Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2024-B-269-z Ribociclib

Stand: November 2024

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

Ribociclib
[Zur adjuvanten Behandlung des HR-positiven, HER2-negativen Mammakarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“. Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für das - Hormonrezeptor (HR)-negative Mammakarzinom - für das HER2/neu-positive Mammakarzinom - für das fortgeschrittene, metastasierte Mammakarzinom
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Strahlentherapie - Radiomenolyse - Ovarektomie

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:**
	- Abemaciclib (in Kombination mit einer endokrinen Therapie): Beschluss vom 20. Oktober 2022
	- Olaparib: Beschluss vom 16.02.2023
	
	Richtlinien
	- Arzneimittel Richtlinie, Anlage VI (Off-Label-Use); in Kraft getreten am 17.07.2024
	  - Teil A - Arzneimittel, die unter Beachtung der dazu gegebenen Hinweise in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind; XXXVII. Bisphosphonate bei Patientinnen mit Hormonrezeptor (HR)-positivem, postmenopausalem Mammakarzinom: Adjuvante Bisphosphonat-Therapie bei Patientinnen mit Hormonrezeptor (HR)-positivem, postmenopausalem Mammakarzinom
	  - Teil B - Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht Verordnungsfähig sind: IV. Gemcitabin in der Monotherapie beim Mammakarzinom der Frau
	- Richtlinie zur Regelung von Anforderungen an strukturierte Behandlungsprogramme nach § 137f Abs. 2 SGB V (DMP-Anforderungen-Richtlinie), Anlage 3 Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen für Patientinnen mit Brustkrebs; in Kraft getreten am 01.07.2024

	- Richtlinie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung), § 4 ausgeschlossene Methoden: Protonentherapie beim Mammakarzinom; in Kraft getreten am 21.06.2024 - Richtlinie Methoden vertragsärztliche Versorgung: Biomarkerbasierte Tests zur Entscheidung für oder gegen eine adjuvante systemische Chemotherapie beim primären Mammakarzinom; in Kraft getreten am 20.01.2021
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:	
Ribociclib L01EF02 Kisqali	Anwendungsgebiet laut Zulassung: Kisqali wird in Kombination mit einem Aromatasehemmer als adjuvante Behandlung bei Patientinnen und Patienten mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen frühen Mammakarzinom mit hohem Rezidivrisiko angewendet (siehe Abschnitt 5.1 für die Kriterien zur Therapieeignung). Bei prä- oder perimenopausalen Frauen und bei Männern sollte der Aromatasehemmer mit einem Luteinisierendes-Hormon- Release Hormon (LHRH = Luteinising Hormone- Releasing Hormone)-Agonisten kombiniert werden.
Antiestrogene	
Tamoxifen L02BA01 generisch	- Adjuvante Therapie nach Primärbehandlung des Mammakarzinoms
Aromataseinhibitoren	
Anastrozol L02BG03 generisch	- Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen. - Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen - Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen, die bereits 2 bis 3 Jahre adjuvant Tamoxifen erhalten haben.
Exemestan L02BG06 generisch	- Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen. - Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen - Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen, die bereits 2 bis 3 Jahre adjuvant Tamoxifen erhalten haben.
Letrozol L02BG04 generisch	- Adjuvante Therapie postmenopausaler Frauen mit hormonrezeptor-positivem primärem Mammakarzinom. - Erweiterte adjuvante Therapie des hormonabhängigen primären Mammakarzinoms bei postmenopausalen Frauen nach vorheriger adjuvanter Standardtherapie mit Tamoxifen über 5 Jahre.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	- First-Line-Therapie des hormonabhängigen fortgeschrittenen Stadiums nach Rezidiv oder Progression der Erkrankung bei Frauen, die sich physiologisch oder nach einem künstlichen Eingriff in der Postmenopause befinden und die zuvor mit Antiöstrogenen behandelt wurden. - Neoadjuvante Behandlung postmenopausaler Frauen mit hormonrezeptor-positivem, HER-2-negativem Mammakarzinom, bei denen eine Chemotherapie nicht in Betracht kommt und ein sofortiger chirurgischer Eingriff nicht indiziert ist. Bei Patientinnen mit hormonrezeptor-negativem Mammakarzinom ist die Wirksamkeit nicht belegt.
Gonadotropin-Releasing-Hormon-Analoga	
Leuprorelin L02AE02 z.B. Enantone-Gyn	- Mammakarzinom prä- und perimenopausaler Frauen, sofern eine endokrine Behandlung angezeigt ist.
Goserelin L02AE03 z.B. Zoladex-Gyn	- Behandlung von Patientinnen mit Mammakarzinom (prä- und perimenopausale Frauen), bei denen eine endokrine Behandlung angezeigt ist.
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 generisch	Brustkrebs Docetaxel ist in Kombination mit Doxorubicin und Cyclophosphamid angezeigt für die adjuvante Therapie von Patientinnen mit: - operablem, nodal positivem Brustkrebs, - operablem, nodal negativem Brustkrebs. Bei Patientinnen mit operablem, nodal negativem Brustkrebs sollte die adjuvante Therapie auf solche Patientinnen beschränkt werden, die für eine Chemotherapie gemäß den international festgelegten Kriterien zur Primärtherapie von Brustkrebs in frühen Stadien infrage kommen.
Doxorubicin L01DB01 generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: - Mammakarzinom. Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Epirubicin L01DB03	Epirubicin wird zur Behandlung verschiedener Neoplasien eingesetzt, einschließlich: - Mammakarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	
Methotrexat L01BA01 generisch	Mammakarzinome: - in Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium.
Paclitaxel L01CD01 generisch	<u>Mammakarzinom</u> Im Rahmen einer adjuvanten Therapie ist Paclitaxel zur Behandlung von Patientinnen mit Lymphknoten-positivem Mammakarzinom nach vorangegangener Therapie mit Anthracyclinen und Cyclophosphamid (AC) angezeigt. Die adjuvante Behandlung mit Paclitaxel kann als Alternative zu einer verlängerten AC-Therapie betrachtet werden.
Vincristin L01CA02 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.
CDK4/6-Inhibitoren	
Abemaciclib L01EF03 Verzenios	<u>Brustkrebs im frühen Stadium</u> Verzenios ist in Kombination mit einer endokrinen Therapie angezeigt für die adjuvante Behandlung von erwachsenen Patientinnen und Patienten mit Hormonrezeptor (HR)-positivem, humanem epidermalem Wachstumsfaktor-Rezeptor-2 (HER2)-negativem, nodal-positivem Brustkrebs im frühen Stadium mit einem hohen Rezidivrisiko (siehe Abschnitt 5.1). Bei prä- oder perimenopausalen Frauen sollte die endokrine Aromatasehemmer-Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone Releasing Hormone) kombiniert werden.
Olaparib L01XK01 Lynparza	<u>Mammakarzinom</u> Lynparza wird angewendet als: Monotherapie oder in Kombination mit einer endokrinen Therapie für die adjuvante Behandlung von erwachsenen Patienten mit Keimbahn-BRCA1/2-Mutationen, die ein HER2-negatives Mammakarzinom im Frühstadium mit hohem Rezidivrisiko haben und zuvor mit neo-adjuvanter oder adjuvanter Chemotherapie behandelt wurden (siehe Abschnitte 4.2 und 5.1).

Quellen: AMIce-Datenbank, Fachinformationen

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABC	Advanced breast cancer
AE	Adverse event
AI	Aromatase-Inhibitor
ANA	Anastrozol
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDK	Cyclin-dependent kinase
CTX	Chemotherapy
dRFS	Distant relapse-free survival
EBC	Early breasr cancer
ECRI	ECRI Guidelines Trust
ER	Estrogen receptor
ESBC	Early-stage breast cancer
ET	Endocrine therapy
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GnRH	Gonadotropin-releasing hormone
GoR	Grade of Recommendations
HER 2	Human epidermal growth factor 2
HR+	Hormone Receptor positive
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LK	Lymphknoten
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
pCR	Pathologisch komplette Remission
PFS	Progression-free survival
PR	Progesterone receptor
RCT	Randomized controlled trials
RR	Relatives Risiko

SAE	Serious adverse events
SIGN	Scottish Intercollegiate Guidelines Network
TAM	Tamoxifen
TC	docetaxel and cyclophosphamide
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Zur adjuvanten Behandlung von Patientinnen und Patienten mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen Mammakarzinom im Frühstadium mit hohem Rezidivrisiko.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Mammakarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*Suchmaschine*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 13.03.2024 durchgeführt, die folgenden am 30.10.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 5747 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 13 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine CR identifiziert werden.

3.2 Systematische Reviews

Keskinkilic M et al., 2024 [8].

The efficacy and safety of CDK4/6 inhibitors combined with endocrine therapy versus endocrine therapy alone in the adjuvant treatment of patients with high-risk invasive HR+/HER2-early breast cancer: A comprehensive updated meta-analysis of randomized clinical trials

Fragestellung

This paper aimed to evaluate the effectiveness of incorporating CDK 4/6 inhibitors (CDK4/6i) into ET for the adjuvant treatment of HR + HER2-resected early-stage breast cancer (ESBC) patients, employing metaanalysis.

Methodik

Population:

- patients with high-risk invasive HR-positive and HER2-negative early-stage breast cancer.

Intervention:

- Endocrine therapy (ET) + CDK4/6i

Komparator:

- ET alone

Endpunkte:

The primary endpoint of interest for the study was identified as iDFS. This study also assessed secondary outcomes, which included distant relapse-free survival (dRFS), overall survival (OS) and any adverse events (aAEs) (all grades and grade 3-4-5).

Recherche/Suchzeitraum:

- The researchers executed an extensive search for published papers by utilizing databases involving PubMed/Medline, Web of Science, and Scopus. The search period was developed until March 23, 2024,

Qualitätsbewertung der Studien:

In the quality evaluation of all clinical trials included in our study, we considered various important factors. These factors include allocation concealment, random sequence generation, blinding, missing information, reporting bias, and other biases. We conducted the evaluation of the clinical trials according to the guidelines provided in the Cochrane Handbook of Systematic Reviews of terventions.

Ergebnisse

Hinweise: Lediglich Abemaciclib ist zugelassen im AWG (monarchE trial).

Anzahl eingeschlossener Studien:

- 4 trials
- These four clinical trials were published between 2020 and 2024

Charakteristika der Population/Studien:

- These trials involved a combined sample size of 17,749 patients diagnosed with breast cancer. Among these patients, 8872 were assigned to the endocrine therapy +CDK4/6 inhibitor group, while 8877 were assigned to the endocrine therapy alone group.

Table 1
Baseline characteristics of the clinical trials incorporated into the meta-analysis.

