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: 2025-B-068-z Trastuzumab deruxtecan

Stand: April 2025

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

Trastuzumab deruxtecan
[Behandlung des HR-positiven, HER2-low oder -ultralow, metastasierten 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 HER2-positive Mammakarzinom
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Grundsätzlich im Anwendungsgebiet in Betracht kommende nicht-medikamentöse Behandlungen: - Operative Resektion - Strahlentherapie - 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: Beschlüsse vom 02.05.2019, 03.09.2020 und 19.05.2022 - Alpelisib (in Kombination mit Fulvestrant): Beschluss vom 18.02.2021 - Elacestrant: Beschluss vom 02.05.2024 - Olaparib: Beschluss vom 16.01.2020 - Palbociclib: Beschlüsse vom 18.05.2017, 22.03.2019 und 15.12.2022 - Ribociclib: Beschlüsse vom 04.07.2019 und 20.08.2020 - Talazoparib: Beschluss vom 20.11.2020 **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind:** - Gemcitabin in der Monotherapie beim Mammakarzinom der Frau **Richtlinie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung):** - Protonentherapie beim Mammakarzinom

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Trastuzumab deruxtecan [Behandlung des HR-positiven, HER2-low oder -ultralow, metastasierten Mammakarzinoms]	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Trastuzumab deruxtecan L01FD04 Enhertu	<u>Anwendungsgebiet laut Zulassung</u> *HER2-low und HER2-ultralow Brustkrebs* Trastuzumab deruxtecan wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem - Hormonrezeptor (HR)-positivem, HER2-low oder HER2-ultralow Brustkrebs, die mindestens eine endokrine Therapie in der metastasierten Situation erhalten haben und die für eine endokrine Therapie als nächste Therapielinie nicht in Frage kommen (siehe Abschnitte 4.2 und 5.1).
Zytostatika	
5-Fluorouracil L01BC02 generisch	Fortgeschrittenes und/oder metastasiertes Mammakarzinom
Capecitabin L01BC06 generisch	• in Kombination mit Docetaxel zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom nach Versagen einer zytotoxischen Chemotherapie. Eine frühere Behandlung sollte ein Anthracyclin enthalten haben. • als Monotherapie zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom, bei denen eine Therapie mit Taxanen und Anthracyclinen versagt hat oder eine weitere Anthracyclinbehandlung nicht angezeigt ist.
Cyclophosphamid L01AA01 Endoxan	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: Endoxan Pulver zur Herstellung einer Injektionslösung: • Palliative Therapie des fortgeschrittenen Mammakarzinoms

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Docetaxel L01CD02 generisch	*Brustkrebs* – TAXOTERE ist in Kombination mit Doxorubicin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs ohne vorausgegangene Chemotherapie angezeigt. – Die TAXOTERE-Monotherapie ist zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die vorausgegangene Chemotherapie sollte ein Anthracyclin oder Alkylanzien enthalten haben. – TAXOTERE ist in Kombination mit Capecitabin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die frühere Behandlung sollte ein Anthracyclin enthalten haben.
Doxorubicin L01DB01 generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: – Mammakarzinom – […] Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Doxorubicin (liposomal) L01DB01 Caelyx Myocet liposomal	Caelyx ist indiziert: Als Monotherapie bei Patientinnen mit metastasierendem Mammakarzinom mit erhöhtem kardialen Risiko. Myocet liposomal in Kombination mit Cyclophosphamid wird angewendet bei der First-line-Behandlung von metastasiertem Brustkrebs bei erwachsenen Frauen.
Epirubicin L01DB03 generisch	Epirubicin wird zur Behandlung folgender neoplastischer Erkrankungen eingesetzt: – Mammakarzinom
Gemcitabin L01BCO5 generisch	Gemcitabin ist angezeigt in Kombination mit Paclitaxel für die Behandlung von Patientinnen mit nicht operablem, lokal rezidiviertem oder metastasiertem Brustkrebs, bei denen es nach einer adjuvanten/neoadjuvanten Chemotherapie zu einem Rezidiv kam. Die vorausgegangene Chemotherapie sollte ein Anthracyclin enthalten haben, sofern dieses nicht klinisch kontraindiziert war.
Ifosfamid L01AA06 generisch	Zur Palliativtherapie bei fortgeschrittenen, therapierefraktären bzw. rezidivierenden Mammakarzinomen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: – fortgeschrittenes und/oder metastasierendes Mammakarzinom
Mitoxantron L01DB07 generisch	– ist indiziert zur Behandlung des metastasierten Mammakarzinoms
Paclitaxel L01CD01 generisch	Paclitaxel ist angezeigt zur First-line-Behandlung des lokal fortgeschrittenen oder metastasierenden Mammakarzinoms entweder in Kombination mit Anthrazyklin bei Patientinnen, für die eine Anthrazyklin-Therapie geeignet ist oder in Kombination mit Trastuzumab bei Patientinnen mit Überexpression des HER-2 (humaner epidermaler Wachstumsfaktorrezeptor 2) (3+ mittels immunhistochemischer Untersuchung) und für die eine Therapie mit Anthrazyklin nicht geeignet ist. Als Monotherapie ist Paclitaxel angezeigt zur Behandlung des metastasierenden Mammakarzinoms bei Patientinnen, die nicht auf eine anthrazyklinhaltige Standardtherapie angesprochen haben oder nicht dafür in Frage kommen.
Vinblastin L01CA01 generisch	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: – rezidivierendes oder metastasierendes Mammakarzinom (wenn eine Behandlung mit Anthracyclinen nicht erfolgreich war)
Vincristin L01CA02 generisch	Vincristin wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: – soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom […].
Vinorelbin L01CA04 generisch	Vinorelbin ist bei erwachsenen Patienten angezeigt zur Behandlung von: – fortgeschrittenem Brustkrebs als Monotherapie oder in Kombination mit anderen Wirkstoffen

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Antikörper	
Bevacizumab L01FG01 generisch	Bevacizumab wird in Kombination mit Paclitaxel zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet. Zu weiteren Informationen wie auch zum humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)- Status siehe Abschnitt 5.1. Bevacizumab wird in Kombination mit Capecitabin zur First-Line-Behandlung von erwachsenen Patienten mit metastasiertem Mammakarzinom angewendet, bei denen eine Behandlung mit anderen Chemotherapie-Optionen, einschließlich Taxanen oder Anthracyclinen, als nicht geeignet angesehen wird. Patienten, die innerhalb der letzten 12 Monate Taxan- und Anthracyclin-haltige Therapieregime im Rahmen der adjuvanten Behandlung erhalten haben, sollten nicht mit Avastin in Kombination mit Capecitabin therapiert werden. Zu weiteren Informationen wie auch zum HER2-Status siehe Ab schnitt 5.1.
Antiöstrogene	
Tamoxifen L02BA01 Nolvadex	• Metastasierendes Mammakarzinom.
Toremifen L02BA02 Fareston[1]	First-line Behandlung des hormonabhängigen metastasierenden Mammakarzinoms bei postmenopausalen Patientinnen. Fareston kann bei Patientinnen mit Östrogenrezeptor-negativen Tumoren nicht empfohlen werden.

Fulvestrant
L02BA03
Faslodex
	Faslodex ist angezeigt als
	• Monotherapie zur Behandlung von Östrogenrezeptor-positivem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom bei postmenopausalen Frauen:
	  • die keine vorhergehende endokrine Therapie erhalten haben, oder
	  • mit Rezidiv während oder nach adjuvanter Antiöstrogen-Therapie oder bei Progression der Erkrankung unter Antiöstrogen-Therapie.
	• in Kombination mit Palbociclib zur Behandlung des Hormonrezeptor-(HR)-positiven humanen Wachstumsfaktor-Rezeptor-2-(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinoms bei Frauen, die eine vorhergehende endokrine Therapie erhalten haben.
	Bei prä- oder perimenopausalen Frauen sollte die Kombinationstherapie mit Palbociclib mit einem Luteinisierungshormon-Releasinghormon-(LHRH)-Agonisten kombiniert werden.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Elacestrant L02BA04 Orserdu	ORSERDU wird angewendet als Monotherapie zur Behandlung von postmenopausalen Frauen sowie von Männern mit Estrogenrezeptor (ER)-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs mit einer aktivierenden ESR1-Mutation, deren Erkrankung nach mindestens einer endokrinen Therapielinie, einschließlich eines CDK 4/6-Inhibitors, fortgeschritten ist.
Aromataseinhibitoren (nicht-steroidal)	
Anastrozol L02BG03 Arimidex	Arimidex ist angezeigt für die: • Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen.
Letrozol L02BG04 Femara	• First-Line-Therapie des hormonabhängigen fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen. • Behandlung des Mammakarzinoms im fortgeschrittenen Stadium nach Rezidiv oder Progression der Erkrankung bei Frauen, die sich physiologisch oder nach einem künstlichen Eingriff in der Postmenopause befinden und die zuvor mit Antiöstrogenen behandelt wurden.
Aromataseinhibitoren (steroidal)	
Exemestan L02BG06 Aromasin	• Behandlung des fortgeschrittenen Mammakarzinoms bei Frauen mit natürlicher oder induzierter Postmenopause nach Progression unter Antiöstrogenbehandlung. Bei Patientinnen mit negativem Östrogenrezeptor-Status ist die Wirksamkeit nicht belegt.
Gestagene	
Megestrolacetat L02AB01 Megestat	Megestat ist angezeigt: • zur palliativen Behandlung fortgeschrittener Mammakarzinome (nicht operable metastasierende bzw. rekurrente Erkrankungen), bei Progression nach einer Therapie mit Aromatasehemmern
Medroxyproges-teronacetat L02AB02 MPA Hexal	Zur palliativen Behandlung bei folgenden hormonabhängigen Tumoren: • metastasierendes Mammakarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Gonadotropin-Releasing-Hormon-Analoga	
Leuprorelin L02AE02 Enantone-Gyn	Mammakarzinom prä- und perimenopausaler Frauen, sofern eine endokrine Behandlung angezeigt ist.
Goserelin L02AE03 Zoladex	Behandlung von Patientinnen mit Mammakarzinom (prä- und perimenopausale Frauen), bei denen eine endokrine Behandlung angezeigt ist.
Proteinkinase-Inhibitoren	
Abemaciclib L01EF03 Verzenios	Verzenios ist angezeigt zur Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie. Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.
Capivasertib L01EX27 Truqap	TRUQAP in Kombination mit Fulvestrant ist indiziert zur Behandlung von erwachsenen Patienten mit Östrogenrezeptor(ER)-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom mit einer oder mehreren PIK3CA/AKT1/PTEN-Alterationen nach Rezidiv oder Progression der Erkrankung während oder nach einer endokrinen Therapie. Bei prä- oder perimenopausalen Frauen sollte TRUQAP plus Fulvestrant mit einem Luteinisierungshormon-Releasinghormon(LHRH)-Agonisten kombiniert werden. Bei Männern sollte die Anwendung eines LHRH-Agonisten gemäß aktueller klinischer Standardpraxis in Betracht gezogen werden.
Everolimus L01EG02 Afinitor	Hormonrezeptor-positives, fortgeschrittenes Mammakarzinom: Afinitor wird in Kombination mit Exemestan zur Therapie des Hormonrezeptor-positiven, HER2/neu-negativen, fortgeschrittenen Mammakarzinoms bei postmenopausalen Frauen ohne symptomatische viszerale Metastasierung angewendet, nachdem es zu einem Rezidiv oder einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.
Palbociclib L01EF01 Ibrance	Ibrance ist angezeigt zur Behandlung von Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen lokal fortgeschrittenen oder metastasierten Brustkrebs: • in Kombination mit einem Aromatasehemmer

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	• in Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinizing Hormone-Releasing Hormone) kombiniert werden.
Ribociclib L01EF02 Kisqali	<u>Fortgeschrittenes oder metastasiertes Mammakarzinom</u> Kisqali wird zur Behandlung von Frauen mit einem Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom in Kombination mit einem Aromatasehemmer oder Fulvestrant als initiale endokrin-basierte Therapie oder bei Frauen mit vorangegangener endokriner Therapie angewendet. Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinising Hormone-Releasing Hormone) kombiniert werden.
PI3K-Inhibitor	
Alpelisib L01EM03 Piqray[1]	Piqray wird in Kombination mit Fulvestrant angewendet zur Behandlung von postmenopausalen Frauen und Männern mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom mit PIK3CA-Mutation bei Fortschreiten der Erkrankung nach endokriner Therapie als Monotherapie.
PARP-Inhibitoren	
Olaparib L01XK01 Lynparza	Mammakarzinom Lynparza wird angewendet als: • Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom haben. Die Patienten sollten zuvor mit einem Anthrazyklin und einem Taxan im (neo)adjuvanten oder metastasierten Setting behandelt worden sein, es sei denn, die Patienten waren für diese Behandlungen nicht geeignet (siehe Abschnitt 5.1). Patienten mit Hormonrezeptor (HR)-positivem Mammakarzinom sollten außerdem eine Krankheitsprogression während oder nach einer vorherigen endokrinen Therapie aufweisen oder für eine endokrine Therapie nicht geeignet sein.

[1] Derzeit nicht auf dem deutschen Markt verfügbar.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Talazoparib L01XK04 Talzenna	Talzenna wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom aufweisen. Die Patienten sollten zuvor mit einem Anthrazyklin und/ oder einem Taxan im (neo)adjuvanten, lokal fortgeschrittenen oder metastasierten Setting behandelt worden sein, es sei denn, sie waren für diese Behandlungen nicht geeignet (siehe Abschnitt 5.1). Patienten mit Hormonrezeptor (HR)-positivem Brustkrebs sollten außerdem bereits eine endokrin-basierte Therapie erhalten haben oder für diese als nicht geeignet eingestuft sein.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-068z (Beratung nach § 35a SGB V) Trastuzumab deruxtecan

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. März 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

a/mBC	advanced/metastatic breast cancer
ABC	Advanced breast cancer
ADCs	antibody-drug conjugates
AEs	Adverse events
AI	aromatase inhibitor
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDK	Cyclin-dependent kinase
CLIA	Clinical Laboratory Improvement Amendments
ECRI	ECRI Guidelines Trust
ER	Estrogen receptor
ESR1	Estrogen receptor 1
ET	Endocrine therapy/endocrine treatment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HER 2	Human epidermal growth factor 2
HR	Hazard Ratio
HR	Hormone receptor
HRQoL	health-related quality of life
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
KM	Kaplan Meyer
LABC	Locally advanced breast cancer
LoE	Level of Evidence
MBC	Metastatic breast cancer
NAC	Neoadjuvante Chemotherapie
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds Ratio
ORR	Overall response rate
ORR	Objective response rate
OS	Overall survival
pCR	Pathologisch komplette Remission

PFS	Progression-free survival
PR	Progesterone receptor
PTEN	phosphatase and tensin homolog
RCT	Randomized controlled trials
RR	Relatives Risiko
RWE	real world evidence
SERD	selective estrogen receptor degrader
SG	anti-Trop2 sacituzumab govitecan
SIGN	Scottish Intercollegiate Guidelines Network
T-DXd	trastuzumab deruxtecan
TEAEs	treatment emergent adverse events
TRIP	Turn Research into Practice Database
VTE	Venous thromboembolism
WHO	World Health Organization

1 Indikation

Adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment.

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 (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 13.03.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 3208 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. *Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet.* 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 12 Referenzen eingeschlossen.

Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten CR identifiziert.

3.2 Systematische Reviews

Su H et al., 2024 [11].

Efficacy and Safety of Cyclin-Dependent Kinase 4/6 Inhibitors in Patients with Breast Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials and Real-World Studies

Fragestellung

We systematically reviewed the large-scale clinical trials and real-world data to investigate the efficacy and safety of CDK4/6 inhibitors in patients with breast cancer.

