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-097 Imlunestrant

Stand: Juni 2025

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

Imlunestrant
[zur Behandlung des HR-positiven, HER2-negativen, lokal fortgeschrittenen oder 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“.
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 - Ovariektomie
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: - Capivasertib: Beschluss vom 03.04.2025 - Elacestrant: Beschluss vom 02.05.2024 - Abemaciclib: Beschlüsse vom 19.05.2022 und 15.06.2023 - Palbociclib: Beschlüsse vom 18.05.2017, 21.03.2019 und 15.12.2022 - Ribociclib: Beschlüsse vom 04.07.2019 und 20.08.2020 - Alpelisib (in Kombination mit Fulvestrant): Beschluss vom 18.02.2021 - Olaparib: Beschluss vom 16.01.2020 - Talazoparib: Beschluss vom 20.11.2020
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:	
Imlunestrant N.N. Inluriyo	Anwendungsgebiet: Imlunestrant ist angezeigt als Monotherapie zur Behandlung erwachsener Patienten mit Östrogenrezeptor (ER)-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs mit einer aktivierenden ESR1-Mutation, deren Erkrankung nach einer vorherigen endokrinen Therapie progredient ist.
Antiöstrogene	
Elacestrant L02BA04 Oserdu	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.
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.
Tamoxifen L02BA01 Nolvadex	Metastasierendes Mammakarzinom

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Toremifen L02BA02 Fareston	First-line Behandlung des hormonabhängigen metastasierenden Mammakarzinoms bei postmenopausalen Patientinnen. Fareston kann bei Patientinnen mit Östrogenrezeptor-negativen Tumoren nicht empfohlen werden.
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.
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.
Capivasertib L01EX27 TRUQAP[1]	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 (siehe Abschnitt 5.1). 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.

[1] Derzeit nicht auf dem deutschen Markt verfügbar.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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 • 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	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.
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.

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-097 (Beratung nach § 35a SGB V) Imlunestrant

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	16. April 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

a/mBC	advanced/metastatic breast cancer
ABC	Advanced breast cancer
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
SIGN	Scottish Intercollegiate Guidelines Network
TEAEs	treatment emergent adverse events
TRIP	Turn Research into Practice Database
VTE	Venous thromboembolism
WHO	World Health Organization

1 Indikation

Behandlung von erwachsenen Patienten mit Hormonrezeptor(HR)-positivem, humanen epidermalen Wachstumsfaktor-Rezeptor 2 (HER2)-negativem, lokal fortgeschrittenem oder metastasiertem Brustkrebs, die für eine endokrine Therapie geeignet sind.

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 31.03.2025 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 6959 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 7 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

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

Hinweis: Aufgrund der erwarteten Heterogenität der Studien wurde keine Metaanalyse durchgeführt. Im Folgenden werden nur die Ergebnisse aus den randomisiert kontrollierten Studien dargestellt.

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 publications reporting results from seven RCTs

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)

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).

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

Treatment Discontinuation

Three RCTs reported treatment discontinuation data for older patients who received palbociclib. 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].

Safety

AE data by age subgroups (younger vs older patients) were reported from three RCTs [19, 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].

Health-Related Quality of Life

Data on HRQoL outcomes by age subgroups (younger versus older patients) were reported in two RCTs (Table 3). Among patients receiving palbociclib in PALOMA-2, there was no significant deterioration in well-being scale or total Functional Assessment of Cancer Therapy – Breast (FACT-B) scores in patients aged 65−74 and ≥ 75 years [27]. Similarly, in PALOMA-3, patients aged 65−74 and ≥ 75 years maintained global quality of life (QoL) and did not show significant differences between treatment arms in functioning or symptoms, except for appetite loss in patients aged ≥ 75 years, for which a greater deterioration was observed in patients who received palbociclib [27].

Table 3 HRQoL outcomes

Study	HRQoL outcomes in older patients
PALOMA-2	• In patients aged 65–74 and ≥ 75 years, baseline HRQoL scores were similar between treatment groups • No significant deterioration in well-being scale or total FACT-B scores was observed among patients aged 65–74 and ≥ 75 years receiving PAL+LET
PALOMA-3	• In patients aged 65–74 and ≥ 75 years, baseline HRQoL scores were similar between treatment groups • PAL+FUL maintained global QoL and did not show significant differences between treatment groups in functioning or symptoms in either age subgroup, except for loss of appetite in patients aged ≥ 75 years, for which a significantly greater deterioration was observed in patients receiving FUL+PBO (− 0.8 vs 17.9; $P = 0.012$) • A statistically significant delay in deterioration in pain scores was observed with PAL+FUL versus FUL+PBO in patients aged 65–74 years (median 19.6 vs 8.0; HR 0.37; $P = 0.003$) • No significant difference between arms in time to deterioration in pain scores was observed in patients aged ≥ 75 years

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

- Keine Meta-Analyse aufgrund hoher Heterogenität der Studien
- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

Luo C et al., 2024 [4].