First author/ study name	Study design	Year	Sample size (n) (ET + CDK4/6i/ ET alone)	CDK4/6 inhibitors	Prior chemotherapy (Neoadjuvant) (n %) (ET + CDK4/6i/ET alone)	Prior chemotherapy (Adjuvant) (n %) (ET + CDK4/6i/ET alone)	Follow-up time (median)	Primary and secondary endpoint(s)
Johnston et al./ monarchE trial	Open-label, randomized, phase III	2020–2022	2808/2829	Abemaciclib, 150 mg twice daily	1039 (37.0)/1048 (37.0)	1642 (58.5)/1647 (58.2)	15,5 months	iDFS, DRFS, aAEs, OS
Mayer et al., Gnant et al./ PALLAS trial	Open-label, randomized, phase III	2021	2884/2877	Palbociclib, 125 mg orally once daily on days 1–21 of a 28-day cycle	965 (33.5)/974 (33.9)	1448 (50.2)/1427 (49.6)	31 months	iDFS, DRFS, LCFS, iBCFS, OS aAEs
Loibl et al./ PENELOPE-B trial	Double-blind, placebo-controlled, phase III	2021	631/619	Palbociclib, 125 mg once daily vs placebo	N/A	N/A	42 months	iDFS, DRFS, LRRFI, OS, aAEs
Slamon et al./ NATALEE trial	Open-label, randomized, phase III	2024	2549/2552	Ribociclib, dose of 400 mg per day for 3 weeks, followed by week off, for 3 years	1085 (42.6)/1095 (42.9)	1223 (48.0)/1220 (47.8)	34 months	iDFS, DRFS, DDFS, OS, aAEs

ET: endocrine therapy, CDK4/6i: CDK4/6 inhibitor, iDFS: invasive disease-free survival, DRFS: distant relapse–free survival, LCFS: locoregional cancer-free survival, iBCFS: invasive breast cancer–free survival, DDFS: distant disease–free survival, OS: overall survival, LRRFI: locoregional relapse-free interval, N/A: not available, aAEs: any adverse events, SD: standard deviation, IQR: interquartile range.

- **Table 2**
Baseline characteristics of the patients that were included in the clinical trials.

First author/ study name	Age, (median (range or min-max)) (ET + CDK4/ 6i/ET alone)	Sex, female, (n %) (ET + CDK4/6i/ET alone)	Menopausal status (premenopausal; postmenopausal) (n %) (ET + CDK4/6i/ET alone)	Histopathological grade at diagnosis (grade 1; grade 2; grade 3) (n %) (ET + CDK4/ 6i/ET alone)	Prior radiotherapy (Neoadjuvant; Adjuvant) (n %) (ET + CDK4/6i/ET alone)	Initial adjuvant endocrine therapy (Aromatase inhibitors; tamoxifen; toremifene or other(s)) (n %) (ET + CDK4/6i/ET alone)
Johnston et al./ monarchE	51 (23–89)/51 (22–86)	2787 (99.3)/ 2814 (99.5)	1221 (43.5)/1232 (43.5); 1587 (56.5)/1597 (56.5)	209 (7.4)/215 (7.6); 1373 (48.9)/1395 (49.3); 1090 (38.8)/1066 (37.7)	71 (2.5)/82 (2.9); 2620 (93.3)/2628 (92.9)	1928 (69.1)/1891 (67.5); 857 (30.7)/898 (32.1); 6 (0.2)/11 (0.4)
Mayer et al., Gnant et al./ PALLAS trial	52.0 (25–90)/52.0 (22–85)	2867 (99.4)/ 2858 (99.3)	1303 (45.2)/1323 (46.0); 1562 (54.2)/1534 (53.3)	300 (10.4)/313 (10.9); 1622 (56.3)/1658 (57.6); 836 (29.0)/767 (26.7)	N/A; 2558 (88.7)/2560 (89.0)	1955 (67.8)/1917 (66.6); 922 (32.0)/950 (33.0); N/A
Loibl et al./ PENELOPE-B trial	49.0 (22.0–76.0)/ 48.0 (19.0–79.0)	631 (100)/ 619 (100)	300 (47.5)/316 (51.1); 331 (52.5)/303 (48.9)	31 (5.0)/36 (5.9); 355 (57.0)/330 (54.0); 237 (38.0)/245 (40.1)	N/A	317 (50.2)/311 (50.2); 314 (49.8)/308 (49.8); 108 (17.1)/113 (18.3)
Slamon et al./ NATALEE trial	52.0 (24.0–90.0)/ 52.0 (24.0–89.0)	2538 (96)/ 2453 (96)	1115 (43.7)/1123(44.0); 1423 (55.8)/1420 (55.6)	218 (8.6)/240 (9.4); 1458 (57.2)/1451 (56.9); 521 (20.4)/549 (21.5)	1085 (42.6)/1095 (42.9); 1223 (48.0)/ 1220 (47.8)	1601 (62.8)/1592 (62.4); N/A; 4 (0.2)/13 (0.5)

ET: endocrine therapy, CDK4/6i: CDK4/6 inhibitor, IDFS: invasive disease-free survival, DRFS: distant relapse–free survival, N/A: not available, SAE: serious adverse events, SD: standard deviation, IQR = interquartile range.

Qualität der Studien:

According to the Cochrane risk of bias tool, in general, the clinical trials included in the meta-analysis were observed to be of high quality. Three of the included studies, PALLAS, monarchE, and NATALEE were deemed to have the risk of bias in some concerns. This was primarily because these studies had an open-label design, which means that the participants and investigators were aware of the treatment assignment. This lack of blinding could potentially influence the outcome assessment and introduce bias into the results. However, without further information or clarification, it is uncertain how much this potential bias may have affected the study out-comes. The other trial, PENELOPE-B, was evaluated and determined to have a low risk of bias.

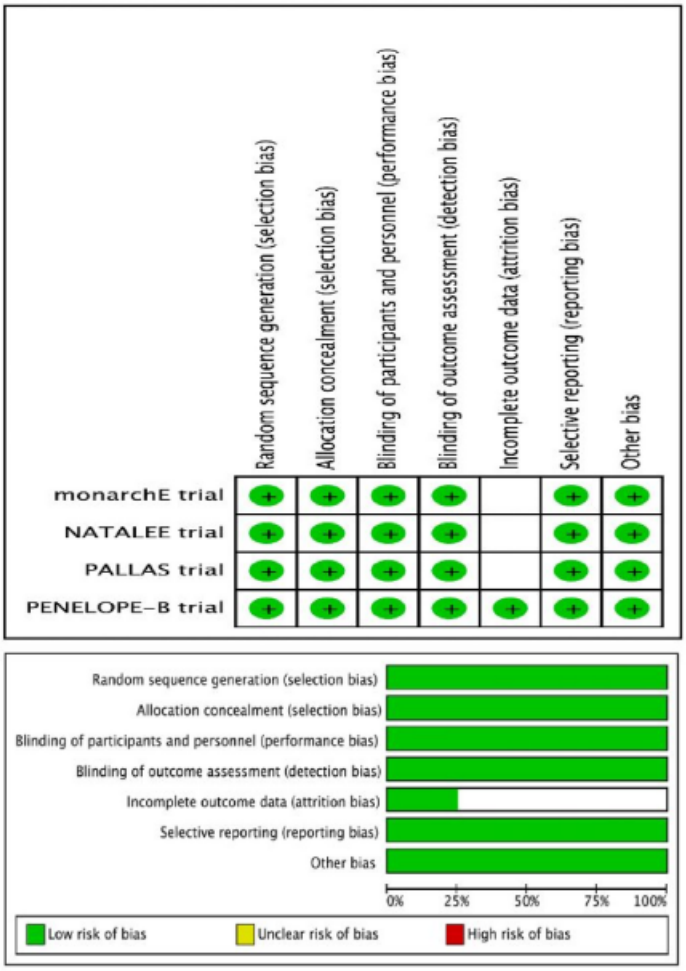
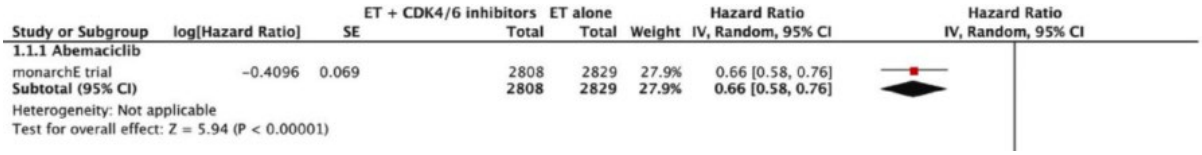


Fig. 2. The summary and methodological quality assessment of the included clinical trial.

Studienergebnisse:

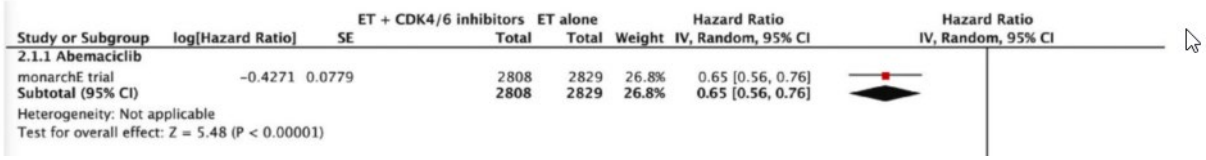
Hinweise: Lediglich Abemaciclib ist zugelassen im AWG, weshalb im Folgenden lediglich diese Ergebnisse dargestellt werden.

iDSF:



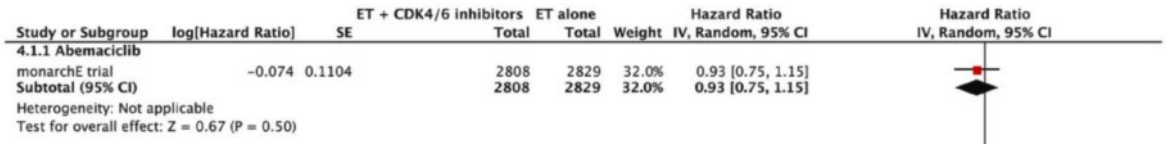
The forest plot of the impact of CDK4/6 inhibitors with endocrine therapy compared to endocrine therapy alone on invasive disease-free survival. CI = confidence interval.

DRFS:

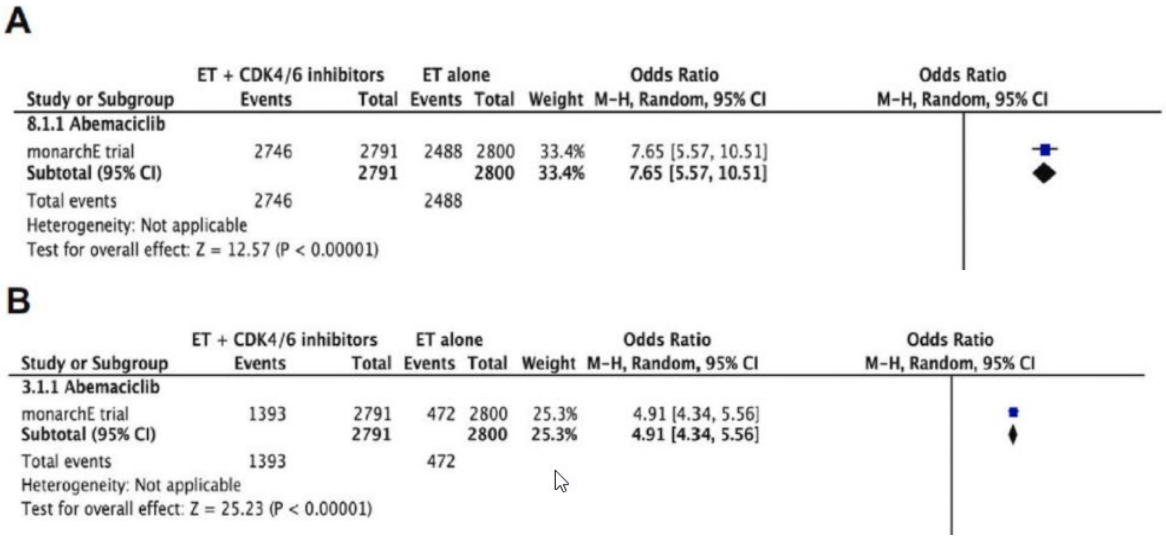


The forest plot of the impact of CDK4/6 inhibitors with endocrine therapy compared to endocrine therapy alone on distant relapse-free survival. CI = confidence interval.