Methodik

Population:

- patients with breast cancer

Intervention/Komparator:

- receiving CDK4/6 inhibitors

Endpunkte:

- survival outcomes (OS, PFS)
- or adverse effects

Recherche/Suchzeitraum:

- PubMed, Embase, and Cochrane Library
- before January 2024

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool […] for RCTs
- Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool for nonrandomized studies
- modified Newcastle–Ottawa Scale (NOS) was used to assess single-arm nonrandomized studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 121 studies
- 41 prospective trials
- 80 retrospective studies

Charakteristika der Population/Studien:

- sample sizes ranged from 101 to 6442
- total of 69,535 patients

- Supplementary Table 1. Characteristics of included studies

Data Source	No. of patients (%)	Age, year, median (range)	Type of breast cancer	Follow-up duration, month	No. of postmenopausal patients (%)	No. of patients with ≥ 2 sites of metastasis (%)	No. of patients with visceral metastases	Type of medication
MONARCH series								
MONARCH 1: phase 2 single-arm, open-label trial	132	58 (36–89)	HR+/HER2-MBC	18	NA	113 (85.6)	119 (90.2)	Abemaciclib
MONARCH 2: global, randomized, double-blind, phase III trial	A: 446 (66.7) C: 223 (33.3)	A: 59 (32-91) C: 62 (32-87)	HR+/HER2-ABC	Median: 19.5	A: 371 (83.2) C: 180 (80.7)	NA	A: 245 (54.9) C: 128 (57.4)	A: Abemaciclib + fulvestrant C: Fulvestrant
MONARCH 3: global, randomized, double-blind, placebo-controlled phase 3 study	A: 328 (66.5) C: 165 (33.5)	A: 63 (38-87) C: 63 (32-88)	HR+/HER2-ABC	Median: 17.8	A: 328 (100) C: 165 (100)	No. of organ sites A: 230 (70.1) C: 117 (70.9)	A: 172 (52.4) C: 89 (53.9)	A: Ribociclib + nonsteroidal AI C: Placebo + nonsteroidal AI

MONARCH plus: Multinational, randomized, double-blind, phase III study; 2016-2019	Cohort A: A: 207 (44.7) C: 99 (21.4) Cohort B: A: 1104 (22.5) C: 53 (11.4)	Cohort A: A: 54 (32-83) C: 54 (27-77) Cohort B: A: 60 (36, 80) C: 60 (30, 80)	HR+/HER2-ABC	Median Cohort A: A: 16 C: 16 Cohort B: A: 12.2 C: 11.1	Cohort A: A: 207 (100) C: 99 (100) Cohort B: A: 104 (100) C: 53 (100)	NA	Cohort A: A: 126 (60.9) C: 59 (59.6) Cohor B: A: 64 (61.5) C: 31 (58.5)	Cohort A: A: Abemaciclib + Non-steroidal AI C: Placebo + Non-steroidal AI Cohort B: A: Abemaciclib + fulvestrant C: Placebo + fulvestrant
monarcHER: Multinational, phase 2, randomised, three-group, open-label trial	A: 79 (33.3) B: 79 (33.3) C: 79 (33.3)	A: 55 (47–62) B: 54 (47–62) C: 57 (47–67)	HR+/HER2-ABC	Median (IQR) 19.0 (14.7-25.1)	NA	NA	A: 58 (73) B: 56 (71) C: 48 (61)	A: Abemaciclib + trastuzumab + fulvestrant B: Abemaciclib + trastuzumab C: trastuzumab + single-agent chemotherapy
NeoMONARCH: multicenter, randomized, open-label, phase II	AA: 74 (33.0) A: 76 (34.0) C: 74	AA: 63 (52–92) A: 62 (51–86) C: 65 (42–	stage I–IIIB HR+/HER2-breast cancer	NA	AA: 74 (100) A: 76 (100) C: 74 (100)	NA	NA	AA: Abemaciclib + anastrozole A: Abemaciclib

study	(33.0)	83)						C: Anastrozole
nextMONARCH: open-label, randomized, controlled, phase 2 study	A + T: 78 (33.3) A-150: 79 (33.4) A-200: 77 (33.3)	A+T: 53 (32-77) A-150: 56 (32–81) A-200: 56 (35-77)	HR+/HER2-MBC	Median: 27.2	NA	NA	NA	A+T: abemaciclib (150 mg BID) with tamoxifen (20 mg daily) A-150: abemaciclib (150 mg BID) A-200: abemaciclib (200 mg BID) + prophylactic loperamide (2 mg daily)
MonarchE: open-label, global, randomized, and phase III trial	A: 2808 (49.8) C: 2829 (50.2)	A: 51 (44-60) [a] C: 51 (44-60) [a]	HR+/HER2-node positive, high risk early breast cancer	Median: 15.5	A: 1587 (56.5) C: 1597 (56.5)	NA	NA	A: Abemaciclib+ET C: ET
PALOMA series								

PALOMA-1: international, phase 2, open-label, multicenter, randomized clinical trial	P: 84 (51.0) C: 81 (49.0)	P: 63 (41–89) C: 64 (38–84)	HR+/HER2- ABC	Median: P: 69.3 C: 59.0	P: 84 (100) C: 81 (100)	NA	P: 38 (45.2) C: 43 (53.1)	P: Palbociclib + letrozole C: Letrozole
PALOMA-2: double-blind, placebo-controlled, multicenter, phase III randomized trial	P: 444 (66.7) C: 222 (33.3)	P: 62 (30–89) C: 61 (28–88)	ER+/HER2- ABC	NA	P: 444 (100) C: 222 (100)	P: 306 (68.9) C: 156 (70.2)	P: 214 (48.2) C: 110 (49.5)	P: Palbociclib + letrozole C: Placebo + letrozole
PALOMA-3: international, multicenter, double- blind, randomized phase 3 trial.	P: 347 (66.6) C: 174 (33.4)	P: 57 (30–88) C: 56 (29–80)	HR+/HER2- ABC	Median (IQR) 8.9 (8.7-9.2)	P: 275 (79.3) C: 138 (79.3)	NA	P: 206 (59.3) C: 105 (60.3)	P: Palbociclib + fulvestrant C: Placebo + fulvestrant
PALOMA-4 international, multicenter, double-blind, randomized phase 3 trial.	P: 169 (49.7) C: 171 (50.3)	P: 54.0 (31-70) C: 54.0 (29-70)	ER+/HER2- ABC	Median: 52.8	P: 169 (100) C: 171 (100)	P: 117 (69.2) C: 121 (70.8)	P: 94 (55.6) C: 96 (56.1)	P: Palbociclib + letrozole C: Placebo + letrozole

MONALEESA series								
MONALEESA-2: global, randomized, double-blind, placebo-controlled, phase III trial	R: 114 (50.2) C: 113 (49.8)	R: 62.5 (37.0–82.0) C: 63.0 (29.0–88.0)	HR+/HER2- MBC	Median: 27	R: 114 (100) C: 113 (100)	R: 80 (70.2) C: 77 (68.1)	R: 53 (46.5) C: 55 (48.6)	R: Ribociclib + letrozole C: Placebo + letrozole
MONALEESA-3 phase III, double-blind, placebo-controlled international study	R: 484 (66.7) C: 242 (33.3)	R: 63.0 (31-89) C: 63.0 (34-86)	HR+/HER2- ABC	NA	R: 484 (100) C: 242 (100)	R: 331 (68.4) C: 168 (69.4)	R: 293 (60.5) C: 146 (60.3)	R: Ribociclib + fulvestrant C: Placebo + fulvestrant
MONALEESA-7 randomized, double-blind, placebo-controlled, phase III trial in 30 countries	R: 335 (49.9) C: 337 (50.1)	R: 43 (25–58) C: 45 (29–58)	HR+/HER2- ABC	Median (IQR) 19.2 (16.2-23.2)	All patients were pre- or peri-menopausal	R: 222 (66.3) C: 220 (65.3)	R: 193 (57.6) C: 188 (55.8)	R: Ribociclib + AI C: AI
Other double-arm trials								

FLIPPER multicenter, double- blind, placebo-controlled, randomized phase II study, Spain & Ireland; 2016-2018	P: 94 (49.7) C: 95 (50.3)	P: 64 (38-81) C: 64 (42-82)	HR+/HER2- ABC	Median: 28.6	189 (100)	P: 71 (75.5) C: 72 (75.8)	P: 57 (60.6) C: 57 (60.0)	P: Palbociclib + fulvestrant C: Placebo + fulvestrant
NEOPAL: multicenter, international, randomised phase 2 trial	P: 53 (50) C: 53 (50)	P: 65 ± 7 [c] C: 62 ± 8 [c]	ER+/HER2- BC	Median (Range) 40.4 (0-56.6)	106 (100)	NA	NA	P: Palbociclib + letrozole C: Chemotherapy
YoungPEARL multicenter, open- label, randomised, controlled, phase 2 study, Korea; 2016-2018	P: 92 (51.7) C: 86 (48.3)	P: 44 [b] C: 44 [b]	HR+/HER2- ABC/ MBC	NA	0 (0)	NA	P: 45 (48.9) C: 43 (50.0)	P: Palbociclib + ET C: Capecitabine
PALLAS randomised, open-label,phase 3 study	P: 2883 (50.1) C: 2877	P: 52 (45-61) C: 52 (45-60)	HR+/HER2- early breast cancer (stage II- III)	Median (IQR) 23.7 (16.9-29.2)	P: 1312 (45.5) C: 1330 (46.2)	NA	NA	P: Palbociclib + ET C: ET

conducted in 21 countries	(50.5)							
PEARL multicenter, international, openlabel, controlled, phase 3 study	Cohort 1: P: 153 (25.5) C: 143 (23.8) Cohort 2: P: 149 (24.8) C: 156 (26.0)	Cohort 1: P: 60 (31-89) C: 60 (38-87) Cohort 2: P: 62 (38-86) C: 60 (33-85)	HR+/HER2- AI-resistant MBC	Median (Range) Cohort 1: NA Cohort 2: 13.5 (0.0-30.7)	601 (100)	NA	Cohort 1: P: 103 (67.3) C: 94 (65.7) Cohort 2: P: 97 (65.1) C: 102 (65.4)	Cohort 1: P: Palbociclib + exemestane C: Capecitabine Cohort 2: P: Palbociclib + fulvestrant C: Capecitabine
GO39932: Phaselа/Ib, multicenter, open- label study, 5 countries; 2017-2021	P: 64 (36.6) C: 111 (63.4)	P: 56.9 ± 10.9 C: 58.6 ± 11.0	ER+/HER2- locally ABC or MBC	NA	NA	NA	P:45 (70.3) C: 72 (64.9)	P: Palbociclib 125 mg + giredestrant 100 mg ± LHRH (if premenopausal) C: Giredestrant 10 mg (n = 6); giredestrant 30 mg (n = 41); giredestrant 90/100 mg ± LHRH (n = 55); giredestrant 250 mg ± LHRH

								(n = 9)
MAINTAIN randomized, phase II, double-blind placebo-controlled, trial; USA	R: 60 (50.4) C: 59 (49.6)	R: 55 (48-67) [a] C: 59 (51.5-65)[a]	HR+/HER2- MBC	Median (IQR); 18.2 (10.1-28.8)	NA	NA	R: 36 (60) C: 35 (59.3)	R: Ribociclib C: Placebo
PENELOPE-B double-blind, placebo-controlled, phase 3 study	P: 631 (50.5) C: 619 (49.5)	49 (19-79)	HR+/HER2- MBC	Median: 42.8	P: 331 (52.5) C: 303 (48.9)	NA	NA	P: Palbociclib + ET C: Placebo + ET
CORALLEEN Parallel-arm, multicenter, randomised, open-label, phase 2 trial, Spain	R: 49 (48.2) C: 52 (51.5)	Median (Range) R: 63.0 (56.5-70.3) C: 64.0 (58.3-71.8)	HR+/HER2- luminal B MBC	Days: Median (IQR) 200.0 (191.2-206.0)	NA	R: 49 (100) C: 52 (100)	NA	R: Ribociclib + letrozole C: Chemotherapy

PRAEGNANT: Prospective; [multicenter; Germany]; 2014-2019	I1 (1st line): 99 C1 (1st line): 132 I2 (2nd line): 71 C2 (2nd line): 125 I3 (3rd line): 41 C3(3rd line): 57	I1: 60.5 ± 13.4[c] C1: 62.9 ± 13.0[c] I2: 60.6± 12.4[c] C2: 61.3 ± 12.8[c] I3: 59.8 ± 11.4[c] C3: 62.4 ± 13.1[c]	HR+/HER2-ABC	NA	NA	NA	NAS	I: CDK4/6 inhibitor + ET C: ET
FUTURE Prospective; [55 institutions, Japan]; 2018-2020	P: 72 (31.3) C: 158 (68.6)	P: 67 (44-80) C: 67 (44-80)	HR+/HER2-ABC/MBC	Median: I: 8.9 C: 23.8	NA	NA	P: 38 (52.8) C: 82 (51.9)	P: Palbociclib + fulvestrant C: Fulvestrant

Qualität der Studien:

Supplementary Table 2. Methodological quality assessment (RoB 2.0) of the randomized trials.

Study	Bias from the randomization process	Bias caused by deviations from intended interventions	Bias caused by missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
MONARCH 2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONARCH 3	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONARCH plus	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
monarcHER	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
NeoMONARCH	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
nextMONARCH	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
MonarchE	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
PALOMA-1	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
PALOMA-2	Low risk [a]	Low risk	Low risk	Low risk	Low risk	Low risk
PALOMA-3	Low risk [a]	Low risk	Low risk	Low risk	Low risk	Low risk
PALOMA-4	Low risk [a]	Low risk	Low risk	Low risk	Low risk	Low risk
MONALEESA-2	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONALEESA-3	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONALEESA-7	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
CORALLEEN	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
FLIPPER	Some concerns [a]	Low risk	Low risk	Low risk	Low risk	Some concerns
Hurvitz [2023]	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
Llombart-Cussac [2021]	Low risk	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
MAINTAIN	Low risk [a]	Low risk	Low risk	Low risk	Low risk	Low risk

NEOPAL	Some concerns [b]	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
PALLAS	Low risk [a]	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
PARSIFAL	Some concerns [b]	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
PEARL	Some concerns [b]	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
PENELOPE-B	Some concerns [a]	Low risk	Low risk	Low risk	Low risk	Some concerns
TREnd	Some concerns [b]	Low risk	Low risk	Some concerns [a]	Low risk	Some concerns
YoungPEARL	Some concerns [a]	Low risk	Low risk	Low risk	Low risk	Some concerns

[a] No information regarding blinding or no blinding process was conducted.

[b] No detailed information regarding concealment or randomization

Studienergebnisse:

Table 1 Summary of the pooled results (double arm studies)

Outcome		Abemaciclib	Palbociclib	Ribociclib	Mix	Total
Survival, HR [95% CI]	OS	0.79 [0.68–0.91]*	0.82 [0.73–0.92]*	0.76 [0.68–0.85]*	0.49 [0.37–0.64]*	0.77 [0.72–0.83]*
	PFS	0.55 [0.44–0.69]*	0.68 [0.60–0.76]*	0.60 [0.54–0.68]*	NA	0.63 [0.58–0.70]*
Adverse effects, RR [95% CI]	≥ Grade 3 adverse effects	2.25 [1.64–3.08]#	2.21 [1.32–3.69]#	1.47 [0.48–4.51]	NA	2.10 [1.58–2.78]#
	Neutropenia	5.62[2.29–3.78]#	7.19 [3.91–13.24]#	6.87 [1.76–26.88]#	NA	6.63 [4.31–10.20]#
	Anemia	4.49 [2.50–8.08]#	2.63 [1.97–3.50]#	1.58 [0.79–3.17]	NA	2.69 [2.07–3.50]#
	Thrombo cytopenia	6.58 [5.20–8.31]#	5.95 [3.65–9.69]#	2.98 [1.27–6.97]#	NA	5.37 [3.92–7.35]#
	Leukopenia	4.82 [2.81–8.25]#	5.54 [2.65–11.58]#	7.62[4.60–12.61]#	NA	5.82 [3.58–9.44]#
	Lymphopenia	4.50 [3.28–6.17]#	2.00 [1.00–4.03]#	NA	NA	3.17 [1.92–5.23]#
	Diarrhea	4.32 [2.29–8.15]#	1.17 [0.74–1.86]	1.26 [0.97–1.63]	NA	1.63 [1.07–2.46]#
	Constipation	1.39 [0.86–2.24]	1.56 [1.19–2.05]#	1.22 [0.80–1.88]	NA	1.44 [1.19–1.74]#
	Vomiting	2.41 [1.66–3.50]#	1.16 [0.76–1.78]	1.54 [1.00–2.39]#	NA	1.70 [1.24–2.35]#
	Nausea	1.64 [1.29–2.07]#	1.17 [0.83–1.65]	1.53 [1.23–1.91]#	NA	1.36 [1.14–1.63]#
	Fatigue	1.46 [1.05–2.03]#	1.42 [1.14–1.77]#	1.04 [0.89–1.23]	NA	1.31 [1.12–1.54]#
	Rash	2.34 [1.81–3.04]#	2.11 [1.54–2.89]#	1.99 [1.36–2.90]#	NA	2.16 [1.83–2.54]#
	QT prolong	1.52 [0.06–37.17]	1.48 [1.03–2.13]	2.69 [1.75–4.13]#	NA	1.89 [1.44–2.50]#
	ALT increase	2.08 [1.60–2.70]#	1.09 [0.89–1.33]	1.58 [0.81–3.06]	NA	1.57 [1.19–2.07]#
	Creatinine increase	9.49 [6.01–14.98]#	2.32 [1.17–4.61]#	NA	NA	7.23 [3.43–15.23]#

NA not available, *CI* confidence interval, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival

*CDK 4/6 inhibitor is significantly better than control or other intervention

#Control or other intervention is significantly better than CDK 4/6 inhibitor

OS

Three double-arm studies that compared abemaciclib with control or other interventions reported OS. The pooled results revealed a significantly higher OS rate in the abemaciclib group [hazard ratio (HR) = 0.79, 95% confidence interval (CI) 0.68–0.91] than in the control group. In addition, eight double-arm studies comparing palbociclib with control or other interventions reported OS. The pooled results revealed a significantly higher OS rate in the palbociclib group (HR = 0.82, 95% CI 0.73–0.92) than in the control group. In addition, three studies comparing ribobiclib with control or other interventions reported OS. The pooled results revealed a significantly higher OS rate in the ribobiclib group (HR = 0.76, 95% CI

0.68–0.85) than in the control group. Another study that treated patients with different CDK4/6 inhibitors also reported significant differences in the OS rate. Overall, the pooled results indicated a significantly higher OS rate in the CDK4/6 inhibitor group (HR = 0.77, 95% CI 0.72–0.83) than in the control group.

