (Pertuzumab/Trastuzumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	24. März 2020

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse Events
AI	Aromatase Inhibitor
AT	adjuvant trastuzumab
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BCT	Breast Conservation Therapy
cCR	complete response rate
DFS	Disease Free Survival
ECRI	Epirubicin
EC-T	ECRI Guidelines Trust
ER+	Estrogen Receptor positive
FEC	Fluorouracil
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard Ratio
HR+	Hormone Receptor positive
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
LRR	local-regional relapse
NCET	Neoadjuvant Chemoendocrine Therapy
NCT/NACT	Neoadjuvant Chemotherapy
NET	Neoadjuvant Endocrine Therapy
NICE	National Institute for Health and Care Excellence
OFS	Ovarian Function Suppression
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
PCR	Pathological Complete Response
QOL	Quality Of Life

RFS	Recurrence-Free Survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Adjuvante/neoadjuvante Behandlung von erwachsenen Patienten mit HER2-positivem Brustkrebs.

2 Systematische Recherche

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

Die Erstrecherche wurde am am 09.11.2018 durchgeführt, die Folgerecherchen am 29.07.2019 und 10.02.2020. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherchen übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 3901 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 23 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2019 [8].

Richtlinie des Gemeinsamen Bundesausschusses zur Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung): in der Fassung vom 21. März 2006; veröffentlicht im Bundesanzeiger 2006 (S. 4 466); in Kraft getreten am 01. April 2006; 20. Dezember 2018; veröffentlicht im Bundesanzeiger (BAnz AT 19.03.2019 B6); in Kraft getreten am 20. März 2019).

Fazit

§ 4 Ausgeschlossene Methoden

(…) 3.5 Protonentherapie beim Mammakarzinom

G-BA, 2019 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: Anlage VI – Off-Label-Use; Teil B: Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind; IV Gemcitabin in der Monotherapie beim Mammakarzinom der Frau.

Anwendungsgebiet

Zweckmäßige Vergleichstherapie

Fazit

- Teil B:
  - Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind:

    (…) Gemcitabin in der Monotherapie beim Mammakarzinom der Frau

G-BA, 2018 [10].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. Dezember 2018 - Pertuzumab (neues Anwendungsgebiet: Brustkrebs, adjuvante Behandlung).

Anwendungsgebiet

Perjeta ist zur Anwendung in Kombination mit Trastuzumab und Chemotherapie indiziert zur adjuvanten Behandlung von erwachsenen Patienten mit HER2-positivem frühem Brustkrebs mit hohem Rezidivrisiko.

Zweckmäßige Vergleichstherapie

Erwachsene Patienten mit HER2-positivem frühem Brustkrebs mit hohem Rezidivrisiko zur adjuvanten Behandlung:

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

Fazit / Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens gegenüber Trastuzumab + Chemotherapie:

- Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2016 [9].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 18. Februar 2016 - Pertuzumab (neues Anwendungsgebiet: Mammakarzinom, entzündlich oder früh mit hohem Rezidivrisiko, Neoadjuvanz, Kombination mit Trastuzumab und Chemotherapie).

Anwendungsgebiet

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).

Zweckmäßige Vergleichstherapie

Die zweckmäßige Vergleichstherapie für Pertuzumab in Kombination mit Trastuzumab und Chemotherapie, bei erwachsenen Patienten zur neoadjuvanten Behandlung von HER2positivem, 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

Ein Zusatznutzen ist nicht belegt.

3.2 Cochrane Reviews

Zaheed M et al., 2019 [22].

Sequencing of anthracyclines and taxanes in neoadjuvant and adjuvant therapy for early breast cancer.

Fragestellung

To assess whether the sequence in which anthracyclines and taxanes are administered affects outcomes for people with early breast cancer receiving adjuvant or neoadjuvant therapy.

Methodik

Population:

- Aged 18 years or older, with early breast cancer suitable for adjuvant or neoadjuvant chemotherapy

Intervention:

- Taxane (docetaxel, paclitaxel or nab-paclitaxel) chemotherapy administered before an anthracycline-based chemotherapy. The same regimen of drugs were administered as the comparator arm in reverse sequence.

Hinweis: We included studies in which concurrent interventions with any other non-anthracycline-based chemotherapy, granulocyte colony stimulating factor or trastuzumab were administered. We excluded studies in which concurrent interventions with radiotherapy or endocrine therapy were administered.

Komparator:

- Anthracycline (doxorubicin, epirubicin or liposomal doxorubicin)-based chemotherapy administered before taxane chemotherapy. The same regimen of drugs was administered as in the intervention arm but in reverse sequence.

  Hinweis: We included studies in which concurrent interventions with any non-taxane chemotherapy or granulocyte colony stimulating factor or trastuzumab were administered. We excluded studies in which concurrent interventions with radiotherapy or endocrine therapy were administered.

Endpunkte:

- Neoadjuvant and adjuvant setting: Overall survival, adverse events, treatment adherence, QoL
- Neoadjuvant setting: DFS, pCR, Standardised Residual Cancer Burden score (RCB), Degree of response after neoadjuvant therapy
- Adjuvant Setting: DFS

Recherche/Suchzeitraum:

- Cochrane Breast Cancer's Specialised Register, CENTRAL, MEDLINE, EMBASE, the World Health Organization's International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 1 February 2018

Qualitätsbewertung der Studien:

- Cochrane approach

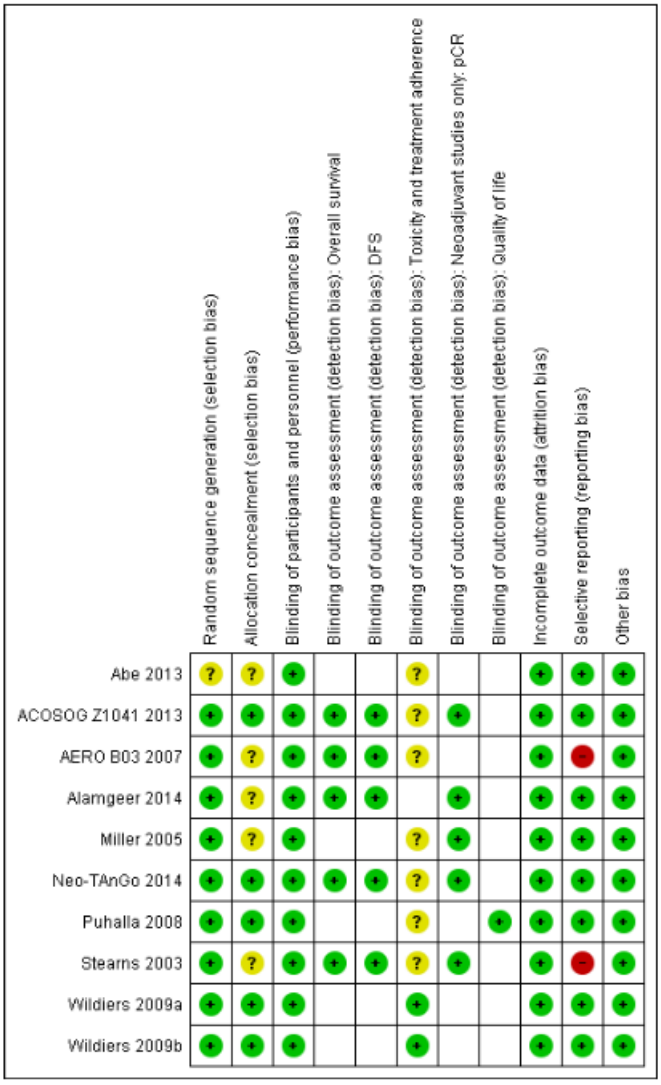
Ergebnisse

Anzahl eingeschlossener Studien:

- 1415 participants in five neoadjuvant studies and 280 participants in four adjuvant studies involving five treatment comparisons

Qualität der Studien:

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Studienergebnisse:

- **Neoadjuvant** studies suggested that the administration of taxanes first probably resulted in little to no difference in overall survival (HR 0.80, 95% CI 0.60 to 1.08; 947 participants; 2 studies; moderate-certainty evidence) and disease-free survival (HR 0.84, 95% CI 0.65 to 1.09; 828 participants; 1 study; moderate-certainty evidence).

- Administration of taxanes first also resulted in little to no difference in pathological complete response (absence of cancer in the breast and axilla: RR 1.15, 95% CI 0.96 to 1.38; 1280 participants; 4 studies; high-certainty evidence). However, there appeared to be a trend in favour of taxanes first.
- Studies reported treatment adherence using a range of measures. Administration of taxanes first probably did not increase the likelihood of requiring dose reductions compared to administration of anthracyclines first (RR 0.81, 95% CI 0.59 to 1.11; 280 participants; 1 study; moderatecertainty evidence). There was probably little to no difference in the risk of grade 3/4 neutropenia (RR 1.25, 95% CI 0.86 to 1.82; 280 participants, 1 study; moderate-certainty evidence) or grade 3/4 neurotoxicity (RR 0.95, 95% CI 0.55 to 1.65; 1108 participants; 2 studies; low-certainty evidence) when taxanes were given first.
- There were no data on quality of life.
- Only one **adjuvant** study collected data on overall survival and disease-free survival but did not report data.
- Administration of taxanes first reduced the risk of grade 3/4 neutropenia (RR 0.62, 95% CI 0.40 to 0.97; 279 participants; 4 studies, 5 treatment comparisons; high-certainty evidence) and appeared to result in little to no difference in grade 3/4 neurotoxicity (RR 0.78, 95% CI 0.25 to 2.46; 162 participants; 3 studies; low-certainty evidence). There was probably little to no difference in the proportions experiencing dose delays when taxanes are given first compared to anthracyclines given first (RR 0.76, 95% CI 0.52 to 1.12; 238 participants; 3 studies, 4 treatment comparisons; moderate-certainty evidence).
- One study reported on quality of life and indicated that scores (using the Functional Assessment ofCancer Therapy - Breast Cancer (FACT-B) validated questionnaire) were similar in both groups though did not provide numerical data.

Anmerkung/Fazit der Autoren

In the neoadjuvant setting, there is high- to low-certainty evidence of equivalent outcomes for the sequence in which taxanes are delivered. In the adjuvant setting, none of the studies reported on overall survival or disease-free survival. In most institutions, standard practice would be to deliver anthracycline followed by taxane, and currently available data do not support a change in this practice. We wait for the full-text publication of a relevant neoadjuvant study for women with HER2-negative breast cancer for inclusion in an update of this review.

3.3 Systematische Reviews

Wang Y et al., 2020 [18].

The tumour response of postmenopausal hormone receptor-positive breast cancers undergoing different types of neoadjuvant therapy: a meta-analysis.