OS:



The forest plot of the impact of CDK4/6 inhibitors with endocrine therapy compared to endocrine therapy alone on overall survival. CI = confidence interval.



The forest plot of the impact of CDK4/6 inhibitors with endocrine therapy compared to endocrine therapy alone on adverse event for all grade (A) and grade 3-4-5 (B). CI = confidence interval.

Anmerkung/Fazit der Autoren

In conclusion, current findings revealed that the application of CDK 4/6 inhibitors in combination with ET in the adjuvant treatment of HR + HER2-resected early stage breast cancer patients provided a significant improvement in iDFS, while specifically abemaciclib and ribociclib also provided a significant increase in dRFS. These results are consistent with previous meta-analysis results and strongly support the role of CDK 4/6 inhibitors in adjuvant therapy. In the future, the results of studies investigating molecular profile-based approaches as well as clinicopathological factors will better illuminate our path in this field.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Zhang Z. et al. 2024 [13]
- Moraes et al. 2024 [10]
- Ergun et al. 2023 [3]
- Zhang M. et al. 2023 [12]
- Gao et al. 2012 [5]

Giffoni de Mello Morais Mata, D et al., 2024 [6].

The Omission of Anthracycline Chemotherapy in Women with Early HER2-Negative Breast Cancer—A Systematic Review and Meta-Analysis

Fragestellung

We reviewed the existing literature comparing the combination of docetaxel and cyclophosphamide (TC) and anthracycline-taxane-containing chemotherapy regimens in patients with stages I–III HER2-negative breast cancer to investigate and compare their impact on DFS, OS and cardiotoxicity.

Methodik

Population:

- adult patients with histologically confirmed HER2-negative, stages I–III breast cancer.

Intervention:

- combination of docetaxel and cyclophosphamide (TC)

Komparator:

- anthracycline-taxane-based chemotherapy

Endpunkte:

- DFS is defined as the time from randomization to the development of breast cancer recurrence or death
- OS was defined as the time from randomization until death from any cause
- Cardiotoxicity was defined as participants who developed signs and symptoms of heart failure (HF) or left ventricular systolic dysfunction (LVSD) in the context of recent or remote chemotherapy administration. Only grade 3 or above cardiotoxic adverse events were extracted, as measured by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 standardized grading system

Recherche/Suchzeitraum:

- We searched Ovid Medline (1946–2024), EMBASE (1974–2024) and Evidence-Based Medicine Reviews: Cochrane Central Register of Controlled Trials (1991–2024) and ClinicalTrials.gov for RCTs.
- We searched trial websites and databases, such as ClinicalTrials.gov, the World Health Organization (WHO) International Clinical Trials Registry Platform, as well as International Standard Randomised Controlled Trial Number (ISRCTN) for additional publication information.
- The literature search included trials published until 11 March 2024

Qualitätsbewertung der Studien:

- Cochrane RoB 2.0 tool for RCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs were included in the qualitative analysis and 7 RCTs in the quantitative (meta) analysis

Charakteristika der Population/Studien:

Table 1. Summary of key clinical trials, systematic reviews and meta-analyses that investigated the role of TC versus anthracycline-taxane in HER2-negative breast cancer.

Randomized Controlled Trial	Eligibility Criteria	Study Population	Median Follow up	DFS (95% CI)	OS (95% CI)
Geyer Jr. et al., 2024 [55]/**J. Blum et al., 2017** [46] Analysis of 3 RCTs * (n = 4242) · TC (6 cycles): docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2, q3 weeks · TaxAC: doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, q2–3 weeks, for four cycles, followed by paclitaxel (80 mg/m^2 weekly (×12) or 175 mg/m^2 q2 weeks for four cycles	• If pN+: pT_{any} • If pN_0: > pT_2 or TNBC. • If pT_{1c} pN_0 and ER+: grade 3 or high-risk score on Oncotype DX	ER+: 69% ER/PR−: 31% LN 0: 41% $LN+_{1–3}$: 44% $LN+_{≥4}$: 16%	3.3 years and 6.9 years (updated analysis)	5-year DFS TC: 85.1% TaxAC: 86.7% HR 1.14 (0.99–1.32), p = 0.08	5-year OS TC: 234 deaths TaxAC: 221 deaths HR 1.05 (0.87–1.26), p = 0.64)
De Gregorio et al., 2022 [54] (n = 3643) · TC (6 cycles): docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2 q3 weeks · FEC-D: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2, q3 weeks for three cycles, followed by docetaxel 100 mg/m^2 q3 weeks for three cycles	Stages I–III high risk (pN+) or if pN0: ≥ pT_2, grade 3, age ≤ 35 years, ER– PLAN B trial: All patients were offered OncotypeDX	ER +: 76.4% Luminal A: 53.4% Luminal B: 23% TNBC: 23.6%	5 years	5-year DFS rate: TC: 89.3% FEC-D: 90% TC vs. FEC-D: HR 1.05 (0.89–1.23), p= 0.565	5-year OS rate: TC: 94.9% FEC-D: 95% TC vs. FEC-D: HR 1.0 (0.79–1.25), p= 0.997
Yu et al., 2021 [33] (n = 1571) · TC (6 cycles): docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2 q3 weeks · FEC-D: fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2, q3 weeks for three cycles, followed by docetaxel 100 mg/m^2 every 3 weeks, for three cycles ·EC-P: epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2, q3 weeks for 3 cycles, followed by weekly (×12) paclitaxel 80 mg/m^2	$pT_{1–4}$, pN+ or $pT_{2–3}$, pN_0 but high-risk (grade 2–3, age ≤ 35 years, or ER–)	Luminal A: TC: 22.9% CEF-T: 19.1% EC-P: 22.3% Luminal B: TC: 69.5% CEF-T: 73.4% EC-P: 69.9%	5.5 years	5-year DFS rate: TC: 85.0% CEF-T: 85.1% EC-P: 85.9 TC vs. EC-P: HR 1.05 (0.79–1.39), p = 0.771	5-year OS rate: TC: 96.5% CEF-T: 94.9% EC-P: 95.4% TC vs. EC-P: HR 0.96 (0.58–1.59), p = 0.893
H. Ishiguro et al., 2020 [53] (n = 195) · TC (6 cycles): docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2 · FEC-TC: 5-fluorouracil (500 mg/m^2), epirubicin (100 mg/m^2), cyclophosphamide (500 mg/m^2), q3 weeks for three cycles, followed by TC q3 weeks, for three cycles	Stages I–III (except pT_{1a} or pT_{1b}	ER+: 100% LN−: 49.2% LN+: 50.8%	5.8 years	No differences in IDFS (p = 0.854) between the treatment groups	No differences in OS (p = 0.911) between the treatment groups

Randomized Controlled Trial	Eligibility Criteria	Study Population	Median Follow up	DFS (95% CI)	OS (95% CI)
U. Nitz et al., 2019 [52] (n = 3198) · TC (6 cycles): docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2, q3 weeks · EC-T: Epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2 q3 weeks, for four cycles, followed by docetaxel 100 mg/m^2, q3 weeks for four cycles	ER+: $pT_{1–4c}$, any pN+ or • If pN_0: grade II-III, TNBC or age < 35	ER+: 81.8% ER−: 18.2% pN_0: 58.8% pN_1: 34% $pN_{2–3}$: 7.2%	5 years	5-year DFS TC: 89.6% EC-T: 89.8% HR 1.00 (0.77–1.3)	5-year OS TC: 94.7% EC-T: 94.5% HR 0.94 (0.65–1.34)
D. Mavroudis et al., 2016 [51] (n = 650) · FEC-D: 5-fluorouracil 500 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 500 mg/m^2, q2 weeks for four cycles, followed by docetaxel 75 mg/m^2, q2 weeks for four cycles · TC (6 cycles): docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2, q3 weeks	$pT_{1–4}$, any pN+	ER+: 88% ER−: 11.4% Unknown: 0.6% $LN+_{1–3}$: 63.7% $LN+_{≥4}$: 33.7%	3.8 years	Median not reached HR 1.15 (0.71–1.84), p = 0.568 3-year DFS rate: FEC-D: 89.5% TC: 91.1%	Median not reached HR 1.16 (0.49–2.72), p = 0.738

RCT: randomized controlled trial; ER: endocrine receptor; TNBC: triple-negative breast cancer; LN: lymph node; * USOR 06090; NSABP B-46-I/07132; NSABP B-49.

Qualität der Studien:

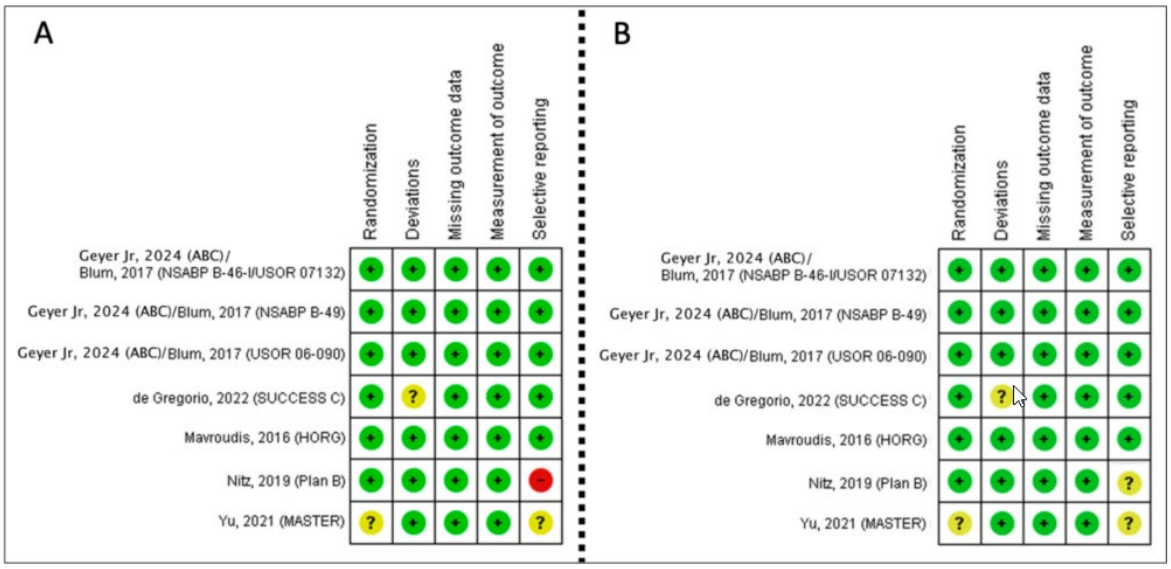


Figure 2. (**A**) Risk of bias summary by domain for disease-free survival. (**B**) Risk of bias summary by domain for overall survival [33,46,51,52,54,55] (color should be used in print version of these figures).