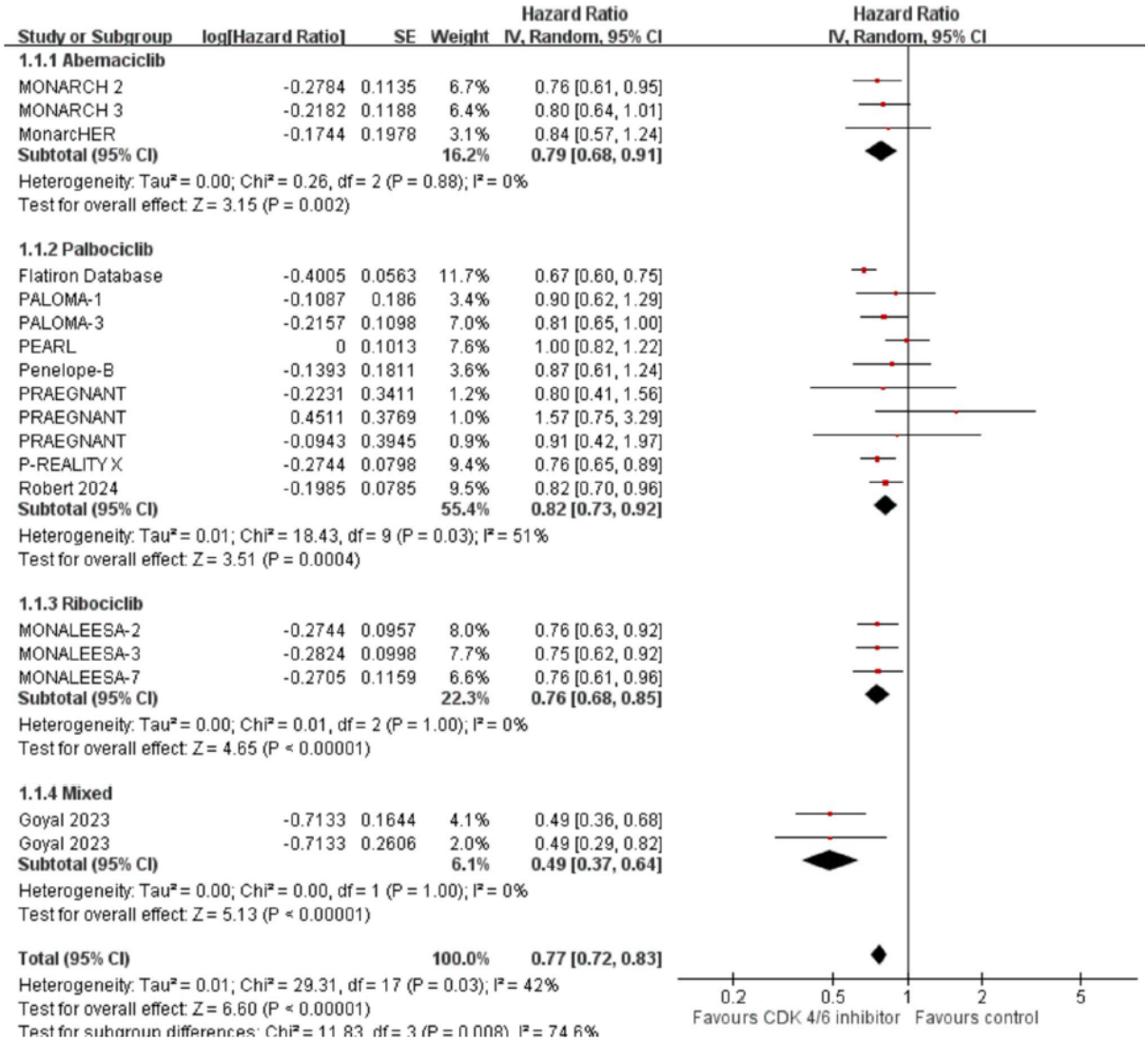


Fig. 2 Forest plot comparing OS in double-arm studies

PFS

Four double-arm studies comparing abemaciclib with control or other interventions reported PFS. The pooled results revealed a significantly higher PFS rate in the abemaciclib group (HR = 0.55, 95% CI 0.44–0.69) than in the control group. In addition, 11 double-arm studies comparing palbociclib with control or other interventions reported PFS. The pooled results revealed a significantly higher PFS rate in the palbociclib group (HR = 0.68, 95% CI 0.60–0.76) than in the control group. Furthermore, four studies comparing ribobiclib with control or other interventions reported OS. The pooled results revealed a significantly higher PFS rate in the ribobiclib group (HR = 0.60, 95% CI 0.54–0.68) than in the control group. Overall, the pooled results revealed a significantly higher PFS rate in the CDK4/6 inhibitor group (HR = 0.63, 95% CI 0.58–0.70) than in the control group (Fig. 4).

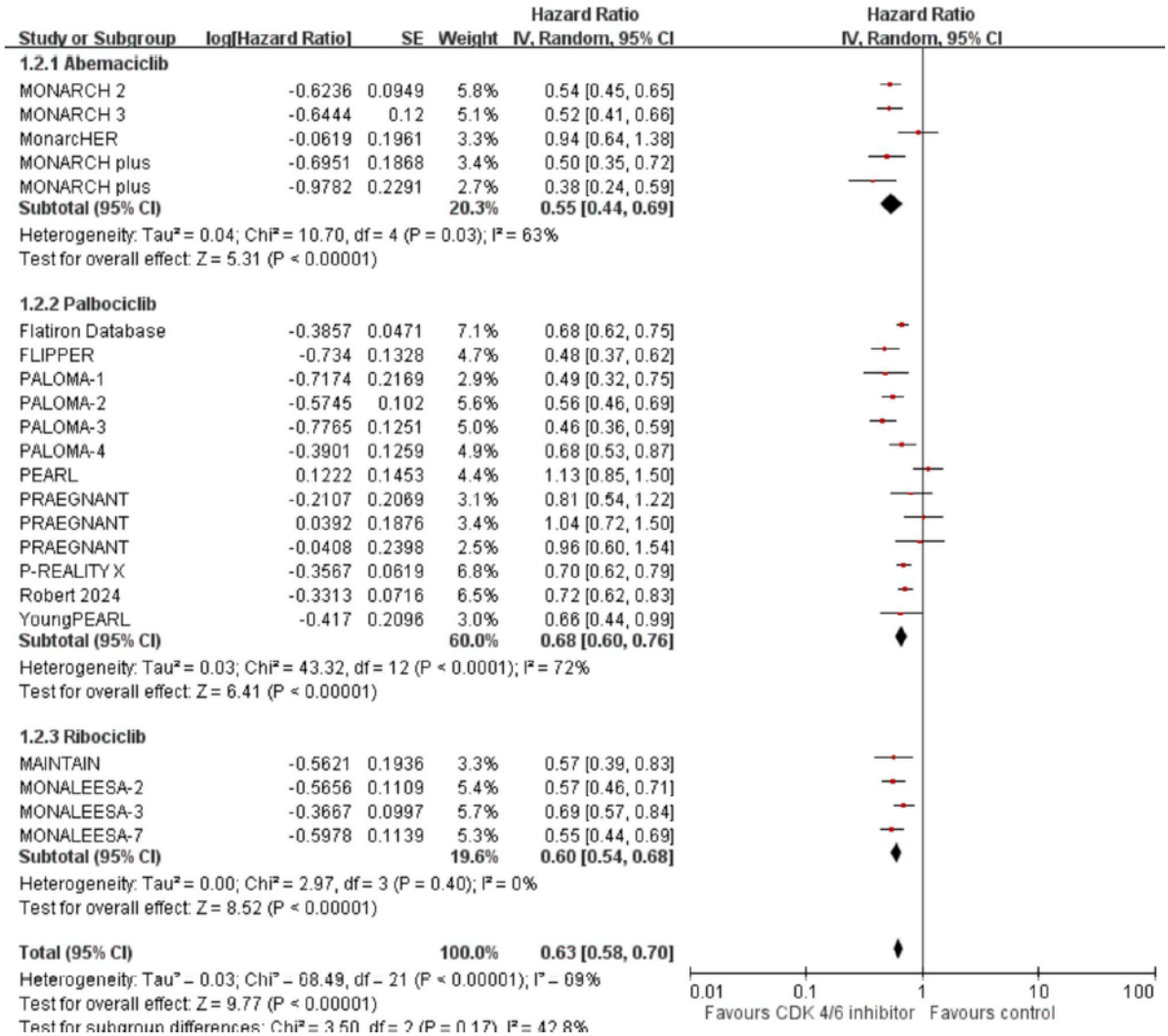


Fig. 4 Forest plot comparing PFS in double-arm studies

Anmerkung/Fazit der Autoren

The findings of this study revealed that CDK4/6 inhibitors can significantly improve both OS and PFS in patients with HR-positive, HER2-negative, advanced or metastatic breast cancer. However, CDK4/6 inhibitors may result in several adverse effects, including hematological and gastrointestinal side effects.

Kommentare zum Review

Studien mit einem n< 100 wurden ausgeschlossen

Luo C et al., 2024 [6].

CDK4/6 inhibitors plus endocrine therapy vs. placebo plus endocrine therapy for HR+/ HER2- advanced breast cancer: a phase III RCTs based meta-analysis

Fragestellung

We compared the antitumor efficacy and adverse effects (AEs) between CDK4/6 inhibitors + ET (CET) and placebo + ET (PET) by conducting a phase III randomized controlled trials (RCTs) based meta-analysis.

Methodik

Population:

- patients diagnosed with HR+/HER2advanced breast cancer

Intervention:

- CDK4/6 inhibitors + ET, defined as the CET group.

Komparator:

- placebo + ET, defined as the PET group

Endpunkte:

- survival, responses, and AEs

Recherche/Suchzeitraum:

- PubMed, Scopus, EMBASE, ScienceDirect, Ovid MEDLINE, the Cochrane Library, and Web of Science
- from their inception until April 1, 2024

Qualitätsbewertung der Studien:

- Jadad scale
- Cochrane Risk of Bias Assessment Tool
- GRADE approach

Ergebnisse

Anzahl eingeschlossener Studien:

- twenty-six studies from seven RCTs (DAWNA-2, MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-3, PALOMA-2, and PALOMA-4)
- The CET group comprised 2,103 patients, while the PET group comprised 1,463 patients

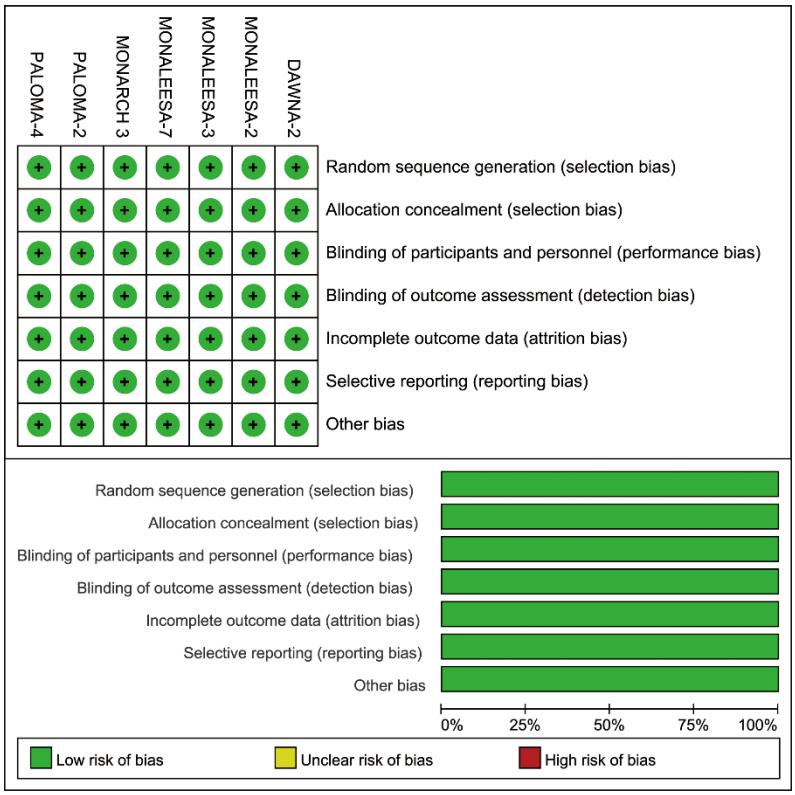
Charakteristika der Population/Studien:

Table 1 Characteristics of the included studies

Study	Register number	Phase	Period	Groups	Patients	Age (Mean, year)	CDK4/6 inhibitor	Endocrine therapy	Menopausal status		ECOG PS			Hormone receptor status		Follow up (months)
									Post-M	Pre-M	0	1	2	ER+	PR+	
DAWNA-2 [9]	NCT03966898	III	2019.07-2020.12	CET group	303	55	Dalpiciclib	Letrozole or Anastrozole	183	120	141	161	0	302	258	21.6
				PET group	153	55			99	54	69	84	0	153	134	
MONALEESA-2 [10,19–23]	NCT01958021	III	2014.01-2015.03	CET group	334	62	Ribociclib	Letrozole	334	0	205	129	0	332	271	80.0
				PET group	334	63			334	0	202	132	0	333	278	
MONALEESA-3 [11,24–26]	NCT02422615	III	2015.06-2016.06	CET group	237	63	Ribociclib	Fulvestrant	237	0	152	92	0	236	173	70.8
				PET group	128	63			128	0	77	44	0	127	88	
MONALEESA-7 [12,27,28]	NCT02278120	III	2014.12-2016.08	CET group	288	43	Ribociclib	Tamoxifen or Letrozole or Anastrozole	0	288	211	75	0	285	249	53.5
				PET group	290	45			0	290	219	67	1	288	248	
MONARCH-3 [13,29–32]	NCT02246621	III	2014.11-2015.11	CET group	328	63	Abemaciclib	Letrozole or Anastrozole	328	0	192	136	0	328	255	70.2
				PET group	165	63			165	0	104	61	0	165	127	
PALOMA-2 [14,33–37]	NCT02246621	III	2013.02-2014.07	CET group	444	62	Palbociclib	Letrozole	444	0	257	178	9	444	-	90.1
				PET group	222	61			222	0	102	117	3	222	-	
PALOMA-4 [15]	NCT02297438	III	2015.03-2020.08	CET group	169	54	Palbociclib	Letrozole	169	0	88	85	0	169	-	52.8
				PET group	171	54			171	0	81	90	0	171	-	

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CDK4/6: Cyclin-dependent kinase 4/6; ECOG PS: Eastern Cooperative Oncology Group Performance Status; M: Menopausal; PET: Placebo plus endocrine therapy

Qualität der Studien:



Studienergebnisse:

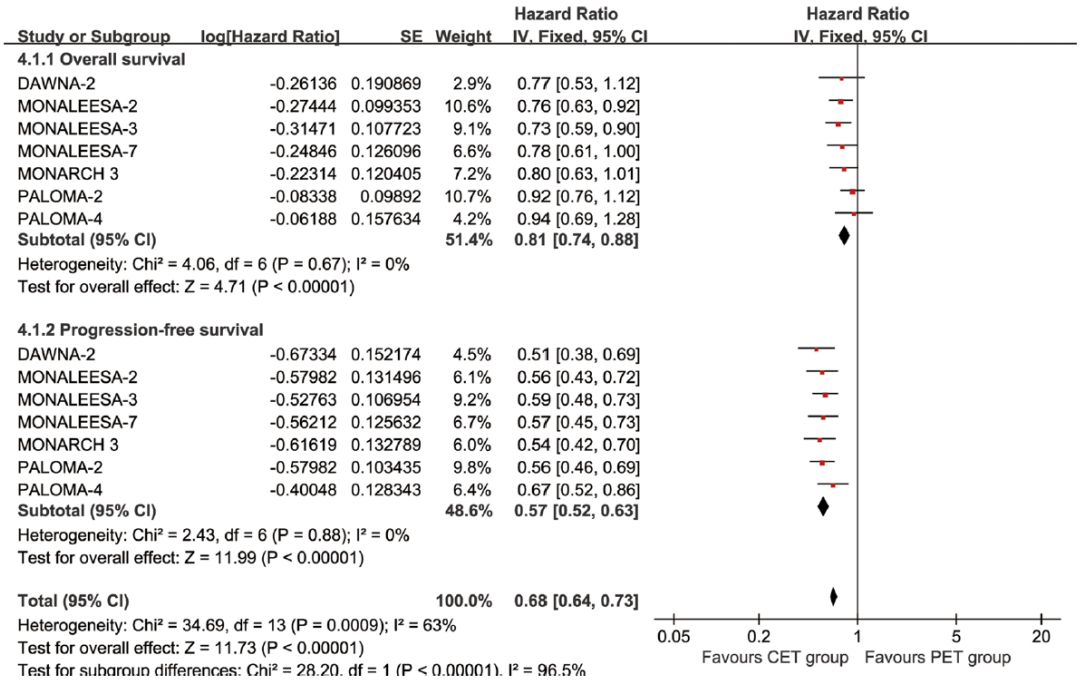


Fig. 2 Forest plots of overall survival and progression-free survival associated with CET group versus PET group

Survival (OS and PFS)

The CET group achieved better OS (HR: 0.81 [0.74, 0.88], p < 0.00001) and PFS (HR: 0.57 [0.52, 0.63], p < 0.00001) (Fig. 2). OSR 24–60 m significantly favored the CET group (Figure

S2). Meanwhile, PFSR 6–60 m significantly favored the CET group (Figure S3). As survival prolonged, CET also exhibited a growing OS and PFS advantage over PET (Fig. 3).