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

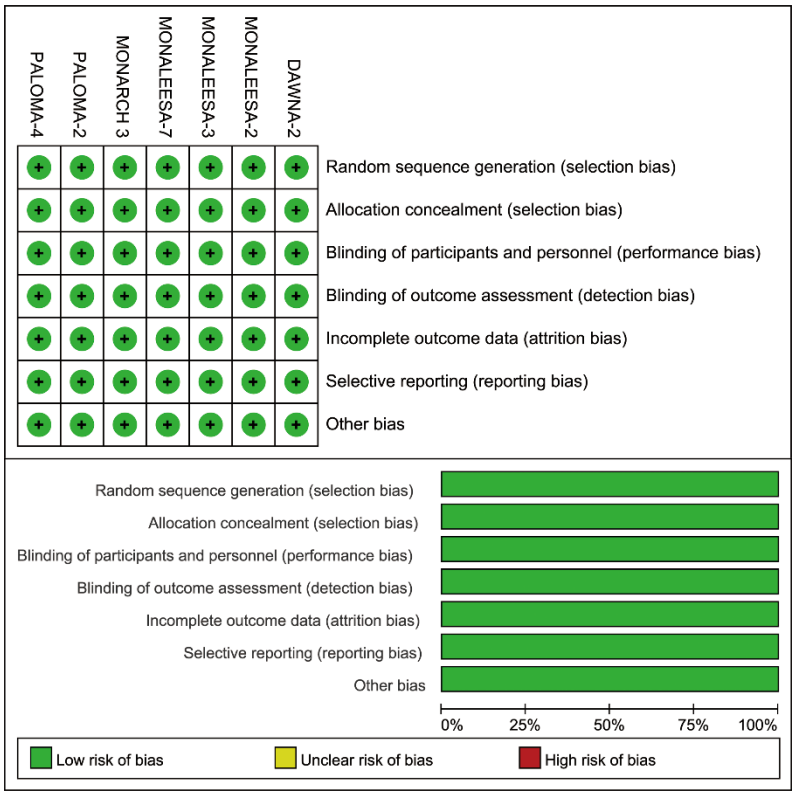
Charakteristika der Population/Studien:

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:

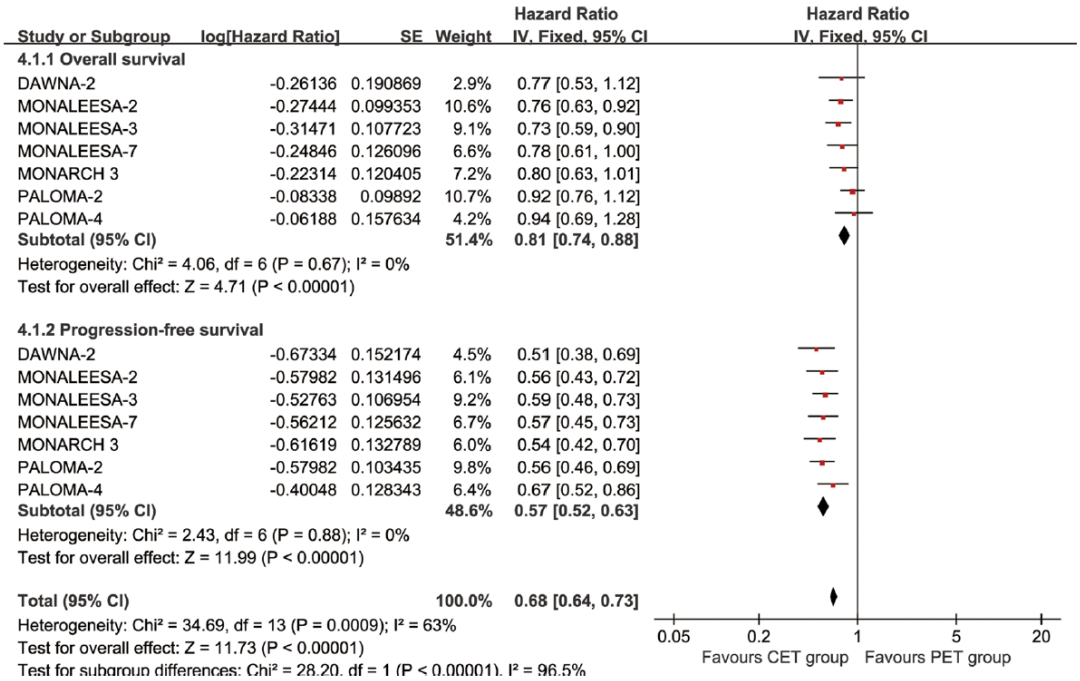


Fig. 2 Forest plots of overall survival and progression-free survival associated with CET group versus PET group

CET: CDK4/6 inhibitors + ET; PET: placebo + ET

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).