- Funnel plots were not generated to assess for reporting bias as there were fewer than
- 10 studies.

Studienergebnisse:

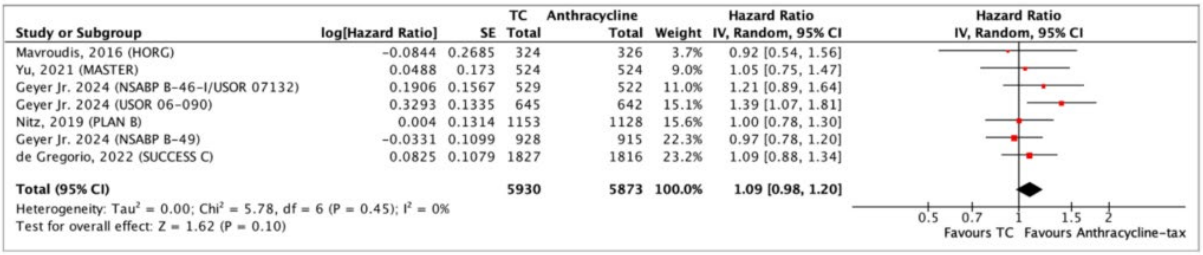
Summary of findings. GRADE Evidence Profile:

Table A1. Summary of findings. GRADE Evidence Profile.

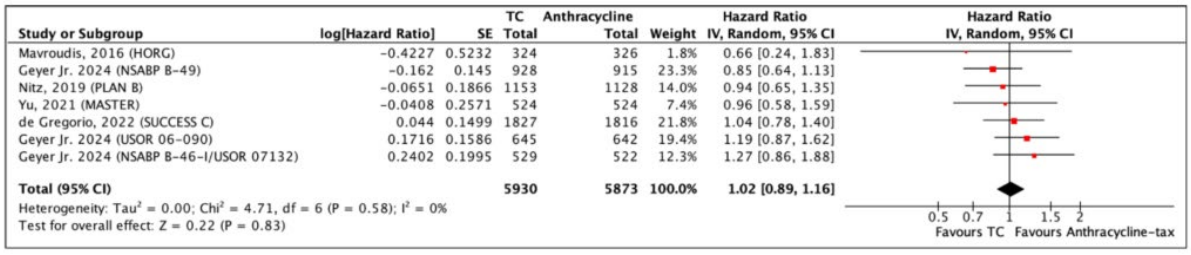
№ of Studies	Study Design	Certainty Assessment: Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	№ of Patients: TC	Anthracycline-Taxane	Effect: Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Disease-free survival (DFS) (follow-up: median 60 months)												
7	Randomized trials	Not serious	Not serious	Not serious	Serious [a]	None	785/5930 (13.2%)	725/5873 (12.3%)	HR 1.09 (0.98 to 1.20)	10 more per 1000 (from 2 fewer to 23 more)	⊕⊕⊕○ Moderate	CRITICAL
Overall survival (OS) (follow-up: median 60 months)												
7	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	411/5930 (6.9%)	400/5873 (6.8%)	HR 1.02 (0.89 to 1.16)	1 more per 1000 (from 7 fewer to 10 more)	⊕⊕⊕⊕ High	CRITICAL
Cardiotoxicity												
5	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	3/4115 (0.1%)	10/4601 (0.2%)	RR 0.54 (0.16 to 1.76)	1 fewer per 1000 (from 2 fewer to 2 more)	⊕⊕⊕⊕ High	CRITICAL

CI: confidence interval; HR: hazard ratio; Explanation: [a]: The 95% CI crosses decision-making thresholds by including the possibility of no meaningful benefit and a meaningful benefit in DFS.

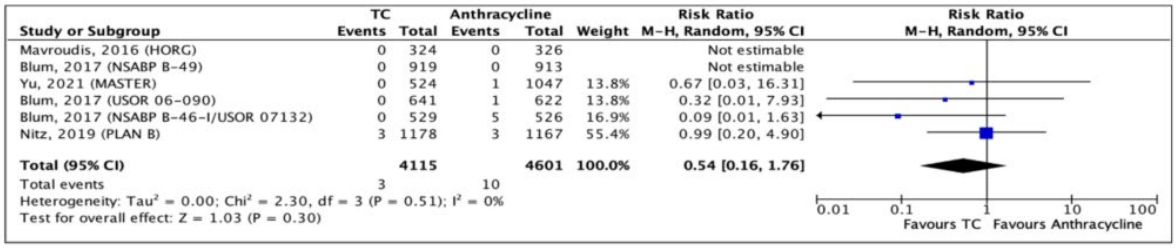
DFS:



OS:



Cardiotxicity:



Subgruppen:

DFS

ER Status

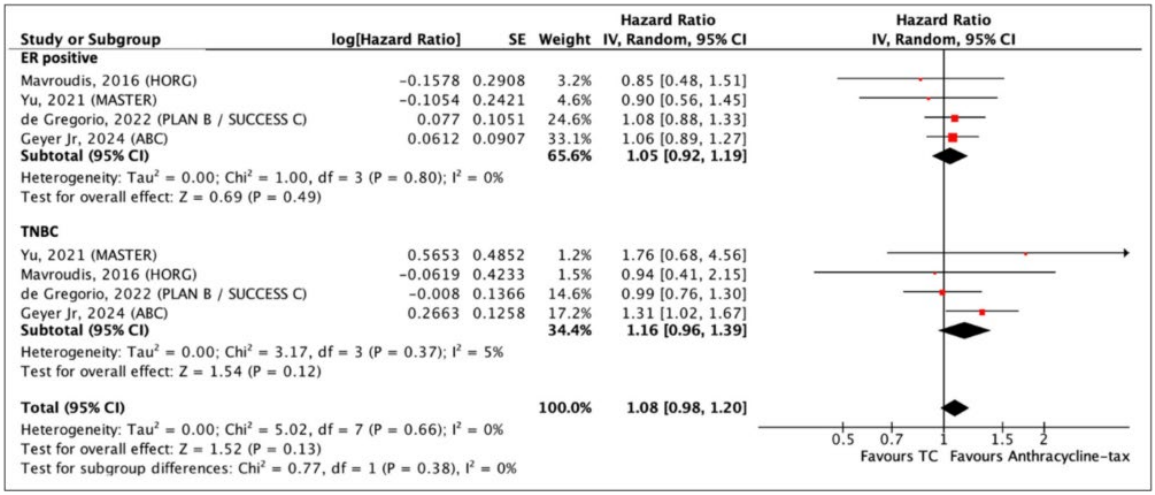


Figure 6. Forest plot of DFS comparing TC and anthracycline-taxane chemotherapy in a subgroup analysis of ER status [33,46,51,54].

Lymph-Node status

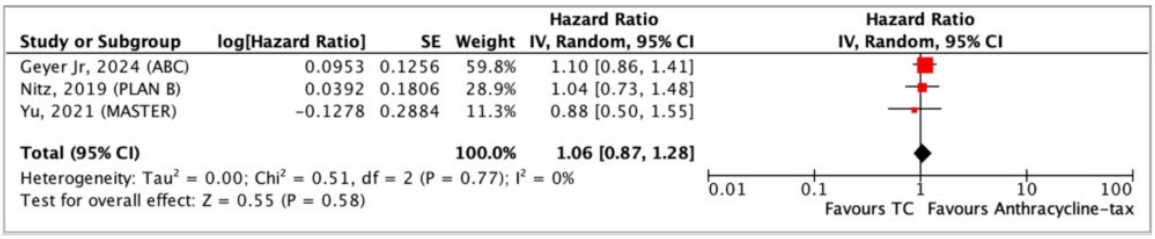


Figure A4. Forest plot of DFS comparing TC and anthracycline-taxane chemotherapy in a subgroup analysis of lymph node-negative [33,52,55].

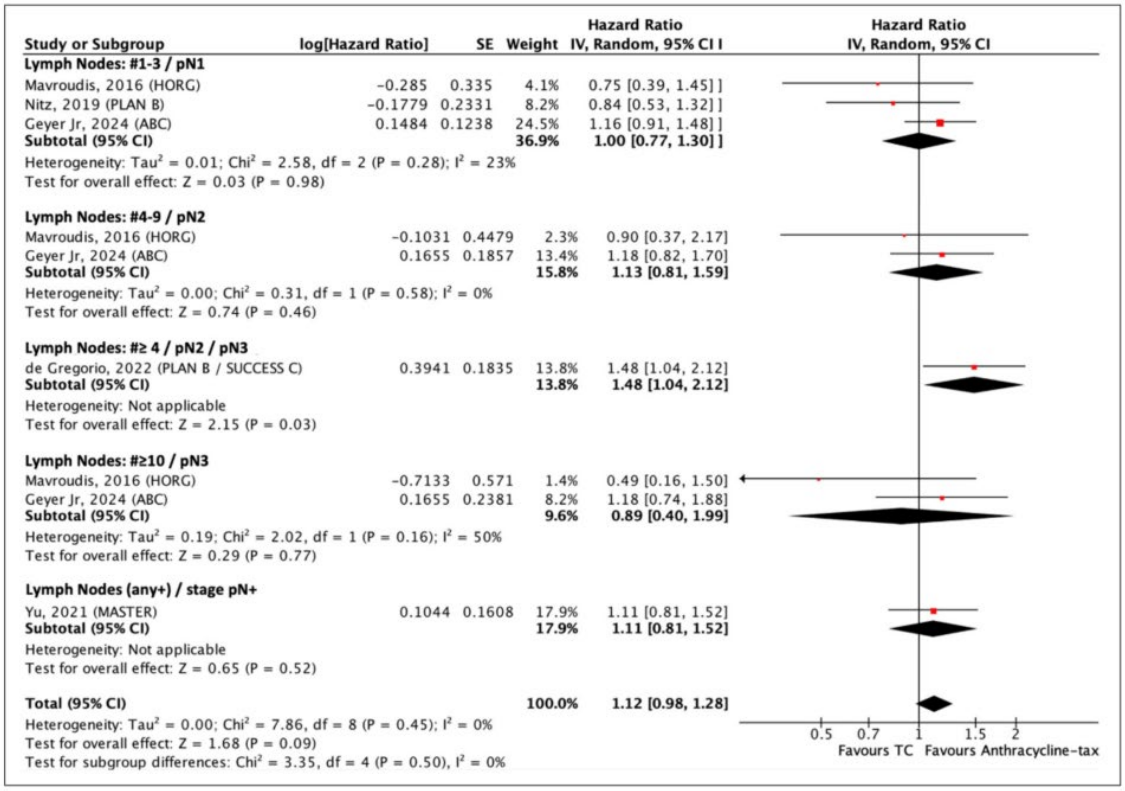


Figure 7. Forest plot of DFS comparing TC and anthracycline-taxane chemotherapy in a subgroup analysis of lymph node-positive [33,51,52,54,55].