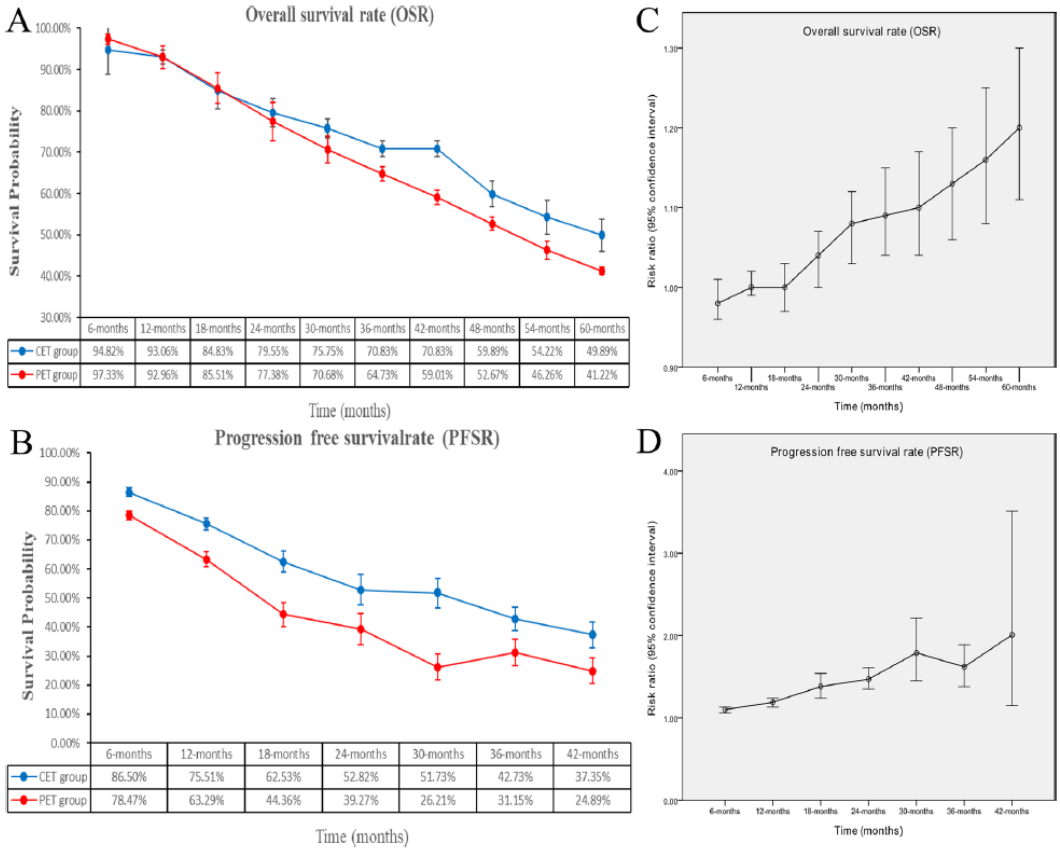


Fig. 3 Comparisons of overall survival rate (6–60 months, **A**: trend of overall survival rate; **C**: trend of risk ratios) and progression-free survival rate (6–42 months, **B**: trend of progression-free survival rate; **D**: trend of risk ratios) associated with CET group versus PET group

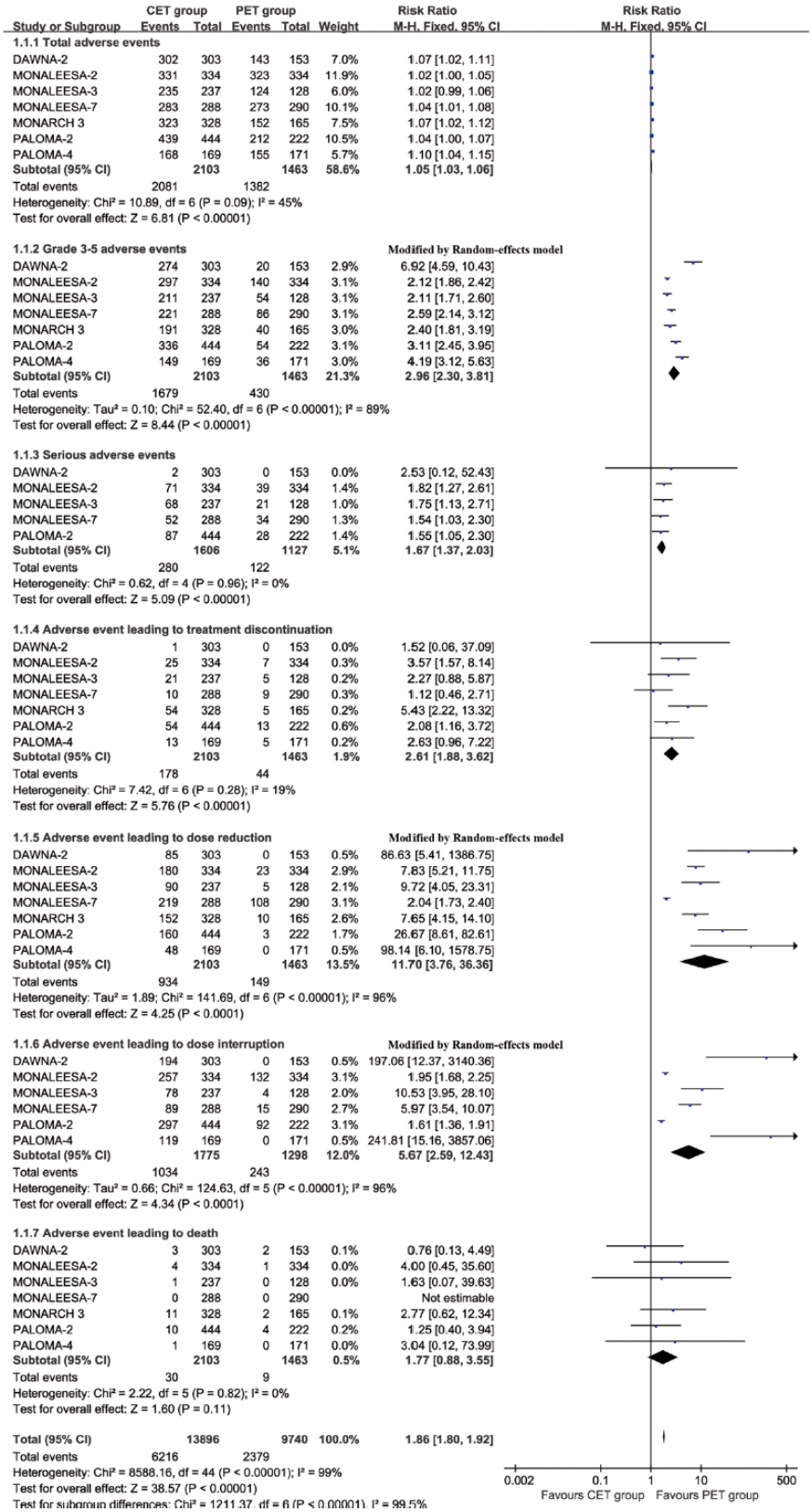
Subgroup analysis of survival (OS and PFS)

We subgroup analyzed survival (OS and PFS) according to Age, Race category, Menopausal status, Hormone receptor status, ECOG PS, Disease-free interval, Metastatic status, CDK4/6 inhibitor therapy partner, ET partner, Previous adjuvant or neoadjuvant ET, Previous ET type, and Previous neoadjuvant or adjuvant chemotherapy. OS and PFS generally favored the CET group in all subgroups (Table 2).

Table 2 Subgroup analysis of overall survival and progression-free survival

Subgroups	No. of studies	Overall Survival		No. of studies	Progression-free survival	
		HR (95% CI)	*P*		HR (95% CI)	*P*
Total	7	0.81 [0.74, 0.88]	< 0.00001	7	0.57 [0.52, 0.63]	< 0.00001
Age						
< 65 years	4	0.79 [0.69, 0.91]	0.001	6	0.55 [0.49, 0.62]	< 0.00001
> 65 years	4	0.80 [0.69, 0.94]	0.007	6	0.55 [0.49, 0.62]	< 0.00001
Race category						
Asian	7	0.78 [0.66, 0.93]	0.005	6	0.51 [0.38, 0.70]	< 0.0001
Others	5	0.81 [0.73, 0.91]	0.0004	4	0.61 [0.53, 0.70]	< 0.00001
ECOG PS						
0	5	0.80 [0.67, 0.96]	0.02	7	0.56 [0.50, 0.64]	< 0.00001
1	5	0.78 [0.67, 0.90]	0.0009	7	0.57 [0.50, 0.66]	< 0.00001
Menopausal status						
Postmenopausal	4	0.78 [0.70, 0.88]	< 0.00001	6	0.58 [0.52, 0.64]	< 0.00001
Premenopausal or perimenopausal	1	0.78 [0.61, 1.00]	0.05	2	0.56 [0.45, 0.70]	< 0.00001
Hormone receptor status						
ER positive + PR positive	4	0.80 [0.70, 0.90]	0.0004	4	0.58 [0.50, 0.67]	< 0.00001
Others	4	0.63 [0.51, 0.79]	< 0.0001	4	0.39 [0.29, 0.52]	< 0.00001
Disease-free interval						
De-novo metastatic disease	4	0.69 [0.48, 1.01]	0.06	6	0.50 [0.42, 0.60]	< 0.00001
Existing disease	3	0.89 [0.76, 1.03]	0.12	4	0.58 [0.49, 0.68]	< 0.00001
Number of metastatic sites						
< 3	3	0.77 [0.66, 0.90]	0.001	3	0.59 [0.49, 0.71]	< 0.00001
> 3	5	0.81 [0.70, 0.94]	0.004	5	0.55 [0.47, 0.64]	< 0.00001
Visceral metastases at study entry						
Yes	2	0.81 [0.66, 0.99]	0.04	4	0.61 [0.52, 0.72]	< 0.00001
No	1	0.98 [0.74, 1.30]	0.89	3	0.53 [0.43, 0.65]	< 0.00001
Presence of liver or lung metastases						
Yes	3	0.39 [0.10, 1.58]	0.19	3	0.57 [0.48, 0.67]	< 0.00001
No	3	0.72 [0.60, 0.86]	0.0003	3	0.58 [0.48, 0.71]	< 0.00001
Bone-only disease						
Yes	5	0.72 [0.58, 0.88]	0.002	5	0.50 [0.40, 0.64]	< 0.00001
No	4	0.81 [0.72, 0.91]	0.0004	4	0.59 [0.52, 0.67]	< 0.00001
CDK4/6 inhibitor therapy partner						
Dalpiciclib	1	0.77 [0.53, 1.12]	0.17	1	0.51 [0.38, 0.69]	< 0.00001
Ribociclib	3	0.75 [0.67, 0.85]	< 0.00001	3	0.58 [0.50, 0.66]	< 0.00001
Abemaciclib	1	0.80 [0.63, 1.01]	0.06	1	0.54 [0.42, 0.70]	< 0.00001
Palbociclib	2	0.93 [0.79, 1.09]	0.36	2	0.60 [0.51, 0.70]	< 0.00001
Endocrine therapy partner						
Letrozole	3	0.85 [0.75, 0.97]	0.01	5	0.58 [0.51, 0.65]	< 0.00001
Anastrozole	-	-	-	2	0.51 [0.37, 0.71]	< 0.0001
Fulvestrant	1	0.73 [0.59, 0.90]	0.003	1	0.59 [0.48, 0.73]	< 0.00001
Tamoxifen	1	0.70 [0.47, 1.04]	0.08	1	0.59 [0.39, 0.89]	0.01
Previous adjuvant or neoadjuvant endocrine therapy						
Yes	4	0.81 [0.70, 0.94]	0.005	5	0.57 [0.49, 0.66]	< 0.00001
No	5	0.79 [0.65, 0.96]	0.02	6	0.56 [0.49, 0.65]	< 0.00001
Previous endocrine therapy type						
Selective oestrogenreceptor modulator	2	0.88 [0.68, 1.14]	0.32	5	0.61 [0.51, 0.74]	< 0.00001
Aromatase inhibitors	2	0.58 [0.40, 0.83]	0.003	5	0.56 [0.47, 0.68]	< 0.00001
Previous neoadjuvant or adjuvant chemotherapy						
Yes	3	0.83 [0.70, 0.98]	0.03	3	0.58 [0.48, 0.70]	< 0.00001
No	3	0.79 [0.59, 1.06]	0.11	3	0.53 [0.43, 0.64]	< 0.00001

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CDK4/6: Cyclin-dependent kinase 4/6; CI: Confidence interval; ECOG PS: Participants, Intervention, Control, Outcome and Study design Performance Status; HR: Hazard ratio; PET: Placebo plus endocrine therapy



Toxicity

In summary, the CET group resulted in more total AEs (RR: 1.05 [1.03, 1.06]), grade 3–5 AEs (RR: 2.96 [2.30, 3.81]), serious AEs (RR: 1.67 [1.37, 2.03]), AEs leading to treatment discontinuation (RR: 2.61 [1.88, 3.62]), AEs leading to dose reduction (RR: 11.70 [3.76,

36.36]), and AEs leading to dose interruption (RR: 5.67 [2.59, 12.43]). However, AEs leading to death (RR: 1.31 [1.21, 1.42]) were similar between the two groups (Fig. 5).

In the assessment of any grade AEs, more cases of neutropenia, decreased white blood cell count, leukopenia, nausea, fatigue, diarrhea, anemia, hyponatremia, thrombocytopenia, alopecia, vomiting, hypokalemia, cough, constipation, decreased appetite, abdominal pain, increased blood creatinine, rash, pruritus, urinary tract infection, hypokalaemia, stomatitis, pyrexia, prolonged electrocardiogram QT, dry skin, hypophosphataemia, dysgeusia, and oropharyngeal pain were observed in the CET group (Table S5). The top 5 any grade AEs were neutropenia (74.66%), decreased white blood cell count (49.55%), leukopenia (42.80%), nausea (37.54%), and fatigue (33.56%) (Table 3). Incidence rate of any grade interstitial lung diseases (ILDs) tended to be higher in the CET group without statistical significance (Figure S5).

In the assessment of grade 3–5 AEs, more cases of leukopenia, decreased white blood cell neutropenia, count, increased alanine aminotransferase, anemia, hyponatremia, increased aspartate aminotransferase, thrombocytopenia, diarrhea, fatigue, and decreased appetite were found in the CET group (Table S6). The top 5 grade 3–5 AEs were neutropenia (59.39%), leukopenia (24.11%), decreased white blood cell count (12.99%), hypertension (7.03%), and increased alanine aminotransferase (5.91%) (Table 4). Incidence rate of grade 3–5 ILDs also tended to be higher in the CET group without statistical significance (Figure S5).

Table 3 Any grade adverse events (> 20% in the CET group)

Adverse events	Studies involved	CET group		PET group		Risk ratio [95% CI]	*P*
		Event/total	%	Event/total	%		
Neutropenia	7	1570/2103	74.66%	106/1463	7.25%	10.92 [7.62, 15.65]	< 0.00001
White blood cell count decreased	2	328/662	49.55%	50/499	10.02%	4.93 [1.74, 13.99]	0.003
Leukopenia	7	900/2103	42.80%	79/1463	5.40%	7.41 [5.69, 9.66]	< 0.00001
Nausea	6	726/1934	37.54%	301/1292	23.30%	1.67 [1.47, 1.90]	< 0.00001
Fatigue	6	604/1800	33.56%	359/1310	27.40%	1.18 [1.05, 1.32]	0.003
Diarrhea	7	697/2103	33.14%	288/1463	19.69%	1.51 [1.16, 1.96]	0.002
Anemia	7	670/2103	31.86%	122/1463	8.34%	3.64 [2.57, 5.14]	< 0.00001
Hypercalcemia	1	96/328	29.27%	50/165	30.30%	0.97 [0.73, 1.29]	0.81
Hyponatremia	1	90/328	27.44%	37/165	22.42%	1.22 [0.88, 1.71]	0.24
Thrombocytopenia	4	328/1204	27.24%	27/836	3.23%	7.59 [4.86, 11.86]	< 0.00001
Alopecia	6	472/1800	26.22%	159/1310	12.14%	2.10 [1.78, 2.48]	< 0.00001
Arthralgia	7	550/2103	26.15%	409/1463	27.96%	0.98 [0.88, 1.09]	0.61
Hot flush	4	305/1303	23.41%	275/974	28.23%	0.86 [0.71, 1.05]	0.05
Headache	5	375/1631	22.99%	257/1139	22.56%	1.05 [0.87, 1.26]	0.50
Vomiting	6	436/1934	22.54%	192/1292	14.86%	1.63 [1.18, 2.25]	0.003
Hypokalemia	2	110/497	22.13%	29/336	8.63%	2.25 [1.51, 3.35]	< 0.0001
Hypocalcemia	1	72/328	21.95%	28/165	16.97%	1.29 [0.87, 1.92]	0.20
Cough	5	320/1472	21.74%	201/1145	17.55%	1.21 [1.03, 1.42]	0.02
Aspartate aminotransferase increased	5	308/1422	21.66%	167/1113	15.00%	1.50 [0.94, 2.41]	0.0002
Constipation	5	349/1631	21.40%	182/1139	15.98%	1.37 [1.16, 1.62]	0.0001
Alanine aminotransferase increased	5	301/1422	21.17%	165/1113	14.82%	1.55 [0.90, 2.66]	0.11
Back pain	5	331/1631	20.29%	229/1139	20.11%	1.04 [0.89, 1.21]	0.64

Abbreviations CET: CDK4/6 inhibitors plus endocrine therapy; CI: Confidence interval; PET: Placebo plus endocrine therapy; RR: Risk ratio

Table 4 Grade 3–5 adverse events (> 1% in the CET group)

Adverse events	Studies involved	CET group		PET group		Risk ratio [95% CI]	*P*
		Event/total	%	Event/total	%		
Neutropenia	7	1249/2103	59.39%	20/1463	1.37%	42.16 [20.45, 86.90]	< 0.00001
Leukopenia	7	507/2103	24.11%	7/1463	0.48%	27.95 [12.00, 65.11]	< 0.00001
White blood cell count decreased	2	86/662	12.99%	3/499	0.60%	21.99 [6.99, 69.19]	< 0.00001
Hypertension	3	65/925	7.03%	57/777	7.34%	1.11 [0.79, 1.54]	0.55
Alanine aminotransferase increased	5	84/1422	5.91%	15/1113	1.35%	3.51 [1.31, 9.44]	0.01
Hypokalemia	2	25/497	5.03%	4/336	1.19%	3.06 [0.04, 240.13]	0.62
Anemia	7	105/2103	4.99%	25/1463	1.71%	2.45 [1.54, 3.89]	< 0.00001
Hyponatremia	1	16/328	4.88%	0/165	0.00%	16.65 [1.01, 275.82]	0.05
Aspartate aminotransferase increased	5	54/1422	3.80%	13/1113	1.17%	3.38 [1.84, 6.21]	< 0.0001
Thrombocytopenia	4	33/1204	2.74%	4/836	0.48%	4.45 [1.41, 14.02]	0.001
Diarrhea	7	51/2103	2.43%	10/1463	0.68%	2.53 [1.16, 5.53]	0.0008
Electrocardiogram QT prolonged	3	18/760	2.37%	3/614	0.49%	2.85 [0.81, 9.95]	0.03
Pneumonia	1	6/303	1.98%	1/153	0.65%	3.03 [0.37, 24.94]	0.30
Fatigue	6	33/1800	1.83%	5/1310	0.38%	3.76 [1.62, 8.76]	0.002
Dyspnea	2	13/778	1.67%	5/556	0.90%	1.77 [0.38, 8.34]	0.20
Back pain	5	27/1631	1.66%	9/1139	0.79%	2.10 [0.97, 4.52]	0.03
γ-Glutamyltransferase increased	3	12/760	1.58%	13/614	2.12%	0.72 [0.33, 1.61]	0.52
Vomiting	6	27/1934	1.40%	12/1292	0.93%	1.39 [0.49, 3.91]	0.14
Hypokalaemia	1	4/303	1.32%	0/153	0.00%	4.56 [0.25, 84.14]	0.31
Asthenia	3	13/1035	1.26%	0/665	0.00%	4.66 [0.82, 26.49]	0.04
Abdominal pain	3	13/1060	1.23%	3/677	0.44%	2.19 [0.67, 7.18]	0.16
Blood creatinine increased	2	7/631	1.11%	0/318	0.00%	7.57 [0.43, 131.71]	0.16
Dyspnoea	1	3/288	1.04%	1/290	0.34%	3.02 [0.32, 28.87]	0.34

Abbreviations: CET: CDK4/6 inhibitors plus endocrine therapy; CI: Confidence interval; PET: Placebo plus endocrine therapy; RR: Risk ratio

Anmerkung/Fazit der Autoren

CET appears to outperform PET in HR+/HER2advanced breast cancer, demonstrating improved survival (OS and PFS) and responses. Survival benefits were consistent across most subgroups. However, the increased incidence of AEs, particularly hematologic AEs, requires careful consideration. Due to the limited number and quality of included studies, these conclusions require further validation through high-quality research.

Kommentare zum Review

Ein weiteres SR hat sich mit einer ähnlichen Fragestellung beschäftigt und kam auf das gleiche Ergebnis [4]

Ravani LV et al., 2024 [10].

Efficacy of Subsequent Treatments After Disease Progression on CDK4/6 Inhibitors in Patients With Hormone Receptor–Positive Advanced Breast Cancer

Fragestellung

What is the efficacy of different treatment options after disease progression in patients with hormone receptor–positive/ human epidermal growth factor receptor 2–negative advanced breast cancer who have been treated with CDK4/6 inhibitors and endocrine therapy (ET)?

Methodik

Population:

- patients with metastatic or advanced HR1 breast cancer who progressed on CDK4/6i plus ET

Intervention/Komparator:

- treated with ET monotherapy, CDK4/6i plus ET, mTOR inhibitors plus ET, chemotherapy, or SERD

Endpunkte:

- PFS or OS with KM curves

Recherche/Suchzeitraum:

- PubMed, Embase, CENTRAL, ClinicalTrials.gov, ASCO, San Antonio Breast Cancer Symposium, and European Society of Medical Oncology
- 2016- December 11, 2023

Qualitätsbewertung der Studien:

- Cochrane Collaboration Risk of Bias 2 tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 studies
- 8 RCTs
- 10 retrospective cohort studies

Charakteristika der Population/Studien:

Table S2. Overview of the included RCTs with relevant patient characteristics

Study	*MAINTAIN 2023*	*PALMIRA 2023*		*PACE 2022*		*postMONARCH 2024*		*EMBER 2023*	*VERONICA 2022*	*ELAINE 1 2023*		*PADA-1 2022*
Subsequent tx post CDK4/6I-progression	Ribo 600 mg QD 21/7 + Switched ET Fulv (n=49) or Exe (n= 11)	Palbo 75/100/125 mg QD 3/1 + Letrozole 2.5 mg QD continuous OR Fulv 500 mg IM (1, 15, 29d) monthly	Letrozole 2.5 mg QD continuous OR Fulv 500 mg IM (1, 15, 29d) monthly	Palbo 125 mg PO QD 1-21d in a 28d cycle + Fulv 500 mg IM C1D1,15, then q28d	Fulv 500 mg IM C1D1,15, then q28d	Abemaciclib + Fulv	Fulv	Imlunestrant 200 (n=21) /400 mg (n=51) (RP2D), 42 at ≥600 mg	Fulv 500 mg IM C1D1,15, then q28d	Lasoxifene 5 mg PO daily	Fulv 500 mg IM (1, 15, 29, q4w)	Palbo 125 mg PO QD 1-21d in a 28d cycle + Fulv 500 mg IM C1D1,15, then q28d
N of patients	60	136	62	111*	55	182	186	48 ‡	52	52	51	88
Follow-up, months	18.2	13.2	13.2	23.6	23.6	NA	NA	NA	9.9	NA	NA	28.2
Median age, years	55	59	61	55	58	58	61	63	59	60 §	61 §	62
White	46 (76.7)	NA	NA	87 (78.4)	47 (85.5)	82 (45.0)	82 (44.1)	NA	46 (88.5)	43 (82.7)	42 (82.4)	NA
Premenopausal¶	NA	18 (13.2)	6 (9.7)	24 (21.6)	8 (14.5)	NA	NA	13 (11)	NA	NA	NA	25 (28·4%)
Previous CDK4/6i	Palbo: 52 (86.7) Ribo: 6 (10) Abema: 2 (3.3)	Palbo: 136 (100)	Palbo: 62 (100)	Palbo: 102 (91.9) Ribo: 5 (4.5) Abema: 3 (2.7)	Palbo: 52 (94.6) Ribo: 1 (1.8) Abema: 2 (3.6)	Palbo: 59 Ribo: 34 Abema: 8	Palbo: 59 Ribo: 33 Abema: 8	NA	Palbo: 39 (75.0) Ribo: 13 (25.0)	Palbo: 48 (92.3) Ribo: 3 (5.8) Abema:1 (1.9)	Palbo: 47 (92.1) Ribo: 3 (5.9) Abema:1 (2.0)	Palbo: 88 (100)
Previous ET with CDKi	F: 11 (18.3) Other ET: 49 (81.7)	F: 16 (11.8) Other ET: 120 (88.2)	F: 4 (6.5) Other ET: 58 (93.5)	NA	NA	AI	AI	NA	NA	AI	AI	AI
Previous CDK4/6i tx duration 6-12 months	6-12m: 18 (30.0) >12m: 35 (58.3)	6-12m: 18 (13.2) >12m: 118 (86.6)	6-12m: 10 (16.1) >12m: 52 (83.9)	6-12m: 26 (23.4) >12m: 84 (75.7)	6-12m: 10 (18.2) >12m: 45 (81.8)	29	22	NA	NA	NA	NA	NA
>2 Lines of therapy in the mBC setting	15 (25.0) †	0	0	21 (18.9)	10 (18.2)	0	0	0 ‡	9 (17.3)	3 (5.8)	3 (5.9)	0
ECOG	0: 40 (66.7) 1: 20 (33.3)	0: 90 (66.2) 1: 45 (33.1) 2: 1 (0.7)	0: 31 (50.0) 1: 31 (50.0)	NA	NA	0: 57 1: 43	0: 58 1: 43	0: 72 (63) 1: 42 (37)	0: 31 (59.6) 1: 21 (40.4)	0: 30 (57.7) 1: 21 (40.4)	0: 26 (51.0) 1: 22 (43.1)	0: 50 (56.8%) 1-2: 38 (43.2%)
Visceral metastasis	36 (60.0)	84 (61.8)	37 (59.7)	70 (63.1)	29 (52.7)	62	59	72 (63)	43 (82.7)	13 (25.0)	10 (19.6)	42 (47·7%)
Bone-only metastasis	13 (21.7)	NA	NA	18 (16.2)	4 (7.3)	18	23	NA	1 (1.9)	13 (25.0)	11 (21.6)	NA
PIKCAm	10 (20.4) δ	NA	NA	39 (35.1)	12 (21.8)	NA	NA	NA	14 (30.4)	NA	NA	NA
ESR1m	18 (36.7)δ	NA	NA	55 (49.5)	23 (41.8)	NA	NA	NA	19 (41.3)	52 (100)	51 (100)	88 (100)
PFS Median, months (95% CI)	5.3 (3.0-8.1)	4.9 (3.6-6.0)	3.6 (2.5-4.2)	4.6 (3.6-5.9)	4.8 (2.1-8.2)	6.0 (5.6-8.6)	5.3 (3.7-5.6)	6.5 (3.7-8.3) ‡	1.9 (1.8–3.5)	6.0 (2.8–8.0)	4.0 (2.9–6.0)	12.8 (9.3-14.7)

Data are n (%), unless stated otherwise. n: number; NA: not available; tx: treatment; Ribo: Ribociclib; ET: Endocrine Therapy; Fulv: Fulvestrant; Exe: Exemestane; Palbo: Palbociclib; IM: Intramuscular; PO: Oral; QD: Once daily; C1D1,15: On the first day of the cycle, days 1 and 15; q28d: Every 28 days; ECOG=Eastern Cooperative Oncology Group; PIKCAm = mutation of the PIKCA gene; ESR1m = mutation of the ESR1 gene; PFS2: progression-free survival in the 2L treatment; CI: confidence interval. ‡ Data regarding the Imlunestrant 2L post-CDK4/6i subgroup, used for quantitative analyses. * Baseline characteristics were published for 110 patients. ¶All studies included premenopausal women with ovarian suppression treatment. § values reported as mean. † estimated maximum value of patients with >2 lines of therapy in the mBC setting, calculated by summing the patients who had received more than 2 lines of previous endocrine therapy with those who had received chemotherapy. δ PIK3 and ESR1 mutation status available for fulvestrant treated patients only.

Table S3. Overview of the included cohort studies with relevant patient characteristics

Study, year	*Choong, 2022 ¶*	*Karacin, 2023*	*Kim, 2023*	*Eziokwu, 2020*	*Waisberg, 2023*	*Li, 2021*	*Xi, 2019*	*Kruse, 2023*	*Martin, 2022*	*Clifton, 2022*
Study design	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective	Retrospective
N of patients in the study	91	202	166	30	91	200	200	165	1210	2795
N of patients included in the analyses	55	70	146	30	91	22	7	165	720	2510
Follow-up; median	25.5	6.2	39.8	27.2	NA	9.2	19.5	39.5	NA	NA
Median age, years	59	55	51	47	52	55	59	63	64*	NA
White	91 (100)	NA	NA	27 (90)	NA	NA	156 (78)	135 (81.8)	840 (69.4)	NA
Premenopausal	NA	NA	NA	NA	32 (35.2)	63 (31.5)	Inclued	NA	NA	NA
Previous CDK4/6i	Palbo	NA	Palbo	Palbo	NA	Palbo	Palbo	NA	Palbo: 1067 (88.2) Ribo: 87 (7.2) Abema: 56 (4.6)	Palbo: 2162 (85.2) Ribo: 144 (5.7) Abema: 229 (9.0)
Previous ET with CDKi in 1L	Letrozole: 74 (81.3) Fulv: 11 (12.1) Exe: 3 (3.3) Anastrozole: 3 (3.3)	NA	Letrozole	Letrozole: 20 (66.7) Fulv: 7 (23.3) Anastrozole: 3 (10)	NA	NA	Letrozole: 39 Fulv: 3	NA	Anastrozole: 59 (4.9) Exe: 28 (2.3%) Fulv: 366 (30.2) Letrozole: 745 (61.6) Tamoxifen: 12 (1.0)	NA
1L CDK4/6i PFS	28.2 (19.6–34.9)	NA	NA	NA	9.4 (6.2-19.3)	NA	20.7	NA	NA	NA
>2 Lines of therapy in the mBC setting	0	0	0	0	0	0 ‡	0 ‡	0	0	0
ECOG	NA	0: 91 (45.0) 1: 98 (48.5) ≥2: 13 (6.4)	0: 104 (57.5) 1: 75 (41.4)	NA	0-1: 71 (78.0) 2-3: 20 (22.0)	NA	NA	0: 52 (31.5) 1: 43 (26.1) 2: 19 (11.5)	0: 360 (37.2) 1: 426 (44.0) 2: 146 (15.1) 3: 33 (3.4)	NA
Visceral metastasis	16 (17.6)	148 (73.2)	52 (28.7)	13 (43.3)	43 (47.2)	164 (82.0)	NA	NA	NA	NA
Bone-only metastasis	NA	46 (22.8)	57 (31.5)	10 (33.3)	NA	NA	NA	NA	NA	NA
PIK3CAm	NA	NA	NA	NA	9 (21.4)§	NA	NA	NA	NA	NA
Subsequent tx post CDK4/6i-progression†	Letrozole: 3 (5.1) Fulvestrant: 15 (22.7) Endoxifen: 2 (3.0) Exemestane: 2 (3.0) Eve+exe: 17 (25.8) Eve+fulv: 1 (0) Alpelisib+fulv: 4 (6.1) Chemo: 11 (16.7)	Exe: 4 (7.3) Fulv: 30 (54.5) Eve+exe: 32 (58.2) Eve+fulv: 4 (7.3)	Fulv: 23 (13.8) Eve+exe: 45 (27.3) Capecitabine: 47 (28.5) Other chemo: 31 (19.8)	Palbo+fulv: 17 (56.7) Palbo+letrozole: 5 (16.7) Palbo+tamoxifen: 4 (13.3) Palbo+anastrozole: 1 (3.3) Palbo+exe: 1 (3.3) Abema+letrozole 1 (3.3) Abema+fulv:- 1 (3.3)	Chemo: 91 (100)	Chemo: 22 (11.0)	Chemo: 7 (3.5)	CDK4/6i switch: 120 (72.7) Same CDK4/6i + changed ET partner: 32 (19.4)	Fulv: 70 (8.3) Palbo: 225 (73.1) Ribo: 34 (11.0) Abema: 49 (15.9%) Eve: 99 (11.7) Chemo: 249 (29.7)	CDK4/6i switch: 213 Same CDK4/6i + changed ET partner: 410 ET monotherapy: 905 Chemotherapy: 982
PFS Median, months	ET monotherapy: 6.0 PIK3/mTOR: 8.5 Chemo: 5.4	ET monotherapy: 5.9 PIK3/mTOR: 11.0	PIK3/mTOR: 5.3 ET monotherapy: 3.7 Capecitanbine: 7.4 Other chemo: 4.8	CDK4/6i: 11.8	Chemo: 6.5	Chemo: 7.2	Chemo: 4.7	CDK4/6i: 12.7	Fulv: 3.2 CDK4/6i: 8.2 Eve: 3.3 Chemo: 3.7	CDK4/6i switch: 214 (7.7) Same CDK4/6i + changed ET partner: 412 (14.7) ET monotherapy: 917 (32.8) Chemotherapy: 992 (35.5)

Data are n (%), unless stated otherwise. n: number; NA: not available; tx: treatment; Ribo: Ribociclib; ET: Endocrine Therapy; Fulv: Fulvestrant; Exe: Exemestane; Palbo: Palbociclib; IM: Intramuscular; PO: Oral; QD: Once daily; C1D1,15: On the first day of the cycle, days 1 and 15; q28d: Every 28 days; ECOG=Eastern Cooperative Oncology Group; PIKCAm = mutation of the PIKCA gene; ESR1m = mutation of the ESR1 gene; PFS2: progression-free survival in the 2L treatment; CI: confidence interval. * Data reported as a mean instead of a median. ‡ Data regarding 2L treatment post-CDK4/6i subgroup, used for quantitative analyses. ¶ Baseline characteristics of patients pre-CDK4/6i 1L treatment. § Only 42 patients were tested for PIK3CAm; † Data regarding patients receiving subsequent treatment with agents that could be included according to the prespecified therapy categories in the meta-analysis and reported in Kaplan-Meier curves amenable to meta-analysis.

Qualität der Studien:

Table S5. Quality assessment for studies included in this systematic review and meta-analysis using: risk of bias summary for non-randomized studies (ROBINS-I) tool for retrospective cohorts and prospective studies (A), and risk-of-bias 2 tool for randomized clinical trials (RoB 2) (B).

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgment
Choong	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Eziokwu	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Low	High
Karacin	Moderate	Low	Moderate	Low	Moderate	Low	Low	Moderate
Kim	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate
Kruse	Low	Low	Moderate	Low	Moderate	Low	Low	Moderate
Li	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Martin	Low	Low	Low	Low	Low	Low	Low	Low
Waisberg	No information	No information	Low	No information	No information	Low	Low	No information
Xi	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Low	Low
Clifton	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate

Study	Bias from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcomes	Bias in selection of the reported result	Overall risk of bias
MAINTAIN	Low	Some concerns	Low	Low	Low	Some concerns
PALMIRA	Low	Some concerns	Low	Low	Some concerns	Some concerns
PACE	Low	Low	Low	Low	Low	Low
postMONARCH	Low	Low	Low	Low	Low	Low
ELAINE 1	Low	Low	Low	Low	Low	Low
VERONICA	Low	Low	Low	Low	Low	Low
PADA-1	Low	Some concerns	Low	Low	Low	Some concerns
EMBER	Low	Low	Low	Low	Low	Low

Studienergebnisse:

PFS

Seventeen studies provided PFS data for subsequent therapy (n 5 2,389), all from patients with progression during 1L treatment. The pooled KM curve for PFS by treatment group is shown in Figure 2. Maintaining treatment with a CDK4/6i (HR, 0.61 [95% CI, 0.53 to 0.70]; P < .01) was associated with longer PFS compared with ET monotherapy. By contrast, subsequent therapy with everolimus (HR, 1.10 [95% CI, 0.90 to 1.35]; P 5 .35), with chemotherapy (HR, 1.09 [95% CI, 0.92 to 1.30]; P 5 .33), or with SERD (HR, 0.94 [95% CI, 0.44 to 2.00]; P 5 .88) achieved similar PFS compared with ET monotherapy.

Subgroup analysis showed that patients receiving CDK4/6i with ET had longer PFS than those on fulvestrant monotherapy after CDK4/6i progression (HR, 0.61 [95% CI, 0.53 to 0.70]; P < .01). Both continuing the same CDK4/6i and switching to a different one showed significantly longer PFS compared with ET monotherapy (HR, 0.67 [95% CI, 0.56 to 0.79]; P < .01 and HR, 0.68 [95% CI, 0.54 to 0.85]; P < .01, respectively; Fig 3). All studies included in this analysis comprised only patients who switched ET, except one where 81.2% switched6 and one lacked baseline treatment information.23

A notable reduction in PFS was identified in approximately 20%-40% of participants during the initial 3 months of the treatment, with the largest drop (35.2%) seen in the ET monotherapy group and the smallest (23.5%) in the CDK4/6i group.

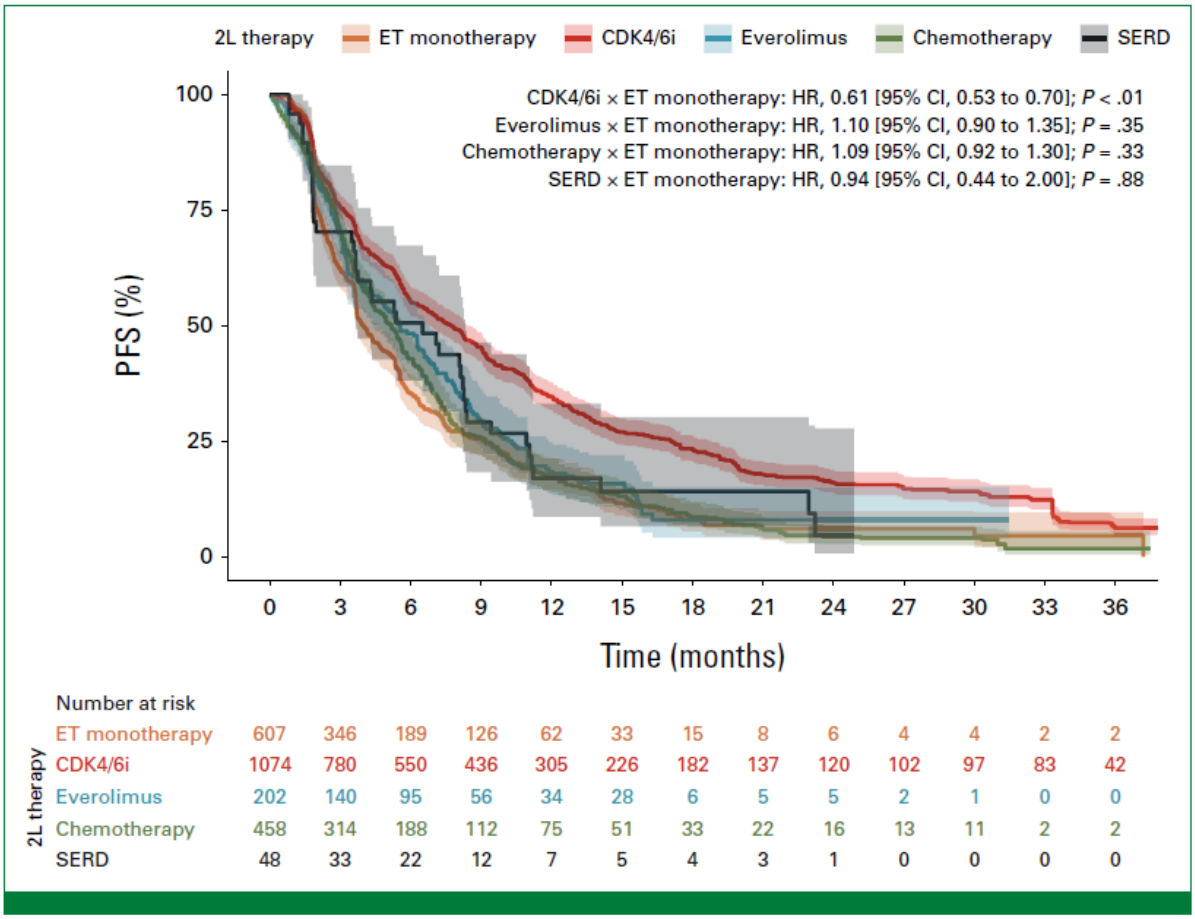


FIG 2. Pooled KM curve of PFS comparing CDK4/6i, chemotherapy, and SERD with ET monotherapy beyond progression on previous CDK4/6i. KM, Kaplan-Meier; PFS, progression-free survival; SERD, selective estrogen receptor degraders; ET, endocrine therapy.

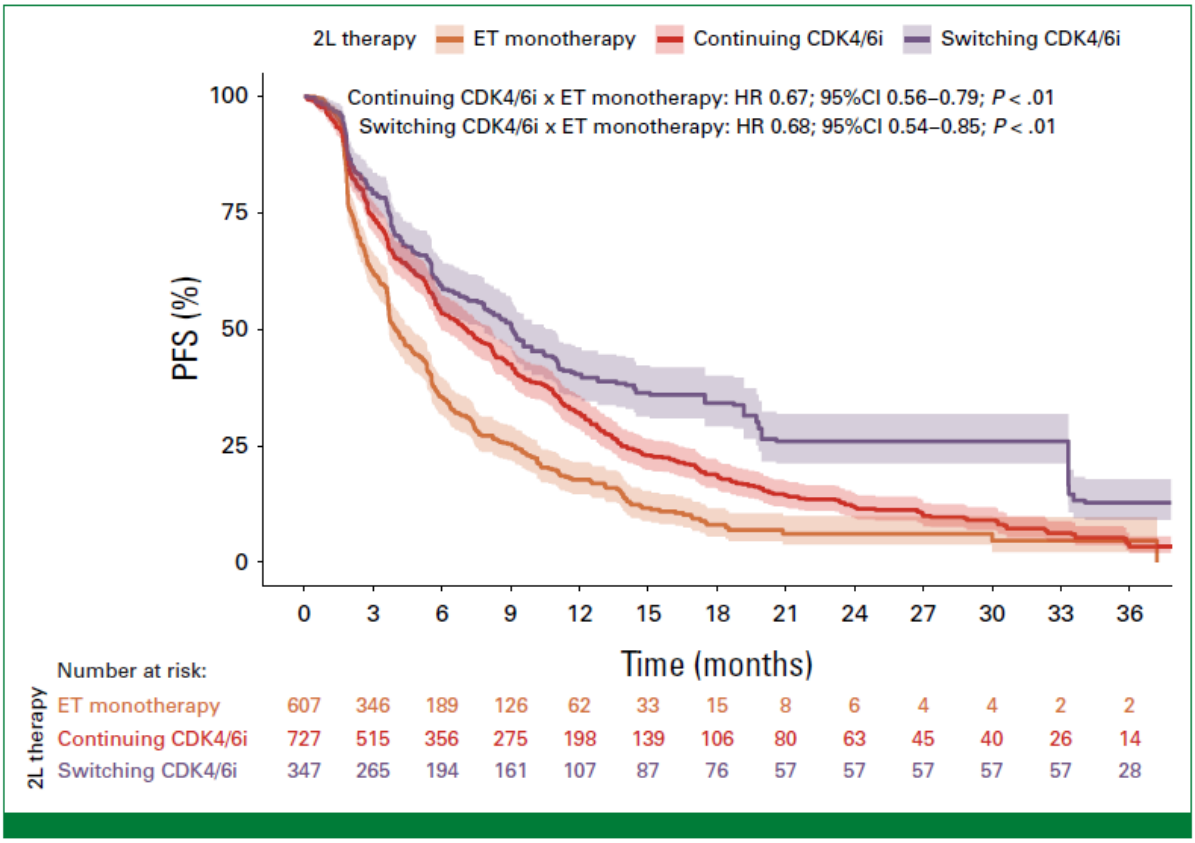


FIG 3. Pooled KM curve of PFS comparing continuing the same CDK4/6i and switching the CDK4/6i agent with ET monotherapy beyond progression on previous CDK4/6i. 2L, second-line; ET, endocrine therapy; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival.

OS

Seven studies reported OS data (n 5 3,822). Of these, one study (n 5 2,510) did not specify whether all patients receiving 2L treatment experienced progression or if some transitioned to 2L because of toxicity.24 The pooled KM curve for OS is shown in Figure 4, revealing that subsequent therapy with CDK4/6i plus ET was associated with prolonged OS compared with ET monotherapy (HR, 0.68 [95% CI, 0.60 to 0.77]; P < .01). Patients receiving everolimus (HR, 1.52 [95% CI, 1.21 to 1.90]; P < .01) or chemotherapy (HR, 1.64 [95% CI, 1.47 to 1.82]; P < .01) had shorter OS compared with 2L ET monotherapy.

Continuing the same CDK4/6I switching the ET combination improved OS (HR, 0.63 [95% CI, 0.55 to 0.74]; P < .01), whereas switching to a different CDK4/6i showed no significant OS difference (HR, 0.90 [95% CI, 0.72 to 1.11]; P5 .33; Fig 5).

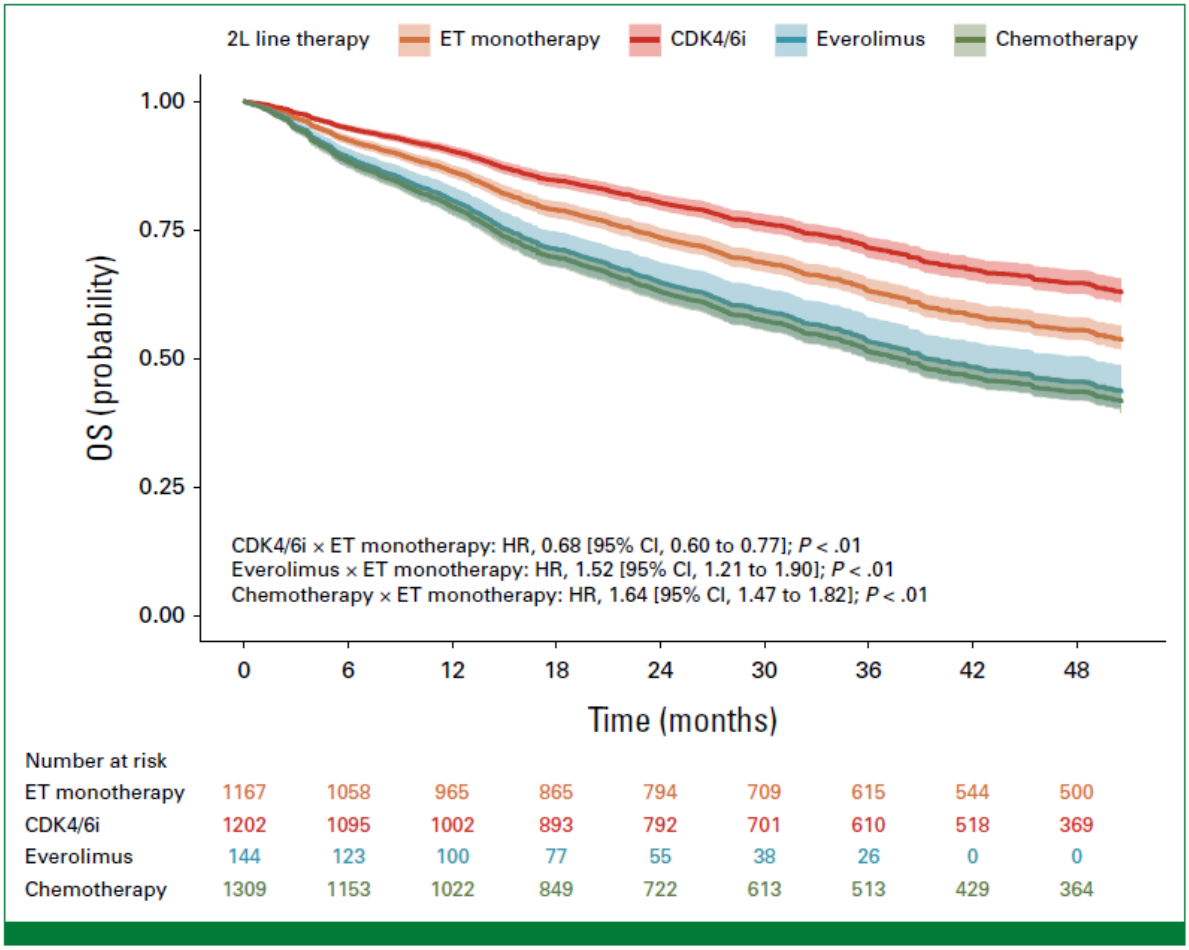


FIG 4. Pooled KM curve of OS comparing CDK4/6i, chemotherapy, with ET monotherapy beyond progression on previous CDK4/6i. 2L, second-line; ET, endocrine therapy; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival.

Anmerkung/Fazit der Autoren

In conclusion, our study reveals that continuing CDK4/6i with ET post-progression improves survival compared with ET alone, supporting guidelines against 2L chemotherapy without endocrine resistance or visceral crisis. It underscores the need for tailored strategies on the basis of clinical and biologic profiles. This analysis, to our knowledge, the largest of its kind, addresses a key clinical challenge, offering a comprehensive foundation for guiding future oncologic strategies and trials in aBC care.

Kommentare zum Review

Ein weiteres SR hat sich mit einer ähnlichen Fragestellung beschäftigt und kam auf das gleiche Ergebnis [9]

Brain E et al., 2024 [1].

Palbociclib in Older Patients with Advanced/Metastatic Breast Cancer: A Systematic Review

Fragestellung

The aim was to systematically review evidence from both clinical trials and real-world studies for palbociclib treatment outcomes in older patients with HR+/HER2− advanced/metastatic breast cancer (a/mBC). Older patients are often underrepresented in clinical trials, and real-world evidence (RWE) will enrich the analysis of palbociclib outcomes in this subgroup of patients.

Methodik

Population:

- older patients (aged 60 years and older based on the United Nations definition for older population)
- with HR+/HER2− a/mBC

Intervention/Komparator:

- palbociclib

Endpunkte:

- efficacy/effectiveness, safety, health-related quality of life (HRQoL), and patient-reported outcomes

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Library
- inception through May 4, 2023
- Google Scholar was used for gray literature searches; targeted searches […] relevant conferences covering the previous 2-year period

Qualitätsbewertung der Studien:

- The modified Jadad scale was used to evaluate quality of RCTs
- Newcastle-Ottawa scale (NOS) was used to assess quality of observational studies

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 publications reporting results from seven RCTs
- 39 publications […] reporting data from 37 RWE studies were included in the qualitative synthesis

Charakteristika der Population/Studien:

Supplementary Table 1. Characteristics of included studies

First author, year of publication	Study name/database	Study phase/design	Study treatment timeframe	Study population	Study treatment; comparator	Older patients sample size (received PAL; did not receive PAL)
RCTs						
Takahashi M, 2020 [17]	–	Phase 2	6/24/2014 to 2/9/2015	Postmenopausal women with ER+/HER2− ABC	1st line PAL + LET; –	16 (16; –)
Albanell J, 2022 [18]	FLIPPER	Phase 2	Feb 2016 to Jan 2018	Postmenopausal women with HR+/HER2− ABC	1st line PAL + FUL; PBO + FUL	92 (47; 45)
Martin M, 2021 [22]; Martin M, 2022 [21]	PEARL	Phase 3	Mar 2014 to Jul 2018	Postmenopausal patients with HR+/HER2− MBC	Any line PAL + EXE or FUL; capecitabine	109 (56; 53)
Finn RS, 2016-1 [19]; Finn RS 2020 [20]; Rugo HS, 2018 [27]	PALOMA-1	Phase 2	12/22/2009 to 5/12/2012	Postmenopausal women with ER+/HER2− ABC	1st line PAL + LET; LET	76 (37; 39)
Finn RS 2016-2 [23]; Rugo HS, 2019 [24]; Finn RS 2022 [29]; Rugo HS, 2018 [27]	PALOMA-2	Phase 3	Feb 2013 to Jul 2014	Postmenopausal women with ER+/HER2− ABC	1st line PAL + LET; PBO + LET	262 (181; 81)
Turner NC, 2018 [25]; Rugo HS, 2018 [27]	PALOMA-3	Phase 3	10/7/2013 to 08/26/2014	HR+/HER2− ABC	Any line PAL + FUL; PBO + FUL	129 (86; 43)
Verma S, 2016 [26]	PALOMA-3	Phase 3	10/7/2013 to 08/26/2014	HR+/HER2− ABC	Any line PAL + FUL; PBO + FUL	NR (50; NR)
Xu B, 2022 [28]	PALOMA-4	Phase 3	3/23/2015 to 08/31/2020	ER+/HER2− ABC	1st line PAL + LET; PBO + LET	38 (14; 24)
RWE studies						
Carola E, 2023 [60]*	PalomAGE: Cohort A	Prospective	Oct 2018 to Jul 2020	HR+/HER2− ABC	1st line PAL + AI or FUL; –	362 (362; –)
Bouteiller F, 2022 [61]; Brain E, 2022 [62]*	PalomAGE: Cohort B	Prospective	Oct 2018 to Jul 2020	HR+/HER2− ABC	Any line PAL + AI or FUL; –	406 (406; –)
Caillet P, 2021 [63]*	PalomAGE: Cohort A+B	Prospective	Oct 2018 to Oct 2020	HR+/HER2− ABC	Any line PAL + AI or FUL; –	807 (807; –)
Bitca V, 2020 [30]	–	Retrospective	Dec 2017 to Mar 2020	HR+/HER2− MBC	1st line PAL + FUL; –	52 (52; –)
Anton FM, 2023 [66]	PALBOSPAIN	Retrospective + prospective	Nov 2017 to Nov 2019	HR+/HER2− ABC	1st line PAL + AI or FUL; –	234 (234; –)
Karuturi MS, 2019 [31]	POLARIS	Retrospective	NR	HR+/HER2− ABC	PAL; –	282 (282; –)
Karuturi M, 2018 [32]	–	Retrospective	NR	ER+ MBC	PAL; –	45 (45; –)
Shah Y, 2022 [33]*	–	Retrospective	NR	ER+/HER2− ABC	1st line PAL + AI; –	15 (15; –)
Skrobo D, 2020 [34]	–	Retrospective	Jan 2010 to Sep 2019	HR+/HER2− MBC	Any line PAL + ET; –	103 (103; –)
Brufsky A, 2023 [35]*	Flatiron Health Analytics database	Retrospective	Feb 2015 to Mar 2020	HR+/HER2− MBC	1st line PAL + AI; AI	961 (313; 648)
Brufsky A, 2021 [36]	Flatiron Health Analytics database	Retrospective	Feb 2015 to Sep 2018	HR+/HER2− MBC	1st line PAL + LET; LET	565 (344; 221)
Rugo H, 2023 [37]*	Flatiron Health Analytics database	Retrospective	Feb 2015 to Sep 2018	HR+/HER2− MBC	1st line PAL + LET; LET	796 (390; 406)

Qualität der Studien:

- Study quality of the 11 full-text RCT publications assessed using the modified Jadad scale showed a median (range) score of 6 (4.5–8).
- Study quality of the 28 full-text RWE publications assessed using NOS showed a median (range) score of 6 (5–8).

Studienergebnisse:

PFS

In three RCTs, PFS was significantly improved with palbociclib (plus fulvestrant in FLIPPER; plus letrozole in PALOMA-1 and PALOMA-2) in the first-line setting compared with control

treatment (fulvestrant in FLIPPER; letrozole in PALOMA-1 and PALOMA-2) in both older and younger patients [18, 19, 24]. In PALOMA-3, PFS was significantly improved with palbociclib plus fulvestrant regardless of line of therapy compared with placebo plus fulvestrant among patients aged < 65 years and 65−74 years but not in those ≥ 75 years; however, there were only 33 patients included in the ≥ 75 years subgroup in that analysis [27]. In PEARL, an RCT with a chemotherapy control arm, palbociclib plus ET (exemestane or fulvestrant) regardless of line therapy showed similar PFS benefit compared to capecitabine in both younger and older patients [22].

a

Study	Age subgroup; n	Intervention, median PFS (95% CI) mo	Control, median PFS (95% CI) mo	HR (95% CI)	*P* value
Takahashi M, 2020	< 65 years; 26	31.9 (13.8-NE)	–	–	
	≥ 65 years; 16	43.0 (20.5-NE)	–	–	
FLIPPER	< 65 years; 97	–	–	0.62 (80% CI: 0.43–0.90)	For interaction: 0.54
	≥ 65 years; 92	–	–	0.51 (80% CI: 0.34–0.75)	
PALOMA-1	< 65 years; 89	18.8 (12.8-26.1)	7.7 (2.8-10.9)	0.315 (0.184–0.539)	
	≥ 65 years; 76	26.2 (12.6-NE)	12.9 (5.7-22.2)	0.505 (0.269–0.948)	
PALOMA-2	< 65 years; 404	23.2 (19.3-27.6)	13.7 (11.0-16.6)	0.55 (0.43–0.70)	< 0.0001
	≥ 65 years; 262	30.6 (27.6-NE)	19.1 (11.0-30.4)	0.60 (0.43–0.86)	< 0.005
PALOMA-1 and -2	< 65 years; 493	22.0 (19.2-24.8)	12.3 (10.5-13.8)	0.50 (0.40–0.64)	< 0.001
	65-74 years; 256	27.5 (24.2-NE)	21.8 (16.3-31.3)	0.66 (0.45–0.97)	< 0.016
	≥ 75 years; 82	NR (19.2-NE)	10.9 (4.9-24.9)	0.31 (0.16–0.61)	< 0.001
PALOMA-3	< 65 years; 392	10.9 (9.1-11.3)	5.4 (3.5-7.3)	0.59 (0.46–0.75)	< 0.001
	65-74 years; 96	16.1 (12.0-NE)	3.7 (1.9-5.3)	0.27 (0.16–0.48)	< 0.001
	≥ 75 years; 33	13.6 (7.5-NE)	7.4 (1.9-NE)	0.59 (0.19–1.8)	< 0.18
PALOMA-4	< 65 years; 302	–	–	0.602 (0.463–0.783)	< 0.001
	≥ 65 years; 38	–	–	1.247 (0.585–2.657)	0.713
PEARL	< 65 years; 196	–	–	1.10 (0.79–1.55)	0.566
	≥ 65 years; 109	–	–	1.06 (0.65–1.72)	0.814

OS

In PALOMA-3, older patients who received palbociclib showed an OS benefit compared with fulvestrant monotherapy control arm, whereas younger patients did not show an OS benefit [25]. In PALOMA-2, the secondary endpoint of OS was numerically longer in patients who received palbociclib compared with the control arm; however, the results were not statistically significant. OS was similar in older patients who received palbociclib versus the control arm (hazard ratio 0.871, 95% confidence interval [CI] 0.624–1.216) [29]. In PALOMA-1, although not statistically significant, OS results were similar in both younger and older patients who received palbociclib [20]. In PEARL, similar OS was seen in younger and older patients, but OS was not different in both age subgroups compared to the control treatment [21].

b

Study	Age subgroup; n	Intervention, median OS (95% CI) mo	Control, median OS (95% CI) mo	HR (95% CI)	*P* value
PALOMA-1	< 65 years; 89	41.8 (28.1-54.6)	35.7 (27.1-48.0)	0.83 (0.51-1.36)	
	≥ 65 years; 76	37.5 (31.4-50.1)	34.4 (26.2-50.5)	0.97 (0.57-1.67)	
PALOMA-2	< 65 years; 404	53.3 (47.0–60.8)	54.4 (44.8–60.2)	1.007 (0.772–1.314)	
	≥ 65 years; 262	58.6 (49.8–66.7)	47.4 (36.2–60.4)	0.871 (0.624–1.216)	
PALOMA-3	< 65 years; 392	31.4 (27.4-39.3)	29.7 (24.0-38.0)	0.91 (0.70-1.20)	For interaction: 0.04
	≥ 65 years; 129	39.7 (30.7-47.0)	23.8 (20.0-33.8)	0.52 (0.33-0.82)	
PEARL	< 65 years; 391	–	–	0.94 (0.73-1.20)	0.613
	≥ 65 years; 210	–	–	1.02 (0.72-1.45)	0.917

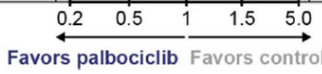


Fig. 2 Progression-free survival (**a**) and overall survival (**b**) in RCTs. *CI* confidence interval, *HR* hazard ratio, *mo* months, *NE* not estimable, *OS* overall survival, *PFS* progression-free survival, *RCT* randomized controlled trial

AEs

In PALOMA-1, treatment discontinuation rate due to AEs was 13% (six of 46) in younger patients and 16.2% (six of 37) in older patients [19]. In the pooled PALOMA analysis, treatment discontinuation rate due to treatment-emergent AEs (TEAEs) was 1.6% (nine of 568), 5.4% (12 of 221), and 6.0% (five of 83) in patients aged < 65 years, 65−74 years, and ≥ 75 years, respectively [27].

In PALOMA-1, the incidence of grade 3/4 AEs was similar in the two age groups (80.4% in < 65 years vs 73.0% in ≥ 65 years) [19]. In the pooled PALOMA analysis, no new safety concerns were identified in older patients. In older patients, hematological TEAEs occurred more frequently in patients receiving palbociclib versus comparator; however, most of these were grade 1 or 2, except for neutropenia and leukopenia [27]. In patients aged ≥ 75 years, myelosuppression was more common; however, incidence of grade 3 or higher AEs was similar across age groups [27].

Anmerkung/Fazit der Autoren

This review indicated that palbociclib in combination with ET is an effective and well tolerated treatment while preserving QoL for older patients with HR+/HER2− a/mBC; the clinical benefit profile of palbociclib in older patients in real-world settings was consistent with results seen in clinical trials.

Kommentare zum Review

Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

3.3 Leitlinien

Tarantino P et al., 2023 [12].

ESMO

ESMO expert consensus statements (ECS) on the definition, diagnosis, and management of HER2-low breast cancer

Zielsetzung/Fragestellung

Human epidermal growth factor receptor 2 (HER2)-low breast cancer has recently emerged as a targetable subset of breast tumors, based on the evidence from clinical trials of novel anti-HER2 antibody-drug conjugates. This evolution has raised several biological and clinical questions, warranting the establishment of consensus to optimally treat patients with HER2-low breast tumors

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, hinsichtlich der Fragestellung zu HER2-low breast cancer, wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium – **trifft teilweise zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – **trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz – **trifft nicht zu**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – **trifft teilweise zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – **trifft teilweise zu**

Regelmäßige Überprüfung der Aktualität gesichert – **trifft nicht zu**

Recherche/Suchzeitraum:

- Keine (consensus statement)

LoE

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well- conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions

GoR

A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Sonstige methodische Hinweise

The experts of each working group, under the lead of the coordinators, reviewed and modified the initial proposal of questions by the addition or revision of topics, then conveying a final list of relevant questions. The virtual meetings were followed by email-based focus group interactions, which led to the development of statements and discussions for each of the relevant questions, based on evidence available or expert opinion.

The list of questions was then voted upon by all the experts of the panel via survey using a modified Delphi voting methodology. A first round of Delphi voting was conducted for each consensus statement. The presence of any disagreement during the first round of voting elicited a check by the working group coordinators for revision, and prompted a second Delphi voting round until there was consensus (90%-100% agreement of all the experts), majority agreement (75%-90% agreement), or no agreement (<75% agreement).

Empfehlungen

QUESTION 2: What is the best position for T-DXd in the treatment of HER2-low metastatic hormone receptor positive breast cancer in clinical practice?

STATEMENT: Patients with HER2-low (IHC 1+ or IHC 2+/ISH-negative), hormone receptor-positive metastatic breast cancer who have received prior CDK4/6 inhibitor therapy and at least one previous line of chemotherapy (or have experienced progression within 6 months of [neo]adjuvant chemotherapy) and are considered to have endocrine refractory disease are candidates for T-DXd if they do not have contraindications. In cases where both T-DXd and SG are available options, T-DXd should be prioritized, given that it was studied in a less pretreated population of patients. [II, A]

DISCUSSION: In the DB-04 trial, 70% of patients with hormone receptor-positive disease had previously received a CDK4/6 inhibitor, and a subgroup analysis suggested that patients derived benefit from T-DXd regardless of previous treatment with a CDK4/6 inhibitor.[19] Given the demonstrated survival advantage,[68] treatment with a CDK4/6 inhibitor in any setting is recommended prior to receiving TDXd, in regions where available. Subgroup analysis in DB-04 also showed similar hazard ratio (HR) for disease progression or death in patients who had received one versus two lines of chemotherapy. Therefore patients should have at least received one line of chemotherapy in the metastatic setting, with the exception of patients experiencing recurrence on or within 6 months of (neo)adjuvant chemotherapy, prior to receiving T-DXd.

Currently, there are no available data with respect to the optimal selection strategy regarding the use of T-DXd and SG, in pretreated patients with HER2-negative, hormone

receptor-positive metastatic breast cancer. However, recent studies support the activity of both agents in this patient population. The DB-04 trial clearly demonstrated the efficacy of T-DXd in pretreated patients with HER2-low metastatic breast cancer.[19] Moreover, the TROPiCS-02 study showed the activity of SG in patients with HER2-negative, hormone receptor-positive disease who had received two to four lines of chemotherapy in the metastatic setting.[69] Furthermore, a post hoc subgroup analysis by HER2 IHC status in the TROPiCS-02 trial demonstrated efficacy for SG, in both HER2-low and HER2-0 groups.[53] The HR of 0.58 with SG in HER2-low disease was similar to the HR of 0.51 with T-DXd in the DB-04 trial, although achieved in a more advanced setting.

Based on the currently available data in pretreated patients with HER2-negative, hormone receptor-positive metastatic breast cancer, T-DXd is the standard of care, while SG is another valid option in cases with HER2-low disease. Although there is some suggestion of activity of T-DXd even in HER2-0 metastatic breast cancer,[34] SG is currently considered the only ADC for HER2-0 disease. There is a greater body of evidence for use of T-DXd in a less pretreated population (one to two prior lines of chemotherapy), whereas SG was tested among patients who had received two to four prior lines of chemotherapy in the metastatic setting, making the preference for use of T-DXd in an earlier line of therapy.

Importantly, data regarding the safety and activity of SG in patients with metastatic breast cancer who have already received an ADC with a different target, such as T-DXd, are lacking. However, there is no biological rationale to suggest that the administration of SG following previous treatment with T-DXd would be either inefficient or unsafe. Consequently, previous treatment with T-DXd should not be considered a contraindication for treatment with SG.

Level of consensus: 90% (n = 27) agree, 10% (n = 3) disagree, (n = 2) abstain.

Referenzen

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34. Mosele MF, Lusque A, Dieras V, et al. LBA1dUnraveling the mechanism of action and resistance to trastuzumab deruxtecan (T-DXd): biomarker analyses from patients from DAISY trial. Ann Oncol. 2022;33: S123-S147.
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68. Schettini F, Giudici F, Giuliano M, et al. Overall survival of CDK4/6inhibitor-based treatments in clinically relevant subgroups of metastatic breast cancer: systematic review and meta-analysis. J Natl Cancer Inst. 2020;112:1089-1097.
69. Rugo H, Bardia A, Marmé F, et al. LBA76 - Overall survival (OS) results from the phase III TROPiCS-02 study of sacituzumab govitecan (SG) vs treatment of physician's choice (TPC) in patients (pts) with HRþ/ HER2- metastatic breast cancer (mBC). Ann Oncol. 2022;33:S808S869.

Burstein HJ et al., 2021 [2,3,5,7,8].

ASCO

Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Update

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt.

- Systematische Suche, Auswahl und Bewertung der Evidenz.
- Keine formalen Konsensusprozesse und ausschließlich internes Begutachtungsverfahren dargelegt.
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt.
- Überprüfung der Aktualität nach Signalen durch Leitliniengruppe beschrieben („For this focused update, phase III randomized trials on alpelisib and additional CDK4/6 inhibitors provided the signals"), keine Gültigkeit angegeben.

Recherche/Suchzeitraum:

- Burstein HJ et al., 2021:
  - RCT und Meta-Analysen: January 1, 2016 to December 31, 2020 in PubMed
  - Lebensqualität: January 1, 2016 to Feb 18, 2021 in PubMed
- Korde L et al., 2021:
  - a systematic review (January 1, 2000-August 31, 2020) of randomized phase II and phase III clinical trials (RCTs) in PubMed.
- Moy B et al., 2023:
  - A targeted electronic literature search was conducted to identify any additional phase III randomized controlled trials of treatment options in this patient population.
- Burstein HJ et al., 2024: nicht angegeben

LoE

Quality of evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits *v* 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

Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a. strong evidence for a true net effect (eg, 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 (eg, 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

- Die eingeschlossenen RCT wurden mittels Cochrane Risk of Bias Tool bewertet. Es wurde keine Angabe zur Bewertung anderer Studien (z.B. der Meta-Analysen) identifiziert.
- Es ist unklar, wie das LoE abgeleitet wurde.

Empfehlungen

THE BOTTOM LINE

Chemotherapy and Targeted Therapy for Patients With Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Update

Guideline Question

What is the optimal chemotherapy and/or targeted therapy for patients with HER2-negative metastatic breast cancer?

Target Population

Women or men with HER2-negative MBC that is HR-positive but endocrine-pretreated or triple negative.

Target Audience

This guideline is targeted to both health care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team) and patients.

Methods

An Expert Panel was reconvened to update clinical practice guideline recommendations on the basis of a systematic review of the medical literature (Appendix Table A1, online only).

Recommendations

Recommendation 1.1. Patients with metastatic triple-negative breast cancer with expression of programmed cell death ligand-1 (PD-L1–positive) and no existing contraindications may be offered the addition of immune checkpoint inhibitor to chemotherapy (atezolizumab plus nab-paclitaxel or pembrolizumab plus chemotherapy) as first-line therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong; Appendix Table A2, online only).

Recommendation 1.2. Patients with metastatic triple-negative breast cancer without expression of programmed cell death ligand-1 (PD-L1–negative) should be offered single-agent chemotherapy rather than combination chemotherapy as first-line treatment, although combination regimens may be offered for symptomatic or immediately life-threatening disease for which time may allow only one potential chance for therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Patients may be offered either platinum-based or nonplatinum-based regimens on the basis of individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 1.3. Patients with metastatic triple-negative breast cancer who have received at least two prior therapies for metastatic disease should be offered treatment with sacituzumab govitecan (Type: evidence based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.4. Patients with metastatic triple-negative breast cancer with germline *BRCA1* or *2* mutations who have previously been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic disease setting may be offered an oral poly (ADP-ribose) polymerase (PARP) inhibitor (olaparib or talazoparib) rather than chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* mutation carriers and somatic *BRCA* mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown.

Recommendation 2.1. Patients with metastatic HR-positive breast cancer with disease progression on a prior endocrine agent with or without targeted therapy may be offered treatment with either ET with or without targeted therapy (refer to the companion ASCO guideline on Endocrine Therapy and Targeted Therapy for Hormone Receptor–Positive Metastatic Breast Cancer[13] for details) or single-agent chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Treatment choice should be based on individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 3.1. Patients with metastatic HR-positive but HER2-negative breast cancer with germline *BRCA1 or 2* mutations who are no longer benefiting from ET may be offered an oral PARP inhibitor in the first-through to third-line setting rather than chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline *PALB2* mutation carriers and somatic *BRCA* mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown.

Recommendation 3.2. Patients with HR-positive HER2-negative MBC no longer benefiting from ET should be offered single-agent chemotherapy rather than combination therapy, although combination regimens may be offered for symptomatic or immediately life-threatening disease for which time may allow only one potential chance for therapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Practical information. Choice of chemotherapy agent should be based on individualized patient and provider assessment of preferences, risks, and benefits.

Recommendation 4.1. No recommendation regarding at which point a patient's care should be transitioned to hospice or best supportive care only is possible at this time (Type: consensus; benefits/harms ratio unknown; Evidence quality: N/A; Strength of recommendation: strong).

Practical information. Given the heterogeneity of breast cancer and the treatment goals of patients with breast cancer, it is not possible to identify a universal optimal time to transition to hospice or best supportive care. When to transition is a decision that should be shared between the patient and clinician in the context of an ongoing conversation regarding goals of care. The conversation about integration of supportive care and eventual consideration of hospice care should start early in the management of MBC.

See the clinical algorithm (Figs 1 and 2) for a graphical representation of the recommendations.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

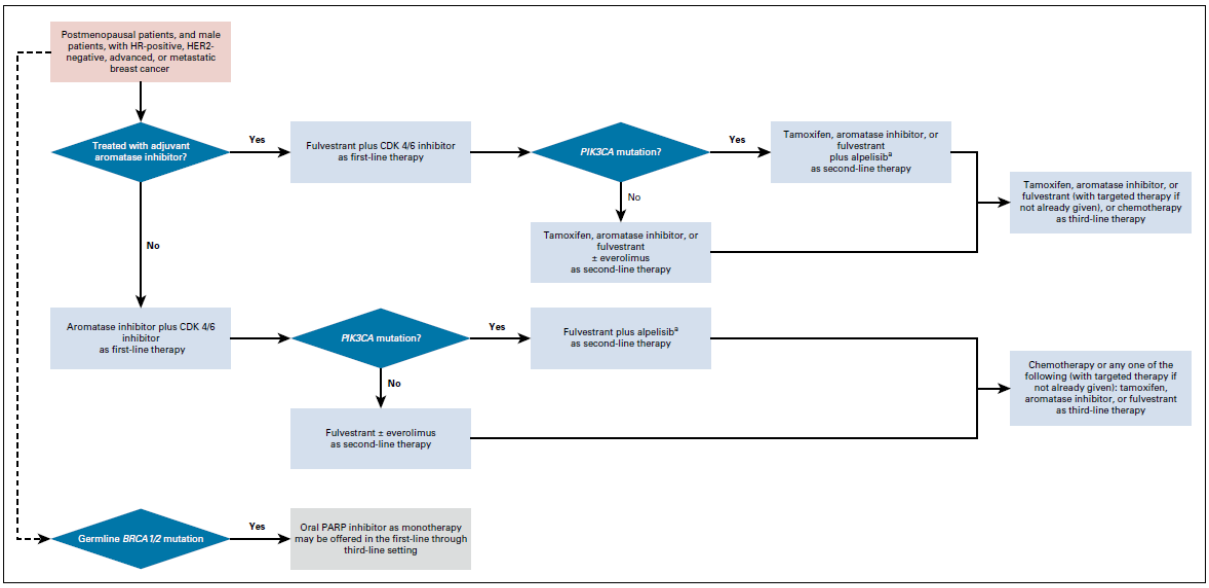

FIG 1. Algorithm for endocrine treatment and targeted therapy for HR-positive, HER2-negative MBC. [a]Patients receiving alpelisib should have laboratory and symptom monitoring weekly for the first 4 weeks of therapy to avoid serious toxicity. CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer.

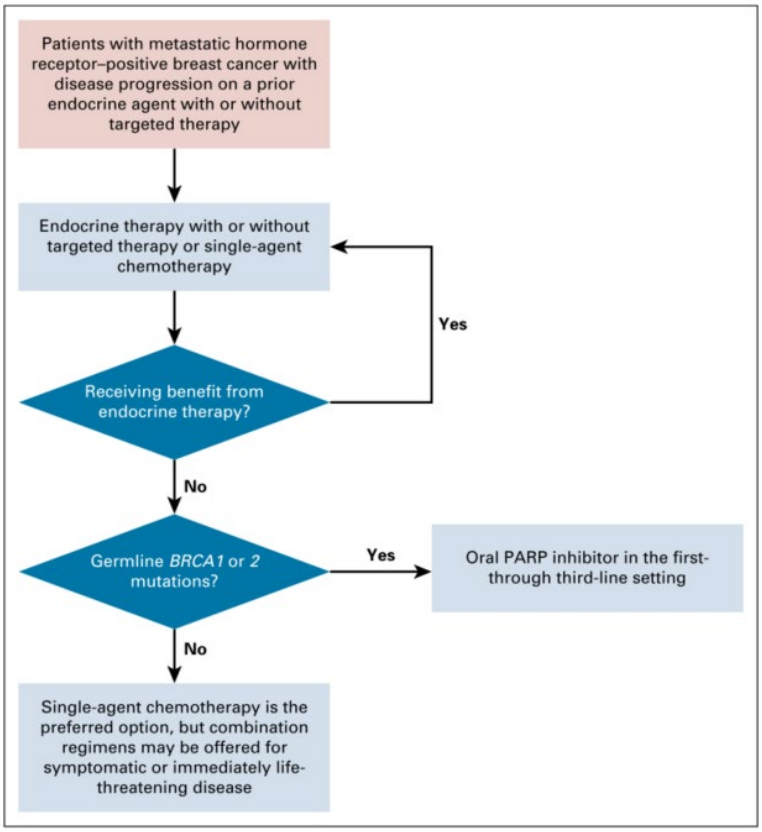

FIG 2. Treatment algorithm for chemotherapy and targeted therapy for patients with HER2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor–negative. HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death ligand-1.

Empfehlungen

THE BOTTOM LINE

Endocrine Treatment and Targeted Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Update

Target Population

Women and men with HR-positive, HER2-negative MBC.

Target Audience

Oncology specialists, other health care providers (including primary care physicians, specialists, nurses, social workers, and any other relevant member of a comprehensive multidisciplinary cancer care team), caregivers, and patients.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

UPDATED RECOMMENDATIONS

Clinical Question 1

Should alpelisib be given to postmenopausal women, and to male patients, with HR-positive, HER2-negative, *PIK3CA*-mutated, ABC, or MBC?

Recommendation 1.1. Alpelisib in combination with ET should be offered to postmenopausal patients in combination with fulvestrant, and to male patients, with HR-positive, HER2-negative, *PIK3CA*-mutated, ABC, or MBC following prior ET including an aromatase inhibitor (AI), with or without a CDK4/6 inhibitor. Careful screening for and management of common toxicities are required (type: evidence-based, benefits outweigh harms; evidence quality: high; strength of recommendation: moderate; Appendix Table A2, online only).

Clinical Question 2

What is the role of biomarkers in treatment selection for patients with HR-positive MBC?

Recommendation 2.1. To guide the decision to use alpelisib in combination with fulvestrant in postmenopausal patients, and in male patients with HR-positive MBC, clinicians should use next-generation sequencing in tumor tissue or cell-free DNA in plasma to detect *PIK3CA* mutations. If no mutation is found in cell-free DNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations (type: evidence-based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Recommendation 2.2. There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for HR-positive, HER2-negative MBC. Existing data suggest reduced efficacy of AIs compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or circulating tumor DNA (ctDNA) with *ESR1* mutations (type: informal consensus; evidence quality: insufficient; strength of recommendation: moderate).

Recommendation 2.3. Patients with metastatic HR-positive but HER2-negative breast cancer with germline *BRCA1* or 2 mutations who are no longer benefiting from ET may be offered an oral poly (ADP-ribose) polymerase (PARP) inhibitor in the first-line through to third-line setting rather than chemotherapy (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong).
Qualifying statements: Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC-encoding DNA repair defects, such as germline *PALB2* mutation carriers and somatic *BRCA* mutations. It should also be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown.

Clinical Question 3

What is the role of CDK4/6 inhibitors in the treatment of patients with HR-positive MBC?

Recommendation 3.1. A nonsteroidal AI and a CDK4/6 inhibitor should be offered to postmenopausal patients and to premenopausal patients combined with chemical ovarian function suppression, and to male patients (with a gonadotropin-releasing hormone analog), with treatment-naïve HR-positive MBC (type: evidence-based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Recommendation 3.2. Fulvestrant and a CDK4/6 inhibitor should be offered to patients with progressive disease during treatment with AIs (or who develop a recurrence within 1 year of adjuvant AI therapy) with or without one line of prior chemotherapy for metastatic disease, or as first-line therapy. Treatment should be limited to those without prior exposure to CDK4/6 inhibitors in the metastatic setting (type: evidence-based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

(continued on following page)

CLINICAL QUESTION 1

Which patients with breast cancer are appropriate candidates for neoadjuvant systemic therapy?

Recommendations

Recommendation 1.1. Neoadjuvant chemotherapy is the treatment of choice for patients with inflammatory breast cancer or those with unresectable or locally advanced disease at presentation whose disease may be rendered resectable with neoadjuvant treatment (Type: informal consensus; Evidence quality: low; Strength of recommendation: strong).

Recommendation 1.2. Tumor histology, grade, stage and estrogen, progesterone, and HER2 expression should routinely be used to guide clinical decisions as to whether or not to pursue neoadjuvant chemotherapy. There is insufficient evidence to support the use of other immunochemical markers, morphological markers (eg, tumor-infiltrating lymphocytes) or genomic profiles to guide a clinical decision as to whether or not to pursue neoadjuvant chemotherapy (Type: informal consensus; Evidence quality: insufficient; Strength of recommendation: moderate).

CLINICAL QUESTION 4

What neoadjuvant treatment is recommended for patients with HR-positive/HER2-negative breast cancer?

Recommendations

Recommendation 4.1. Neoadjuvant chemotherapy can be used instead of adjuvant chemotherapy in any patient with HR-positive, HER2-negative breast cancer in whom the chemotherapy decision can be made without surgical pathology data and/or tumor-specific genomic testing (Type: informal consensus; Evidence quality: low; Strength of recommendation: moderate).

Recommendation 4.2. For postmenopausal patients with HR-positive/HER2-negative disease, neoadjuvant endocrine therapy with an aromatase inhibitor may be offered to increase locoregional treatment options. If there is no intent for surgery, endocrine therapy may be used for disease control (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 4.3. For premenopausal patients with HR-positive/HER2-negative early-stage disease, neoadjuvant endocrine therapy should not be routinely offered outside of a clinical trial (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

UPDATED RECOMMENDATION

Patients with hormone receptor–positive HER2-negative metastatic breast cancer who are refractory to endocrine therapy and have received at least two prior lines of chemotherapy for metastatic disease may be offered SG. (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong.)

TABLE 1. Treatment Options According to Prior Endocrine Therapy

Line of Therapy	Tumor Genomic Findings	Prior Endocrine Therapy[a]	
		None, tamoxifen only, or no prior recent AI therapy (anastrozole, exemestane, letrozole)	Recurrence on or within recent exposure to AI therapy
First-line treatment		AI + CDK4/6 inhibitor	Fulvestrant + CDK4/6 inhibitor
Tumor genomic testing[b]			
Second-line treatment	No targetable mutations	Fulvestrant or fulvestrant + everolimus	Fulvestrant + everolimus, or chemotherapy
	ESR1 mutation	Elacestrant, or fulvestrant + everolimus	Elacestrant
	PIK3CA mutation	Fulvestrant + capivasertib, fulvestrant + alpelisib,[d] or fulvestrant	Fulvestrant + capivasertib, or fulvestrant + alpelisib[d]
	AKT1 mutation or *PTEN* inactivation	Fulvestrant + capivasertib, or fulvestrant	Fulvestrant + capivasertib
Third-line treatment and beyond[c]	No targetable mutations or targeted therapy already given	Chemotherapy or further endocrine-based treatments	Chemotherapy or further endocrine-based treatments
	ESR1 mutation	Elacestrant[e] or chemotherapy	Elacestrant[e] or chemotherapy
	PIK3CA mutation	Fulvestrant + capivasertib,[e] or fulvestrant + alpelisib,[d,e] or chemotherapy	Fulvestrant + capivasertib,[e] or fulvestrant + alpelisib,[d,e] or chemotherapy
	AKT1 mutation or *PTEN* inactivation	Fulvestrant + capivasertib,[e] or chemotherapy	Fulvestrant + capivasertib,[e] or chemotherapy

[a]All contemporary studies for ER-positive advanced breast cancer have been based on outcomes in postmenopausal women or women who were premenopausal at the time of diagnosis of advanced cancer and then underwent medically induced menopause. For premenopausal women diagnosed with advanced, ER-positive breast cancer, ovarian function suppression should be initiated and then treatment proceeds as in the Table.
[b]Tumor genomic testing includes sequencing for targetable mutations, accomplished through large panel tumor genomic testing in a CLIA-certified laboratory performed on tissue or plasma obtained either at the time of progression or from archival tissue. In addition to selecting patients whose tumors have increased *PIK3CA* or *AKT1* activity because of the presence of activating mutations, it is also important to identify those whose tumors have inactivation of PTEN protein. PTEN inactivation can be identified based on the presence of premature stop codons, frameshift alterations, splice site mutations, *PTEN* homozygous deletion, *PTEN* rearrangements that disrupt protein function, or specific missense mutations (C124R, C124S, G129E, G129V, G129R, R130Q, R130G, R130L, R130P, C136R, C136Y, S170R, and R173C) on next-generation sequencing.
[c]There are few data on the value of older ET options after therapy with modern treatment regimens such as AIs, SERDs, CDK4/6 inhibitors, and/or other targeted agents. In select patients—typically those with indolent cancers, limited disease burden or symptoms, and demonstrated clinical benefit from prior ETs—therapies such as tamoxifen, megestrol acetate, or reintroduction of previously administered treatments may be of clinical value.
[d]Alpelisib is an option for patients with tumors harboring *PIK3CA*-activating mutations but not *AKT*1-activating mutations or PTEN inactivation.
[e]If not previously given.

Recommendation 1.1

The Expert Panel recommends multiple lines of endocrine treatment (ET), frequently paired with targeted agents, with choices informed by prior treatments and by routine testing for activating mutations in ESR1, PIK3CA,or AKT1 or inactivation of PTEN (Table 1). Panelists recommend inclusion of CDK4/6 inhibitor therapy with ET in the first line. Second- and third-line therapies reflect targeted options based on tumor genomics. Combining ET with the AKT pathway inhibitor capivasertib is appropriate for tumors harboring PIK3CA or AKT1 mutations or PTEN inactivation while ET combined with the PI3 kinase inhibitor alpelisib is an option for tumors harboring PIK3CA mutations, but not AKT1 mutations. Other options include ET with mammalian target of rapamycin inhibitor everolimus irrespective of tumor genomics (Table 1). Monotherapy with the oral selective estrogen receptor degrader elacestrant is an option for tumors with ESR1 mutation (Evidence quality: High; Strength of recommendation: Strong).

Recommendation 1.2

There are no comparative efficacy data for choosing a PIK3CA targeted option for those who are potential candidates for capivasertib or alpelisib treatment. For such patients, the Panel recommends selecting the targeted agent based on perceived risk-benefit considerations such as hyperglycemia, diarrhea, or treatment discontinuation for AEs (Evidence quality: Low; Strength of recommendation: Weak).

Qualifying Statement for Recommendations 1.1 and 1.2

Both capivasertib and alpelisb can cause rash and/or diarrhea. Grade 3 or greater AEs included diarrhea (9.3% capivasertib v 6.7% alpelisib), rash (12.1% capivasertib v 9.9% alpelisib), and hyperglycemia (2.3% capivasertib v 36.6% alpelisib). Clinicians may mitigate symptoms with antihistamines, anti-diarrheal agents, or other supportive measures. Most patients with estrogen receptor–positive, HER2-negative breast cancers will be candidates for multiple lines of ET and/or targeted agents prior to chemotherapy or antibody-drug conjugate therapy. While newer agents have been added to the armamentarium, there remain few studies on the optimal timing or sequence of treatments, comparisons of targeted agents within a class, or studies that compare one class of agents against another. Such trials are an important clinical priority, as are studies to mitigate side effects of these agents.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2025) am 13.03.2025

#	Suchschritt
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 malignan*):ti,ab,kw
4	((local* NEXT advanced) OR metastat* OR metastas* OR recurren* OR relaps* OR progression*):ti,ab,kw
5	(#1 OR (#2 AND #3)) AND #4
6	#5 with Cochrane Library publication date from Jan 2020 to Feb 2023
7	#5 with Cochrane Library publication date from Mar 2023 to present

Leitlinien und systematische Reviews in PubMed am 13.03.2025

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

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	breast neoplasms[majr]
2	breast[ti] OR mamma*[ti]
3	(#2) AND (cancer*[ti] OR tumour*[ti] OR tumor[ti] OR tumors[ti] OR carcinom*[ti] OR neoplas*[ti] OR malignan*[ti])
4	(#1 OR #3) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
5	((((#4) AND ("2020/03/01"[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]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
6	breast neoplasms/TH[majr] AND (local*[tiab] OR advance*[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR relaps*[tiab] OR progession[tiab] OR progressive*[tiab] OR neoplasm metastasis/TH OR neoplasm recurrence, local/TH)
7	breast*[tiab] OR mamma*[tiab]

#	Suchschritt
8	(#7) AND (local*[tiab] OR advance*[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR relaps*[tiab] OR progession[tiab] OR progressive*[tiab] OR neoplasm metastasis/TH OR neoplasm recurrence, local/TH)
9	(#8) 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 malignan*[tiab])
10	(#9) 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 chemotherapy[tiab] OR chemotherapies[tiab] OR immunotherapy[tiab] OR immunotherapies[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab] OR Combined Modality Therapy/TH)
11	#6 OR #10
12	(#11) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] 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 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"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
13	(((#12) AND ("2020/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
14	(#13) NOT (#5)
15	(#14) AND ("2023/03/01"[PDAT] : "3000"[PDAT])
16	#14 NOT #15

Iterative Handsuche nach grauer Literatur, abgeschlossen am 13.03.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- 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)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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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