Fragestellung

To investigate the efficacy of neoadjuvant chemotherapy (NCT), neoadjuvant endocrine therapy (NET) and neoadjuvant chemoendocrine therapy (NCET)

Methodik

Population:

- Postmenopausal women with HR-positive breast cancer

Intervention/Komparator:

- NET with NCT or NCET with NET or NCT alone

Endpunkte:

- tumour response rate: pCR, ORR

Recherche/Suchzeitraum:

- PubMed, Embase and Cochrane Library databases were used to identify eligible trials published from inception to 7 May 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- ten eligible clinical trials with 971 unique HR-positive breast cancer patients

Table 2 The treatment regimen of neoadjuvant therapy

Study	Year	NET	NCT	NCET
Chae [24]	2016	Letrozole qd	FEC, a switch to docetaxel if PD or SD	
Wright [25]	2015	AIs or tamoxifen qd	PAT or AT	
Palmieri [26]	2014	Letrozole qd	FE100C or FE75C, a switch to docetaxel if PD or SD	
Semiglazov [27]	2007	Exemestane or anastrozole qd	Doxorubicin + paclitaxel	
Marcus [28]	2013	AIs or tamoxifen qd	Anthracycline-based or non-anthracycline-based	
Ellis [29]	2017	AIs qd[a]	Anthracycline-based or non-anthracycline-based	
Nakayama [30]	2018	Anastrozole qd		Anastrozole qd + UFT
Sato [31]	2018	Exemestane qd		Exemestane qd + cyclophosphamide
Sugiu [32]	2015		FEC-T	Exemestane qd + EFC-T
Mohammad [33]	2012		FAC	Letrozole qd + FAC

Explanation of regimen: *FEC*, 5-fluorouracil, epirubicin, and cyclophosphamide; *FE100C*, 5-fluorouracil 500 mg/m^2, cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2; *FE75C*, 5-fluorouracil 600 mg/m^2, cyclophosphamide 600 mg/m^2, epirubicin 75 mg/m^2; *UFT*, tegafur/uracil combination in 1:4 M ratio; 270 mg/m^2/day in two divided doses; *FEC-T*, 80 mg/m^2 of paclitaxel followed by a combination of fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2; *FAC*, 5-Fluorouracil 600 mg/m^2, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2

Abbreviations: *NET* Neoadjuvant endocrine therapy, *NCT* Neoadjuvant chemotherapy, *NCET* Neoadjuvant chemoendocrine therapy, *AIs* Aromatase inhibitors, *PD* Progressive disease, *SD* Stable disease

[a]These aromatase inhibitors include letrozole, anastrozole and exemestane

Charakteristika der Population:

- the baseline clinical stages were mainly in T1/2 (n = 3), T3/4 (n = 3) and unknown (n = 4); the lengths of neoadjuvant treatment were different, ranging from 9 to 24 weeks; the HER2 status was negative (n = 4), or negative/positive (n = 5) or undescribed (n = 1), however, the number of patients with HER2-positive disease was scarce, with a total number of 29 (ranged from 2 to 18)

Qualität der Studien:

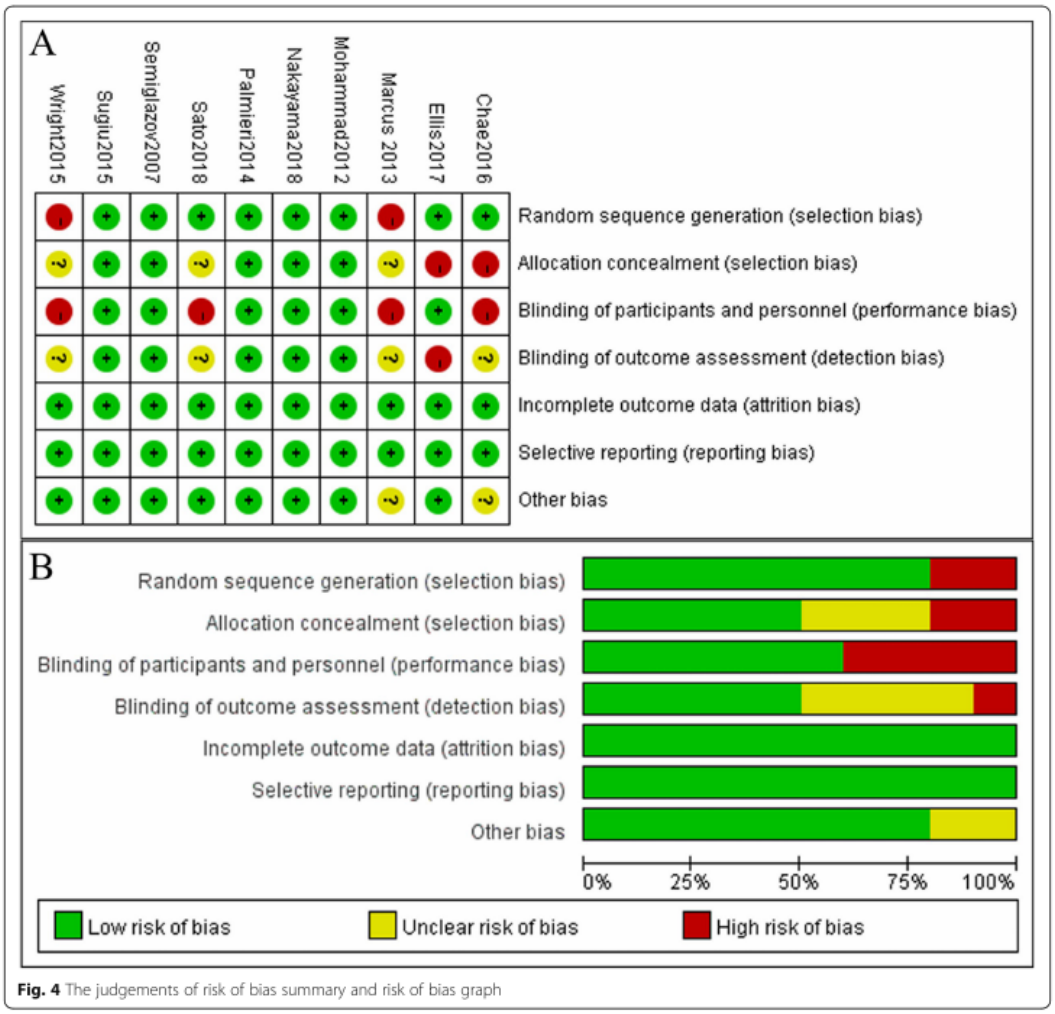


Fig. 4 The judgements of risk of bias summary and risk of bias graph

Studienergebnisse:

- The pooled results indicated that the pCR rate of those patients undergoing NET was significantly lower than those undergoing NCT (pooled OR, 0.48; 95% CI, 0.26–0.90), whereas the difference of ORR between both therapies was not statistically significant (pooled OR, 1.05; 95% CI, 0.73–1.52).
- The combined paradigm of NCET compared with the monotherapy of NET or NCT did not present a significantly improved pCR rate or ORR (pooled OR, 2.61; 95% CI, 0.94– 7.25; and 2.25; 95% CI, 0.39–13.05; respectively).

Anmerkung/Fazit der Autoren

Postmenopausal HR-positive breast cancer patients may benefit more tumour response from NCT than NET, but may be devoid of the improved prognostic outcomes from NCET when compared to NET or NCT alone.

Pathak M et al., 2019 [17].

Effectiveness of Added Targeted Therapies to Neoadjuvant Chemotherapy for Breast Cancer: A Systematic Review and Meta-analysis.

Fragestellung

to assess the effect of these targeted therapies on tumor response rates, breast conserving surgeries, and long-term survival outcomes.

Methodik

Population:

- female patients with non-metastatic breast cancer

Intervention:

- addition of targeted therapy to NACT

Komparator:

- NACT

Endpunkte:

- CR, overall response, clinical complete response (cCR), breast conserving surgery, OS, DFS, loco-regional recurrence, distant metastasis, and toxicity

Recherche/Suchzeitraum:

- PubMed and the Cochrane Central Register of Controlled Trials: Assed on and up to April 28, 2017

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

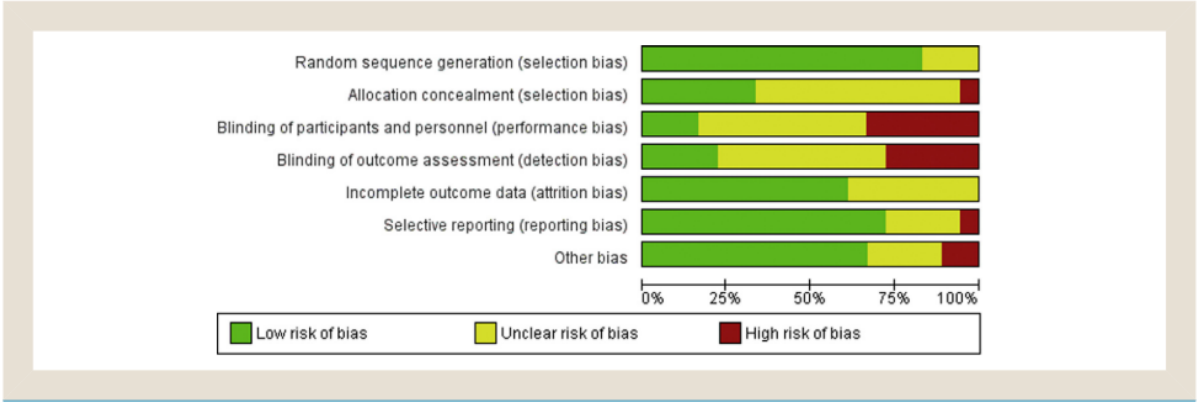
- Of the total 17 RCTs, 5 RCTs involving 491 patients with breast cancer compared the effectiveness of the addition of trastuzumab; 7 RCTs randomizing 4784 women compared the effectiveness of bevacizumab; and 5 RCTs having 501 patients compared the effectiveness of other targeted therapies like gefitinib, evirolimus, iniparib, and erubiline. Four RCTs assessed the effectiveness of trastuzumab along with anthracycline- and taxane-based NACT. However, 1 RCT compared trastuzumab along with non-anthracycline (ie, taxanebased) NACT with NACT alone. Further, 1 RCT compared the effectiveness of epirubicine (taxane + epirubicine + cyclophosphamide) with trastuzumab (taxane + cyclophosphamide +trastuzumab), with taxane in both the arms

Charakteristika der Population:

- The average age of the patients involved in the trials was around 50 years, except for one trial in which it was 38 years. All the RCTs assessing the effectiveness of trastuzumab included only patients with HER2+ breast cancer. On the other hand, 6 of 7 trials assessing the effectiveness of bevacizumab enrolled only patients with HER2- breast cancer. Of these 6 RCTs, 1 RCT enrolled only patients with triple negative breast cancer. However, a small RCT involved 22% ofpatients who were HER2+. A RCT assessed the effectiveness of iniparib only in patients with triple negative breast cancer. Further, RCTs assessing other targeted therapies had mixed molecular profiles.

Qualität der Studien:

Figure 2 Individual Study Risk of Bias Assessment



Studienergebnisse:

- Pathologic complete response was significantly higher with trastuzumab (relative risk [RR], 2.20; 95% confidence interval [CI], 1.62-2.99) and bevacizumab (RR, 1.23; 95% CI, 1.11-1.37), but not with other targeted therapies.
- Bevacizumab for human epidermal growth factor receptor 2 (HER2)-negative breast cancer was found to be associated with improved overall (hazard ratio, 0.69; 95% CI, 0.53-0.90) and disease-free survival (hazard ratio, 0.83; 95% CI, 0.671.03).
- The addition of targeted therapies may not significantly increase breast conserving surgery rates (RR, 1.04; 95% CI, 0.97-1.12).
- Toxicities: The overall addition of targeted therapies to anthracycline- and taxane-based chemotherapy. However, only 1 trial17 comparing the addition of gefitinib to anthracycline alone reported a similar risk of toxicities. In reference to the anthracycline and taxane combination, additional targeted therapies were found to be associated with a higher risk of hematologic toxicities like neutropenia (n = 10; RR, 1.07; 95% CI, 1.02-1.12), febrile neutropenia (n = 6; RR, 1.80; 95% CI, 1.46-2.21), infection (n = 7; RR, 1.82; 95% CI, 1.472.24), leucopenia (n = 6; RR, 1.08; 95% CI, 1.02-1.15), and thrombosis (n = 4; RR, 1.88; 95% CI, 1.20-2.93), as well as for hand-foot syndrome (n = 3; RR, 1.31; 95% CI, 1.00-1.71). However, analytical results regarding hypertension, arthelgia, abrupt cardiac left ventricular function, headache, and death remained imprecise.