OS

Lymph-Node status

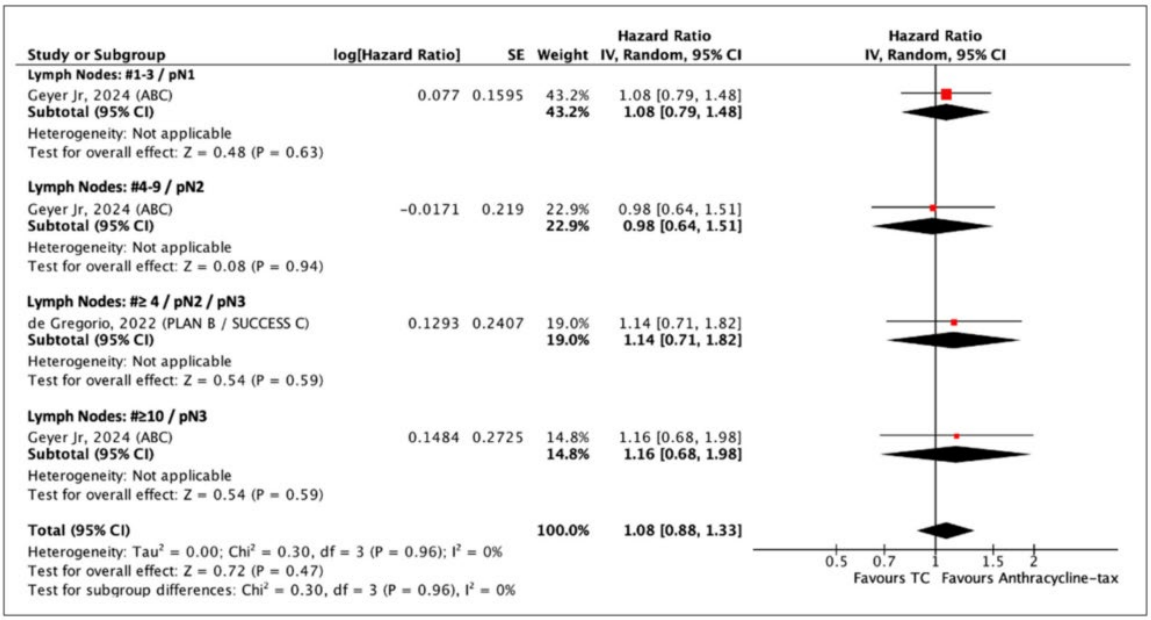


Figure A5. Forest plot of OS comparing TC and anthracycline-taxane chemotherapy in a subgroup analysis of lymph node-positive [54,55].

Anmerkung/Fazit der Autoren

This review indicates that TC is a reasonable alternative to anthracycline-taxane chemotherapy for stages I–III, high-risk, HER2-negative breast cancer, with no meaningful difference in DFS or OS. However, in women with four or more positive lymph nodes (pN2/pN3), anthracycline-taxane was associated with a substantial reduction in relapse events compared with TC. Further studies of breast cancer patients treated with chemotherapy after having undergone a gene signature diagnostic assay are needed to better determine the lenses of genomic expressions, of which breast cancer populations would benefit the most from de-escalating anthracycline chemotherapy

Liao H et al., 2022 [9].

Efficacy and Safety of Initial 5 Years of Adjuvant Endocrine Therapy in Postmenopausal Hormone Receptor-Positive Breast Cancer: A Systematic Review and Network Meta-Analysis

Fragestellung

To identify the optimal initial 5 years of adjuvant endocrine therapy for hormone receptor-positive postmenopausal early breast cancer (EBC) patients

Methodik

Population:

- postmenopausal adult female patients (≥18 years old) with histologically confirmed invasive breast cancer
- positive for estrogen receptors and/or progesterone receptors (≥1% of tumor nuclei positive in immunohistochemistry)
- local treatment with curative intent including surgery and radiation has been completed;

Intervention/Komparator:

- initial endocrine therapy with 5 years of regimens of TAM, AIs, or sequential TAM and an AI

Endpunkte:

- DFS, OS, and SAEs

Recherche/Suchzeitraum:

- PubMed, Web of Science, and EMBASE to obtain relevant studies published between January 2000 and January 2022

Qualitätsbewertung der Studien:

- Cochrane Risk ofBias tool

Ergebnisse

Hinweis: Aus methodischen Gründen werden lediglich die Ergebnisse der Metaanalyse nicht jedoch der NMA dargestellt

Anzahl eingeschlossener Studien:

- Eleven studies with 49,987 subjects were included

Charakteristika der Population/Studien:

TABLE 1 | Basic characteristics of included studies.

Study	Publication year	Design	Patient population	Treatment arms	Population(n) arm 1:arm 2	Median follow-up	Main outcomes
GIM3-FATA (De Placido et al., 2018)	2018	Phase III, open-label	Postmenopausal women with HR+ EBC	(Sung et al., 2021) 5 years of AIs (DeSantis et al., 2019) 2 years of TAM followed by 3 years of AIs (ANA, EXE, LET)	1850:1847	5 years	1, 2, 3
FACE (Smith et al., 2017)	2017	Phase III, open-label	Postmenopausal women with HR+ and node-positive stage IIA-IIIC EBC	(Sung et al., 2021) 5 years of LET (DeSantis et al., 2019) 5 years of ANA	2061:2075	5.4 years	1, 2, 3, 4, 8
TEAM (Derks et al., 2017)	2017	Phase III, open-label	Postmenopausal women with HR+ EBC	(Sung et al., 2021) 2.5–3.0 years of TAM followed by EXE for a total of 5 years (DeSantis et al., 2019) 5 years of EXE	4868:4898	9.8 years	1, 2, 3, 5
N-SAS BC03 (Mouridsen et al., 2009)	2014	Phase III, open-label	Postmenopausal women with HR+ EBC	(Sung et al., 2021) 1–4 years of TAM followed by ANA for a total of 5 years (DeSantis et al., 2019) 5 years of TAM	345:351	8.1 years	1, 3, 5
ITA (Coombes et al., 2007)	2013	Phase III, open-label	Postmenopausal women with HR+ and node-positive EBC	(Sung et al., 2021) TAM followed by ANA for 5 years (DeSantis et al., 2019) 5 years of TAM	223:225	10.7 years	1, 2, 3, 6
MA27 (Goss et al., 2013)	2013	Phase III, open-label	Postmenopausal women with HR+ EBC	(Sung et al., 2021) 5 years of EXE (DeSantis et al., 2019) 5 years of ANA	3789:3787	4.1 years	1, 2, 3, 4, 6, 7
ABCSG-8 (Dubsky et al., 2012)	2012	Phase III, open-label	Postmenopausal women with HR+ EBC	(Sung et al., 2021) 2 years of TAM followed by 3 years of ANA (DeSantis et al., 2019) 5 years of TAM	1865:1849	5 years	1, 2, 3, 5, 10
ATAC (Cuzick et al., 2010)	2010	Phase III, double-blind	Postmenopausal women with EBC	(Sung et al., 2021) 5 years of ANA (DeSantis et al., 2019) 5 years of TAM	3125:3116 (2618: 2598 for HR+ patients)	10 years	1, 2, 3, 7, 8, 9, 11
BIG1-98 (Aihara et al., 2014)	2009	Phase III, double-blind	Postmenopausal women with HR+ EBC	(Sung et al., 2021) 5 years of LET (DeSantis et al., 2019) 5 years of TAM	4003:4007	6.3 years	1, 2, 3, 4
IES (Boccardo et al., 2013)	2007	Phase III, double-blind	Postmenopausal women with EBC	(Sung et al., 2021) 2–3 years of TAM followed by 2–3 years of EXE (DeSantis et al., 2019) 5 years of TAM	2352:2372	4.6 years	1, 2, 3, 7
ARNO95 (Kaufmann et al., 2007)	2007	Phase III, open-label	Postmenopausal women with HR+ EBC	(Sung et al., 2021) 2 years of TAM followed by 3 years of ANA (DeSantis et al., 2019) 5 years of TAM	489:490	2.5 years	1, 2, 3

*Notes: *Main outcomes: 1, DFS; 2, OS; 3, safety; 4, distant DFS; 5, RFS; 6, EFS; 7, contralateral breast cancer; 8, time to distant recurrence; 9, time to recurrence; 10, distant RFS; 11, death with or without recurrence. Abbreviations: HR+, hormone receptor-positive; EBC, early breast cancer; AIs, aromatase inhibitors; TAM, tamoxifen; LET, letrozole; ANA, anastrozole; EXE, exemestane.*

Qualität der Studien:

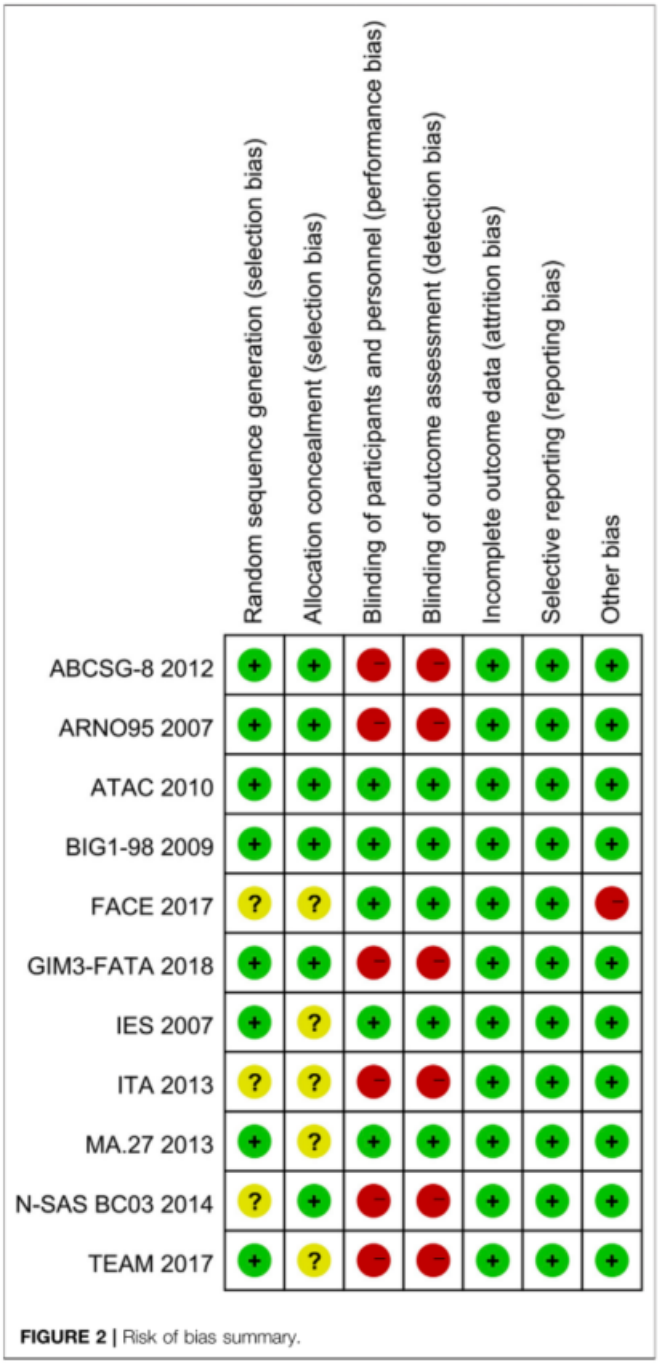


FIGURE 2 | Risk of bias summary.