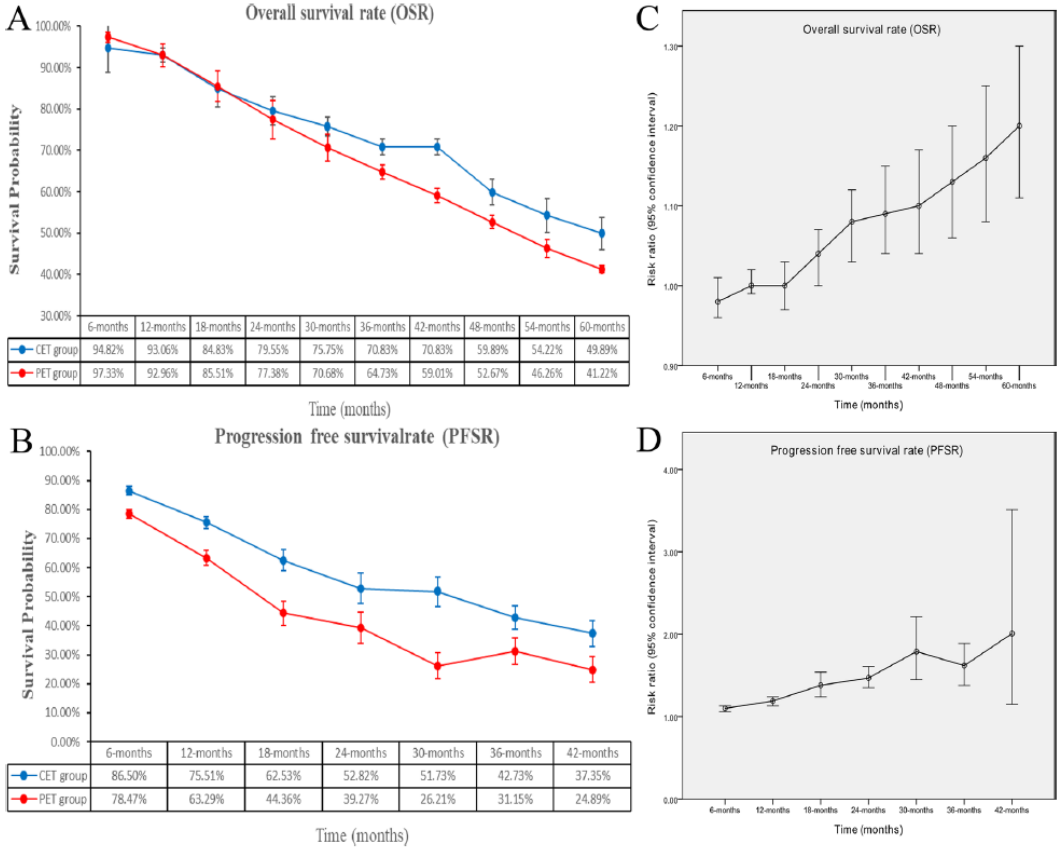


Fig. 3 Comparisons of overall survival rate (6–60 months, **A**: trend of overall survival rate; **C**: trend of risk ratios) and progression-free survival rate (6–42 months, **B**: trend of progression-free survival rate; **D**: trend of risk ratios) associated with CET group versus PET group

CET: CDK4/6 inhibitors + ET; PET: placebo + ET

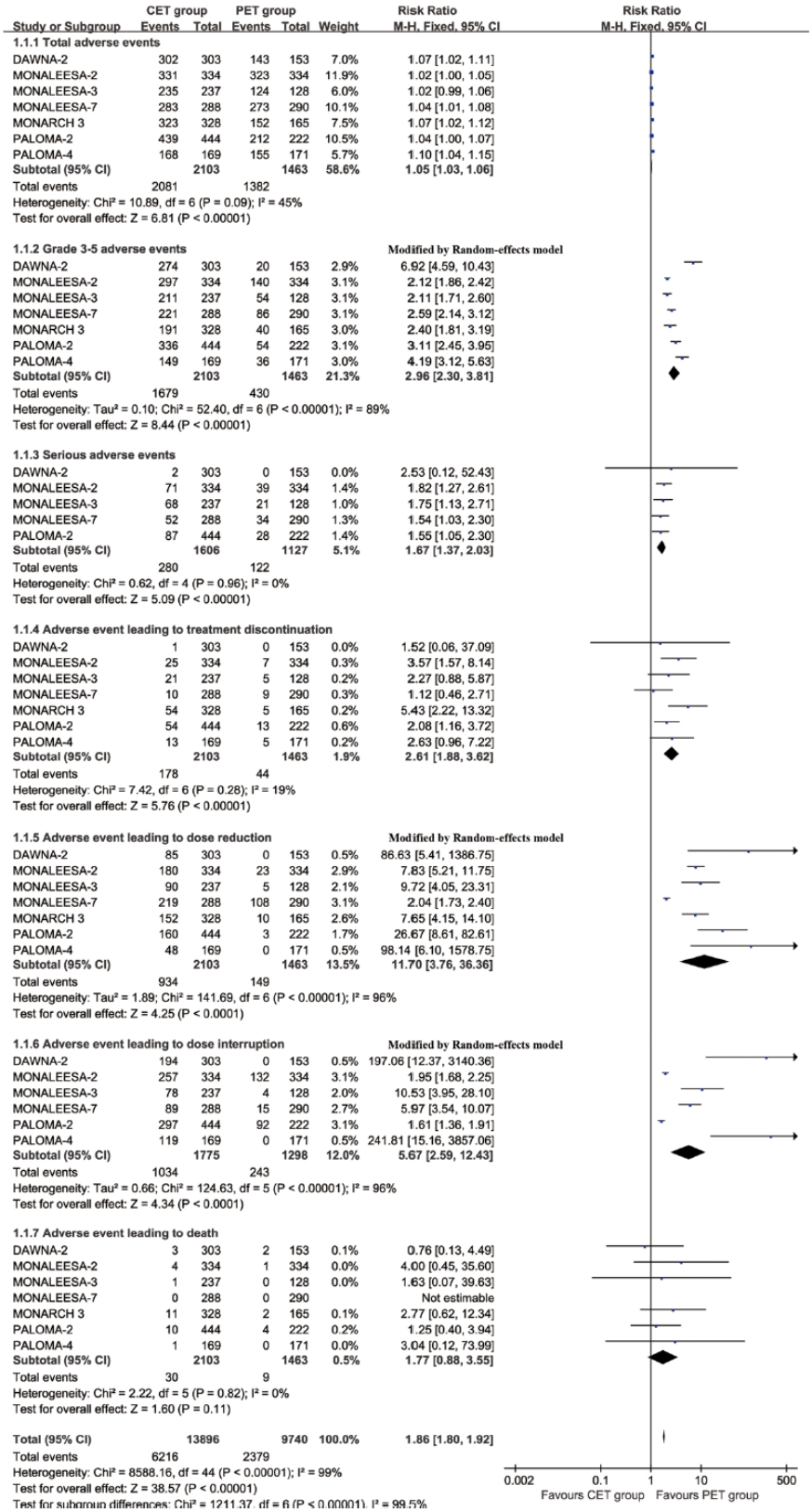
Subgroup analysis of survival (OS and PFS)

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.

Ravani LV et al., 2024 [7].

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:

- 8 RCTs
- 10 retrospective cohort studies

Hinweis: Im Folgenden werden nur die Ergebnisse aus den randomisiert kontrollierten Studien dargestellt. Der Einschluss war beschränkt auf Studien, die Ergebnisse zu den Endpunkten OS und PFS als KM Kurven berichteten. Aus den KM Kurven wurden für die Meta-Analysen der vorliegenden Studie die Rohdaten zu OS und PFS extrahiert.

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.

Qualität der Studien:

Table S5. Quality assessment for studies included in this systematic review and meta-analysis using: […] risk-of-bias 2 tool for randomized clinical trials (RoB 2) (B).

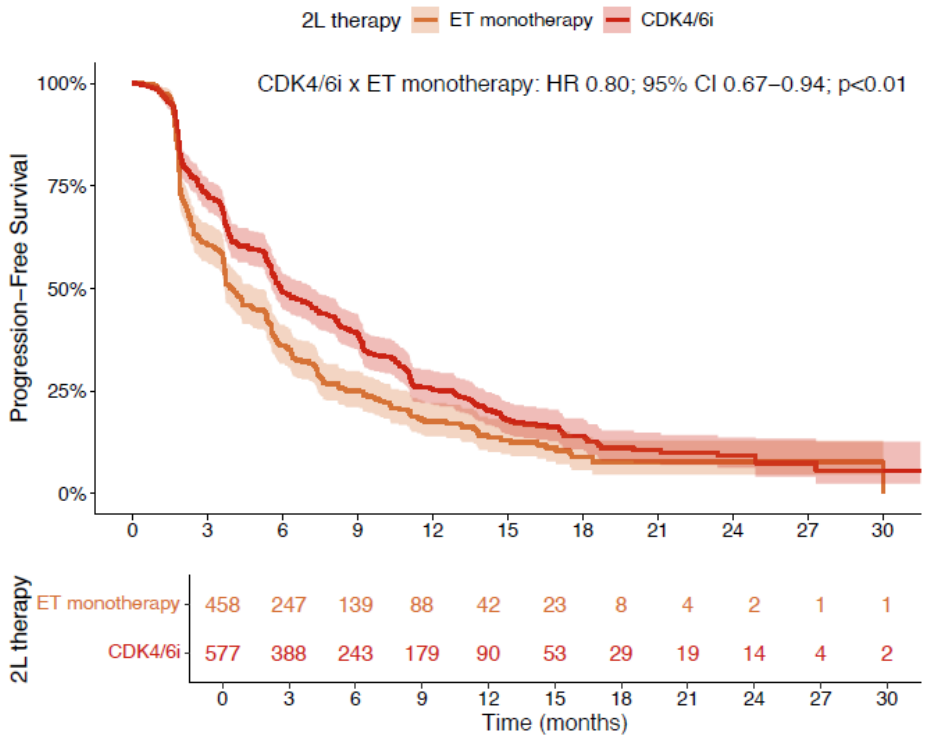
Study	Bias from randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcomes	Bias in selection of the reported result	Overall risk of bias
MAINTAIN	Low	Some concerns	Low	Low	Low	Some concerns
PALMIRA	Low	Some concerns	Low	Low	Some concerns	Some concerns
PACE	Low	Low	Low	Low	Low	Low
ostMONARCH	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 and OS

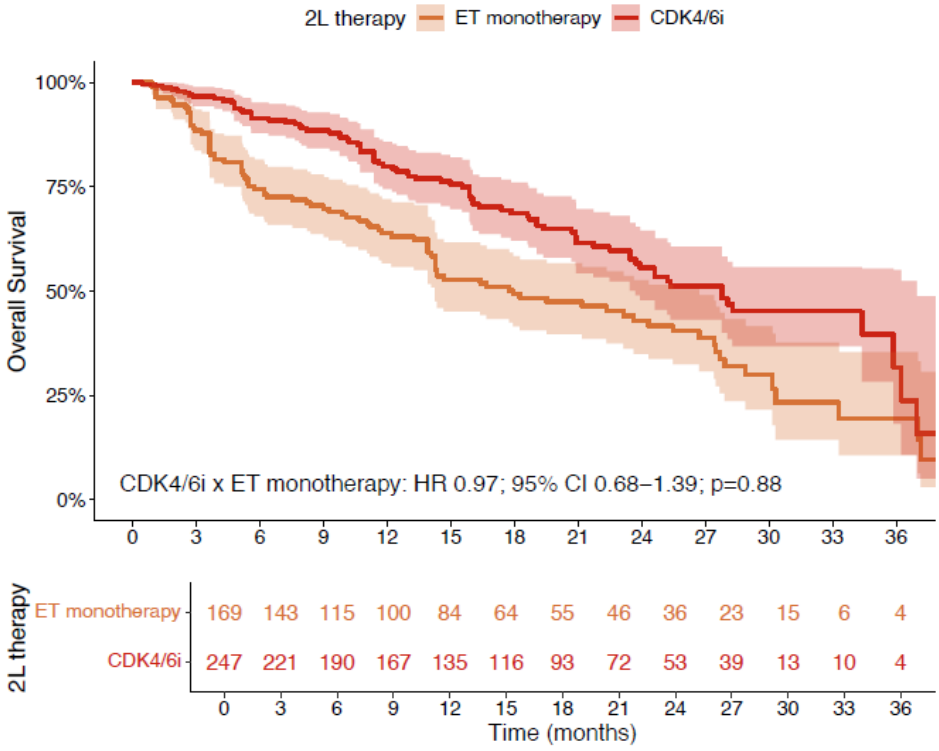
A sensitivity analysis limited to RCTs showed a PFS benefit for maintaining CDK4/6i plus ET compared with ET monotherapy (HR, 0.80 [95% CI, 0.67 to 0.94]; P < .01; Data Supplement, Fig S4), but no significant difference in OS between the two strategies (HR, 0.97, [95% CI, 0.68 to 1.39]; P = .88; Data Supplement, Fig S5).

Figure S4. Sensitivity analysis - Pooled Kaplan-Meier curves of PFS including only data from RCTs



OS

Figure S5. Sensitivity analysis - Pooled Kaplan-Meier curves of OS including only data from RCTs



Anmerkung/Fazit der Autoren

In conclusion, our study reveals that continuing CDK4/6i with ET postprogression 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

- Die Schlussfolgerungen der Autoren beziehen sich auf die gepoolten Analysen mit Daten aus RCT und retrospektiven Kohortenstudien. In den gepoolten Analysen, welche lediglich Daten aus den RCT beinhalten, zeigte sich ein Vorteil für CDK4/6i mit ET gegenüber ET-Monotherapie für den Endpunkt PFS, nicht aber für das den Endpunkt OS.
- Es liegt ein weiterer SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor: Ramos-Esquivel a et al., 2024 [6]

3.3 Leitlinien

Burstein HJ et al., 2021 [3].

ASCO

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

Burstein HJ et al., 2024 [2]

ASCO

Endocrine and Targeted Therapy for Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer-Capivasertib-Fulvestrant: ASCO Rapid Recommendation Update

Zielsetzung/Fragestellung

- To update recommendations of the ASCO systemic therapy for hormone receptor (HR)-positive metastatic breast cancer (MBC) guideline.
- 2021:
  - This focused update of the 2016 guideline provides a new recommendation for the use of alpelisib in the treatment of patients with HR-positive MBC; addresses the role of biomarkers in treatment selection for this patient population; and amends prior recommendations concerning the use of CDK4/6 inhibitors in the treatment of these patients. The remaining recommendations from the 2016 guideline are unchanged because there were no new potentially practicechanging data to support substantive revisions
  - […] this guideline provides recommendations for ET and targeted therapy, including CDK4/6 and PI3 kinase inhibition for patients with HR-positive MBC.
- 2024:
  - The CAPItello-291 phase III, double-blind, randomized controlled trial (RCT) evaluating fulvestrant with the AKT pathway inhibitor capivasertib3 and subsequent US Food and Drug Administration approval of capivasertib and a companion diagnostic device on November 16, 2023, constituted strong signals for updating ASCO MBC guidelines

Methodik

<u>Grundlage der Leitlinie</u>

- 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
- Burstein HJ et al., 2024: „targeted electronic literature search“, keine weiteren Angaben

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.

Empfehlungen
Aus dem Update 2021

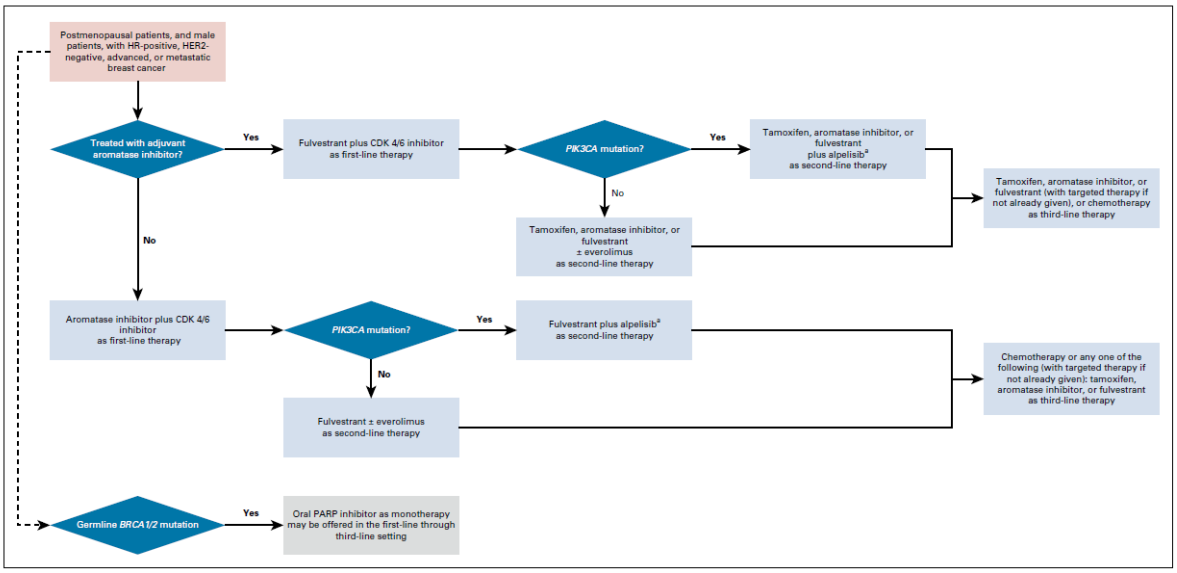


FIG 1. Algorithm for endocrine treatment and targeted therapy for HR-positive, HER2-negative MBC. [a]Patients receiving alpelisib should have laboratory and symptom monitoring weekly for the first 4 weeks of therapy to avoid serious toxicity. CDK, cyclin-dependent kinase; HER2, human epidermal growth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

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).

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.

Aus dem Update 2024

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).

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

NOTE. 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.

Abbreviations: AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; CLIA, Clinical Laboratory Improvement Amendments; ER, estrogen receptor; ESR1, estrogen receptor 1; ET, endocrine treatment; PTEN, phosphatase and tensin homolog; SERD, selective estrogen receptor degrader.

[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 *AKT1*-activating mutations or PTEN inactivation.

[e]If not previously given.

Moy B et al., 2021 [5].

ASCO

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

Zielsetzung/Fragestellung

The purpose of this guideline update is to gather and examine the evidence published since the 2014 guideline by Partridge et al2 and offer a series of updated recommendations for advanced human epidermal growth factor receptor 2 (HER2)–negative breast cancer, if warranted.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Überprüfung der Aktualität nach Bedarf oder alle 3 Jahre; keine Gültigkeit angegeben.

Recherche/Suchzeitraum:

- Systematic review of PubMed (January 1, 2014-February 29, 2020; updated with a targeted search in April 2021)

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

Empfehlungen

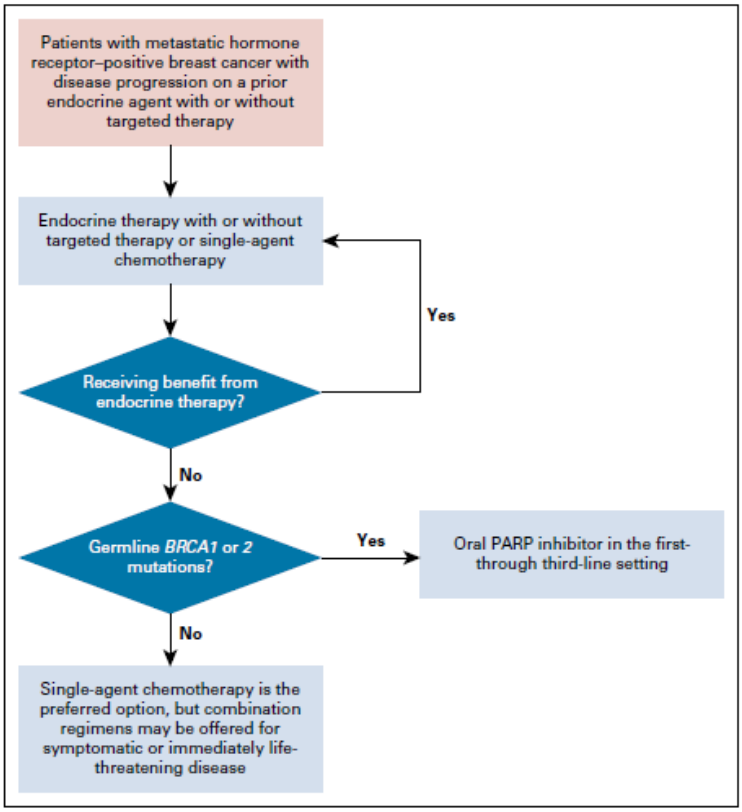


FIG 2. Treatment algorithm for chemotherapy and targeted therapy for patients with HER2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor–negative. HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death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

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 for Hormone Receptor–Positive Metastatic Breast Cancer13 for details) or single-agent chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Hintergrundinformation

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

Literature update and analysis. The systematic review identified three clinical trials and a meta-analysis addressing optimal therapy for women with metastatic HR-positive breast cancer with progressive disease on a nonsteroidal AI. The phase II BOLERO-63 trial randomly assigned 309 patients whose disease had progressed on nonsteroidal Ais to three treatment regimens: everolimus plus exemestane versus everolimus alone versus capecitabine alone. The primary objective of the study was PFS for everolimus plus exemestane versus everolimus alone. Everolimus plus exemestane improved PFS compared with everolimus alone with hazard ratio of 0.74 (90% CI, 0.57 to 0.97). Everolimus plus exemestane had similar PFS compared with capecitabine with hazard ratio of 1.26 (90% CI, 0.96 to 1.66). The investigators noted potential informative cen- soring between treatment arms and therefore performed a stratified multivariate Cox regression model to account for imbalances in baseline characteristics. This demonstrated a consistent hazard ratio for everolimus plus exemestane versus everolimus (hazard ratio, 0.73; 90% CI, 0.56 to 0.97), but the hazard ratio approached one for everolimus plus exemestane versus capecitabine (hazard ratio, 1.15; 90% CI, 0.86 to 1.52). Grade 3 to 4 adverse events were more frequent with capecitabine (74%; n 5 75) versus everolimus plus exemestane (70%; n 5 73) or everolimus alone (59%; n

5 61). Serious adverse events were more frequent with everolimus plus exemestane (36%; n 5 37) versus ever- olimus alone (29%; n 5 30) or capecitabine (29%; n 5 30).
The phase III randomized PEARL4 trial for patients with metastatic HR-positive breast cancer resistant to AIs enrolled two cohorts. In cohort 1, 296 patients were allocated to palbociclib plus exemestane versus capecitabine. Because of concern regarding acquired ESR1 mutations and resistance to AIs, the protocol was amended and a second cohort of 305 patients were allocated to palbociclib plus fulvestrant versus capecitabine. The trial failed to meet either primary superiority end point, finding that palbociclib plus fulvestrant was not superior to capecitabine (median PFS: 7.5 v 10.0 months; adjusted hazard ratio, 1.13; 95% CI, 0.85 to 1.50), nor was palbociclib plus ET superior to capecitabine in wild-type ESR1 patients (median PFS: 8.0 v 10.6 months; adjusted hazard ratio, 1.11; 95% CI: 0.87 to 1.41). The most frequent grade 3- 4 toxicities with palbociclib plus exemestane, palbociclib plus fulvestrant, and capecitabine were neutropenia (57.4%, 55.7% and 5.5%), hand-foot syndrome (0%, 0%, and 23.5%), and diarrhea (1.3%, 1.3%, and 7.6%), respectively. Palbociclib plus ET demonstrated better QoL compared with capecitabine (adjusted hazard ratio for time to deterioration of global health status 5 0.67; 95% CI, 0.53 to 0.85).
The randomized phase II KCSG-BR15-1018 trial compared safety and efficacy of palbociclib plus ET versus capecita- bine in premenopausal women with HR-positive breast cancer who had progressed on tamoxifen. This study ran- domly assigned 184 premenopausal women to receive ei- ther aromatase inhibitor-ovarian function suppression (AI- OFS) (exemestane plus leuprolide) plus palbociclib versus capecitabine. Treatment with AI-OFS plus palbociclib demonstrated improved PFS compared with capecitabine (20 v 14 months; hazard ratio, 0.66; 95% CI, 0.44 to 0.99). Nonhematologic toxicities were less common with AI-OFS plus palbociclib compared with capecitabine (grade 1-4: diarrhea, 13% v 39%; hand-foot syndrome, 1% v 100%, respectively), but hematologic toxicity was more common (grade $ 3 neutropenia, 64% v 16%, respectively).
A systematic review16 compared ET plus palbociclib versus chemotherapy in metastatic HR-positive disease. In this review, a meta-analysis of 60 randomized controlled trials published from January 2000 to January 2016 demonstrated in the first line, palbociclib plus letrozole showed statistically significant improvements in PFS/TTP versus capecitabine (intermittent: hazard ratio, 0.28; 95% CI, 0.11 to 0.72) and mitoxantrone (hazard ratio, 0.28; 95% CI, 0.13 to 0.61) and trended toward improvements versus paclitaxel (hazard ratio, 0.59; 95% CI, 0.19 to 1.96), docetaxel (hazard ratio, 0.51; 95% CI, 0.14 to 2.03), and other monotherapy or combination agents (hazard ratios ranging from 0.24 to 0.99). In the second line, palbociclib plus fulvestrant showed statistically significant improvements in PFS/TTP versus capecitabine (intermittent: hazard ratio, 0.28; 95% CI, 0.13 to 0.65), mitoxantrone (hazard ratio, 0.26; 95% CI, 0.12 to 0.53), and pegylated liposomal doxorubicin (hazard ratio, 0.19; 95% CI, 0.07 to 0.50) and trended toward improvements versus paclitaxel (hazard ratio, 0.48; 95% CI, 0.16 to 1.44), docetaxel (hazard ratio, 0.71; 95% CI, 0.24 to 2.13), and other monotherapy or combination agents (hazard ratios ranging from 0.23 to 0.89).
Clinical interpretation. The treatment choice between ET with targeted agents such as CDK 4/6 inhibitors, ever- olimus, and alpelesib and single-agent chemotherapy should be based on individualized assessments of risks and benefits, prior treatment response, tumor burden, pace of disease, and patient preferences. Individual considerations should include the robustness of the patient's prior re- sponse to ET, QoL, side effects, comorbid conditions, and out-of-pocket treatment costs. Notably, the results of the systematic review should be interpreted with caution since there were significant limitations, including stage migration and unmeasured variables that might have led to patients enrolling in a chemotherapy rather than an ET clinical trial.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2025) am 31.03.2025

#	Suchschritt
1	[mh ”Breast Neoplasms”]
2	(breast OR mamma*):ti,ab,kw
3	#2 AND (cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	{OR #1, #3} with Cochrane Library publication date from Mar 2020 to Feb 2023
5	{OR #1, #3} with Cochrane Library publication date from Mar 2023 to present

Leitlinien und systematische Reviews in PubMed am 31.03.2025

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 (tumor[ti] OR tumors[ti] OR tumour*[ti] OR carcinoma*[ti] OR adenocarcinoma*[ti] OR neoplas*[ti] OR sarcoma*[ti] OR cancer*[ti] OR lesion*[ti] OR malignan*[ti])
4	(#1 OR #3) 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/therapy[majr]
7	(breast[tiab]) OR mamma*[tiab]
8	(#7) AND (tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab])

#	Suchschritt
9	(#8) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
10	(#6 OR #9) 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])
11	(((#10) 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
12	(#11) NOT (#5)
13	(#12) AND ("2023/03/01"[PDAT] : "3000"[PDAT])
14	#12 NOT #13

Iterative Handsuche nach grauer Literatur, abgeschlossen am 31.03.2025

- 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)
- American Society of Clinical Oncology (ASCO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2025-B-097

Verfasser	
Institution	Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) der Deutschen Krebsgesellschaft (DKG) Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) Deutsche Gesellschaft für Senologie (DGS)
Datum	6. Juni 2025

Indikation
Behandlung von erwachsenen Patienten mit Östrogenrezeptor (ER)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor 2 (HER2)-negativem, Östrogenrezeptor 1 (ESR1)-mutiertem, fortgeschrittenem oder metastasiertem Brustkrebs, die zuvor mit einem endokrinen Therapieschema behandelt wurden Behandlung von erwachsenen Patienten mit ER-positivem, HER2-negativem, fortgeschrittenem oder metastasiertem Brustkrebs, die zuvor mit einem endokrinen Therapieschema behandelt wurden
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?
Zusammenfassung Aktueller Standard bei Patientinnen und Patienten (Pat.) mit HR+/HER2- Mammakarzinom nach Rezidiv oder Progression der Erkrankung während oder nach einer erweiterten endokrinen Therapie mit Einsatz von CDK4/6i ist eine Therapie nach ärztlicher Maßgabe unter besonderer Berücksichtigung der - Biologie der Erkrankung - Krankheitsaktivität / Symptomatik - Vortherapie - Komorbidität.

Die zugrundeliegende Evidenz wurde auch in aktuellen Verfahren der frühen Nutzenbewertung präsentiert. Innerhalb der verschiedenen Strategien stehen folgende Arzneimittel zur Verfügung [1-3]:

Entsprechend dem ersten Teil der Fragestellung

- bei endokriner Sensitivität und Nachweis aktivierender *ESR1*-Mutation: Elacestrant [4]

Entsprechend dem zweiten Teil der Fragestellung, falls keine ESR1-Mutation nachgewiesen wurde

- bei Nachweis von *PIK3CA/AKT1/PTEN*-Alterationen: Fulvestrant + Capivasertib, Fulvestrant + Alpelisib [5, 6]
- bei Nachweis von *gBRCA*mut: Olaparib [7, 8] oder Talazoparib [9, 10]
- bei endokriner Sensitivität für alle: Wechsel der endokrinen Therapie: Aromatasehemmer, Fulvestrant, ggf. die Kombination mit GnRH bei prämenopausalen Patientinnen [1-3]
- bei endokriner Sensitivität für alle: Exemestan + Everolimus
- bei endokriner Resistenz für alle: Chemotherapie ggf. in Kombination mit Bevacizumab [1-3]
- bei endokriner Resistenz und nachfolgendem Versagen von mindestens einer Chemotherapie und Nachweis von HER2 niedrig: Trastuzumab Deruxtecan [11]

Bei Konzeption einer Studie für Pat., die nicht für endokrine Therapie geeignet sind, ist eine Definition der Nicht-Eignung und insbesondere der Kriterien für endokrine Resistenz erforderlich [1-3]. Die Optionen sind oben integriert.

Fragestellung

Die Empfehlungen haben sich seit unseren letzten gutachterlichen Expertisen in dieser Indikation nicht grundlegend geändert.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ja, diese sind oben dargestellt.

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