Anmerkung/Fazit der Autoren

In summary, to achieve pathologic response and better survival, based on results under the present systematic review, it may be recommended that the addition of trastuzumab for patients with HER2+ breast cancer and of bevacizumab for patients with HER2- breast cancer, with a planned management of hematologic toxicities, may be a better choice.

Ma W et al., 2019 [14].

Targeted neoadjuvant therapy in the HER-2-positive breast cancer patients: a systematic review and meta-analysis.

Fragestellung

To evaluate efficacy and safety of lapatinib or trastuzumab alone or both plus chemotherapy for the treatment of breast cancer patients with positive HER-2 expression.

Methodik

Population:

- women at age 18 or older, with histologically proven stages I, II, III or inflammatory breast cancer; Patients with positive HER-2 expression

Intervention:

- chemotherapy plus lapatinib or chemotherapy plus lapatinib and trastuzumab

Komparator:

- chemotherapy plus trastuzumab

Endpunkte:

- PCR, tPCR, adverse events

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials, PubMed, MEDLINE, OVID, EMBASE, Chinese Biomedical Literature Database, and China Academic Journals Database were searched from 1994 through December 2017

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 studies

Qualität der Studien:

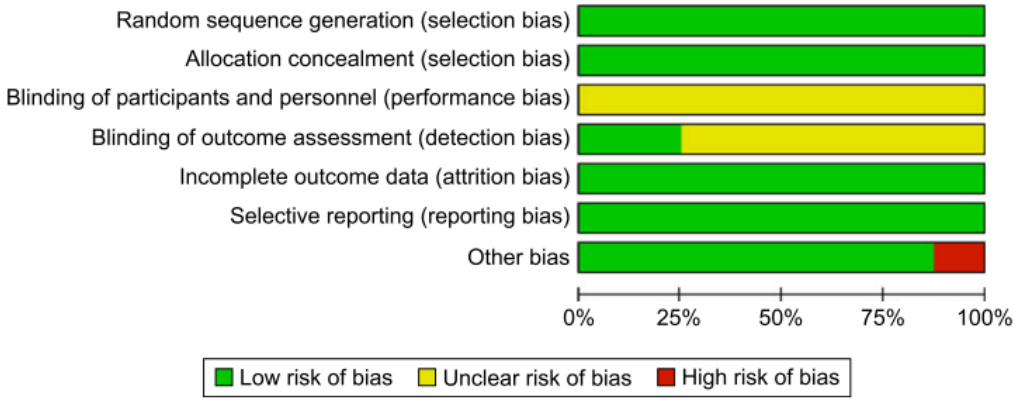


Figure 2 Risk of bias graph.
Note: Review of the authors' judgments about each risk of bias item was presented as percentages across all included studies.

Studienergebnisse:

- Meta-analysis found that pathological complete response (PCR; risk ratio [RR]=0.82, 95% CI: 0.72–0.93) and tall PCR (tPCR; RR=0.77, 95% CI: 0.67–0.88) of chemotherapy plus lapatinib were significantly less effective or safe compared to that of chemotherapy plus trastuzumab (P,0.05).
- PCR (RR=1.30, 95% CI: 1.15–1.47) and tPCR (RR=1.32, 95% CI: 1.16–1.50) of chemotherapy plus both lapatinib and trastuzumab were significantly superior to that of chemotherapy plus trastuzumab alone (P,0.05).
- There was no significant difference in breast reservation rate between chemotherapy plus lapatinib vs chemotherapy plus trastuzumab (RR=0.91, 95% CI: 0.72–1.16) or chemotherapy plus both lapatinib and trastuzumab (RR=1.11, 95% CI: 0.73–1.68, P.0.05).
- Incidence of diarrhea, hepatic toxicity, and skin rash in the groups of chemotherapy plus lapatinib or chemotherapy plus both lapatinib and trastuzumab was significantly higher than that in chemotherapy plus trastuzumab (P,0.05).

Anmerkung/Fazit der Autoren

Taken together, the current meta-analysis revealed that lapatinib caused higher occurrence rate of side effects, but lower rate of PCR and breast conservation in comparison to trastuzumab. When lapatinib was used in combination with trastuzumab, neither OS rate nor breast conservation rate was improved, although the combination did increase PCR or tPCR rate. These findings indicated that lapatinib is not recommended as single anti-HER-2-treatment in combination with chemotherapy and that combination of lapatinib with trastuzumab was not superior to that of trastuzumab alone.

He L et al., 2019 [12].

Do early HER2-overexpression breast cancer patients benefit from undergoing neoadjuvant trastuzumab and mastectomy? A meta-analysis.

Fragestellung

To assess the overall survival (OS) of early human epidermal growth factor receptor 2 (HER2)-enriched breast cancer patients after receiving neoadjuvant trastuzumab (NAT) compared to adjuvant trastuzumab (AT) treatment and the difference in local-regional relapse (LRR) rate with this tumor and treatment between women after mastectomy and women after breast-conserving therapy (BCT).

Methodik

Population:

- Early HER2-enriched breast cancer patients

Intervention:

- NAT or mastectomy

Komparator:

- AT or BCT treatment

Endpunkte:

- OS, local-regional relapse (LRR)

Recherche/Suchzeitraum:

- PubMed, EMBASE, Web of Science, and Cochrane Library. The searching of citation was terminated as of 28th May 2019.

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 clinical studies
- The sample size ranged from 43 to 748 (median: 81.5), with a total number of 2366 subjects. The year range of included studies was 2008 to 2018.

Qualität der Studien:

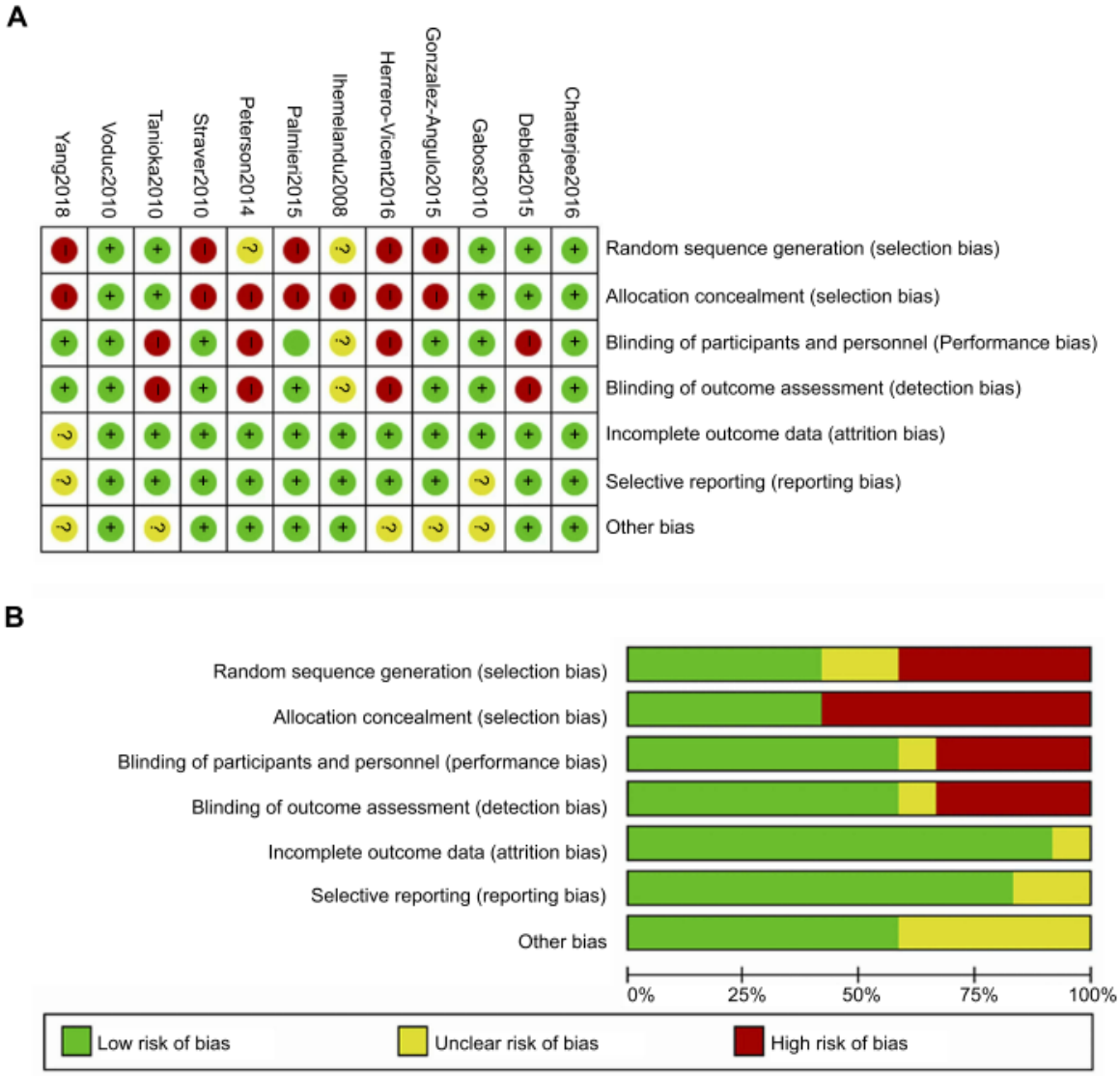


Figure 4 The assessment of risk of bias by the new Cochrane tool. (**A**) The risk of bias summary; (**B**) The risk of bias graph.

Studienergebnisse:

- The OS of NAT compared with that of AT was not significantly different (pooled OR=1.04; 95% CI, 0.47–2.33).
- There was a significantly lower LRR rate for patients with mastectomy compared to those with BCT (pooled OR=0.58; 95% CI, 0.38–0.89); however, subgroup analysis revealed that the significant advantage of LRR for mastectomy compared to BCT was only represented in women without trastuzumab treatment (pooled OR=0.52; 95% CI, 0.31–0.88) compared to those who received trastuzumab treatment (pooled OR=0.71; 95% CI, 0.34–1.49).

Anmerkung/Fazit der Autoren

The OS of HER2-amplified breast tumor patients treated with NAT is equivalent to those with AT treatment. The LRR rate of those women who undergo mastectomy compared to BCT is

identical in the absence of trastuzumab treatment, but mastectomy reduces the LRR rate compared to BCT in women who receive trastuzumab treatment.

Kommentare zum Review:

- Siehe auch: Chen, Y. et al., 2018 [3]

Genuino AJ et al., 2019 [11].

Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis.

Fragestellung

to update the pooling of the relative treatment efficacy and safety of adjuvant trastuzumab plus chemotherapy compared to chemotherapy alone in HER2positive EBC patients.

Methodik

Population:

- participating patients were HER2-positive EBC covering stage I, IIA, IIB, and IIIA

Intervention/Komparator:

- adjuvant trastuzumab plus any chemotherapy regimen (i.e., anthracycline-taxane regime, anthracycline-only regimen, taxane-only regimen)

Endpunkte:

- OS, DFS, LVEF

Recherche/Suchzeitraum:

- from inception to 8 July 2017 was performed through two electronic databases (i.e. Medline via PubMed and Scopus)

Qualitätsbewertung der Studien:

- Cochrane approach / NOS

Ergebnisse

Anzahl eingeschlossener Studien:

- eight studies

Charakteristika der Population:

- The percentage of node-positive patients ranged from 52% to 100%, and hormone-receptor (HR)-positive patients were 40% to 73%. The percentage of patients who underwent mastectomy ranged from 36% to 67%.

Qualität der Studien:

- Among eight studies, most studies, 5/8 were rated as low risk for random sequence generation (N = 5), selective reporting (N = 7), and incomplete outcomes (N = 5). However,

most studies (N = 6) were unclear whether they had applied allocation concealment, whereas none of the studies applied blinding.

Studienergebnisse:

- OS: The pooled HR was 0.67 (95% CI: 0.61, 0.73, P < 0.001) with a degree of heterogeneity of 0%, which could be interpreted that the risk of death was decreased by about 33% in the trastuzumab-chemotherapy group compared to the chemotherapy alone group.
- DFS: The relative treatment effects of trastuzumab-chemotherapy regimen versus chemotherapy alone regimen on recurrence were moderately heterogeneous with the I2 of 61.1% as shown in Figure 3. The pooled HR was 0.65 (95% CI: 0.55, 0.75, P < 0.001), suggesting significantly lower risk of recurrence in the trastuzumab-chemotherapy group, about 35% when compared to the chemotherapy alone group.
  - For the subgroup analysis based on intervention type, four RCTs administered trastuzumab with anthracycline-taxane chemotherapy regimens while two RCTs administered trastuzumab with any/mixed chemotherapy regimens (i.e., anthracycline-taxane chemotherapy, anthracycline-based chemotherapy, or taxane-based chemotherapy). The pooled subgroup HR for trastuzumab with any/mixed chemotherapy regimen type was significantly higher (HR 0.77; 95% CI: 0.68, 0.85, P < 0.001) compared to the pooled subgroup HR for trastuzumab with anthracycline-taxane chemotherapy regimen (HR 0.60; 95% CI: 0.54, 0.66, P < 0.001).
- CHF: The pooled RR for CHF was 3.71 (95% CI: 2.41, 5.71, P < 0.001), which could be interpreted that the risk of CHF in the trastuzumab-chemotherapy group increased by 3.71 times more compared to the chemotherapy alone group.
- LEVF: The pooled RR was 2.17 (95% CI: 1.11, 4.24, P < 0.001), suggesting a significantly higher risk of LVEF decline in the trastuzumab/chemotherapy group by 2.17 times more when compared to chemotherapy alone group.
  - For the subgroup analysis of LVEF decline based on intervention type, three RCTs administered trastuzumab with anthracycline-taxane chemotherapy regimen while two RCTs administered trastuzumab with any/mixed chemotherapy regimen type yielding the I2 values of 40% and 0%, respectively. The pooled RRs of these two corresponding subgroups were 4.70 (95% CI: 2.98, 7.41, P < 0.001) and 1.32 (95% CI 0.74–2.36, P = 0.350), respectively.

Anmerkung/Fazit der Autoren

In the light of the most current and longest trial evidence available to date, combining adjuvant trastuzumab with chemotherapy is able to gain the benefits of OS and DFS over the risk of CHF but not for LVEF decline when compared to chemotherapy alone in HER2-positive EBC women. The currently available evidence under the subgroup analyses showed that administering adjuvant trastuzumab in a weekly cycle concurrently with anthracycline-taxane chemotherapy regimen is able to lower cardiogenetic toxicity than 3-week cycle given not much differences in the benefit of OS and DFS.

Kommentare zum Review:

- Siehe auch: Davari, M. et al., 2017 [4]

Chen S et al., 2019 [2].

Efficacy and safety of HER2 inhibitors in combination with or without pertuzumab for HER2-positive breast cancer: a systematic review and meta-analysis.

Fragestellung

This systematic review evaluates the efficacy and safety of H (trastuzumab or trastuzumab emtansine ± chemotherapy) + P (pertuzumab) compared with those of H in HER2+ breast cancer patients.

Methodik

Population:

- patients with HER2+ breast cancer

Intervention:

- H (trastuzumab or trastuzumab emtansine ± chemotherapy) + P (pertuzumab)

Komparator:

- H (trastuzumab or trastuzumab emtansine ± chemotherapy)

Endpunkte:

- CR, PFS, OS, and the incidence of all-grade or grade ≥ 3 AEs or cardiac toxicity

Recherche/Suchzeitraum:

- PubMed, COCHRANE, Science Direct, EMBASE, the clinical trial registry. Databases were searched for studies published between 2005 (based on the first reported trial of pertuzumab efficacy in humans) and December 30, 2018.

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- Twenty-six studies (9872 patients)
- Of these 26 studies, the 14 single-arm trials with 1098 patients included 13 studies describing pertuzumab combined with trastuzumab for the treatment of HER2+ breast cancer patients nd one study describing pertuzumab combined with T-DM1 for the treatment of HER2+ breast cancer patients, and the 12 controlled trials with 8774 participants (4015 patients and 4759 patients in the experimental and control arms, respectively) included seven studies describing the treatment of patients with pertuzumab combined with trastuzumab versus trastuzumab alone and four studies describing the treatment of patients with pertuzumab combined with T-DM1 versus T-DM1 alone.

Qualität der Studien:

Table 2 Quality assessment of included studies

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Bias from other resources
Shruti R. Tiwari 2016 [25]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Sandra M.Swain 2015 [19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Sabino De Placido 2018 [33]	Low risk	High risk	Unclear	Low risk	Low risk	Low risk	Low risk
Rashmi K. Murthy 2018 [17]	Low risk	Unclear	Low risk	Low risk	High risk	Low risk	Low risk
Peter Beitsch 2017 [10]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nicholas J. Robert 2017 [32]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear
Nadia Hussain 2018 [35]	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Mothaffar Rimawi 2017 [18]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Andersson M 2017 [26]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Manish Gupta 2013 [11]	High risk	Low risk	Low risk	Low risk	High risk	High risk	Unclear
M. Martin 2016 [13]	High risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Luca Gianni 2018 [22]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	High risk
Luca Gianni 2012 [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kazuhiro Araki 2017 [14]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	High risk
Kathy D. Miller 2014 [34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Julia Foldi 2017 [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
José Baselga 2010 [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
JASMEET C. SINGH 2017 [24]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear
Ian E.Krop 2016 [20]	Low risk	Unclear	Low risk	Low risk	Low risk	High risk	Low risk
Gunter von Minckwitz 2017 [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Edith A. Perez 2017 [21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Edith A. Perez 2016 [27]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Chia C. Portera 2008 [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chau Dang 2015 [28]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Bao D Dao 2015 [29]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Unclear
Ander Urruticoechea 2017 [9]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Studienergebnisse:

- Neoadjuvant setting: Four single-arm trials that included 205 patients were analyzed for the pCR rate in stage -III HER2+ breast cancer patients treated with neoadjuvant H+ P. The pCR rates ranged from 0.27 to 0.62 in the four studies, and the pooled results using a random effects model showed that the absolute pCR rate was 0.56 (95% CI, 0.45–0.63). Significant heterogeneity was observed (I2 = 82.4%; P < 0.001). In the sensitivity analysis, the estimated absolute rate equaled 0.59 (95% CI, 0.36–0.63) after removing the studies conducted by Luca Gianni and Jasmeet C. Singh.
- Four controlled trials including 1448 patients (n = 383 in the experimental H+ P groups and n = 1065 in the control H groups) were analyzed for the pCR rate in stage -III HER2+ breast

cancer patients. The pooled results using a fixed-effects model demonstrated that the pCR rate of the H+ P group was significantly higher than that of the H group (OR = 1.33; 95% CI, 1.08–1.63; P= 0.006). Low heterogeneity was found among the included individual studies (I2 = 0.0%; P= 0.78). Moreover, the absolute pCR rates of the H+ P and H groups were estimated to equal 55 and 44%, respectively.

- A subgroup analysis based on the HR was conducted.
  - The analysis of pCR outcomes stratified by HR status revealed that the HR status contributes to the difference in efficacy between H+ P and H. A subgroup analysis of the four single-arm trials showed that the efficacy of H+ P in HR- (pCR rate range, 0.69–0.85; absolute rate = 0.77; 95% CI, 0.67–0.87; P < 0.001) was more significant than that in HR+ (pCR rate range, 0.26–0.68; absolute rate = 0.46; 95% CI, 0.21–0.70; P < 0.001). Significant heterogeneity was observed in the HR+ group (I2 = 86.4%; P= 0.001)). The sensitivity analysis yielded an estimated absolute rate of 0.35 (95% CI, 0.21–0.70) after sequential exclusion of the study conducted by Jasmeet C. Singh. The subgroup analysis based on HR was performed in three studies, the results of the benefit ratio showed that there was a trend towards better pCR of HR- patients treated with H+ P compared to that of HR+ patients [absolute rate (HR-) = 0.68; absolute rate (HR+) = 0.39]. However, the results of comparison between group H+ P and group H on the efficacy of HR+/ HR- breast cancer patients showed that the efficacy of H+ P was not significantly better than that of H in HR+ (absolute rate = 0.39 versus 0.30) or HR- (absolute rate = 0.68 versus 0.51) breast cancer patients, and the pooled estimates using a fixed-effects model indicated no significant difference between HR+ (OR = 1.37; 95% CI, 0.88–2.13; P= 0.162) and HR- (OR = 1.37; 95% CI, 0.91– 2.07; P= 0.126) breast cancer patients.
- Rash, diarrhea, epistaxis, mucosal inflammation, and anemia were significantly more frequently observed with H + P than with H, whereas myalgia was less frequent (OR = 0.91; 95% CI, 0.82–1.01; p = 0.072), and no significant difference in cardiac toxicity was observed between these therapies (OR = 1.26; 95% CI, 0.81–1.95; P = 0.309). (→ Hinweis: Setting unklar)

Anmerkung/Fazit der Autoren

In conclusion, the results of this systematic review and meta-analysis provide the first opportunity to compare the efficacy and safety of HER2 inhibitors with (H + P) or without pertuzumab (H) for patients with HER2+ breast cancer. Our meta-analysis confirms that H+ P is superior to H in the (neo)adjuvant treatment of HER2+ breast cancer, and increase the risk of acceptable and tolerable toxicity (rash, diarrhea, epistaxis, mucosal inflammation, and anemia). Based on the subgroup analysis of pCR, H+ P is a correct choice for the treatment of patients with HER2+/HR- breast cancer. The combined application of pertuzumab and HER2-targeted drugs is thus promising and potent.

Kommentare zum Review

- Siehe auch: Zhang, J. et al., 2017 [23] & Wu, D. et al., 2019 [19]

Wu YT et al., 2018 [21].

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

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:

Intervention/Komparator:

- concurrent vs nonconcurrent use of trastuzumab and anthracycline-based NAC

Endpunkte:

- pCR, CED, CF, CR, PR, BCS, OS, RFS

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane databases from inception until July 1, 2017

Qualitätsbewertung der Studien:

- Newcastle–Ottawa scale (NOS)

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 studies

Qualität der Studien:

- All of the included studies were of moderate or high quality.

Studienergebnisse:

- The pCR rate was significantly higher in the concurrent use of trastuzumab and anthracycline group (45%) than that in the nonconcurrent use group (32%) (OR: 2.36, 95% CI: 1.69–3.30, P,0.0001).
- The pooled absolute rate of breast conservation surgery (BCS) was 48% (95% CI: 0.35–0.61) and 38% (95% CI: 0.14–0.62) in the experimental and control groups, respectively (OR: 1.10, 95% CI: 0.64–1.90, P=0.73).
- No significant differences were found in the left ventricular ejection fraction (LVEF), which decreased by .10% (OR: 1.26, 95% CI: 0.55–2.88, P=0.59), and in terms of cardiac failure (OR: 2.17, 95% CI: 0.24–19.84, P=0.49), when comparing the concurrent use of trastuzumab and anthracyclines with their non-concurrent use.

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 anthracyclinebased 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.

Kommentare zum Review

- Siehe auch: Wu, Yu-Tuan et al., 2018 [20]

Ding W et al., 2018 [6].

Anthracycline versus nonanthracycline adjuvant therapy for early breast cancer: A systematic review and meta-analysis.

Fragestellung

to compare treatment outcomes for patients with EBC receiving adjuvant chemotherapy with non–anthracycline-contained regimens or anthracycline-contained regimens.

Methodik

Population:

- patients with EBC that had not spread out of the breast or the axillary lymph nodes; previously untreated patients who had undergone curative surgical resection

Intervention:

- non– anthracycline-contained regimens

Komparator:

- anthracycline-contained regimens

Hinweis: patients with standard postoperative radiotherapy and adjuvant hormonal treatment, in which tamoxifen or aromatase inhibitors were allowed, whereas trastuzumab or other targeted drugs were not allowed.

Endpunkte:

- DFS, OS, adverse events

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library. Trials were eligible if they were randomized, presented before April 2018.

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 studies / 14,451 patients

Charakteristika der Population:

Table 1

Characteristics of included studies and outcome events.

Trials	Jones 2009[11]	Shulman 2014[12]	Minckwitz 2015[13]	Mavroudis 2016[14]	Ejlertsen 2017[15]	Goetz 2017[16]	Harbeck 2017[17]
Information of the included trials							
Trials	USOR 9735	CALGB 40101	ICE II-GBG 52	HORG	DBCG 07-READ	USOR 06–090, NSABP B-46-I/USOR 07132, NSABP B-49	WSG PlanB
Phases	III	III	II	III	III	III	III
Accrual dates	Between July 1, 1997, and January 5, 2000	Between 2002 and 2010	Between April 2009 and April 2013	Between October 2007 and December 2013	Between June 2008 and December 2012	Between May 29, 2007 and November 21, 2013	Between 2009 and 2011
Patient characteristics and study designs							
Inclusion criteria	Age 18 to 75 years; operable stage I-III invasive breast cancer	Age ≥18 years; operable breast cancer; pN0 ER+ T≥1cm; ER-; pN+;	Age ≥65 years; CCI≤2; cM0; pT1/2 pN0/1 high-risk; pT3/4 pN2/3;	Age 18 to 75 years; free margins; N+; HER2-	pN0 high-risk; pN+; TOP2A-Normal operable breast cancer;	pN0 high-risk; pN+; free margins; pT1-3; cM0;	Age ≤75 years; HER2-; cM0; free margins; pN0 high-risk; pN+
Study designs	AC 60/600 * 4 TC 75/600 * 4	AC 60/600 * 4 or 6 P 175 * 4 or 6	EC 90/600 * 4/CMF 500/40/600 * 6 nPX 100/2000 * 6	FEC 75/50/500 * 4 → T 75 * 4 TC 75/600 * 6	EC 90/600 *3→T 100 * 3 TC 75/600 * 6	TAC 75/50/500 * 6 TC 75/600 * 6	EC 90/600 * 4→T 100 * 4 TC 75/600 * 6
Medium follow-up, mo	84	73.2	22.8	46	69	39.6	60
No. patients	AC: 510 TC: 506	AT: 1931 P: 1940	EC/CMF: 185 nPX: 124	FEC→T: 326 TC: 324	EC→T: 994 TC: 1006	TAC: 2062 TC: 2094	EC→T: 1227 TC: 1222
Outcomes assessment							
Primary end point	Disease-free survival; overall survival	Disease-free survival	Safety	3-Year disease-free survival rate	Disease-free survival	Invasive disease-free survival	Disease-free survival
Secondary end point	Disease-free survival (age, HER2 status, and hormone receptor status)	Overall survival	Invasive disease-free survival and overall survival	Overall survival	Overall survival;	Overall survival and safety	Overall survival and safety

+ = positive, − = negative, AC = doxorubicin and cyclophosphamide, AT = doxorubicin and doxorubicin, CALGB = Cancer and Leukemia Group B, CCI = Charlson Comorbidity Index, CMF = cyclophosphamide, methotrexate, and 5-fluorouracil, DBCG = Danish Breast Cancer Cooperative Group, EC = epirubicin and cyclophosphamide, ER = estrogen receptor, FEC = 5-fluorouracil, epirubicin, and cyclophosphamide, HER2 = human epidermal growth factor receptor 2, HORG = Hellenic Oncology Research Group, ICE II-GBG = Investigational Chemotherapy for Elderly patients II —German Breast Group, nPX = Nab-paclitaxel and capecitabine, NSABP = National Surgical Adjuvant Breast and Bowel Project, P = paclitaxel, TAC = docetaxel, doxorubicin, and cyclophosphamide, TC = docetaxel and cyclophosphamide, TOP2A = topoisomerase II a, USOR = United States Oncology Research, WSG = West German Study Group.

Qualität der Studien:

- For allocation concealment, the risk of bias was unclear in 2 RCTs with an allocation scheme which was not mentioned in the trials; and in the other 5 studies, the risk of bias was high. For random sequence generation, the risk of bias was unclear in 3 RCT studies and high in another one. For the attrition bias, the risk was high in 1 study.

Studienergebnisse:

- Significant differences in favor of anthracycline-contained regimens were seen in DFS (HR: 0.86; 95% CI: 0.78–0.95; P= .003) and in OS (HR: 0.85; 95% CI: 0.75–0.97; P=.01).
  - Subgroup analyses of DFS showed similar treatment effects by hormone-receptor status and nodal status, but differential effects by human epidermal growth factor receptor 2 status, menopausal status, and malignancy grade. Sensitive analysis showed that the DFS of taxanes and cyclophosphamide (TC) was noninferior to anthracycline-contained regiments.

Table 2

Subgroup analysis and sensitivity analysis for disease-free survival.

	HR (95% CI)	*P*	I^2%
1. Subgroup analysis			
Hormone-receptor status			
ER and PR (–)	0.98 (0.71, 1.35)	.09	55
ER and/or PR (+)	1.02 (0.86, 1.21)	.43	0
HER2 status			
HER2 –	1.01 (0.82,1.26)	.19	35
HER2 +	1.37 (0.59,3.16)	.46	–
Malignancy grade			
Grade ½	0.73 (0.53,1.00)	.29	20
Grade 3	1.36 (1.01,1.85)	.59	0
Nodal status			
0	0.97 (0.69, 1.36)	.86	–
1–3	0.95 (0.58, 1.54)	.16	50
4–10	0.80 (0.52,1.21)	.40	0
>10	0.80 (0.46,1.40)	.06	72
Menopausal status			
Postmenopausal	0.87 (0.63,1.20)	.29	10
Premenopausal	1.29 (0.92,1.79)	.88	0
2. Sensitivity analysis			
A vs TC	0.89 (0.79,1.00)	.26	24

+ = positive, – = negative, A = anthracycline contained regimen, CI = confidence interval, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, PR = progesterone receptor, TC = docetaxel and cyclophosphamide.

Anmerkung/Fazit der Autoren

Despite failing to show noninferior to the non-A in patients with EBC, it provided evidence that both regimens significantly improved the DFS and OS, and TC regimen may be noninferior to anthracycline-contained regimens.

3.4 Leitlinien

Leitlinienprogramm Onkologie, 2017 [13].

Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 4.3 (Februar 2020)

Leitlinienorganisation/Fragestellung

Management des Mammakarzinoms.

Methodik

- 3. Aktualisierung der Leitlinie von 2017
- Repräsentatives Gremium: Interdisziplinäre LL-Entwicklergruppe, Beteiligung von Patientenvertreterinnen;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt. Es wurde ein durch die AWMF moderierter, mehrteiliger Nominaler Gruppenprozess durchgeführt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: Die S3-Leitlinie ist bis zur nächsten Aktualisierung gültig, die Gültigkeitsdauer wird auf 5 Jahre geschätzt.

Recherche/Suchzeitraum:

- Recherche nach Leitlinien, die nach Nov. 2013 veröffentlicht wurden, in Datenbanken von G-I-N, NGC, NICE, Library NHS, SIGN u.a. im Juni 2015 und Oktober 2015 (inkl. Abgleich mit LL-Bericht des IQWiG),
- AGREE-II-Bewertung der identifizierten LL; Einschlusskriterium: Erfüllen von ≥ 50% der Domäne 3 (Rigour of Development) des AGREE II (Bewertung durch 2 Begutachter)
- Recherche nach Primärliteratur und systematischen Reviews in Medline, CDSR, CENTRAL, DARE; Zeitraum: 06. April – 2. November 2016
- Methodische Bewertung der Literatur: SIGN-Checklisten für SR, RCT, Observational Studies (jeweils Version 2004) sowie Studies of Diagnostic Accuracy (Version 2006)

LoE/GoR

- Schema der Evidenzgraduierung (in Anlehnung an das Schema des Oxford Centre of Evidences-based Medicine)
- In der Leitlinie werden zu allen evidenzbasierten Statements und Empfehlungen das Evidenzlevel der zugrundeliegenden Studien sowie bei Empfehlungen zusätzlich die Stärke der Empfehlung (Empfehlungsgrad) ausgewiesen. Hinsichtlich der Stärke der Empfehlung werden in dieser Leitlinie drei Empfehlungsgrade unterschieden, die sich auch in der Formulierung der Empfehlungen jeweils widerspiegeln.

Schema der Empfehlungsgraduierung

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

Konsensusstärke:

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

- Statements/Empfehlungen, für die eine Bearbeitung auf der Grundlage von Experten-konsens der Leitliniengruppe beschlossen wurde, sind als „Expertenkonsens“ ausgewiesen. Für die Graduierung der auf Expertenkonsens beruhenden Empfehlungen wurden keine Symbole bzw. Buchstaben verwendet, die Stärke ergibt sich hier aus der verwendeten Formulierung (soll/sollte/kann).

Sonstige methodische Hinweise

- Februar 2020, Version 4.3: Umfassende redaktionelle Überarbeitung der Empfehlungskästen. Zusammengefasste Empfehlungen wurden in separate Empfehlungskästen übertragen. Durch die Überarbeitung wurden die Empfehlungsnummern geändert. Inhaltliche Änderungen fanden nicht statt.

Empfehlungen

Radiotherapie des DCIS

4.33.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Die adjuvante Radiotherapie verringert das Lokalrezidivrisiko nach brust-erhaltender Therapie um bis zu 50%, bei niedrigem Risiko ist der Benefit für die Patientin jedoch gering. Die Möglichkeit einer Radiotherapie sollte der Patientin in Abhängigkeit vom individuellen Risikoprofil angeboten werden.
Level of Evidence **1a**	Quellen: [231, 281-284]
	Starker Konsens

Brusterhaltende Therapie

4.43.	Evidenzbasiertes Statement
Level of Evidence **1a**	Ziel der operativen Therapie ist die Tumorentfernung im Gesunden. Dabei ist eine brusterhaltende Therapie (BET) mit nachfolgender Radiotherapie der gesamten Brust bezüglich des Überlebens der alleinigen Mastektomie gleichwertig.
	Leitlinienadaptation: [358, 359], Quellen: [363-369]
	Starker Konsens

4.44.	Konsensbasierte Empfehlung
EK	Es sollen alle entsprechenden Patientinnen mit oder ohne vorausgegangene primäre Systemtherapie über die Möglichkeit der brusterhaltenden Therapie (BET) und der Mastektomie mit der Option einer primären oder sekundären Rekonstruktion aufgeklärt werden.
	Konsens

Mastektomie

4.45.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Eine Mastektomie soll bei folgenden Indikationen durchgeführt werden: • inkomplette Entfernung des Tumors (inkl. intraduktale Komponente), auch nach Nachresektion • inflammatorisches Mammakarzinom (in der Regel auch bei pathologischer Komplettremission) • bei Kontraindikationen zur Nachbestrahlung nach brusterhaltender Therapie bei absoluter Indikation zur Bestrahlung • Wunsch der aufgeklärten Patientin
Level of Evidence **2b**	Leitlinienadaptation: [370] Quellen: [180, 371, 372]
	Konsens

4.46.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Unter Berücksichtigung von tumorfreien Resektionsrändern kann die Mastektomie auch als hautsparend mit oder ohne Erhalt des MAK durchgeführt werden.
Level of Evidence **2a**	Quellen: [387-390]
	Starker Konsens

4.47.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Unter Berücksichtigung der Tumorlokalisation und Tumorgröße kann bei multizentrischem Sitz im Einzelfall auf eine Mastektomie verzichtet werden.
Level of Evidence **2a**	Quellen: [374-381]
	Starker Konsens

4.48.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Eine kontralaterale prophylaktische Mastektomie sollte bei Nicht-Mutationsträgerinnen bzw. bei Patientinnen ohne Nachweis einer familiären Hochrisikosituation zur Reduktion des kontralateralen Mammakarzinomrisikos nicht durchgeführt werden.
Level of Evidence **2b**	Leitlinienadaptation: [359] Quellen: [160, 170, 391]
	Starker Konsens

Prädiktion adjuvanter systemischer Therapien

4.80.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Zur Einschätzung der voraussichtlichen Wirkung adjuvanter systemischer Therapien (Prädiktion) soll der Östrogen-/Progesteronrezeptorstatus für eine endokrine Systemtherapie erhoben werden.
Level of Evidence **1a**	Quellen: [417, 554, 555]
	Starker Konsens

4.81.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Zur Einschätzung der voraussichtlichen Wirkung adjuvanter systemischer Therapien (Prädiktion) soll der HER2-Status für eine zielgerichtete Anti-HER2-Therapie erhoben werden.
Level of Evidence **1b**	Quellen: [422, 461-463]
	Starker Konsens

4.82.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Zur Einschätzung der voraussichtlichen Wirkung adjuvanter systemischer Therapien (Prädiktion) soll der Menopausenstatus für den Einsatz einer antiöstrogenen Therapie erhoben werden.
Level of Evidence **1c**	Quellen: [556]
	Starker Konsens

Prädiktive Faktoren im Rahmen einer neoadjuvanten Systemtherapie

4.83.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Verschiedene prädiktive Faktoren besitzen einen signifikanten Vorhersagewert für das Eintreten einer pathologischen Komplettremission (pCR). Im Vorfeld einer neoadjuvanten Systemtherapie sollen erhoben werden: • Alter • cT* • cN* • histologischer Typ • histologisches Grading • ER- und PgR-Status • HER2-Status *Klinische Parameter
Level of Evidence **1a**	Quellen: [557, 558]
	Starker Konsens

Adjuvante Strahlentherapie des Mammakarzinoms

4.86.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Nach brusterhaltender Operation wegen eines invasiven Karzinoms soll eine Bestrahlung der betroffenen Brust durchgeführt werden. Bei Patientinnen mit eindeutig begrenzter Lebenserwartung (<10 Jahre) und einem kleinen (pT1), nodal-negativen (pN0), Hormon-rezeptorpositiven HER2-negativen Tumor mit endokriner adjuvanter Therapie, freie Schnittränder vorausgesetzt, kann unter Inkaufnahme eines erhöhten Lokalrezidivsrisikos nach individueller Beratung auf die Strahlentherapie verzichtet werden. Hinweis für alle Empfehlungen: Alle Einzelpositionen sind „oder"-Verknüpfungen. „Und"-Verknüpfungen sind mit einem „und" dargestellt.
Level of Evidence **1a**	Quellen: [575-582]
	Starker Konsens

4.88.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A/B**	Eine lokale Dosisaufsättigung (Boost-Bestrahlung) des Tumorbettes senkt die lokale Rezidivrate in der Brust, ohne dadurch einen signifikanten Überlebensvorteil zu bewirken. Die Boostbestrahlung • soll daher bei allen </= 50 Jahre alten Patientinnen und • sollte bei > 51 Jahre alten Patientinnen nur bei erhöhtem lokalen Rückfallrisiko erfolgen (G3, HER2-positiv, tripelnegativ, > T1).
Level of Evidence **1a**	Quellen: [613-616]
	Starker Konsens

4.89.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Eine alleinige Teilbrustbestrahlung (als Alternative zur Nachbestrahlung der ganzen Brust) kann bei Patientinnen mit niedrigem Rezidivrisiko durchgeführt werden.
Level of Evidence **1a**	Quellen: [624-629]
	Starker Konsens

4.90.	Evidenzbasiertes Statement
Level of Evidence **1a**	Die postoperative Radiotherapie der Brustwand nach Mastektomie senkt das Risiko eines lokoregionären Rezidivs und verbessert das Gesamtüberleben bei lokal fortgeschrittenen und nodal-positiven Mammakarzinomen.
	Quelle: [650]
	Starker Konsens

4.91.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A/B**	Bei folgenden Situationen soll die Strahlentherapie der Brustwand nach Mastektomie indiziert werden: • pT4 • pT3 pN0 R0 bei Vorliegen von Risikofaktoren (Lymphgefäßinvasion (L1), Grading G3, prämenopausal, Alter < 50 Jahre) • R1-/R2-Resektion und fehlender Möglichkeit der sanierenden Nachresektion a) Bei mehr als 3 befallenen axillären Lymphknoten soll eine Postmastektomiebestrahlung regelhaft durchgeführt werden b) Bei 1-3 tumorbefallenen axillären Lymphknoten soll eine Postmastektomiebestrahlung durchgeführt werden, wenn ein erhöhtes Rezidivrisiko vorliegt (z. B. wenn HER2-positiv, triple-negativ, G3, L1, Ki-67 > 30%, > 25% der entfernten Lymphknoten tumorbefallen; Alter ≤ 45 Jahren mit zusätzlichen Risikofaktoren wie medialer Tumorlokalisation oder Tumorgröße > 2cm, oder ER-negativ). c) Bei 1-3 tumorbefallenen axillären Lymphknoten und Tumoren mit geringem Lokalrezidivrisiko (pT1, G1, ER-positiv, HER2-negativ, wenigstens 3 Eigenschaften müssen zutreffen) sollte auf die PMRT verzichtet werden. d) Bei allen anderen Patientinnen mit 1-3 tumorbefallenen axillären Lymphknoten soll die individuelle Indikation interdisziplinär festgelegt werden.
Level of Evidence **1a**	Quellen: [270, 650-663]
	Konsens

Postmastektomie-Radiotherapie nach primär systemischer Therapie

4.92.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Nach primärer (neoadjuvanter) systemischer Therapie soll sich die Indikation zur Postmastektomie-Radiotherapie am prätherapeutischen klinischen Stadium orientieren; bei pCR (ypT0 und ypN0) soll die Indikation im interdisziplinären Tumorboard abhängig vom Risikoprofil festgelegt werden.
Level of Evidence **1a**	Quellen: [664-667]
	Starker Konsens

Radiotherapie bei lokal weit fortgeschrittenem Tumor und bei primärer Inoperabilität

4.104.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Bei Patientinnen mit primär inoperablen bzw. inflammatorischen Karzinomen soll eine primäre Systemtherapie, gefolgt von Operation und postoperativer Strahlentherapie, oder bei weiter bestehender Inoperabilität alleiniger oder präoperativer Strahlentherapie durchgeführt werden.
Level of Evidence **1b**	Quellen: [700, 701]
	Starker Konsens

Therapiesequenz von adjuvanter Systemtherapie und Radiotherapie

4.105.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Postoperative Chemotherapie und Radiotherapie sollen sequentiell erfolgen. Hinweis: die Überlegenheit einer speziellen Sequenz (erst Chemotherapie bzw. erst Radiotherapie) ist nicht belegt. Für die klinische Praxis hat sich die Sequenz von Chemotherapie mit nachfolgender Radiotherapie etabliert.
Level of Evidence **1b**	Quellen: [710-713]
	Starker Konsens

4.106.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Bei alleiniger RT sollte diese innerhalb einer 8-wöchigen Frist postoperativ eingeleitet werden.
Level of Evidence **2b**	Quellen: [714, 715]
	Starker Konsens

4.107.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	Eine adjuvante endokrine Therapie kann unabhängig von der Radiotherapie eingeleitet werden. (Evidenzgrad 1a) Eine Therapie mit Trastuzumab kann während einer Strahlentherapie fortgeführt werden. Bei einer simultanen A.-mammaria-Lymphknoten-Bestrahlung soll das Vorgehen interdisziplinär festgelegt werden. (Evidenzgrad 4)
Level of Evidence **1a/4**	Quellen: [593, 686, 687, 716]
	Starker Konsens

Systemische adjuvante Therapie (endokrine, Chemo-, Antikörpertherapie)

4.108.	Evidenzbasierte Empfehlung
Empfehlungsgrad **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

4.109.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Eine endokrine Therapie soll erst nach Abschluss der Chemotherapie begonnen werden, kann aber parallel zur Strahlentherapie erfolgen.
Level of Evidence **1a**	Quellen: [29, 580, 726-729]
	Starker Konsens

4.110.	Evidenzbasierte Empfehlung
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 therapieassoziierten Nebenwirkungen (Toxizität, verminderte Adhärenz) erfolgen (Empfehlungsgrad B). Bei der Wahl der endokrinen Therapie soll der aktuelle Menopausenstatus der Patientin berücksichtigt werden.
Level of Evidence **1a**	Leitlinienadaptation: [737]
	Starker Konsens

4.111.	Evidenzbasierte Empfehlung
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 Patientin abhängig.
Level of Evidence **1a**	Quellen: [726, 727, 738, 739, 741]
	Starker Konsens

4.112.	Konsensbasierte Empfehlung
EK	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

4.113.	Evidenzbasierte Empfehlung
Empfehlungsgrad 0	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.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

4.114.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	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

4.115.	Evidenzbasierte Empfehlung
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

Adjuvante Chemotherapie

4.116.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	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., Ki-67 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

4.117.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	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

4.118.	Evidenzbasierte Empfehlung
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: [760-765]
	Starker Konsens

4.119.	Evidenzbasierte Empfehlung
Empfehlungsgrad **B**	Die adjuvante Chemotherapie sollte ein Taxan und ein Anthrazyklin enthalten.
Level of Evidence **1b**	Quellen: [760-765]
	Starker Konsens

4.120.	Evidenzbasierte Empfehlung
Empfehlungsgrad **0**	6 Zyklen TC (Docetaxel/Cyclophosphamid) können bei einem mittleren klinischen Risiko (≤ 3 befallene Lymphknoten) eine Alternative darstellen.
Level of Evidence **1b**	Quellen: [760-765]
	Konsens

4.121.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Eine adjuvante Standard-Chemotherapie soll 18–24 Wochen dauern.
Level of Evidence **1a**	Quellen: [751, 761, 766-774]
	Konsens

Neoadjuvante Therapie

4.122.	Konsensbasiertes Statement
EK	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

4.123.	Konsensbasierte Empfehlung
EK	Wenn die gleiche postoperative, adjuvante Chemotherapie indiziert ist, sollte eine neoadjuvante systemische Therapie bevorzugt werden.
	Starker Konsens

Neoadjuvante oder adjuvante Chemotherapie

4.124.	Evidenzbasierte Empfehlung
Empfehlungsgrad 0	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.
Level of Evidence 1a	Quellen: [558, 560, 793]
	Starker Konsens

4.125.	Evidenzbasiertes Statements
Level of Evidence 1a	Der Effekt (pathohistologische Remission) ist bei Hormonrezeptor-negativen Karzinomen am Größten.
	Quellen: [558, 560, 794, 795]
	Starker Konsens

4.126.	Konsensbasiertes Statement
EK	Eine Resektion in den neuen Tumorgrenzen ist möglich, wenn eine R0-Resektion erreicht werden kann.
	Starker Konsens

Primäre Hormontherapie bei postmenopausalen Patientinnen

4.127.	Konsensbasierte Empfehlung
EK	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

4.128.	Konsensbasierte Empfehlung
EK	Die neoadjuvante endokrine Therapie ist keine Standardtherapie, in speziellen Situationen (inoperabel, multimorbide Patientin) kann eine neoadjuvante endokrine Therapie erwogen werden.
	Starker Konsens

Neoadjuvante Chemotherapiekombination

4.129.	Konsensbasierte Empfehlung
EK	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

4.130.	Konsensbasiertes Statement
EK	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

Postneoadjuvante Behandlung

4.131.	Konsensbasierte Empfehlung
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

Antikörpertherapie

4.132.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Patientinnen mit HER2-überexprimierenden Tumoren mit einem Durchmesser ≥ 1 cm (immunhistochemisch Score 3+ und/oder ISH-positiv) sollen eine (neo-)adjuvante Behandlung mit Anthrazyklin gefolgt von einem Taxan in Kombination mit Trastuzumab erhalten. Trastuzumab soll über eine Gesamtdauer von einem Jahr verabreicht werden.
Level of Evidence 1b	Leitlinienadaptation: [29, 180] De-novo-Recherche: [809]
	Starker Konsens

4.133.	Evidenzbasierte Empfehlung
Empfehlungsgrad B	Die adjuvante Behandlung mit Trastuzumab sollte vorzugsweise simultan mit der Taxan-Phase der adjuvanten Chemotherapie begonnen werden.
Level of Evidence 2a	Quelle: [810]
	Starker Konsens

4.134.	Konsensbasierte Empfehlung
EK	Wenn die Indikation für eine Chemotherapie bei HER2+-Tumoren </= 5 mm vorliegt, sollte zusätzlich Trastuzumab gegeben werden. TCH (Docetaxel, Carboplatin, Trastuzumab) kann über 6 Zyklen alle 3 Wochen adjuvant ebenfalls empfohlen werden. Die Kardiotoxizität ist geringer als nach Anthrazyklinen.
	Konsens

Adjuvante Therapie zur Verbesserung des knochenmetastasenfreien und Gesamtüberlebens

4.143.	Evidenzbasiertes Statement
Level of Evidence 1	Eine adjuvante Bisphosphonattherapie verlängert das knochenmetastasenfreie Überleben und das Gesamtüberleben bei postmenopausalen Brustkrebspatientinnen sowie bei prämenopausalen Patientinnen unter Ovarsuppression (außerhalb des Zulassungsstatus).
	Quellen: [866, 867]
	Starker Konsens

4.144.	Evidenzbasiertes Statement
1b	Für prämenopausale Patientinnen ohne Ovarsuppression kann derzeit keine Empfehlung für den adjuvanten Einsatz von Bisphosphonaten oder Denosumab gegeben werden.
	Quellen: [857, 866, 867]
	Starker Konsens

NICE, 2018 [15].

National Institute for Health and Care Excellence (NICE)

Early and locally advanced breast cancer: diagnosis and management.

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.

Methodik

Grundlage der Leitlinie

- Leitlinien-Update; neue Empfehlungen gekennzeichnet
- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert. We have reviewed the evidence and made new recommendations on the diagnosis and treatment of people with early and locally advanced breast cancer. These recommendations are marked [2018].
- For full details of the evidence and the guideline committee's discussions, see the evidence reviews. Information about how the guideline was developed, including details of the committee: https://www.nice.org.uk/guidance/NG101/history

Recherche/Suchzeitraum:

- Unterschiedlich für verschiedene Leitlinienabschnitte (z.B. adjuvante Chemotherapie: September 2017)

LoE/ GoR:

- GRADE-Methodik

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.

Recommendations

Adjuvant endocrine therapy for invasive breast cancer

- Offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER-positive invasive breast cancer. [2009, amended 2018]
- Offer an aromatase inhibitor as the initial adjuvant endocrine therapy for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk at low risk of disease recurrence. Offer tamoxifen to women who are of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated. [2009, amended 2018]

Ovarian function suppression

- Consider ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer. [2018]
- Discuss the benefits and risks of ovarian function suppression in addition to endocrine therapy with premenopausal women with ER-positive invasive breast cancer. Explain to women that ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy. [2018]

Extended endocrine therapy

- Offer extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor ER-positive invasive breast cancer who are at medium or high risk recurrence and who have been taking tamoxifen for 2 to 5 years. [2018]
- Consider extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at low risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. [2018]
- Consider extending the duration of tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER-positive invasive breast cancer. [2018]
- Discuss the benefits and risks of extended endocrine therapy with women.

Endocrine therapy for ductal carcinoma in situ

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

- 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]

Adjuvant chemotherapy for invasive breast cancer

- For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline. [2018]
- Discuss with people the benefits and risks of adding a taxane to anthracycline-containing regimens. Topics to discuss include e.g.:
  - 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]
- 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

- 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]
- 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]
- Assess cardiac function before starting treatment with trastuzumab [2009]
- 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]
- 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]

Adjuvant bisphosphonate therapy

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

- Offer whole-breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins. [2018]
- 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]
- 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]
- When delivering partial breast radiotherapy, use external beam radiotherapy. [2018]
- 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]
- 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]

Radiotherapy after mastectomy

- Offer adjuvant postmastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins. [2018]
- Consider adjuvant postmastectomy radiotherapy for people with node-negative T3 or T4 invasive breast cancer. [2018]
- Do not offer radiotherapy following mastectomy to people with invasive breast cancer who are at low risk of local recurrence (for example, most people who have lymph node-negative breast cancer). [2018]

Neoadjuvant chemotherapy

- Offer neoadjuvant chemotherapy to people with ER-negative invasive breast cancer as an option to reduce tumour size. [2018]
- 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]
    - Recommendation from the NICE appraisal: Pertuzumab, in combination with trastuzumab and chemotherapy, is recommended, within its marketing authorisation, as an option for the neoadjuvant treatment of adults with human epidermal growth factor receptor 2 (HER2)-positive breast cancer; that is, in patients with HER2-positive, locally advanced, inflammatory or early-stage breast cancer at high risk of recurrence. It is recommended only if the company provides pertuzumab with the discount agreed in the patient access scheme. [16]
- 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

- For people with triple-negative invasive breast cancer, consider a neoadjuvant chemotherapy regimen that contains both a platinum [2018] and an anthracycline.
- Discuss the benefits and risks of adding a platinum to an anthracycline-containing neoadjuvant chemotherapy regimen. Topics to discuss include those in table 6, and particularly the risk of increased toxicity. [2018]

Neoadjuvant endocrine therapy

- 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]
- 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]
- Discuss with women the benefits and risks of neoadjuvant endocrine therapy compared with neoadjuvant chemotherapy. [2018]

Radiotherapy after neoadjuvant chemotherapy

- Offer local treatment with mastectomy (or, in exceptional cases, breast-conserving surgery) followed by radiotherapy to people with locally advanced or inflammatory breast cancer that has been treated with neoadjuvant chemotherapy. [2009]
- Offer postmastectomy radiotherapy after neoadjuvant chemotherapy if post-treatment histology shows node-positive (macrometastases) breast cancer or involved resection margins. [2018]
- Offer postmastectomy radiotherapy after neoadjuvant chemotherapy if pretreatment investigations show node-positive (macrometastases) breast cancer. [2018]
- Consider postmastectomy radiotherapy after neoadjuvant chemotherapy if post-treatment histology shows node-negative T3 breast cancer. [2018]

- Consider postmastectomy radiotherapy after neoadjuvant chemotherapy if pretreatment investigations show node-negative T3 breast cancer. [2018]

Burstein, H. J. et al., 2019 [1]

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.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- from 2012 to 2018

LoE/GoR

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.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (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.

Guide for Rating Strength of Evidence

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

Recommendations

<u>1a What adjuvant endocrine treatments should be offered to postmenopausal women with hormone receptor–positive breast cancer?</u>

- Women diagnosed with hormone receptor–positive breast cancer who are postmenopausal should be offered adjuvant endocrine therapy with one of the following initial options:
  - 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.
  - Women with node-positive breast cancer should be offered extended AI therapy for up to a total of 10 years of adjuvant endocrine treatment.

- Women who receive extended adjuvant endocrine therapy should receive no more than 10 years of total treatment.
- As prevention of secondary or contralateral breast cancers is a major benefit of extended AI therapy and overall survival is not, the risk of second breast cancers (or not) based on prior therapy should inform the decision to pursue extended treatment.
- 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.

<u>If tamoxifen is administered first, how long should it be continued before the switch to an AI?</u>

- Tamoxifen for an initial duration of 5 years, then a switch to an AI for up to 5 years, for a total duration of up to 10 years of adjuvant endocrine therapy. (Evidence Quality: High, Strength of recommendation: Strong); or
- Tamoxifen for a duration of 2-3 years and a switch to an AI for up to 5 years, for a total duration of up to 7-8 years of adjuvant endocrine therapy. (Evidence Quality: High, Strength of Recommendation: Strong)

<u>Are there specific patient populations that derive different degrees of benefit from an AI compared with tamoxifen?</u>

- A specific marker or clinical subset that predicts which adjuvant treatment strategy (tamoxifen alone, AI alone, or AI and tamoxifen based) is best has not been identified. Among men with breast cancer, tamoxifen remains the standard adjuvant endocrine treatment. The CYP2D6 genotype is not recommended to select adjuvant endocrine therapy. Caution with concurrent use of CYP2D6 inhibitors (such as bupropion, paroxetine, or fluoxetine) and tamoxifen is recommended because of drug-drug interactions.

<u>What are the toxicities and risks of adjuvant endocrine therapy?</u>

- Clinicians should consider adverse effect profiles, patient preferences, and pre-existing conditions when they discuss adjuvant endocrine strategies. Adverse effect profiles should be discussed with patients when available treatment options are presented. Clinicians may recommend that patients change treatments if adverse effects are intolerable or patients are persistently noncompliant with therapy.

<u>Are AIs effective adjuvant therapy for women who are premenopausal at the time of diagnosis?</u>

- Women diagnosed with hormone receptor–positive breast cancer who are pre/ perimenopausal should be offered adjuvant endocrine therapy as follows:
  - Tamoxifen for an initial duration of 5 years.
  - After 5 years, women should receive additional therapy based on menopausal status:
  - If women are pre/perimenopausal, or if menopausal status is unknown or cannot be determined, they should be offered continued tamoxifen for a total duration of 10 years. (Evidence Quality: High, Strength of Recommendation: Strong); or

- o If women have become definitively postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or should switch to up to 5 years of AI for a total duration of up to 10 years of adjuvant endocrine therapy. (Evidence Quality for tamoxifen: High, Evidence Quality for AI: High; Strength of Recommendation: Strong)

Can the third generation AIs be used interchangeably? / What is the appropriate sequence of adjuvant endocrine therapy?

- Women who are postmenopausal and are intolerant of either tamoxifen or an AI should be offered the alternative type of adjuvant endocrine therapy.
- If women have received an AI but discontinued treatment at , 5 years, they may be offered tamoxifen for a total of 5 years. (Type: Informal consensus, Evidence Quality: Low, Strength of Recommendation: Weak)
- If women have received tamoxifen for 2-3 years, they should be offered a switch to an AI for up to 5 years, for a total duration of up to 7-8 years of adjuvant endocrine therapy.
- Women who have received 5 years of tamoxifen as adjuvant endocrine therapy should be offered additional adjuvant endocrine treatment.
- If women are postmenopausal, they should be offered continued tamoxifen for a total duration of 10 years or should switch to up to 5 years of AI for a total duration of up to 10 years of adjuvant endocrine therapy. (Type: Evidence-Based, Evidence Quality: High, Strength of Recommendation: Strong)
- If women are pre/perimenopausal or menopausal status cannot be ascertained, they should be offered 5 additional years of tamoxifen for a total of 10 years of adjuvant endocrine therapy. (Type: Evidence-Based, Evidence Quality: High, Strength of Recommendation: Strong)

Should premenopausal women with ER-positive tumors receive adjuvant ovarian suppression in addition to standard adjuvant therapy and, if so, in which subsets of patients?

- The Panel recommends that higher-risk patients should receive ovarian suppression in addition to adjuvant endocrine therapy, whereas lower-risk patients should not.

Qualifying statement: The Panel notes that two prospective studies did not show overall clinical benefit for the addition of ovarian suppression to tamoxifen in premenopausal, ER-positive breast cancer. However, in a large subset of women with higher-risk cancers, nearly all of whom received chemotherapy but remained premenopausal, ovarian suppression added to tamoxifen reduced the risk of breast cancer recurrence. Because of the design of the clinical trials, there are few definitive criteria by which to define risk.

- Women with stage II or III breast cancers who would ordinarily be advised to receive adjuvant chemotherapy should receive ovarian suppression in addition to endocrine therapy.
- Women with stage I or II breast cancers at higher risk of recurrence, who might consider chemotherapy, may also be offered ovarian suppression in addition to endocrine therapy.
- Women with stage I breast cancers that do not warrant chemotherapy should receive endocrine therapy but not ovarian suppression.
- Women with node-negative cancers ≤ 1 cm (T1a, T1b) should receive endocrine therapy but not ovarian suppression.

Qualifying statements: The standard duration of ovarian suppression in the included trials was 5 years. With no comparative data available on alternative durations, the Panel supports ovarian suppression for 5 years.

To date, there is no adequate evidence to assess the benefit of adjuvant ovarian suppression in women at sufficient risk to warrant chemotherapy compared with 10 years of tamoxifen.

There is no current role for ovarian suppression as adjuvant therapy in ER-negative breast cancers.

There are substantial adverse effects to ovarian suppression. Clinicians and patients should consider the tradeoffs of adverse effects when they choose ovarian suppression.

The long-term effects of ovarian suppression on breast cancer risk and survival are not yet established.

If ovarian suppression is recommended, should ovarian suppression be administered in combination with tamoxifen or an AI?

- Ovarian suppression may be administered with either tamoxifen or an AI.

Qualifying statements: Tamoxifen and AI therapy differ in their adverse effect profiles, which may affect patient preferences. Clinicians should be alert to the possibility of incomplete ovarian suppression with GnRH agonist therapy and should evaluate patients in whom there is concern for residual ovarian function.

Denduluri N et al., 2018 [5].

American Society of Clinical Oncology (ASCO)

Diagnosis, staging and treatment of patients with breast cancer.

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.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- PubMed search for reports published from July 2015 to December of 2017

LoE/GoR

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.

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (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.

Guide for Rating Strength of Evidence

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

Recommendations

- Recommendations from 2016 ASCO Guideline Adaptation and from the ASCO 2018 Focused Guideline Update

Recommendation	Evidence Rating
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 *Qualifying Statements.* If clinicians decide to use capecitabine, then the Expert Panel preferentially supports the use of adjuvant capecitabine in patients with hormone receptor-negative, HER2-negative breast cancer. The capecitabine dosage used in the CREATE-X study (1,250 mg/m^2 twice daily) is associated with higher toxicity in patients ≥ 65 years old.	Type: evidence-based, benefits outweigh harms Evidence quality: intermediate Strength of recommendation: moderate
Clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy for patients with early-stage, HER2-positive breast cancer. *Qualifying Statements.* The Expert Panel preferentially supports pertuzumab in the node-positive, HER2-positive population in view of the clinically insignificant absolute benefit observed among node-negative patients. After a median follow-up of 3.8 years, pertuzumab was found to offer a modest disease-free survival benefit; the first planned interim analysis did not show an overall survival benefit. There are no data to guide the duration of pertuzumab treatment for patients who received neoadjuvant pertuzumab and achieved a pathologic complete response.	Type: evidence-based, benefits outweigh harms Evidence quality: high Strength of recommendation: moderate
Clinicians may use extended adjuvant therapy with neratinib for patients with early-stage, HER2-positive breast cancer. Neratinib causes substantial diarrhea, and diarrhea prophylaxis must be used. *Qualifying Statements.* The Expert Panel preferentially favors use of neratinib treatment for hormone receptor–positive and node-positive patients. At 5.2-years of follow-up, no overall survival benefit has been observed. Patients who began receiving neratinib within 1 year of trastuzumab completion appeared to derive the greatest benefit. There are no data on the added benefit of neratinib treatment for patients who also received pertuzumab in the neoadjuvant or adjuvant setting.	Type: evidence-based, benefits outweigh harms Evidence quality: high Strength of recommendation: moderate

- Recommendations Unchanged From 2016 Guideline Adaptation

In patients who can tolerate it, use of a regimen containing anthracycline-taxane is considered the optimal strategy for adjuvant chemotherapy, particularly for patients deemed to be at high risk.

For patients with high-risk disease who will not receive a taxane, an optimal-dose, anthracycline, three-drug regimen (cumulative dose of doxorubicin ≥ 240 mg/m^2 or epirubicin ≥ 600 mg/m^2 but not > 720 mg/m^2) that contains cyclophosphamide is recommended. The cumulative dose of doxorubicin in two-drug regimens should not exceed 240 mg/m^2.

The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen is not recommended for adjuvant chemotherapy.

In patients age ≥ 65 years, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of standard regimens such as doxorubicin-cyclophosphamide or cyclophosphamide-methotrexate-fluorouracil (with oral cyclophosphamide).

For patients in whom anthracycline-taxane is contraindicated, cyclophosphamide-methotrexate-fluorouracil (with oral cyclophosphamide) is an acceptable chemotherapy alternative to doxorubicin-cyclophosphamide. Of note, the ASCO Panel recommends classic cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide days 1 to 14 with IV methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (eg, TAILORx) on the basis of convenience and tolerability despite the absence of efficacy data from randomized controlled trials.

These adjuvant chemotherapy regimens can be used for patients with early breast cancer:

- Fluorouracil-epirubicin-cyclophosphamide × 3 → docetaxel × 3 (superior to fluorouracil-epirubicin-cyclophosphamide × 6)
- Doxorubicin-cyclophosphamide × 4 → docetaxel × 4 (superior to doxorubicin-cyclophosphamide × 4)
- Docetaxel-doxorubicin-cyclophosphamide × 6 (superior to fluorouracil-doxorubicin-cyclophosphamide × 6)
- Doxorubicin-cyclophosphamide × 4 → paclitaxel administered once per week
- Dose-dense doxorubicin-cyclophosphamide → paclitaxel administered once every 2 weeks
- Dose-dense epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles → paclitaxel 175 mg/m^2 every 2 weeks for 4 cycles

Docetaxel-cyclophosphamide × 4 is recommended as an alternative to doxorubicin-cyclophosphamide × 4 and offers improved disease-free survival and overall survival. Classic cyclophosphamide-methotrexate-fluorouracil with oral cyclophosphamide for six cycles is another option. As mentioned, the ASCO Panel recommends classic cyclophosphamide-methotrexate-φλuorouracil (oral cyclophosphamide days 1 to 14 with IV methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (eg, TAILORx) on the basis of its convenience and tolerability despite the absence of efficacy data from randomized controlled trials.

Only patients with HER2-positive breast cancer (overexpressed based on immunohistochemistry [3+] or amplified based on in situ hybridization [ratio ≥ 2.0 or average HER2 copy number ≥ 6.0]) should be offered adjuvant trastuzumab.

Trastuzumab plus chemotherapy is recommended for all patients with HER2-positive, node-positive breast cancer and for patients with HER2-positive, node-negative breast cancer (> 1 cm)

Trastuzumab therapy can be considered in small, node-negative tumors (≤ 1 cm).

Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.

The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is not recommended, because of the potential for increased cardiotoxicity.

Trastuzumab should be preferentially administered concurrently (not sequentially) with a nonanthracycline chemotherapy regimen.

Less cardiotoxicity is seen with docetaxel-carboplatin-trastuzumab than with doxorubicin-cyclophosphamide → docetaxel-trastuzumab, and docetaxel-carboplatin-trastuzumab is recommended for patients at higher risk for cardiotoxicity.

No phase III evidence exists for the addition of trastuzumab to some chemotherapy regimens, such as docetaxel-cyclophosphamide. However, those regimens might be in use and are reasonable options, particularly for mitigating cardiotoxicity in certain patients.

Patients should be offered 1 year total of adjuvant trastuzumab with regular assessments of cardiac function during that period.

Abbreviations: IV, intravenous; TAILORx, Trial Assigning Individualized Options for Treatment (Rx).

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 2 of 12, Feb 2020) am 04.02.2020

#	Suchfrage
1	[mh "Breast Neoplasms"]
2	(breast OR mamma*):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Feb 2015 to present

Systematic Reviews in Medline (PubMed) am 04.02.2020

#	Suchfrage
1	breast neoplasms/therapy[majr]
2	(breast[ti]) OR mamma*[ti]
3	(((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]) OR malignan*[ti]
4	(treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[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 management[tiab] OR drug*[tiab])
5	#2 AND #3 AND #4
6	#1 OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) 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]))))))
8	((#7) AND ("2015/02/01"[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 04.02.2020

#	**Suchfrage**
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	(((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]) OR malignan*[ti]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
7	(((#6) AND ("2015/02/01"[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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