Studienergebnisse:

ll 11 studies reported survival outcomes in postmenopausal patients with HR+ EBC treated with initial 5 years of adjuvant endocrine therapy. Among them, nine (Coombes et al., 2007; Kaufmann et al., 2007; Mouridsen et al., 2009; Cuzick et al., 2010; Dubsky et al., 2012; Boccardo et al., 2013; Aihara et al., 2014; Derks et al., 2017; De Placido et al., 2018) and eight (Coombes et al., 2007; Kaufmann et al., 2007; Cuzick et al., 2010; Dubsky et al., 2012; Boccardo et al., 2013; Aihara et al., 2014; Derks et al.,2017; De Placido et al., 2018) studies could be used for the direct meta-analysis of DFS and OS, respectively. For DFS, both AIs (HR 0.87, 95%CI 0.80–0.94, p = 0.0003) and TAM followed by an AI (0.79, 0.72–0.87, p < 0.00001) were significantly better than TAM (Figures 3A,B), with low heterogeneity (I2 = 0

and 9%, respectively). However, AIs did not significantly improve DFS than TAM followed by an AI (HR 0.95, 95%CI 0.88–1.03, p = 0.19) (Figure 3C). For OS, TAM followed by an AI was superior than TAM (HR 0.82, 95%CI 0.71–0.94, p = 0.005), with a low heterogeneity of I2 =0% (Figure 3E). Nevertheless, there was no significance between AIs and TAM (HR 0.92, 95%CI 0.83–1.01, p = 0.07), and AIs and TAM followed by an AI (0.96, 0.87–1.05, p = 0.37) (Figures 3D,F).

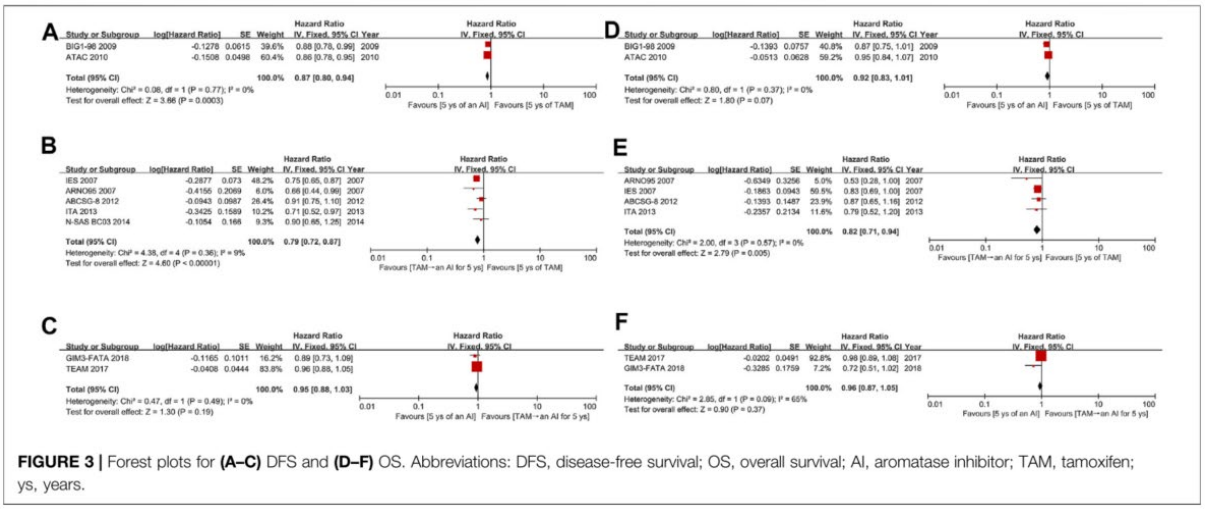


FIGURE 3 | Forest plots for **(A–C)** DFS and **(D–F)** OS. Abbreviations: DFS, disease-free survival; OS, overall survival; AI, aromatase inhibitor; TAM, tamoxifen; ys, years.

Anmerkung/Fazit der Autoren

In summary, any regimens involving AIs improved the DFS of postmenopausal hormone receptor-positive EBC patients compared with TAM alone. Only the sequential use of AIs especially ANA was superior than TAM alone in OS. No significant difference of survival was found in the direct comparison between the upfront use and the sequential use of AIs, or in the indirect comparisons among different AIs. In terms of safety, the sequential use of AIs was generally associated with less SAEs than the upfront use of AIs, with the categories of SAEs varying among different regimens. From a longterm perspective, the sequential use of Ais may be the best treatment mode for postmenopausal hormone receptor-positive EBC patients. Therefore, when making clinical decisions, physicians need to balance short-term and long-term benefits, and select suitable agents according to patients' clinical characteristics and potential risk of side effects.

3.3 Leitlinien

National Institute for Health and Care Excellence (NICE), 2018 (Update: Januar 2024) [11].
Early and locally advanced breast cancer: diagnosis and treatment

Zielsetzung/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

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

Recherche/Suchzeitraum:

- Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. […] All searches were conducted in MEDLINE, Embase and The Cochrane Library, with some additional database searching in AMED, PsycINFO and CINAHL for certain topic areas.

LoE

Tabelle 5: Levels of overall quality of outcome evidence in GRADE

Overall quality of outcome evidence in GRADE	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

GoR

- NICE reflects the strength of the recommendation in the wording. NICE uses 'offer' (or words such as 'measure', 'advise', or 'refer') to reflect a strong recommendation usually where there is clear evidence of benefit. […] uses 'consider' to reflect a recommendation for which the evidence of benefit is less certain.

Sonstige methodische Hinweise

- This guideline updates and replaces NICE guideline CG80 (February 2009), and NICE technology appraisal guidance 107, 108, 109 and 112 (published 2006).
- Anmerkung: Breast cancer affects women and men, and can affect those who have undergone a gender reassignment or who are non-binary. […] used the term 'women' in this guideline for recommendations that usually only relate to women (such as breast-conserving surgery) and 'people' in all other cases.

Recommendations

Adjuvant therapy planning

1.6.6 Consider adjuvant therapy after surgery for people with invasive breast cancer, and ensure that recommendations are recorded at the multidisciplinary team meeting. [2009]

1.6.7 Base recommendations about adjuvant therapy on multidisciplinary team assessment of the prognostic and predictive factors, and the possible risks and benefits of the treatment. Make decisions with the person after discussing these factors. [2009, amended 2018]

Endocrine therapy

1.7.1 Treat all people with invasive breast cancer with surgery and appropriate systemic therapy, rather than endocrine therapy alone, unless a significant comorbidity means surgery is not suitable for them. [2009]

Adjuvant endocrine therapy for invasive breast cancer

1.7.2 Offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER-positive invasive breast cancer. [2009, amended 2018]

1.7.3 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 of disease recurrence. Offer tamoxifen to women who are at low risk of disease recurrence, or if aromatase inhibitors are not tolerated or are contraindicated. [2009, amended 2018]

Ovarian function suppression

1.7.4 Consider ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer. [2018]

1.7.5 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

1.7.6 Discuss the benefits and risks of extended endocrine therapy with people who this treatment may be suitable for (see table 2). [2018, amended 2023]

1.7.7 Offer extended endocrine therapy (past the 5-year point) with an aromatase inhibitor for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk of disease recurrence and who have been taking tamoxifen for 2 to 5 years. Medium or high risk may include people who have lymph node-positive breast cancer, with tumours that are T2 or greater and higher grade. [2018]

1.7.8 Consider extended endocrine therapy (past the 5-year point) 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. Low

risk may include people with lymph node-negative breast cancer, with smaller or lower-grade tumours. [2018]

1.7.9 Consider extending the duration of tamoxifen therapy for longer than 5 years for people with ER-positive invasive breast cancer. [2018]

Table 2 Effects of extended endocrine therapy

Category	Extended tamoxifen therapy (after an initial 5 years of tamoxifen therapy)	Extended endocrine therapy with an aromatase inhibitor (after 5 years of tamoxifen therapy)
Definition	Continuing to take tamoxifen after 5 years of tamoxifen therapy	Switching to an aromatase inhibitor after 5 years of tamoxifen therapy
Who can take this therapy	People with ER-positive invasive breast cancer	Postmenopausal women with ER-positive invasive breast cancer
Effect on breast cancer recurrence: The benefit for an individual person will depend on the risk of their cancer returning. For people with a low risk of recurrence, the benefits may not outweigh the risks or side effects Medium or high risk may include people who have lymph node-positive breast cancer, with tumours that are T2 or greater and higher grade. Low risk may include people with lymph node-negative breast cancer, with smaller or lower-grade tumours	Evidence shows lower rates of breast cancer recurrence compared with 5 years of tamoxifen therapy in women	Lower rates of breast cancer recurrence compared with 5 years of tamoxifen therapy In postmenopausal women, switching to an aromatase inhibitor may be more effective at reducing recurrence than continuing with tamoxifen

Endocrine therapy for ductal carcinoma in situ

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

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

Adjuvant chemotherapy for invasive breast cancer

1.8.1 For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline. Please refer to the summaries of product characteristics for individual taxanes and anthracyclines because there are differences in their licensed indications. [2018]

1.8.2 Discuss with people the benefits and risks of adding a taxane to anthracycline-containing regimens […]:

- 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.

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

Background

There was good evidence of improved survival when taxanes are added to anthracycline-based chemotherapy in people with node-positive and node-negative breast cancer. In both groups, the benefits and risks of treatment should be discussed because of the potential side effects associated with taxanes. Three-weekly docetaxel was identified as a regimen with potentially more toxicity than weekly or fortnightly paclitaxel.

Adjuvant bisphosphonate therapy

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

1.9.2 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. Risk can be estimated using a range of standardised tools and clinical expertise. [2018]

Background

There was good evidence that treatment with sodium clodronate and zoledronic acid improved disease-free and overall survival in postmenopausal women with node-positive invasive breast cancer.

There was little evidence of benefit for other bisphosphonates. The committee recommended considering zoledronic acid or sodium clodronate treatment for other high-risk populations (such as postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence), based on the evidence that sodium clodronate has overall survival benefits in mixed populations.

Although there is evidence that intravenous (IV) bisphosphonates have a higher risk of osteonecrosis of the jaw, oral bisphosphonates have a higher risk of gastrointestinal problems.

There is also a risk of atypical femoral fractures and osteonecrosis of the external auditory canal with bisphosphonates. Because each drug and regimen has different risks, the potential benefits and risks should be discussed with women to help them make an informed choice.

There was little evidence on survival, particularly for premenopausal women on ovarian suppression, those with node-positive or node-negative disease, and those with positive or negative oestrogen or progestogen statuses. There was not enough evidence to make a recommendation relating to the use of adjuvant bisphosphonates in premenopausal women. The committee agreed that further research is needed to determine the long-term survival benefits and the groups of people most likely to benefit from adjuvant bisphosphonates. So they made a research recommendation on groups of people who would benefit from the use of adjuvant bisphosphonates.

The committee did not look at the evidence relating to the use of bisphosphonates for bone health or for the use of baseline dual-energy X-ray absorptiometry (DEXA) scanning, so did not make any new recommendations.

Radiotherapy

1.10.1 Use a radiotherapy technique that minimises the dose to the lung and heart. [2018]

1.10.2 Use a deep inspiratory breath-hold radiotherapy technique for people with left-sided breast cancer to reduce the dose to the heart. [2018]

Background

There was good evidence that radiotherapy to the internal mammary nodes reduced locoregional recurrence and improved survival. However, the committee took into account the potential for lung and heart toxicity, so recommended using a radiotherapy technique that minimises this risk.

There was evidence that deep inspiratory breath-hold radiotherapy techniques reduce the mean radiotherapy heart dose for adults with left-sided invasive breast cancer receiving whole-breast radiotherapy. The committee did not identify any harms. There was also evidence that deep inspiration breath-hold radiotherapy techniques did not reduce the target coverage of whole-breast radiotherapy.

There was no evidence about the use of deep inspiration breath-hold radiotherapy techniques for people with right-sided breast cancer, so the committee did not make separate recommendations for this subgroup.

Radiotherapy after breast-conserving surgery

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

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

- have a low absolute risk of local recurrence (defined as women aged 50 and over with tumours that are 3 cm or less, N0, ER-positive, HER2-negative and grade 1 to 2) and
- have been advised to have adjuvant endocrine therapy for a minimum of 5 years. [2018]

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

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

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

1.10.7 Consider omitting radiotherapy for women who:

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

1.10.8 When considering omitting radiotherapy for the population in recommendation 1.10.7, discuss the benefits and risks […] and explain that:

- without radiotherapy, local recurrence occurs in about 50 women per 1,000 at 5 years, and with radiotherapy, occurs in about 10 women per 1,000 at 5 years
- overall survival at 10 years is the same with or without radiotherapy

- there is no increase in serious late effects if radiotherapy is given (for example, congestive cardiac failure, myocardial infarction or secondary cancer. [2018]

1.10.9 Consider adjuvant radiotherapy for women with DCIS following breast-conserving surgery with clear margins. Discuss the possible benefits and risks of radiotherapy (also see the section on surgery to the breast) and make a shared decision about its use. [2009]

Background

There is evidence that whole-breast radiotherapy after breast-conserving surgery reduces the risk of recurrence and increases overall survival. It also decreases rates of depression and anxiety.

However, because the risk of breast cancer recurring at 5 years is very low and there are harms associated with radiotherapy, the benefits of radiotherapy for women with a very low risk of recurrence are less certain. For these women, the committee agreed that healthcare professionals should fully discuss the benefits and risks with women before a decision is made.

Good evidence showed that partial breast radiotherapy led to similar results to whole-breast radiotherapy after breast-conserving surgery in women with a low risk of local recurrence. In addition, it may have fewer treatment-related adverse effects. There was evidence for multicatheter interstitial brachytherapy but this was not recommended because it is not currently available in England.

Radiotherapy after mastectomy

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

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

1.10.12 Do not offer radiotherapy following mastectomy to people with invasive breast cancer who are at low risk of local recurrence (for example, most people who have lymph node-negative breast cancer). Risk can be estimated using a range of standardised tools and clinical expertise. [2018]

Background

The committee agreed that adjuvant postmastectomy radiotherapy should be offered to people who have macroscopically node-positive invasive breast cancer or have involved resection margins. This is because the evidence showed a beneficial effect on survival and local recurrence. Although the evidence was limited and the committee acknowledged that radiotherapy is associated with lung and cardiac morbidity, they concluded that for this group of women, the benefits of radiotherapy outweigh the harms.

There was evidence of a beneficial effect of postmastectomy radiotherapy on local recurrence and overall survival for people with node-negative invasive breast cancer. However, the committee agreed that there was a risk of over-treatment if all people with node-negative invasive breast cancer received postmastectomy radiotherapy. Therefore, the committee recommended that adjuvant postmastectomy radiotherapy should be considered for people with node-negative T3 or T4 invasive breast cancer. There was no evidence for this specific subgroup but they would be considered at increased risk of recurrence and mortality relative to smaller, node-negative invasive breast cancers because of the size of the tumour.

The committee agreed that radiotherapy after mastectomy should not be offered to women with early invasive breast cancer who are at low risk of local recurrence (for example, most women who are lymph node-negative) because the evidence showed limited benefit in survival and local recurrence.

Dose fractionation for external beam radiotherapy

1.10.13 Offer 26 Gy in 5 fractions over 1 week for people with invasive breast cancer having partial-breast, whole-breast or chest-wall radiotherapy, without regional lymph node irradiation, after breast-conserving surgery or mastectomy. [2023]

1.10.16 Offer 40 Gy in 15 fractions over 3 weeks for people with invasive breast cancer having regional lymph node irradiation, with or without whole-breast or chestwall radiotherapy, after breast-conserving treatment or mastectomy. [2023]

Breast boost following breast-conserving surgery

1.10.17 Offer an external beam boost to the tumour bed for women with invasive breast cancer and a high risk of local recurrence, following whole-breast radiotherapy. Risk can be estimated using a range of standardised tools and clinical expertise. [2009, amended 2018]

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

Radiotherapy to nodal areas

1.10.19 Do not offer adjuvant radiotherapy to regional lymph nodes to people with invasive breast cancer who have been shown to have histologically lymph node-negative breast cancer. [2009, amended 2018]

1.10.20 Do not offer people with invasive breast cancer adjuvant radiotherapy to the axilla after axillary clearance. [2009, amended 2023]

1.10.21 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 4 or more involved axillary lymph nodes. [2009]

1.10.22 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 1 to 3 positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status. [2009]

1.10.23 Consider including the internal mammary chain within the nodal radiotherapy target for people with node-positive (macrometastases) invasive breast cancer. [2018]

Background

There was good evidence that radiotherapy to the internal mammary nodes reduced locoregional recurrence and improved survival. However, the committee took into account the potential for lung and heart toxicity, and agreed the importance of using a radiotherapy technique that minimises this risk.

Denduluri N et al., 2021 [2].

American Society of Clinical Oncology (ASCO)

Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO Guideline Update.

sowie

Freedman R.A. et al., 2024 [4] mit clinical insights Caswell-Jin J.L. et al., 2024 [1]

ASCO (American Society of Clinical Oncology)

Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer-Cyclin-Dependent Kinase 4 and 6 Inhibitors: ASCO Guideline Rapid Recommendation Update

Zielsetzung/Fragestellung

The aim of this work is 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 – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft teilweise zu (Für die in Vorgängerversionen der Leitlinie publizierten Empfehlungen konnten keine Empfehlungsstärken, Evidenzgrade oder Evidenz identifiziert werden. Sie sind jedoch in den ursprünglichen Versionen der Leitlinie publiziert.);
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- systematic review–based guideline
- Literature searches of selected databases, including The Cochrane Library and Medline (via PubMed) are performed.

LoE/GoR

- GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Sonstige methodische Hinweise

- Das ASCO Guidelines Methodology Manual ist hier zu finden: https://www.asco.org/practice-patients/guidelines/guideline-methodology

Recommendations

TABLE 1. Complete List of Recommendations From 2018 ASCO Guideline Adaptation and From the ASCO 2020 Focused Guideline Update

Recommendation	Evidence Rating
New Recommendations From 2020 Focused Guideline Update	
Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant T-DM1, unless there is disease recurrence or unmanageable toxicity.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Recommendations Unchanged From 2018 Guideline Adaptation[a]	
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 no higher than 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 or older, 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; Trial Assigning Individualized Options for Treatment) 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 four cycles → paclitaxel 175 mg/m^2 every 2 weeks for four 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 before, 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 its convenience and tolerability, despite the absence of efficacy data from randomized controlled trials.	
Only patients with HER2-positive breast cancer (overexpressed on the basis of immunohistochemistry [3+] or amplified on the basis of 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.	
Patients with early-stage, HER2-negative breast cancer with pathologic invasive residual disease at surgery after 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 the hormone receptor–negative, HER2-negative patient subgroup. The capecitabine dose used in the CREATE-X study (1,250 mg/m^2 twice daily) is associated with higher toxicity in patients age ≥ 65 years.	
Clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy in 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 in patients who received neoadjuvant pertuzumab and achieved a pathologic complete response.	
Clinicians may use extended adjuvant therapy with neratinib in 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 the use of neratinib in hormone receptor–positive and node-positive patients. At 5.2-year follow up, no overall survival benefit has been observed. Patients who began neratinib within 1 year of trastuzumab completion seemed to derive the greatest benefit. There are no data on the added benefit of neratinib in patients who also received pertuzumab in the neoadjuvant or adjuvant setting.	

Abbreviations: HER2, human epidermal growth factor receptor 1; IV, intravenous; T-DM1, trastuzumab emtansine.

[a]Evidence and analysis for recommendations unchanged from 2018 are described in Eisen et al,[5] and later by Denduluri et al,[1,3] in ASCO's adaptation of the Cancer Care Ontario guideline in 2016 and in the 2018 focused update of that adaptation.

2024 Updated Recommendation

Recommendation 1

Abemaciclib for 2 years plus ET for ≥5 years may be offered to patients meeting the criteria of the ITT monarchE population with resected, hormone receptor-positive, HER2- negative, node-positive, early breast cancer at high risk of recurrence, defined as having ≥4 positive axillary lymph nodes (ALNs) or as having 1-3 positive ALNs plus at least one of the following features: grade 3 disease, tumor size ≥5 cm, or Ki-67 index ≥20%. Although the FDA's

language is broad, the Panel promotes the use of abemaciclib primarily in those who would have been eligible for monarchE based on that trial's eligibility criteria (**Evidence quality: High; Strength of recommendation: Strong**).

Recommendation 2

The Panel recommends, based on the phase III NATALEE trial, that adjuvant ribociclib (400 mg once daily, 3 weeks on followed by 1 week off) for 3 years plus ET may be offered to patients with anatomic stage II or III breast cancer who would have met criteria for study entry and have a high risk of recurrence (**Evidence quality: High; Strength of recommendation: Conditional**).

Qualifying Statements for Recommendations 1 and 2 on the Use of Adjuvant Abemaciclib and Ribociclib

The Panel believes that adjuvant CDK4/6 inhibitor therapy may not provide meaningful clinical benefit to all patients who would have been eligible for the available trials, especially the lower-risk patients who were included in the NATALEE trial. For example, for most patients with node-negative disease, the risks of ribociclib may outweigh the benefits, with the exception of some patients with the highest risk, node-negative disease. However, the Panel acknowledges that there are insufficient data to specify which subgroups of patients do or do not warrant therapy. The Panel thus recommends considering the benefits, risks, costs, and preferences for each individual patient when deciding whether to recommend therapy.

Among patients meeting criteria for both monarchE and NATALEE, the Panel also notes that, of the two CDK4/6 inhibitors, abemaciclib has longer follow-up, a deepening benefit over time, a shorter duration of therapy, and FDA approval in the adjuvant setting. In this case, the Panel favors using abemaciclib, reserving use of ribociclib in patients who have a contraindication to (e.g., preexisting high-grade diarrhea) or intolerance of abemaciclib. The Panel characterized the strength of the ribociclib recommendation as conditional, pending future efficacy data and regulatory updates. Although a formal cost-effectiveness analysis was out of scope for this update, it could be informative for some decision makers considering the costs of both medications. Results from longer-term follow-up will further inform adjuvant therapy decision making.

Weitere Empfehlungen aus den clinical insights:

SPECIAL POPULATIONS: SHOULD CLINICIANS RECOMMEND ADJUVANT CDK4/6 INHIBITORS IN PATIENTS WITH GERMLINE BRCA1/BRCA2 PATHOGENIC VARIANTS?

The OlympiA trial included an especially high-risk population of patients with hormone receptor–positive, HER2-negative breast cancer and germline BRCA1/BRCA2 variants, requiring at least four involved nodes or a poor response to neoadjuvant chemotherapy (clinical and pathologic stage [CPS] and estrogen receptor status and histologic grade [EG] score of three or higher).[11] For high-risk patients outside those criteria, we do not have sufficient evidence to recommend olaparib, and shared decision making is essential. In general, we prioritize adjuvant olaparib over a CDK4/6 inhibitor for high-risk patients given the degree of benefit seen in OlympiA in the BRCA1/BRCA2 population,[11] and the uncertainty about the degree of CDK4/6 inhibitor benefit specifically in BRCA1/BRCA2 germline carriers. There are no data for sequential CDK4/6 inhibitor after olaparib. However, given that monarchE allowed initiation of adjuvant abemaciclib up to 16 months after definitive breast cancer surgery and NATALEE allowed initiation of adjuvant ribociclib up to 12 months after starting ET, sequential therapy could be an option in the highest-risk and very motivated patients.

SPECIAL POPULATIONS: SHOULD CLINICIANS RECOMMEND ADJUVANT CDK4/6 INHIBITORS IN MEN?

There were 20 men (0.4%) included in NATALEE and 36 men (0.6%) included in monarchE. Although the trials cannot speak to the utility of adjuvant CDK4/6 inhibition in men, we recommend adjuvant CDK4/6 inhibitors in men, using similar guidelines to women.[12]

11. Tutt ANJ, Garber JE, Garber CE Jr: Adjuvant olaparib in BRCA-mutated breast cancer. Reply. N Engl J Med 385:1440, 2021
12. (siehe unten) Hassett MJ, Somerfield MR, Baker ER, et al: Management of male breast cancer: ASCO guideline. J Clin Oncol 38:1849-1863, 2020

Hasset MJ et al., 2020 [7].

ASCO

Management of Male Breast Cancer: ASCO Guideline

Zielsetzung/Fragestellung

To develop recommendations concerning the management of male

Guideline Question: What is the optimal management for men with breast cancer including use of adjuvant endocrine therapy, use of endocrine therapy for advanced or metastatic disease, targeted therapies, management of treatment-related adverse effects, genetic testing, and post-treatment surveillance?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium enthält PatV;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz beschrieben;
- 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: January 1, 1998 - September 20, 2019

LoE

Strength of Total Body of Evidence

Rating	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (e.g., balance of benefits versus harms) and further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Intermediate 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 the magnitude and/or direction of 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. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available.

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 an online 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.

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

Sonstige methodische Hinweise

- Because of the limited evidence available for most of the clinical questions, recommendations were developed using the ASCO modified Delphi formal consensus methodology. […] Ratings for the type and strength of recommendation and quality of evidence are provided with each recommendation. A "strong" rating was assigned when the observed consensus agreement was between 90% and 100%; otherwise, a "moderate" rating was assigned.

Empfehlungen

Clinical questions (1) Which adjuvant endocrine therapy should be offered to men with earlystage, hormone receptor–positive breast cancer?

Recommendation 1.1. Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy should be offered tamoxifen (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 1.2. Men with hormone receptor–positive breast cancer who are candidates for adjuvant endocrine therapy but have a contraindication to tamoxifen may be offered gonadotropin-releasing hormone agonist/antagonist and an aromatase inhibitor (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis.

Most male breast cancers are hormone receptor positive; about 99% are estrogen receptor positive and about 81% are progesterone receptor positive.[26]

Data on the use of AIs in the treatment of men with earlystage breast cancer are sparse. Population-based series comparing AI and tamoxifen have reported inferior survival among men with breast cancer who were treated with an AI.[9,10,24] Adjuvant endocrine therapy is thus the mainstay of systemic treatment in men with early-stage breast cancer. Tamoxifen is the preferred adjuvant endocrine therapy based on observational studies that have suggested a survival benefit.[12,24,25] For this reason, treatment of men with an AI alone is generally not preferred. However, use of an AI in combination with a GnRH analog is an acceptable alternative, especially for men who have a contraindication to tamoxifen (eg, a history of thrombosis).[17]Adding the GnRH analog may help overcome the lack of complete estradiol suppression sometimes seen in men treated with an AI alone.[2] Some have argued in favor of using an AI alone in selected patients, such as those who are unlikely to tolerate combined therapy, although concerns about the efficacy of this approach persist.

Clinical questions (2) What is the optimal duration of adjuvant endocrine treatment of men with early-stage, hormone receptor–positive breast cancer?

Recommendation 2.1. Men who are treated with adjuvant endocrine therapy should be treated for an initial duration of five years (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 2.2. Men who have completed five years of tamoxifen, have tolerated therapy, and still have a high risk of recurrence may be offered an additional five years of tamoxifen therapy (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).

Literature review and analysis.

There is no evidence from clinical trials in men with breast cancer to inform clinical questions regarding the duration of adjuvant endocrine therapy.

Clinical questions (3) What is the role of bone-modifying agents in men with early-stage, hormone receptor–positive breast cancer?

Recommendation 3. Men with early-stage breast cancer should not be treated with bone-modifying agents to prevent recurrence but could still receive these agents to prevent or treat osteoporosis (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate).

Literature review and analysis.

There is no evidence from clinical trials in men with breast cancer to inform clinical questions regarding the use of bone-modifying agents to prevent breast cancer recurrence.

Referenzen aus Leitlinien
2. Giordano SH: Breast cancer in men. N Engl J Med 378:2311-2320, 2018
9. Eggemann H, Altmann U, Costa SD, et al: Survival benefit of tamoxifen and aromatase inhibitor in male and female breast cancer. J Cancer Res Clin Oncol 144: 337-341, 2018
10. Eggemann H, Ignatov A, Smith BJ, et al: Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat 137:465-470, 2013
12. Giordano SH, Perkins GH, Broglio K, et al: Adjuvant systemic therapy for male breast carcinoma. Cancer 104:2359-2364, 2005
17. Eggemann H, Bernreiter AL, Reinisch M, et al: Tamoxifen treatment for male breast cancer and risk of thromboembolism: Prospective cohort analysis. Br J Cancer 120:301-305, 2019
24. Harlan LC, Zujewski JA, Goodman MT, et al: Breast cancer in men in the United States: A population-based study of diagnosis, treatment, and survival. Cancer 116:3558-3568, 2010
25. Goss PE, Reid C, Pintilie M, et al: Male breast carcinoma: A review of 229 patients who presented to the Princess Margaret Hospital during 40 years: 1955-1996. Cancer 85:629-639, 1999

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2024) am 28.10.2024

#	Suchfragen
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 lesion* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Okt 2019 to present

Systematic Reviews in PubMed am 28.10.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfragen
1	breast neoplasms/therapy[majr]
2	(breast[ti]) OR mamma*[ti]
3	(#2) AND (tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab])
4	(#3) AND (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	#1 OR #4
6	(#5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR

#	Suchfragen
	overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
7	((#6) AND ("2019/10/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 28.10.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	(#2) AND (((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesion*[ti]) OR malignan*[ti]
4	#1 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
6	(((#5) AND ("2019/10/01"[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]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 29.10.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- *Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)*
- *Alberta Health Service (AHS)*
- *European Society for Medical Oncology (ESMO)*
- *National Comprehensive Cancer Network (NCCN)*
- *National Cancer Institute (NCI)*

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Caswell-Jin JL, Freedman RA, Hassett MJ, Tang H, Garrett-Mayer E, Somerfield MR, et al.** Optimal adjuvant chemotherapy and targeted therapy for early breast cancer-CDK4/6 Inhibitors: ASCO rapid guideline update clinical insights. JCO Oncol Pract 2024:Op2400663.

2. **Denduluri N, Somerfield MR, Chavez-MacGregor M, Comander AH, Dayao Z, Eisen A, et al.** Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO guideline update. J Clin Oncol 2021;39(6):685-693.

3. **Ergun Y, Dogan M, Ucar G, Karacin P, Karacin C.** Efficacy of adjuvant CDK4/6 inhibitors in hormone receptor-positive breast cancer: a systematic review and meta-analysis. Expert Opin Pharmacother 2023;24(17):1901-1909.

4. **Freedman RA, Caswell-Jin JL, Hassett M, Somerfield MR, Giordano SH.** Optimal adjuvant chemotherapy and targeted therapy for early breast cancer-Cyclin-Dependent Kinase 4 and 6 inhibitors: ASCO guideline rapid recommendation update. J Clin Oncol 2024;42(18):2233-2235.

5. **Gao HF, Lin YY, Zhu T, Ji F, Zhang LL, Yang CQ, et al.** Adjuvant CDK4/6 inhibitors combined with endocrine therapy in HR-positive, HER2-negative early breast cancer: a meta-analysis of randomized clinical trials. Breast 2021;59:165-175.

6. **Giffoni de Mello Morais Mata D, Rush MB, Smith-Uffen M, Younus J, Lohmann AE, Trudeau M, et al.** The omission of Anthracycline chemotherapy in women with early HER2-negative breast cancer-a systematic review and meta-analysis. Curr Oncol 2024;31(8):4486-4506.

7. **Hassett MJ, Somerfield MR, Baker ER, Cardoso F, Kansal KJ, Kwait DC, et al.** Management of male breast cancer: ASCO guideline. J Clin Oncol 2020;38(16):1849-1863.

8. **Keskinkilic M, Arayici ME, Basbinar Y, Ellidokuz H, Yavuzsen T, Oztop I.** The efficacy and safety of CDK4/6 inhibitors combined with endocrine therapy versus endocrine therapy alone in the adjuvant treatment of patients with high-risk invasive HR+/HER2- early breast cancer: a comprehensive updated meta-analysis of randomized clinical trials. Breast 2024;78:103815.

9. **Liao H, Pei W, Zhong J, Shao B, Liu X, Liu Y, et al.** Efficacy and safety of initial 5 years of adjuvant endocrine therapy in postmenopausal hormone receptor-positive breast cancer: a systematic review and network meta-analysis. Front Pharmacol 2022;13:886954.

10. **Moraes FCA, de Oliveira Almeida G, Alves VFC, Priantti JN, Gomes GDC, Carnevalli SVB, et al.** Cyclin-dependent kinase 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone for HR-positive, HER-2-negative early breast cancer: meta-analysis of phase III randomized clinical trials. J Pers Med 2024;14(5).

11. **National Institute for Health and Care Excellence (NICE).** Early and locally advanced breast cancer: diagnosis and treatment [online]. Last updated 16.01.2024. London (GBR): NICE; 2018. [Zugriff: 29.10.2024]. (NICE guideline; Band 101). URL: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605.

12. **Zhang M, Song J, Guo S, Jin F, Zheng A.** Adjuvant and neoadjuvant therapy with cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer: a systematic review and meta-analysis. Endocr Relat Cancer 2023;30(8).

13. **Zhang Z, Zhao X, Chen J.** Adjuvant and neoadjuvant therapy with or without CDK4/6 inhibitors in HR+/HER2- early breast cancer: a systematic review and meta-analysis. Front Pharmacol 2024;15:1438288.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. Node

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO