Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2024-B-284-z Capivasertib

Stand: November 2024

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

Capivasertib
[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 • 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: Beschluss vom 02.05.2019, 03.09.2020 und 19.05.2022 • Alpelisib (in Kombination mit Fulvestrant): Beschluss vom 18.02.2021 • Olaparib: Beschluss vom 16.01.2020 • Palbociclib: Beschluss vom 18.05.2017, 22.03.2019 und 15.12.2022 • Ribociclib: Beschluss vom 04.07.2019 und 20.08.2020 • 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:	
Capivasertib L01EX27 TRUQAP	<u>Zugelassenes Anwendungsgebiet</u> Capivasertib 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.
Antiöstrogene	
Tamoxifen L02BA01 Nolvadex®	• […] • Metastasierendes Mammakarzinom.
Toremifen L02BA02 Fareston®	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.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	• 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.
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.
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Medroxyproges-teronacetat L02AB02 MPA Hexal®	Zur palliativen Behandlung bei folgenden hormonabhängigen Tumoren: • metastasierendes Mammakarzinom • […].
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.
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	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.
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 nach § 35a SGB V

Vorgang: 2024-B-180-z

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. August 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABC	Advanced breast cancer
AE	Adverse event
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDK	Cyclin-dependent kinase
ECRI	ECRI Guidelines Trust
ER	Estrogen receptor
ET	Endocrine therapy
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
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LABC	Locally advanced breast cancer
LoE	Level of Evidence
MBC	Metastatic breast cancer
NAC	Neoadjuvante Chemotherapie
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
pCR	Pathologisch komplette Remission
PFS	Progression-free survival
PR	Progesterone receptor
RCT	Randomized controlled trials
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
VTE	Venous thromboembolism
WHO	World Health Organization

1 Indikation

Erwachsene Personen mit einem Hormonrezeptor(HR)-positiven, HER2-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom nach Rezidiv oder Progression der Erkrankung während oder nach einer endokrinen Therapie.

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.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 05.05.2023 durchgeführt, die folgende am 03.01.2024 und 01.08.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 4480 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 20 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Tian Q et al., 2021 [18].

Overall survival and progression-free survival with cyclin-dependent kinase 4/6 inhibitors plus endocrine therapy in breast cancer: an updated meta-analysis of randomized controlled trials

Fragestellung

We conducted this meta-analysis to better define the efficacy and safety of CDK4/6i in HR+, Her2- ABC patients and aimed to identify a suitable patient population for CDK4/6i therapy through subgroup analysis.

Methodik

Population:

- HR+, Her2- ABC

Intervention/ Komparator:

- combined use of CDK4/6i and ET vs. Endocrine monotherapy

Endpunkte:

- PFS, OS, objective response rate (ORR) and the incidence of adverse events

Recherche/Suchzeitraum:

- Original articles published from Jan 2014 to Jan 2020
- searched in the MEDLINE, EMBASE and the Cochrane Library databases

Qualitätsbewertung der Studien:

- methodological quality assessment followed the Quality of Reporting of Meta-analyses and Cochrane Collaboration guidelines

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of eight RCTs (1 phase 2 and 7 phase 3) and 4580 HR+, Her2- ABC patients were enrolled in this meta-analysis.
- Five trials[5-8,10] estimated the efficacy and safety of CDK4/6i plus ET in HR+, Her2- ABC patients who had no prior systemic therapy in the advanced setting, two trials[9,16] in patients whose disease progressed during prior ET, and one trial[19] included patients in both settings.

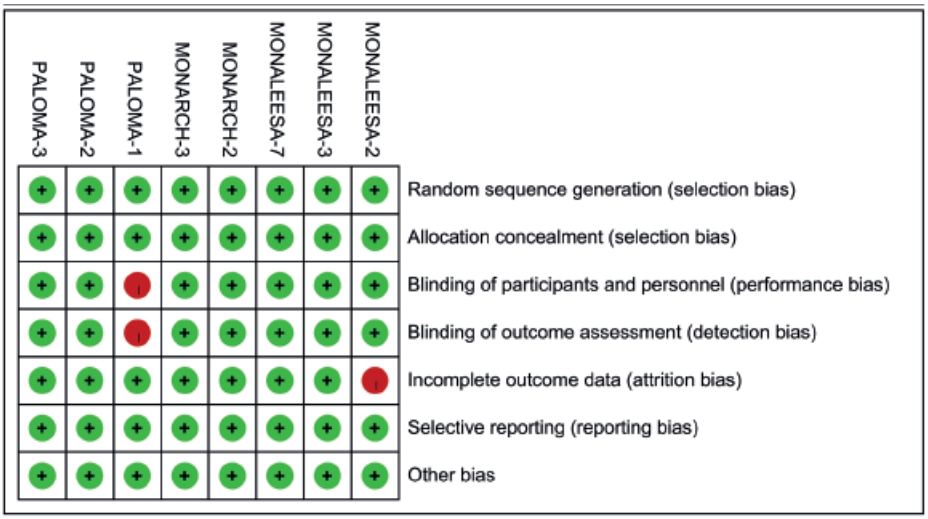
Charakteristika der Population:

Table I. Main characteristics of the randomized studies included in this meta-analysis.

Clinical trail	Recruitment period	Sample size	Design	Phase	Setting	Arms	PFS	OS	TTC
PALOMA1	2009.12-2012.5	165	Open-label, randomized study	2	1 line	P+L group L group	HR=0.488 95%CI:0.319-0.748	HR=0.897 95%CI:0.623-1.294	NA
PALOMA2	2013.2-2014.7	666	Randomized, double-blind, placebo-controlled study	3	1 line	P+L group L group	HR=0.58 95%CI:0.46-0.72	NA	40.4(34.7-47.3) HR=0.735 29.9(25.6-35.1) 95%CI:0.589-0.917
PALOMA3	2013.10-2014.8	521	Randomized, double-blind, placebo-controlled study	3	2 line	P+F group F group	HR=0.42 95%CI:0.32-0.56	HR=0.81 95%CI:0.64-1.03	17.6(15.2-19.7) HR=0.58 8.8(7.3-12.7) 95%CI:0.47-0.73
MONALEESA2	2014.1-2015.3	668	Randomized, double-blind, placebo-controlled study	3	1 line	R+L group L group	HR=0.56 95%CI:0.43-0.72	HR=0.746 95%CI:0.517-1.078	NA
MONALEESA3	2015.6-2016.6	726	Randomized, double-blind, placebo-controlled study	3	1 & 2 line	R+F group F group	HR=0.587 95%CI:0.488-0.705	HR=0.724 95%CI:0.568-0.924	NR HR=0.696 29.5 95%CI:0.551-0.879
MONALEESA7	2014.12-2016.8	672	Randomized, double-blind, placebo-controlled study	3	1 line	R+T/AI+OFS group T/AI+OFS group	HR=0.55 95%CI:0.44-0.96	HR=0.71 95%CI:0.54-0.95	NA
MONARCH2	2014.8-2015.12	669	Randomized, double-blind, placebo-controlled study	3	2 line	A+F group F group	HR=0.536 95%CI:0.445-0.645	HR=0.757 95%CI:0.606-0.945	50.2 HR=0.625 22.1 95%CI:0.501-0.779
MONARCH3	2014.11-2015.11	493	Randomized, double-blind, placebo-controlled study	3	1 line	A+AI group AI group	HR=0.54 95%CI:0.418-0.698	NA	NA

Notes: *P*, Palbociclib; *L*, Letrozole; *F*, Fulvestrant; *R*, Ribociclib; *T*, Tamoxifen; *AI*, Aromatase Inhibitors; *OFS*, Ovarian function suppression; *A*, Abemaciclib; *PFS*, Progression-free survival; *HR*, Hazard ratio; *CI*, Confidence interval; *OS*, Overall survival; *TTC*, Time to chemotherapy.

Qualität der Studien:



Studienergebnisse:

- The combination treatment improved **OS** outcomes in patients with treatment-naïve advanced disease (HR=0.74; 95% CI: 0.61–0.87) […]
- Improvements in **PFS** outcomes were consistent among all subgroups. […] The PFS advantage was obtained regardless of whether the treatments were applied as first-line (HR=0.55; 95% CI: 0.49–0.61) or subsequent-line (HR=0.53; 95% CI: 0.46–0.60) therapies
- In the ITT population, a total of 1045 **ORR** events occurred in 2802 patients in the CDK4/6i plus ET group, while 464 ORR events occurred in 1778 patients in the ET group. The combination of CDK4/6i and ET significantly improved the ORR compared to that obtained with ET alone (RR=1.47; 95% CI: 1.29–1.67) in the ITT population. In patients with measurable disease, a total of 1037 ORR events occurred in 2160 patients in the CDK4/6i group, 459 ORR events occurred in 1372 patients in the ET group, and the pooled RR for the ORR was 1.47 (95% CI: 1.30-1.67).
- Subgroup Analysis:

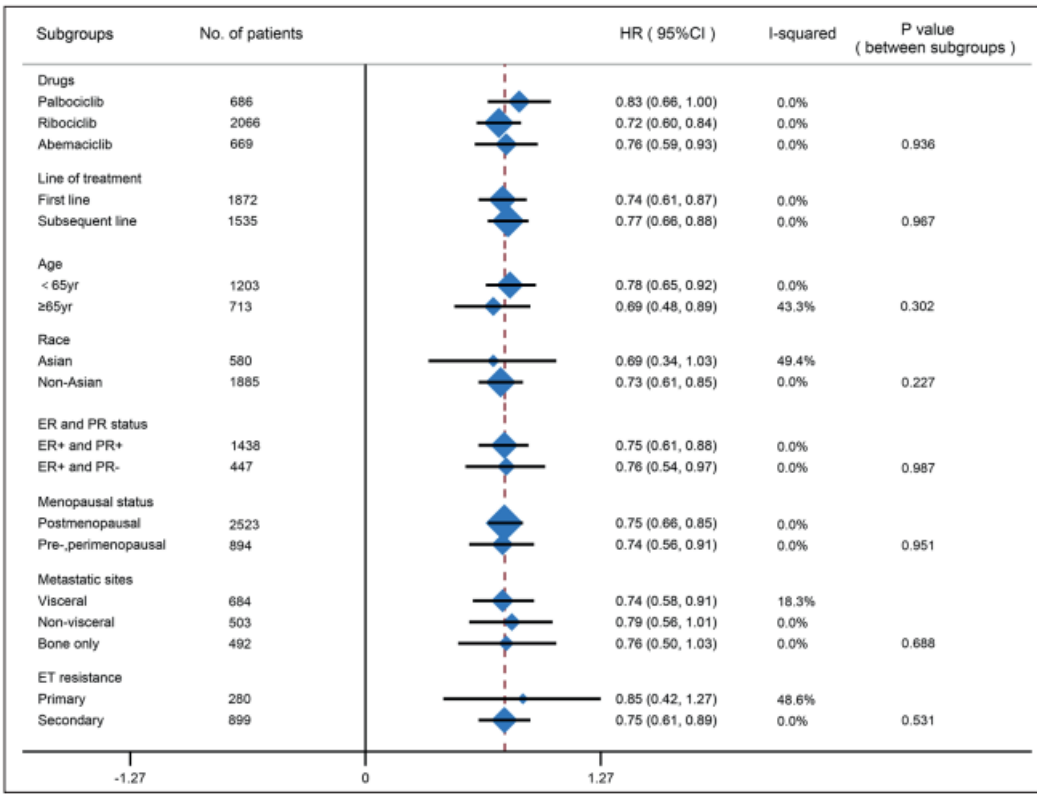


Figure 3. Subgroup analyses of pooled hazard ratios for overall survival.

- Adverse events:
  - Seven trials[5-10,16] included in our study reported any **G3/4 aes** in the intervention and control groups. A total of 1660 out of 2309 patients in the CDK4/6i group developed any G3/4 aes compared with 416 out of 1522 patients in the ET alone group. The pooled RR was 2.69 (95% CI: 2.43–2.97), indicating a much higher probability of developing G3/4 aes in the CDK4/6i group. The pooled data of G3/4 common aes were extracted from 4555 participants across all eight enrolled trials.
  - The G3/4 haematologic toxicities were increased in the CDK4/6i group compared with those in the ET alone group. For G3/4 neutropenia, the RR was 32.40 (95% CI: 17.42-60.25) (Figure 6B); for G3/4 leucopenia, the RR was 20.96 (95% CI: 11.81-37.22); and for G3/4 anaemia, the RR was 2.42 (95% CI: 1.55-3.77). For G3/4 nonhaematologic toxicity, the RR of G3/4 diarrhoea was 2.88 (95% CI: 1.01-8.22), and the RR of G3/4 fatigue was 3.69 (95% CI: 1.88-7.26), indicating a higher incidence of developing G3/4 diarrhoea and fatigue in the intervention group.
  - Subgroup analyses of G3/4 aes based on the drugs administered showed that the incidence of G3/4 neutropenia was much higher in the palbociclib and ribociclib subgroups, and the incidence of developing G3/4 diarrhoea was much higher in the abemaciclib subgroup. The pooled rrs for G3/4 aes are summarized in Table III.

Table III. Grade 3/4 adverse events in advanced breast cancer patients treated with CDK4/6 inhibitors.

G3/4 aes	RR	95% CI	*p*
Any	2.69	2.43-2.97	<0.001
Neutropenia	32.40	17.42-60.25	<0.001
Leucopenia	20.96	11.81-37.22	<0.001
Anemia	2.42	1.55-3.77	<0.001
Diarrhea	2.88	1.01-8.22	<0.05
Fatigue	3.69	1.88-7.26	<0.001
Nausea	1.39	0.63-3.06	=0.42

- Notes: G3/4 aes, Grade 3/4 adverse events; RR, Risk ratio; CI, Confidence interval.

Anmerkung/Fazit der Autoren

Based on the results of the present meta-analysis, we conclude that the combination of CDK4/6i and ET is superior to ET alone in terms of OS and PFS outcomes, irrespective of the drug administered, treatment line, age distribution, race, PR status, menopausal status, site of metastasis and endocrine resistance status. CDK4/6i meaningfully improved the ORR in both the ITT population and patients with measurable disease; however, they also increased the incidence of G3/4 aes. More mature OS results are awaited to consolidate our study.

Kommentare zum Review

- Es wurden vor allem Studien im Erstliniensetting eingeschlossen. Die Subgruppenergebnisse für Zweitlinie und Resistenz bezüglich der endokrinen Therapie sind konsistent mit den Gesamtergebnissen.
- Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Li J et al., 2020 [10].
  - Lin M et al., 2020 [11].
  - Zheng J et al., 2020 [20].
  - Huang T et al., 2023 [8].
  - Hermansyah et al., 2022 [7].
  - Dai et al., 2022 [4].

Becherini C et al., 2023 [1].

Safety profile of cyclin-dependent kinase (CDK) 4/6 inhibitors with concurrent radiation therapy: A systematic review and meta-analysis

Fragestellung

As part of the European Society for Radiotherapy and Oncology (ESTRO) Guidelines Committee's consensus recommendations on the integration of RT with targeted treatments for breast cancer, we conducted a systematic review and meta-analysis to assess the safety profile of combining CDK4-6i with palliative and ablative RT in both the metastatic and early breast cancer settings.

Methodik

Population:

- hormone receptor-positive (HR +) and human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer
- adjuvant or metastatic setting

- involved cohorts of breast cancer patients with more than five consecutive patients
- RT was delivered for intracranial or extracranial disease

Intervention:

- CDK4/ 6i in combination with either palliative or ablative RT

Komparator:

- Nicht präspezifiziert

Endpunkte:

- proportions of patients experiencing grade 3 + toxicities, both haematological and non-haematological toxicities, were calculated for each individual study

Recherche/Suchzeitraum:

- Medline, Scopus, and Embase databases; from January 1, 2000, to November 1, 2022

Qualitätsbewertung der Studien:

- RoB 2, ROBINS-I, GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- eleven retrospective studies, which collectively evaluated a total of 382 patients who received concurrent RT for a total of 558 lesions.

Charakteristika der Population/Studien:

- The median age of the patients was 57 years, ranging from 30 to 91 years. The reported median follow-up period across the studies was 12 months, with a range of 6 to 19 months.

Table 1
Main characteristics of eligible studies included in the systematic review and *meta*-analysis.

Author, Year	No. of patients	CDK4/6i (No. of patients)	Site of radiation (No. of irradiated lesions)	RT timing with CDK4/6i * (%)	Median follow-up (months)	Median total dose and fractions (range)	TRAE G3+ (% of patients)	CDK 4/6i dose reduction (No. of patients)	CDK 4/6i discontinuation due to toxicity (No. of patients)
Hans S, et al. [15], 2018	5	Palbociclib (5)	Bone (4) Liver (1)	Concurrent (100)	NR	20 Gy (20–60) 5 fractions (5–10)	Neutropenia (40) Anaemia (20) Thrombocytopenia (20)	1	0
Meattini I, et al. [16], 2018	5	Ribociclib (5)	Bone (5)	Concurrent (100)	NR	20 Gy (20–30) 5 fractions (5–10)	Neutropenia (20) Diarrhoea, vomiting (20)	0	0
Ippolito E, et al. [17], 2019	16	Palbociclib (13) Ribociclib (3)	Bone (22) Breast/chest wall (2)	Concurrent (100)	6.3	30 Gy (20–60) 10 fractions (7–25)	Neutropenia (31.3)	1	0
Chowdhary M, et al. [18], 2019	16	Palbociclib (16)	Bone (11) Brain (4) Mediastinal nodes (1)	Concurrent (100)	17.6	30 Gy (18–36) 10 fractions (1–18)	None reported	0	0
Figura NB, et al. [19], 2019	15	Palbociclib (10) Abemaciclib (5)	Brain (42)	Concurrent (100)	9.2	20 Gy (18–20) 1 fraction	Radionecrosis (4.8)	0	0
Beddok A, et al. [20], 2020	30	Palbociclib (30)	Bone (25) Brain (1) Breast/chest wall (14)	Concurrent (100)	12.5	20 Gy (8–64) 5 fractions (1–26)	Pain (3.3) Radiodermatitis (3.3) Febrile neutropenia (3.3)	0	2
Ratosa I, et al. [21], 2020	46	Palbociclib (30) Ribociclib (15) Abemaciclib (1)	Bone (50) Brain (3) Breast/chest wall (2) Visceral (7)	Concurrent (100)	6	20 Gy (8–63) 5 fractions (1–26)	Diarrhoea (2.2) Neutropenia (13)	5	0
Guerini AE, et al. [22], 2020	18	Palbociclib (9) Ribociclib (6) Abemaciclib (3)	Bone (32)	Concurrent (100)	6	30 Gy (8–30) 10 fractions (1–10)	Enterocolitis (5.6)	2	0
Howlett S, et al. [23], 2021	42	Palbociclib (28) Ribociclib (6) Abemaciclib (6)	Bone (40) Brain (2)	Concurrent (100)	NR	NR	Neutropenia (9.5) Dermatitis (4.8)	NR	0
Al-Rashdan A, et al. [24], 2022	185 (n = 132 CDK4/6i + RT n = 53 RT only)	Palbociclib (124) Ribociclib (8)	Bone (157) Brain (20) Breast/chest wall (39) Lung, liver (9)	Concurrent n = 104 (46.2) Sequential n = 121 (53.8)	18	NR	Non haematological (3.7)	69 (12 in the concurrent cohort)	13 (1 in the concurrent cohort)
Visani L, et al. [25], 2022	132 (n = 57 CDK4/6i + RT n = 75 CDK4/6i only)	Palbociclib (NR) Ribociclib (NR) Abemaciclib (NR)	Bone (54) Brain (4) Breast/chest wall (4) Lung, liver (8)	Concurrent (100)	18.8	20 Gy (8–55) 5 fractions (1–10)	Asthenia (1.8) Nausea (1.8), diarrhoea (1.8) Anaemia (3.5), neutropenia (54.4), thrombocytopenia (1.8) Hypertransaminasemia (3.5)	67	1

Abbreviations: RT, radiation therapy; NR, not reported; TRAE, treatment-related adverse event; G3+, grade equal or more than 3.
* Irradiated lesions were considered treated concurrent with CDK4/6i if received irradiation within 5 half-lives of the CDK4/6i.

Radiation details of patients included in the eligible studies.

Author	RT setting (No. of treated lesions)			RT technique (No. of treated patients)				RT Dose (Gy/fraction) (No. of treated lesions)	RT dose EQD2 (Gy) (No. of treated lesions) *		
	Adjuvant	Palliative	Ablative	SBRT/ SRS	IMRT/ VMAT	3DCRT	NR		≤32.5 Gy	>32.5 Gy	NR
Hans S, et al. [15]	0	4	1	0	0	0	5	20/5 (4); 60/10 (1)	4	1	0
Meattini I, et al. [16]	0	5	0	0	1	4	0	30/5 (1); 20/5 (4)	4	1	0
Ippolito E, et al. [17]	0	19	5	1	4	19	0	30/10 (11); 36/13 (1); 20/5 (6); 39.6/ 18 (1); 50/25 (2); 60/30 (1); 21/7 (1)	19	6	0
Chowdhary M, et al. [18]	0	16	0	3	2	15	3	30/3 (1); 25/5 (1); 35/14 (5); 36/18 (1); 18/1 (1); 30/10 (7)	9	7	0
Figura NB, et al. [19]	0	0	42	42	0	0	0	18/1 (5); 20/1 (9); 21/1 (8); 24/1 (4); 20/5 (3); 25/5 (8); 30/5 (5)	11	31	0
Beddok A, et al. [20]	0	34	1	1	10	24	0	20/5 (13); 30/10 (10); 8/1 (3); 18/1 (1); 50/25 (7); 64.4/26 (2)	25	10	0
Ratosa I, et al. [21]	0	62	0	7	1	41	13	Median total dose 20 Gy (8–63); median dose per fraction 4 (2–18)	0	0	62
Guerini AE, et al. [22]	0	30	2	0	2	29	1	20/5 (13); 30/10 (14); 8/1 (5)	32	0	0
Howlett S, et al. [23]	0	NR	NR	0	0	0	42	NR	0	0	42
Al-Rashdan A, et al. [24]	0	292	28	28	43	114	0	NR	222	42	52
Visani L, et al. [25]	0	56	14	14	16	40	0	45–54/3 (3); 30–55/5 (6); 21–24/3 (2); 30/10 (7); 20/5 (42); 8/1 (2); NR (8)	56	14	0

Abbreviations: RT, radiation therapy; NR, not reported; SBRT, stereotactic body radiation therapy; SRS, stereotactic radiation surgery; IMRT, intensity. modulated radiation therapy; VMAT, Volumetric-modulated Arc Therapy; 3DCRT, 3-dimensional conformal radiation therapy; Gy, Gray; EQD2, equivalent. dose in 2 Gy fractions.
* a/b ratio of 10 for acute toxicity.

Qualität der Studien:

- According to examined domains of risk-of-bias tools for nonrandomized trials, most studies were judged at moderate overall risk [17–19,21,22,25], and only one study was deemed to be at low risk [24]. The remaining articles [15,16,20,23] were judged at serious overall risk of-bias (Appendix, Table S1). The GRADE Working Group grades of evidence was reported in the Appendix.

Studienergebnisse:

- We extrapolate data regarding grade 3 + toxicity derived from concurrent treatment from all the studies. The pooled incidence of all grade 3 + toxicity was 22% (95% CI, 0.08––0.39), with a substantial heterogeneity between the studies (I2 90.7%) (Fig. 2a). Grade 3 + haematological toxicity was mostly represented by neutropenia (40/68; 58.8% of events). However, the onset of this toxicity rarely caused treatment discontinuation. Only four patients required definitive discontinuation of CDK4/6i treatment: one due to hematological toxicity (neutropenia) [25], one due to grade 3 radiodermatitis and febrile neutropenia, one due to grade 2 dysphagia [20], and one due to unspecified non-hematological toxicity [24]. In the study by AlRashdan A et al [24], the authors reported discontinuation of CDK4/6i treatment due to toxicity in 13 patients, although only one patient was included in the concurrent cohort. The resulting pooled incidence of grade 3 + hematologic toxicity rate was 14% (95% CI, 0.03––0.30), with a substantial heterogeneity between the studies (I2 91.7%) (Fig. 2b). Regarding non-haematological toxicity, the pooled incidence of grade 3 + toxicity rate was 3% (95% CI, 0.01––0.05) with a minimal heterogeneity between the studies (I2 0%) (Fig. 2c). Gastrointestinal toxicity was quite frequent, mostly represented by diarrhoea (4/19; 21% of events).
- Use of concurrent RT on intracranial disease was reported in seven studies [18–20,23–26]. There was only one specific study on concurrent SBRT for intracranial lesions plus CDK4/6i [19]. All other studies did not specify radiation technique and/or fractionation for this setting of patients. Overall, intracranial treatments were performed in 13.6% of cases (76/558 total treatments), reporting a low incidence of radionecrosis (2.6%).

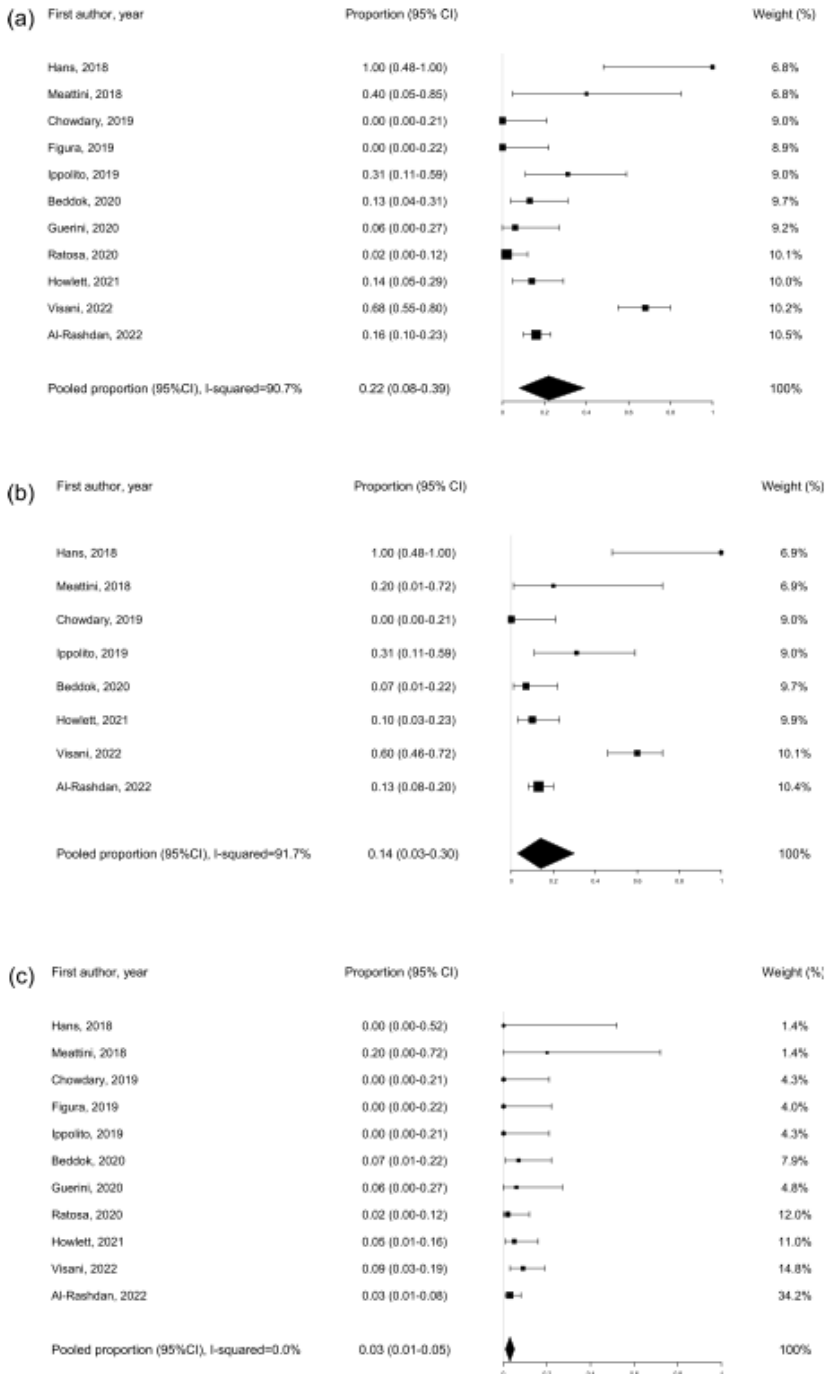


Fig. 2. Meta-analysis results concerning any toxicity of grade 3+ (a), haematological toxicity of grade 3+ (b), and non-haematological toxicity of grade 3+ (c).

Anmerkung/Fazit der Autoren

Published data on the feasibility of concurrent RT and CDK4/6i are based on a low level of evidence derived from small retrospective series. These studies exhibit heterogeneity in reporting RT doses to targets and organs at risk, schedules, techniques, and treatment intent. There is currently no available data on the safety or efficacy of concurrent RT and CDK4/6i in the early breast cancer setting, and therefore, it is advisable to avoid such combination. However, in cases of metastatic disease, it may be possible to consider administering them on a case-by-case basis, taking into consideration factors such as the total dose and irradiated volumes, and carefully weighing the risks and benefits in

collaboration with the patient. It is important to note that reliable reporting of RT details and toxicity is essential for both early and advanced settings when combining new agents with RT.

Kubeczko M et al., 2023 [9].

Safety and feasibility of CDK4/6 inhibitors treatment combined with radiotherapy in patients with HR-positive/HER2-negative breast cancer. A systematic review and meta-analysis

Fragestellung

The addition of cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) to endocrine therapy in hormone receptor-positive (HR+) human epidermal growth factor 2-negative (HER2-) breast cancer has led to practice-changing improvements in overall survival. However, there are conflicting data concerning the safety of CDK4/6i combination with radiotherapy, and no consensus guidelines exist to guide practice. We conducted a meta-analysis to assess the safety and feasibility of CDK4/6i treatment with radiotherapy.

Methodik

Population:

- advanced HR+/HER2- breast cancer patients

Intervention:

- CDK4/6i therapy combined with endocrine therapy (aromatase inhibitor or fulvestrant or tamoxifen) and receiving radiotherapy

Komparator:

- Nicht präspezifiziert

Endpunkte:

- safety outcomes with adverse events (AEs) rates reported
- The primary outcome measure was the incidence of grade 3 hematologic and non-hematologic adverse events.
- The secondary outcome measure was CDK4/6i dose reduction and discontinuation due to toxicity.

Recherche/Suchzeitraum:

- A comprehensive search was conducted in PubMed/MEDLINE, Web of Science, and Scopus, on January 31, 2023.

Qualitätsbewertung der Studien:

- The bias was assessed independently by two reviewers (M.K. and M.J.) with ROBINS-I (‘‘Risk Of Bias In Non-randomised Studies - of Interventions”) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- The fifteen studies included an aggregate of 1133 patients with
- HR+/HER2- advanced breast cancer. Among 1133 pts enrolled in the study, 1080 pts received CDK4/6i.

Charakteristika der Population/Studien:

- The majority of pts received palbociclib (795 pts, 74%), followed by ribociclib (229 pts, 21%) and abemaciclib (56 pts, 5%). 617 pts received CDK4/6i and radiotherapy. The median age was 58.8 years (IQR 55.5 – 62.5) and the median follow-up was 17 months (IQR 9.2 – 18). In this group, 412 pts were treated with palbociclib, 108 pts with ribociclib, and 40 pts with palbociclib (data lacking for 57 pts). For endocrine treatment, 289 pts received aromatase inhibitor and 81 pts fulvestrant (data lacking in 6 studies).

Table 1
Baseline characteristics of the included studies.

Author Publication year Study characteristics	Enroll.	Nb. of pts CDK +RT	mAge	mFu	Palbo-ciclib	Ribo-ciclib	Abema-ciclib	Nb. of pts Control group
Kubeczko et al. 2023 [15] RT prior 54 pts; RT conc 42 pts;	2017–2022	100	58.5	17.0	27	65	8	188 CDK alone
Norman et al. 2021 [16] RT prior 47 pts;	2015–2019	47	56	NR	47	0	0	200 CDK alone
Al-Rashdan et al. 2022 [17] RT prior; RT conc; RT post;	2016–2020	132	60	18.0	124	8	0	53 RT alone
Visani et al. 2022 [18] RT conc 57 pts	2017–2020	57	49.9	18.8	NR	NR	NR	75 CDK alone
Kawamoto et al. 2022 [19] RT prior 19 pts; RT conc 29 pts; RT post 4 pts; RT prior & post 8 pts	2018–2020	60	62.0	18.0	45	0	15	NA
Ratosa et al. 2020 [20] RT conc 46 pts	2017–2020	46	57.9	NR	30	15	1	NA
Howlett et al. 2021 [21] RT prior; RT conc	2016–2019	40	NR	NR	28	6	6	NA
Kim et al. 2021 [22] RT prior; RT conc; RT post	2010–2021	30	59	22.3	28	0	2	NA
Beddok et al. 2020 [23] RT conc 30 pts	2017–2019	30	66.0	17.0	30	0	0	NA
Guerini et al. 2020 [24] RT conc 18 pts	2016–2020	18	64.1	12.0	9	6	3	NA
Chowdhary et al. 2019 [25] RT prior 7 pts; RT conc 5 pts; RT post 4 pts	2015–2018	16	59.6	14.7	16	0	0	NA
Ippolito et al. 2019 [26] RT conc 15 pts	2017–2018	16	54.0	6.3	13	3	0	NA
Figura et al. 2019 [27] RT prior; RT conc; RT post	2015–2018	15	54.0	9.2	10	0	5	NA
Meattini et al. 2018 [28] RT conc 5 pts	NR	5	71.0	3.0	0	5	0	NA
Hans et al. 2018 [29] RT conc 5 pts	2017	5	57.2	NR	5	0	0	NA

Abbreviations: Enroll. – enrolment; mAge – median age; mFU – median follow up in months; Nb.– number; pts – patients; CDK – cyclin-dependent kinase 4/6 inhibitor; NR – data not reported. RT – radiation therapy; RT prior – RT prior to CDK, RT conc – RT concurrent with CDK, RT post – RT post CDK, number of patients in each category provided if specified in the study; Control – control group; data regarding the control group are underlined; NA – not applicable (studies without control arm).

Table 2
Radiation details of the CDK4/6i treated patients in the included studies.

Author Nb. of pts treated with CDK+RT	RT Technique				RT site								tot
	SBRTSRS CK GK	IMRT VMAT	3D CRT	oth*	bone spine	bone pelvis	bone oth	breastLR	brain	lung	liver	oth/ unsp	
Kubeczko et al. [15] [n=100]	32	107			66	22	20	11	11	1	3	5	139
Norman et al. [16] [n=47]	5	3	39		37		10	0	0	0	0	0	47
Al-Rashdan et al. [17] [n=132]	18		114	0	86		46					132	
Visani et al. [18] [n=57]	15		55		26	28		2	4	3	3	4	70
Kawamoto et al. [19] [n=60]	1	4	61	0	38	4	9	5	5	0	0	5	66
Ratosa et al. [20] [n=46]	7	1	41	13	31	11	8	2	3	7			62
Howlett et al. [21] [n=40]	NR	NR	NR	NR	24	16		0	2	0	0	0	42
Kim et al. [22] [n=30]	7	6	29	1	19	9	6	0	5	0	0	4	43
Beddok et al. [23] [n=30]	1	10	24	0	17	2	5	9	1	0	0	1	35
Guerini et al. [24] [n=18]	0	2	29	1	11	9	12	0	0	0	0	0	32
Chowdhary et al. [25] [n=16]	3	2	15	3	9	4	5	0	4	0	0	1	23
Ippolito et al. [26] [n=16]	1	4	19	0	8	6	8	0	0	0	0	2	24
Figura et al. ** [27] [n=15]	42	0	0	0	0	0	0	0	42	0	0	0	42
Meattini et al. [28] [n=5]	0	1	4	0	2	1	2	0	0	0	0	0	5
Hans et al. [29] [n=5]	5				2	1	1	0	0	0	1	0	5

Abbreviations: Nb. – number; pts – patients; RT – radiation therapy; CDK - cyclin-dependent kinase 4/6 inhibitor; SBRT – Stereotactic Body Radiation Therapy; SRS – Stereotactic Radiosurgery; CK – CybeKnife; GK – GammaKnife; 3DCRT – Three-dimensional conformal radiotherapy; IMRT – Intensity Modulated Radiation Therapy; VMAT – Volumetric Modulated Arch Therapy; oth – other; breast/LR – breast or locoregional site; unsp – unspecified treatment site; tot – total; oth* – Two-Dimensional Radiotherapy, helical thomotherapy, electron; **Figura: 15 pts, 42 lesions in the brain, 19 treatment sessions.

Qualität der Studien:

- There was a serious bias due to baseline confounding across included studies since the clinical state of patients requiring RT may be prognostic, such as brain metastases, bone

lesions with impending pathologic fracture, or massively advanced local disease with bleeding ulceration. On the other hand, patients with the oligometastatic disease may also receive RT. Furthermore, toxicity might differ from the population of advanced breast cancer patients who did not require RT. These are different clinical scenarios in which radiotherapy is used, and no randomized clinical trials exist to assess whether they harbor prognostic significance in advanced breast cancer patients treated with CDK4/6i and RT. Therefore, it is hard to assess whether the true effect estimate is predicted to be greater or less than the estimated effect in the study.

Studienergebnisse:

- Adverse events were scored in eight studies according to CTCAE v5.0 [15,16,18–20,22,23,25]. CTCAE v4.0 was used in three studies [17,24,29]. In one study radiation-related AEs were scored according to the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) scales [18]. Three studies did not report the data scale used [21,27,28].

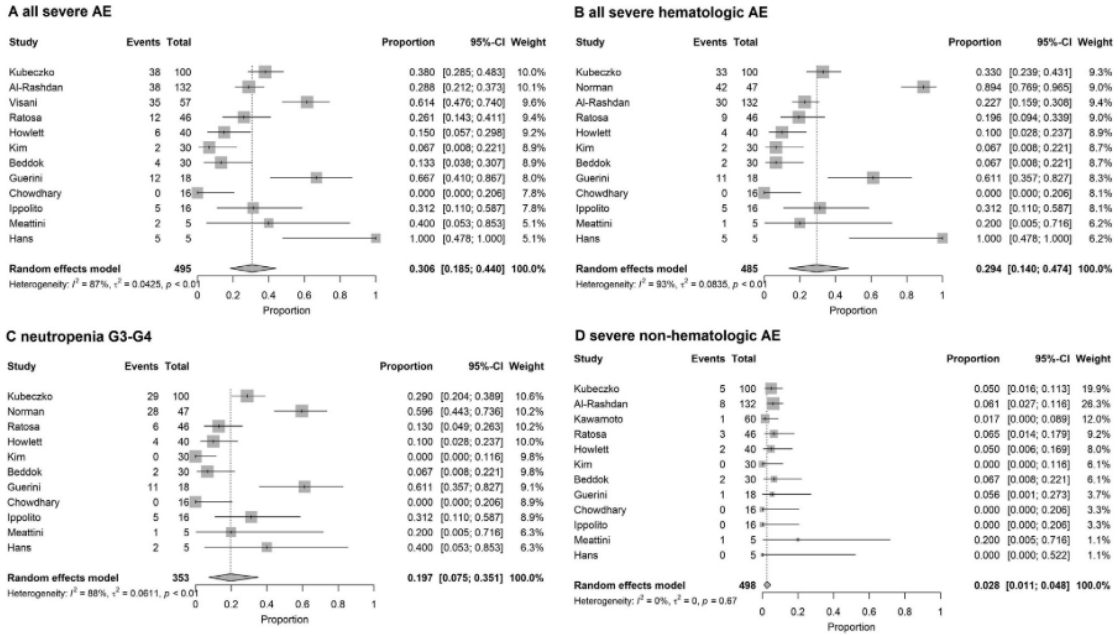
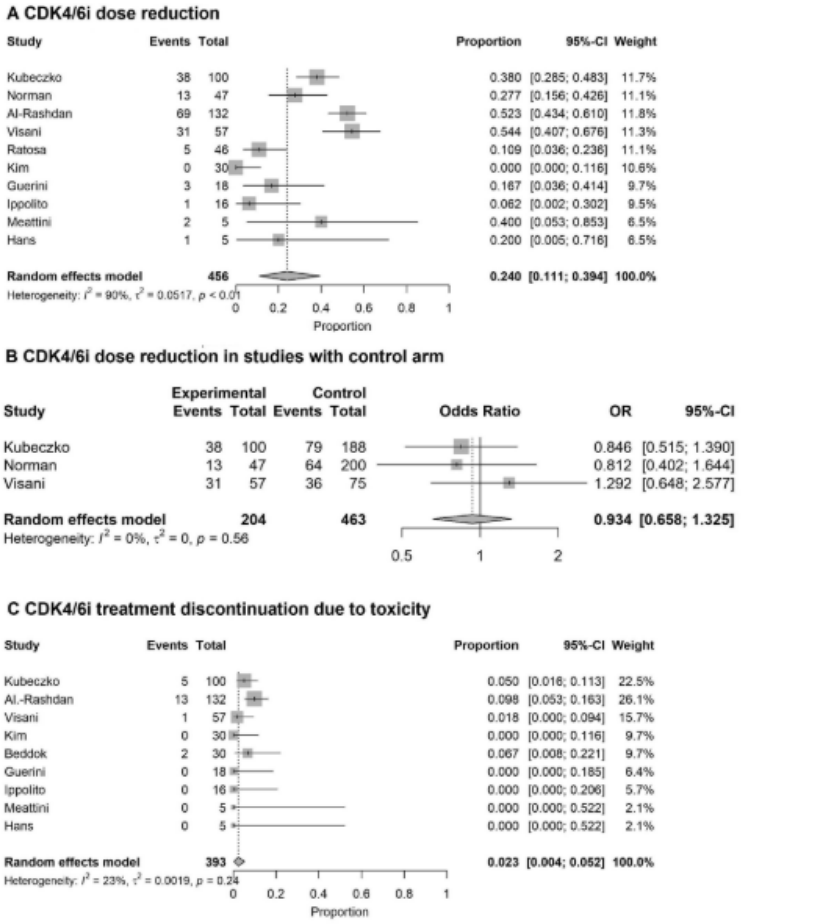


Fig. 2. Severe adverse events (AE): a) all severe AE b) all severe hematologic AE c) neutropenia G3-G4, d) severe non-hematologic AE.

- The pooled prevalence of severe hematologic toxicity was 29.4% (95% CI 14.0% – 47.4%; I2 = 93%; s2 = 0.084; p < 0.01 and severe nonhematologic toxicity was 2.8% (95% CI 1.1% – 4.8%; I2 = 0%; s2 = 0.0; p = 0.67). The pooled prevalence of CDK4/6i dose reduction was 24.0% (95% CI 11.1% – 39.4%; I2 = 90%; s2 = 0.052; p < 0.01) with no difference between CDK4/6i plus RT vs. CDK4/6i (odds ratio of 0.934; 95% CI 0.66 – 1.33; I2 = 0%; s2 = 0.0; p = 0.56). The pooled prevalence of CDK4/6i discontinuation due to toxicity was 2.3% (95% CI 0.4% – 5.2%; I2 = 23%; s2 = 0.002; p = 0.24).



ig. 3. CDK3/6i dose reductions and treatment discontinuations; a) CDK4/6i dose reduction, b) CDK4/6i dose reduction in studies with control arm, c) CDK4/6i treatment iscontinuation due to toxicity.

Anmerkung/Fazit der Autoren

The findings of this study suggest that adding radiotherapy to CDK4/6i treatment in advanced breast cancer patients is generally safe and well tolerated and remains a viable treatment option, with toxicity rates comparable to CDK4/6i treatment alone. However, most data concerns palliative RT regimens with limited details regarding RT timing. Prospective data will be important to further establish safety of RT with CDK4/6i, especially when RT with higher doses are performed.

Liu Y et al., 2023 [12].

Comparative efficacy and safety of different combinations of three CDK4/6 inhibitors with endocrine therapies in HR+/HER2 − metastatic or advanced breast cancer patients: a network meta-analysis

Fragestellung

This network meta-analysis aimed to assess the comparative efficacy and safety of combinations involving three cyclin-dependent kinase 4/6 (CDK4/6) inhibitors and endocrine therapies (ETs) in patients with metastatic or advanced breast cancer (BC) who are hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-).

Methodik

Population:

- HR+/HER2- metastatic or advanced BC

Intervention:

- various combinations of three CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) and two endocrine therapies (AI and fulvestrant)

Komparator:

- nicht präspezifiziert

Endpunkte:

- at least one of the following outcomes must have been reported: progression-free survival (PFS), overall survival (OS), and severe treatment-related adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, Embase (Ovid), and the Cochrane Central Register for Controlled Trials (CENTRAL) to retrieve additional studies published between February 2020 and September 2021

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Among the 9 studies included in this analysis, 2 studies [45, 46] were phase II design, while the remaining 7 studies [41–44, 47–49] were phase III designs.

Charakteristika der Population/Studien:

Table 1 Reported HR for PFS and OS and severe AEs rate of each eligible study

Study	Study	Control	HR for PFS	HR for OS	Severe AEs rate, %
PALOMA-1	P + AI	AI	0.488 (0.319, 0.748)	0.9897 (0.623, 1.294)	75.90 vs. 20.78
PALOMA-2	P + AI	AI	0.563 (0.461, 0.687)	n.r.	79.28 vs. 28.38
PALOMA-3	P + F	F	0.50 (0.40, 0.62)	0.81 (0.64, 1.03)	72.33 vs. 21.84
MONALEESA-2	R + AI	AI	0.568 (0.457, 0.704)	0.746 (0.517, 1.078)	82.04 vs. 32.73
MONALEESA-3	R + F	F	0.593 (0.480, 0.732)	0.73 (0.59, 0.90)	28.51 vs. 16.53
MONALEESA-7	R + AI	AI	0.55 (0.44, 0.69)	0.71 (0.54, 0.95)	82.09 vs. 29.67
MONARCH-2	A + F	F	0.553 (0.449, 0.681)	0.757 (0.606, 0.945)	65.99 vs. 26.91
MONARCH-3	A + AI	AI	0.540 (0.418, 0.698)	n.r.	58.41 vs. 24.84
MONARCH plus (cohort A)	A + AI	AI	0.499 (0.346, 0.719)	n.r.	59.02 vs. 23.23
MONARCH plus (cohort B)	A + F	F	0.376 (0.240, 0.588)	n.r.	51.92 vs. 15.09

P, palbociclib; R, ribociclib; A, abemaciclib; AI, aromatase inhibitor; F, fulvestrant; AEs, adverse events; HR, hazard ratio; PFS, progression-free survival; OS, overall survival; n.r., not reported

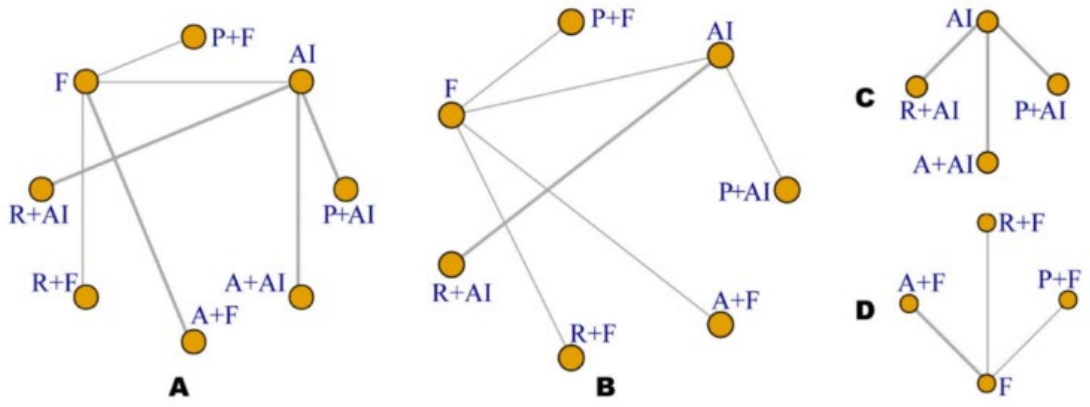
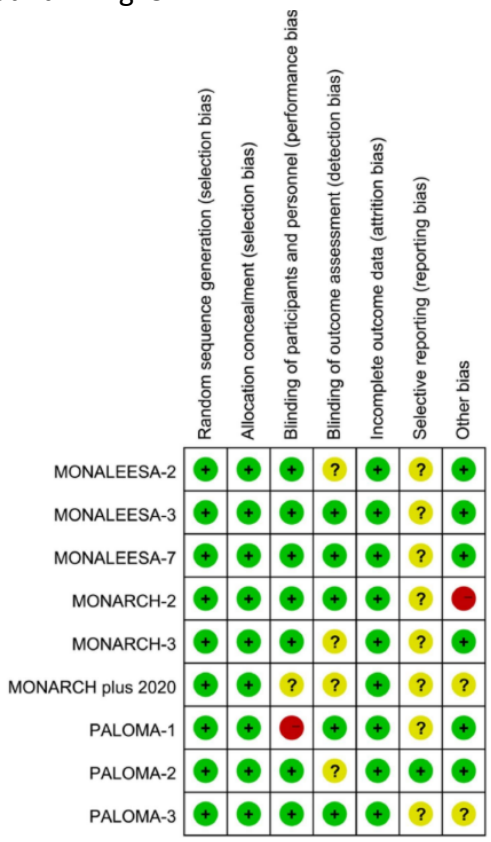


Fig. 2 Network of the comparisons for the Bayesian network meta-analysis. As shown in the figure, the thickness of the lines is proportional to the number of comparisons, and the diameter of the circles is proportional to the number of treatments included in the meta-analysis. Network of PFS (A), OS (B), and severe AEs based on different endocrine therapies including AI (C) and fulvestrant (D)

Qualität der Studien:

- Among the identified studies [41–49], all were considered to have a low risk of selection bias. Most studies effectively minimized performance and detection bias through double-blind designs, except for one study that used an open-label design [46]. Since attrition bias did not affect our estimates significantly, we categorized all studies as low risk in this domain. Regarding outcome reporting and other biases, most studies were

either unclear or at low risk. A summary of the individual study-level assessment can be found in Fig. 3.



ig. 3 Risk of bias summary: reviewers' judgments of each risk of bias item for each eligible study

Studienergebnisse:

- Meta-analysis of progression-free survival

  All 9 eligible studies [41–49] involving 5043 patients reported hazard ratios (HR) for PFS. The pairwise metaanalysis results indicated a reduced hazard risk of PFS for each treatment combination (Supplementary Fig. 1). This finding was further supported by the network metaanalysis (Fig. 4). However, when comparing the available treatment combinations of three CDK4/6 inhibitors and various endocrine therapies, no statistical differences were observed for PFS (Fig. 4).

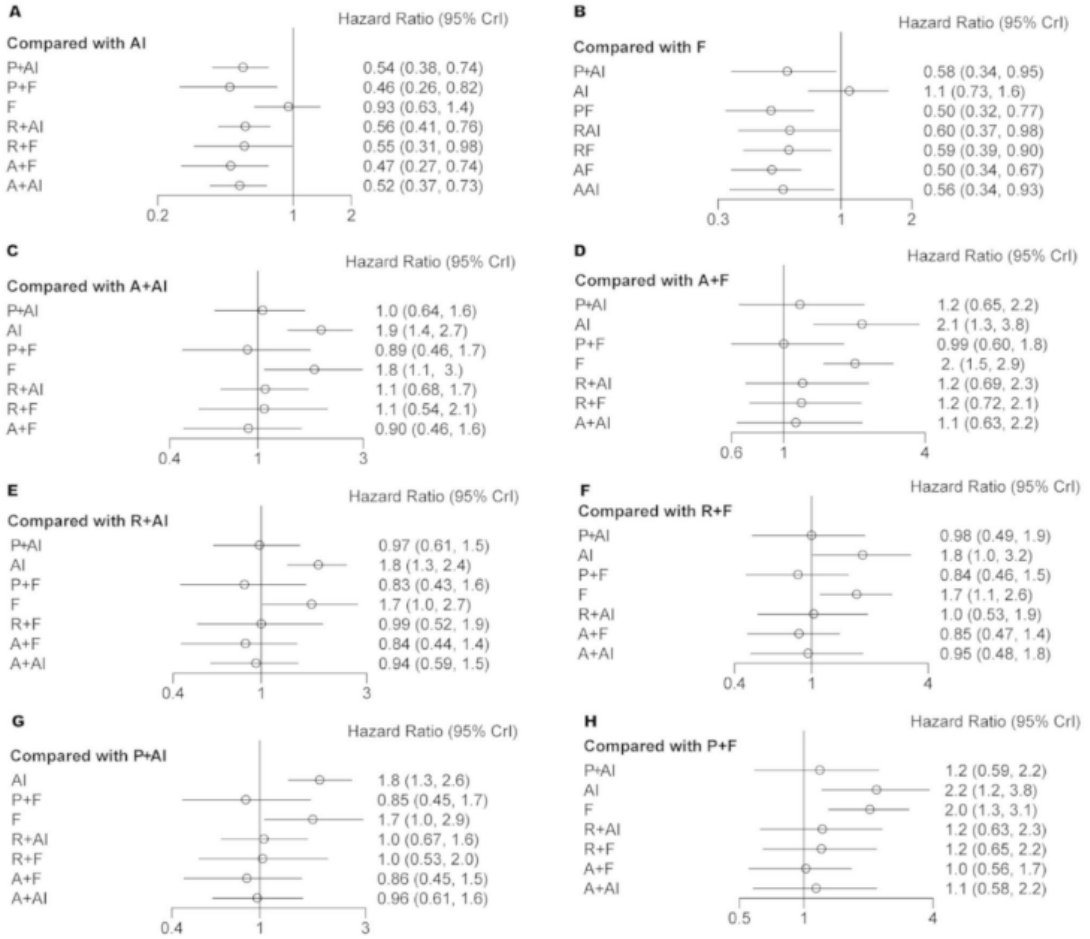


Fig. 4 Forest plot of the hazard ratios for PFS based on different pairwise comparisons

- Meta-analysis of overall survival

  Among the 9 included studies, 6 studies [41–43, 46, 47] involving 3421 patients reported the HR for OS. The pairwise meta-analysis suggested that the combination of abemaciclib plus fulvestrant (HR = 0.76, 95% CI = 0.61 to 0.94) and ribociclib plus AI (HR = 0.73, 95% CI = 0.58 to 0.91) or fulvestrant (HR = 0.73, 95% CI = 0.59 to 0.90) was associated with improved OS (Supplementary Fig. 2). However, these findings were not supported by the network meta-analysis (abemaciclib plus fulvestrant: HR = 0.76, 95% CI = 0.50 to 1.15; ribociclib plus AI: HR = 0.73, 95% CI = 0.52 to 1.02; ribociclib plus fulvestrant: HR = 0.73, 95% CI = 0.48 to 1.11) (Fig. 5). Similarly, the network meta-analysis indicated no statistical difference between the available treatment combinations of three CDK4/6 inhibitors and different endocrine therapies for OS (Fig. 5).

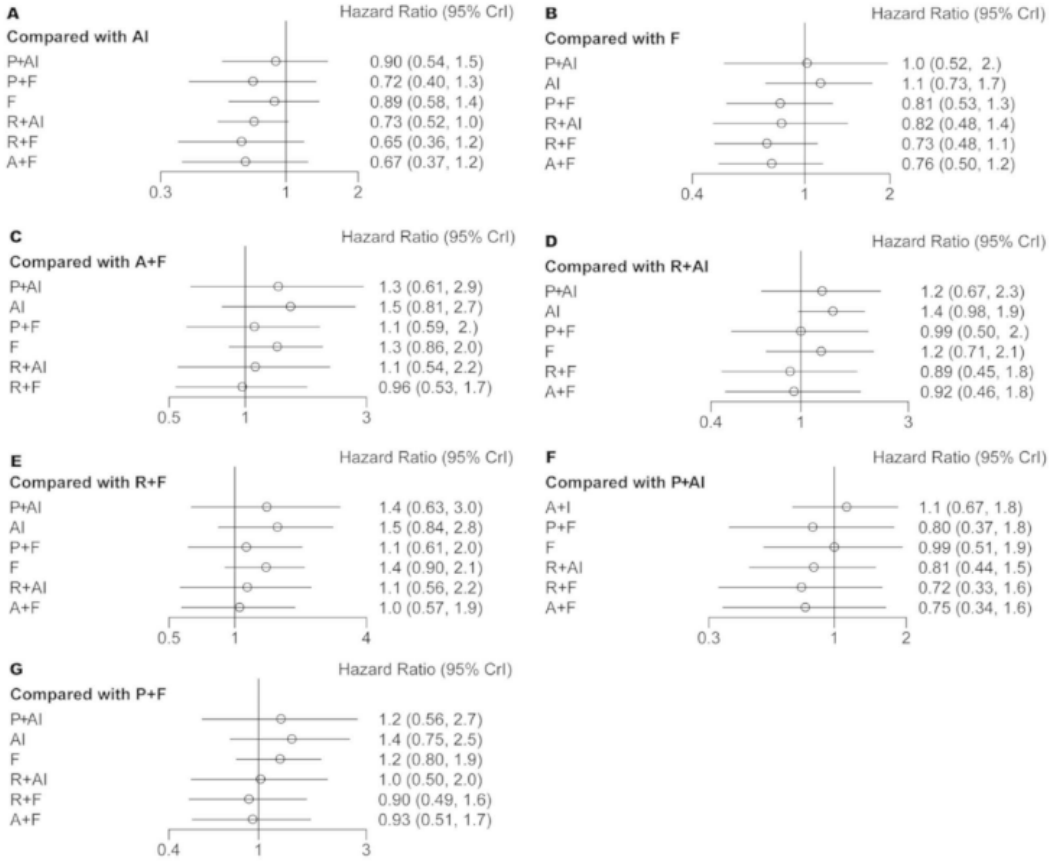


Fig. 5 Forest plot of the hazard ratios for OS based on different pairwise comparisons

- Meta-analysis of severe adverse events

  All eligible studies [41–49] reported the incidence of severe adverse events. The pairwise meta-analysis revealed that treatment combinations involving three CDK4/6 inhibitors plus AI or fulvestrant were associated with a higher incidence of severe adverse events compared to AI or fulvestrant alone (Supplementary Fig. 3). However, the network meta-analysis confirmed increased incidence only for specific combinations: ribociclib (OR = 9.46, 95% CI = 2.07 to 43.14) or palbociclib (OR = 10.83, 95% CI = 2.36 to 50.93) plus AI and abemaciclib (OR = 4.79, 95% CI = 1.40 to 16.13) or palbociclib (OR = 6.30, 95% CI = 1.03 to 40.68) plus fulvestrant (Supplementary Fig. 4). However, no statistically significant differences were observed between the available treatment combinations of the three CDK4/6 inhibitors and different endocrine therapies in the network metaanalysis (Supplementary Fig. 4).

- Rank Probabilities

  The rankings of all available treatment combinations are presented in Fig. 6. Regarding PFS, palbociclib plus fulvestrant had the highest likelihood of being the most effective regimen (SUCRA = 37.65%), followed by abemaciclib plus fulvestrant (SUCRA = 28.76%) (Fig. 6a). For OS, ribociclib plus fulvestrant was identified as the most effective regimen (SUCRA = 34.11%), with abemaciclib plus fulvestrant ranking second (SUCRA = 25.75%) (Fig. 6b). In terms of severe adverse events, the least desirable regimens were palbociclib plus AI (SUCRA = 53.98%) (Fig. 6c) and palbociclib plus fulvestrant (SUCRA = 51.37%) (Fig. 6d).

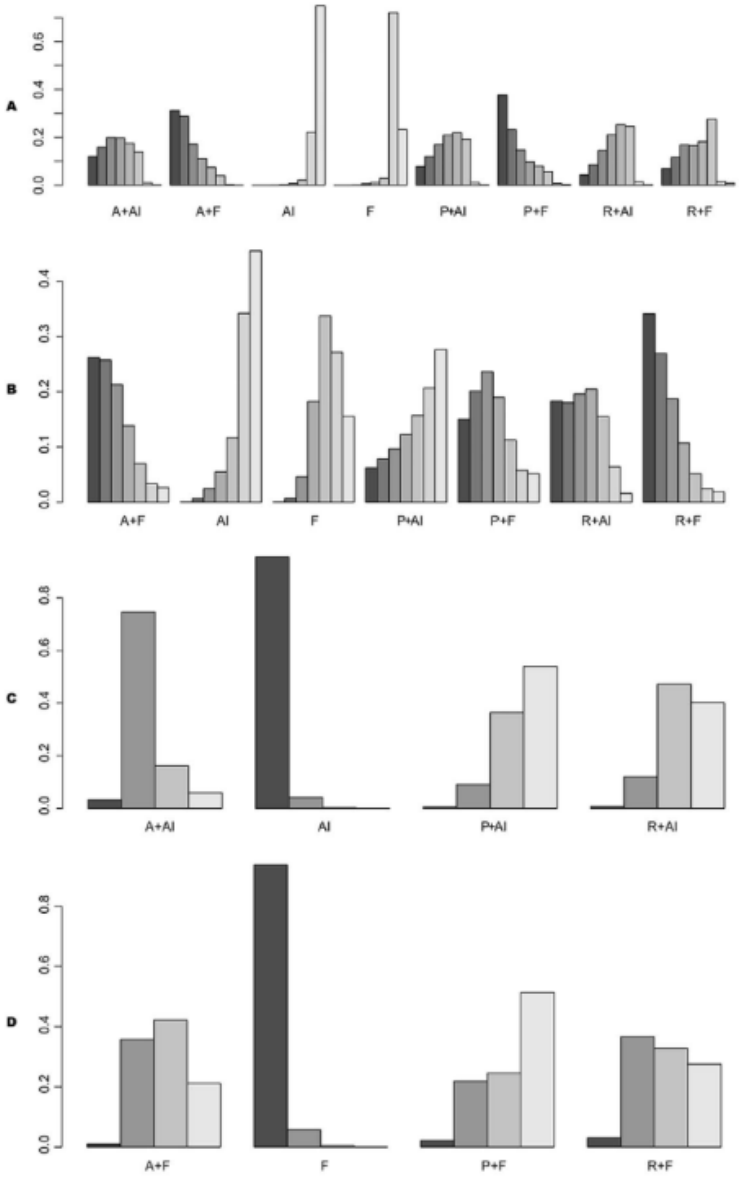


Fig. 6 Ranking plot based on the probabilities of interventions in the analysis of secondary outcomes. PFS (A), OS (B), and severe AEs based on different endocrine therapies including AI (C) and fulvestrant (D). Treatments are ranked according to their chance of being the best treatment, and the height of each column reflects the probability of the rank

- Convergence Assessment

  To assess the convergence of the Markov Chain Monte Carlo (MCMC) simulation in our network meta-analysis, we calculated the potential scale reduction factor (PSRF) value. The PSRF value was close to 1, indicating satisfactory convergence of the MCMC simulation.

Anmerkung/Fazit der Autoren

In conclusion, based on our network meta-analysis, the combinations of abemaciclib plus fulvestrant or ribociclib plus AI appear to be promising options for the treatment of HR+/HER2- metastatic or advanced breast cancer. These combinations demonstrate superior efficacy and safety compared to other available treatment options. However, further randomized controlled trials (RCTs) are necessary to provide more robust evidence

and compare the efficacy and safety of different treatment combinations involving three CDK4/6 inhibitors and two endocrine therapies.

Kommentare zum Review

- Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Tong et al., 2024 [19]

Rahmani J et al., 2024 [15].

Locoregional therapy containing surgery in metastatic breast cancer: Systematic review and meta-analysis

Fragestellung

The role of locoregional therapy (LRT) containing surgery and systematic therapy in metastatic breast cancer patients remains controversial. This study investigated the effect of LRT in patients who were initially diagnosed with metastatic breast cancer (MBC) on overall survival (OS), locoregional progression-free survival (PFS), and distant systemic PFS.

Methodik

Population:

- patients with stage IV breast cancer

Intervention:

- breast surgery was performed in the intervention group

Komparator:

- nicht präspezifiziert

Endpunkte:

- nicht präspezifiziert

Recherche/Suchzeitraum:

- MEDLINE/PubMed, SCOPUS, and Web of Science databases up to August 15th, 2022

Qualitätsbewertung der Studien:

- The Cochrane Collaboration's tool and the Newcastle Ottawa Quality Assessment Scale (NOS) were used to assess the quality of randomized control trials and the quality of observational studies, respectively

Ergebnisse

Anzahl eingeschlossener Studien:

- five randomized controlled trials and two prospective observational studies
- A total of 1626 participants were included in this meta-analysis, ranging from 55 to 505 participants per study.

Charakteristika der Population/Studien:

Table 1 – Baseline characteristics of trials and participants.

First Author	Year	Country	Study name Identifier	Duration of study	n of Population		Age		Overall Survival (%)		Therapy schedule	Design Follow up (month)	Triple Negative (%)	
					In[1]	Co[2]	In	Co	In	Co			In	Co
Khan, S. A.	2022	US	E2108 NCT01242800	2011–2015	125	131	55	56	Three-year OS 68.4	67.9	ST-LRT	RCT 53	7.5	8.5
Soran, Atilla	2021	Turkey	MF07-01 NCT00557986	2007–2012	140	138	51	51	Five-year OS 42	24	LRT-ST	RCT 40	7	18
Soran, Atilla	2021	Turkey	BOMET MF14-01 NCT02125630	2014–2019	265	240	51	54	Five-year OS 72	33	ST-LRT /LRT-ST	Observational 34	6	8
Fitzal, Florian	2019	Austria	ABCSG-28 POSYTIVE NCT01015625	2011–2015	45	45	63	64	– –	–	LRT-ST	RCT 37.5	9	9
King, Tari A	2016	US	TBCRC 013 NCT00941759	2009–2016	39	51	51		Three-year OS 77	76	ST-LRT	Observational 54	–	–
Abo-Touk, NA	2016	Egypt	– –	2012–2013	27	30	45	44	Two-year OS 46	22	LRT-ST	RCT 15	–	–
Badwe, Rajendra	2015	India	Tata NCT00193778	2005–2013	173	177	48	48	Two-year OS 41.9	43	ST-LRT	RCT 23	–	–

In: Intervention group, Co: Control group, ST: Systemic therapy, LRT: Locoregional therapy.

Qualität der Studien:

- The overall risk of bias was mostly unclear or high due to selection bias, performance bias, and detection bias. Furthermore, none of the studies mention blinding their assessors.

Studienergebnisse:

- The effect of LRT compared with primary
- ST on OS in patients with de novo MBC was reported in all seven articles (1626 participants). The combined results showed no difference (p = 0.28) in overall survival between the LRT and ST groups (HR: 0.83, 95% CI: 0.60, 1.16) (Fig. 2-a). High heterogeneity (I^2 = 80.3%) was detected among the studies. Pooled results revealed that LRT significantly improved locoregional progression-free survival compared to ST (HR: 0.31, 95% CI: 0.15, 0.60, p = 0.001) (Fig. 2-b). LRT compared to ST showed no significant difference in improving distant systemic PFS (HR: 1.03, 95% CI: 0.42, 2.52, p = 0.94) (Fig. 2-b).

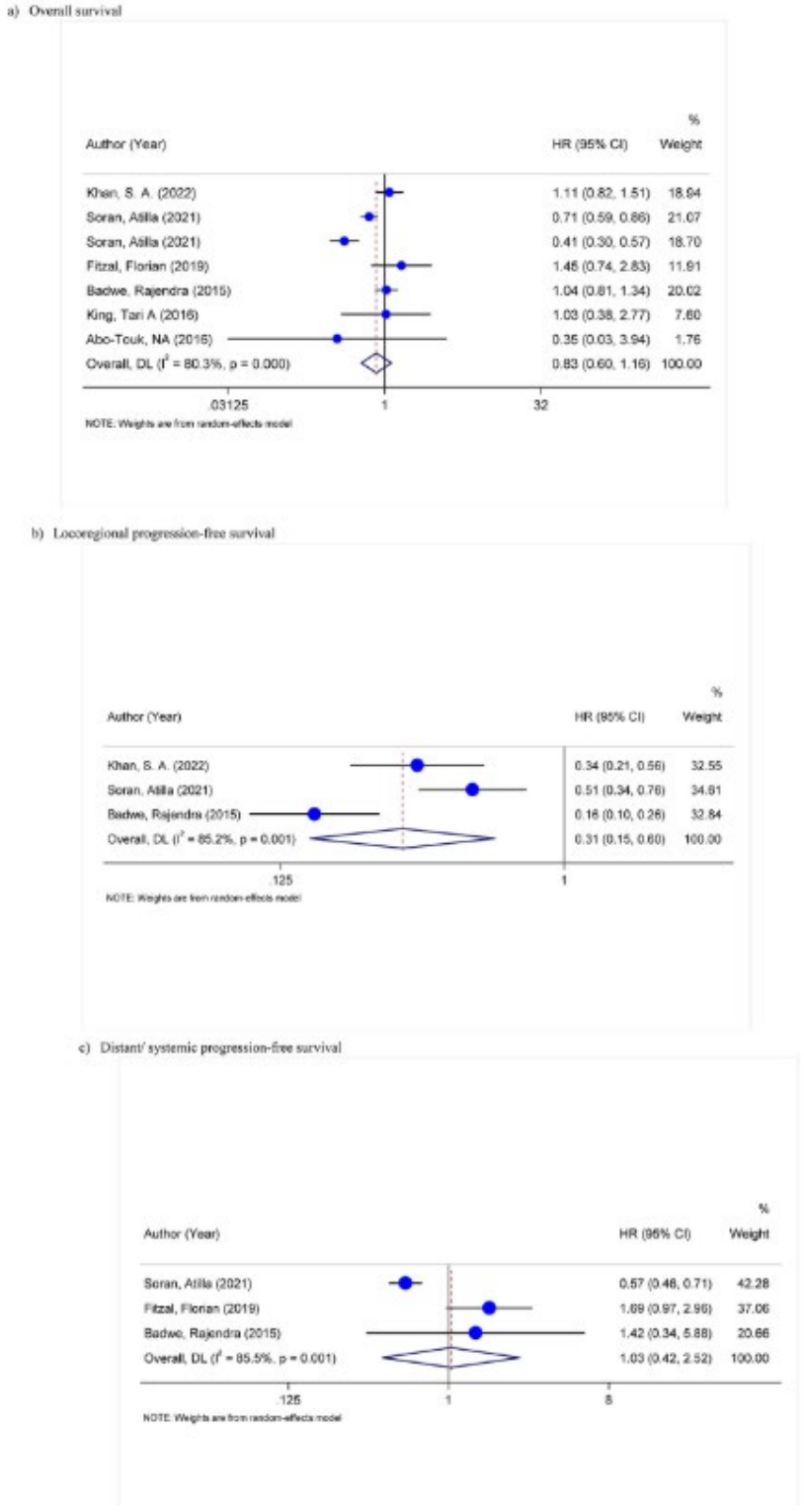


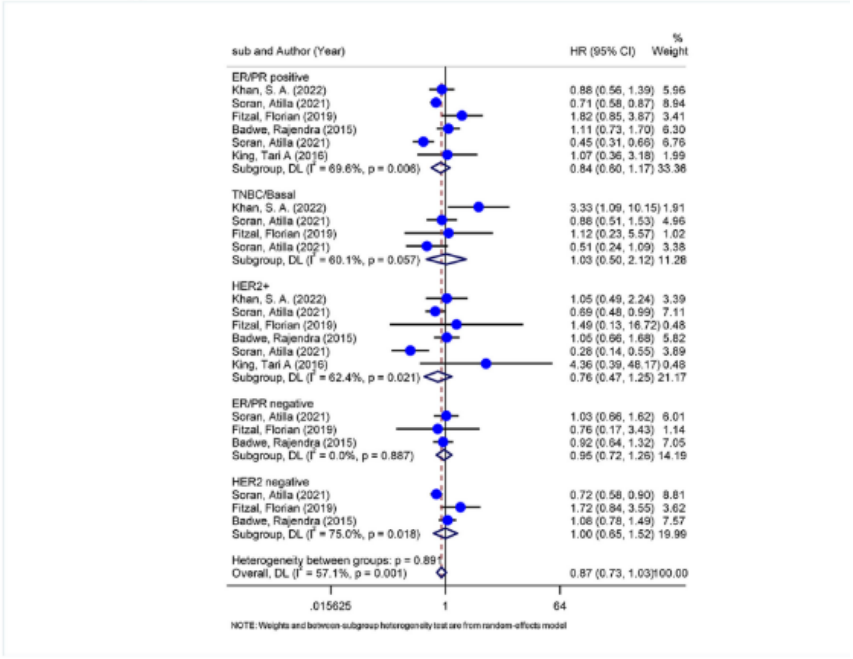
Fig. 2 e Forest plot of studies investigating the effects of Locoregional therapy on: a) Overall survival, HR: Hazard ratio; CI: Confidence interval; DL: DerSimonian and Laird. b) Locoregional progression-free survival, HR: Hazard ratio; CI: Confidence interval; DL: DerSimonian and Laird. c) Distant/systemic progression-free survival, HR: Hazard ratio; CI: Confidence interval; DL: DerSimonian and Laird.

- Subgroup analysis

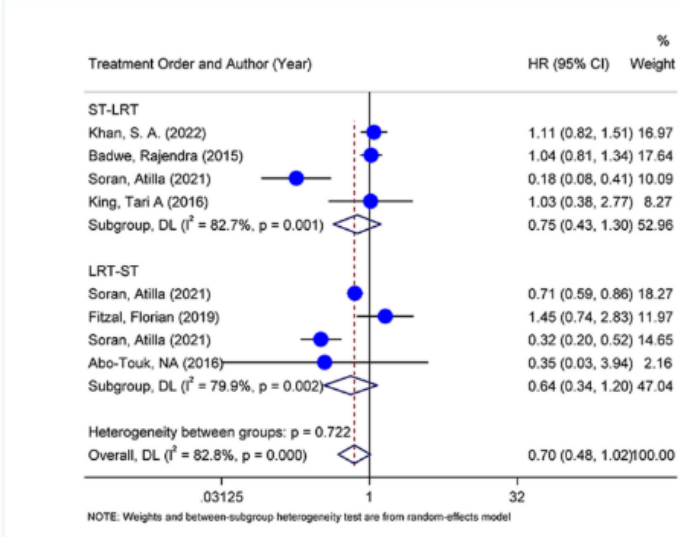
  Figure 3 summarizes the results of the subgroup analyses. Overall survival did not improve in any molecular subtypes in LRT (HR of overall survival in ER/PR positive patients was 0.84 (95% CI: 0.60-1.17, p = 0.41). LRT did not improve overall survival of

TNBC (Triple-negative breast cancer)/Basal (HR: 1.03, 95% CI: 0.50-2.12, p = 0.93), HER2 positive (HR: 0.76, 95% CI: 0.47-1.26, p = 0.28), ER/PR negative (HR: 0.95, 95% CI: 0.72-1.26, p = 0.73), and HER2 negative breast cancer subtypes (HR: 1.00, 95% CI: 0.65-1.52, p = 0.99) (Fig. 3-a). Furthermore, subgroup analyses of the therapy scheme revealed insignificant differences between the two treatment groups (HR of overall survival in ST-surgery was 0.75 (95% CI: 0.43-1.30, p = 0.30) and in surgery-ST (HR: 0.64, 95%CI: 0.34-1.20, p = 0.17) (Fig. 3-b). The location of metastasis did not affect overall survival in either the LRT group or the ST group (Fig. 3c). Additionally, significant heterogeneity (I2= 72.9%, p = 0.001) was detected between the studies. LRT significantly (p = 0.001) improved overall survival in patients with solitary bone metastases (HR = 0.48; 95% CI: 0.35-0.67) (Fig. 3-d). However, LRT had no effect (p =0.19) on overall survival in patients with multiple bone metastases (HR = 0.63; 95% CI: 0.32-1.27) (Fig. 3-d).

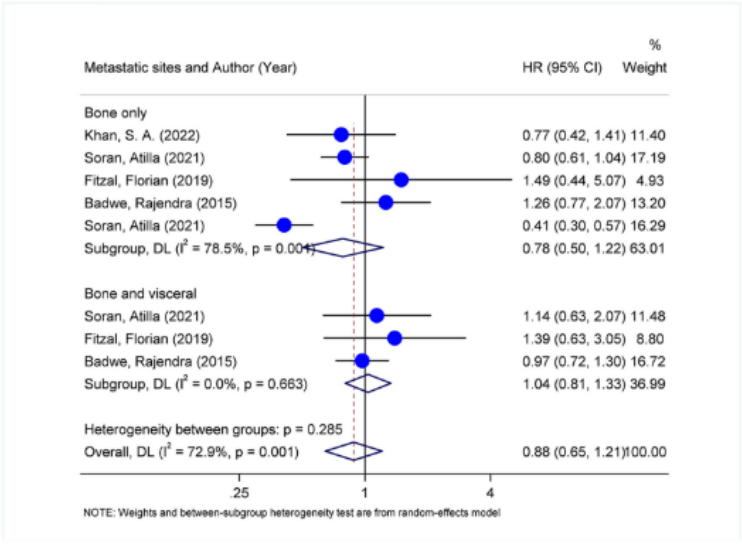
a) Molecular subtypes



b) Therapy scheme



c) Metastasis location



d) Metastasized bones number

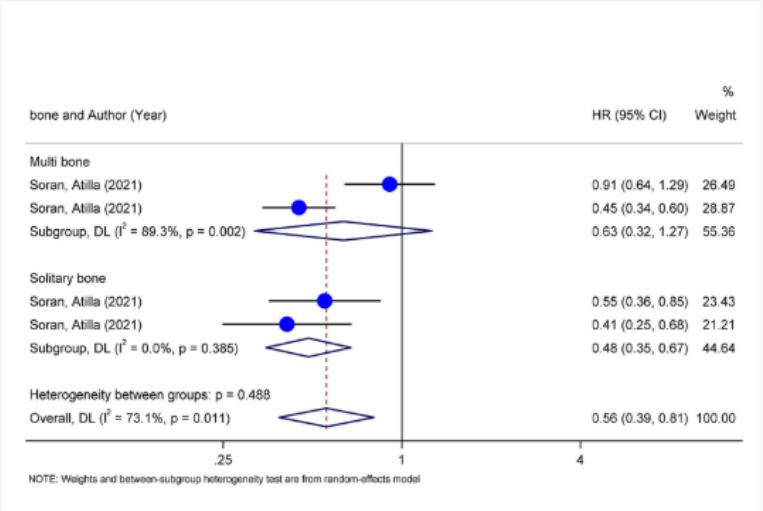


Fig. 3 e Sub-grouped analysis of studies investigating the effects of locoregional therapy on overall survival based on: a) Molecular subtypes, HR: Hazard ratio; CI: Confidence interval; ER: Estrogen receptor; PR: Progesterone receptor; TNBC: Triplenegative breast cancer; HER: Human epidermal growth factor receptor; DL: DerSimonian and Laird. b) Therapy scheme, HR: Hazard ratio; CI: Confidence interval; LRT: Locoregional therapy; ST: Systemic therapy; DL: DerSimonian and Laird. c) Metastasis location, HR: Hazard ratio; CI: Confidence interval; DL: DerSimonian and Laird. d) Metastasized bones number.

Anmerkung/Fazit der Autoren

LRT improves locoregional PFS. Furthermore, LRT improves OS in patients with solitary bone metastases.

Ren C et al., 2024 [16].

Breast surgery for patients with de novo metastatic breast cancer: A meta-analysis of randomized controlled trials

Fragestellung

Our objective was to undertake a meta-analysis based on RCTs, exploring the role of breast surgery in the management of de novo metastatic breast cancer (dnMBC), and to examine whether there is an improved survival and quality-of-life outcomes in patients with dnMBC.

Methodik

Population:

- pathologically confirmed operable stage IV breast cancer at initial presentation and had not received any previous anticancer therapy

Intervention:

- primary tumor resection

Komparator:

- no surgery

Endpunkte:

- nicht präspezifiziert

Recherche/Suchzeitraum:

- Embase, Google Scholar, MEDLINE, Scopus, Web of Science and unpublished sources including Clinicaltrials.gov and the Cochrane Central Register of Controlled Trials from inception until March 30, 2022

Qualitätsbewertung der Studien:

- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Finally, we included seven studies in the quantitative synthesis (Fig.A1 and Table A.5). A total of seven studies [24–26,28,29,53,54], consisting of 1018 patients combined, were eligible to be assessed in this meta-analysis.

Charakteristika der Population/Studien:

Table 1
Baseline characteristics of included studies.

Author, year	Period of enrolment	Study location	Age (year)†	Sample size (n)	Molecular subtype (n)	Follow-up (month)†	Trial number	Initial therapy	Primary outcome	Effect size (95%CI)
Badwe,2015	2005–2013	India	48.0	350	ER/PR+ (208) ER/PR- (142) HER2+ (107) HER2- (232)	23.0	NCT00193778	Systemic therapy	OS	HR:1.04(0.81–1.34)
Abo-Touk,2016	2012–2013	Egypt	45.0	57	ER+ (30) PR+ (26)	15.0	N/A	Surgery	OS	HR:0.35(0.03–3.82)
Fitzal,2018	2010–2015	Austria	64.0	90	Luminal A (46) Luminal B (12) HER2 enriched (20) Triple-negative (8)	37.5	NCT01015625 (ABCSG 28)	Surgery	OS	HR:0.69(0.36–1.33)
Soran,2021	2007–2012	Turkey	51.9[a]	265	ER/PR+ (210) HER2+ (77) Triple negative (33)	46.0	NCT00557986 (MF07-01)	Surgery	OS	HR:0.71(0.59–0.86)
Khan,2022	2011–2015	USA	56.0	256	ER/PR+/HER2- (222) Triple-negative (40) HER2+ (113)	53.0	NCT01242800 (ECOG2108)	Systemic therapy	OS QoL	HR:1.09(0.75–1.57) SMD:0.49(0.14–0.83)
Bjelic-Radisic,2020	2010–2015	Austria	64.0	90	ER/PR+ (65) ER/PR- (14) HER2+ (15) HER2- (63)	37.5	NCT01015625 (ABCSG 28)	Surgery	QoL	SMD: 0.29(-0.73 to 0.15)
Soran,2020	2007–2012	Turkey	51.8[a]	274	ER/PR+ (205) HER2+ (84) Triple-negative (33)	46.0	NCT00557986 (MF07-01Q)	Surgery	QoL	SMD: 0.23(-0.69 to 0.24)

Abbreviations: ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; OS, overall survival; QoL, quality of life; CI, confidence interval; HR, hazard ratio; SMD, standardized mean difference; †, median; [a], mean.

Qualität der Studien:

Nicht verfügbar

Studienergebnisse:

- OS, LPFS and DPFS

Five RCTs were included in the comparison of breast surgery (adding breast surgery to ST) with no surgery (ST only) in women with dnMBC, and the pooled median follow-up was 39.7 months. The pooled results showed no statistically significant difference between the two groups in terms of OS (HR = 0.87, 95 % CI 0.68–1.11, p = 0.265; moderate certainty; Fig. 1a). Moreover, the results showed no benefit of breast surgery in terms of 2-year OS (relative risk [RR] = 1.08; 95 % CI 0.75–1.56, p = 0.663; moderate certainty; Fig. 2a), and 3-year OS (RR = 1.08; 95 % CI 0.83–1.41, p = 0.573; moderate certainty; Fig. 2b). Only one study reported a significant increase in OS in the surgical group at 5 and 10 years of follow-up [29].In a subset of three studies with available data on PFS, the pooled results indicated that breast surgery was associated with a significant improvement in LPFS (HR = 0.27, 95 % CI 0.19–0.38, p < 0.001; moderate certainty; Fig. 1b), while there was no significant difference in DPFS among the groups (HR = 1.20, 95 % CI 0.94–1.54, p = 0.136; low certainty; Fig. 1c). Based on the five studies included, Galbraith plot shows that the included studies were all within the confidence intervals and no potential outliers were detected (Fig.A2). Leave-one-out forest plot displays that there are no studies that substantially influence the results of our meta-analysis (Fig.A3). Inspection and statistical tests of the funnel plot revealed that there was little heterogeneity in the included studies showing a symmetrical distribution (Fig.A4). However, as per the TSA analysis, the optimal information size was not reached for OS, contributing to the assessment of imprecision and overall moderate certainty (Fig.A5).

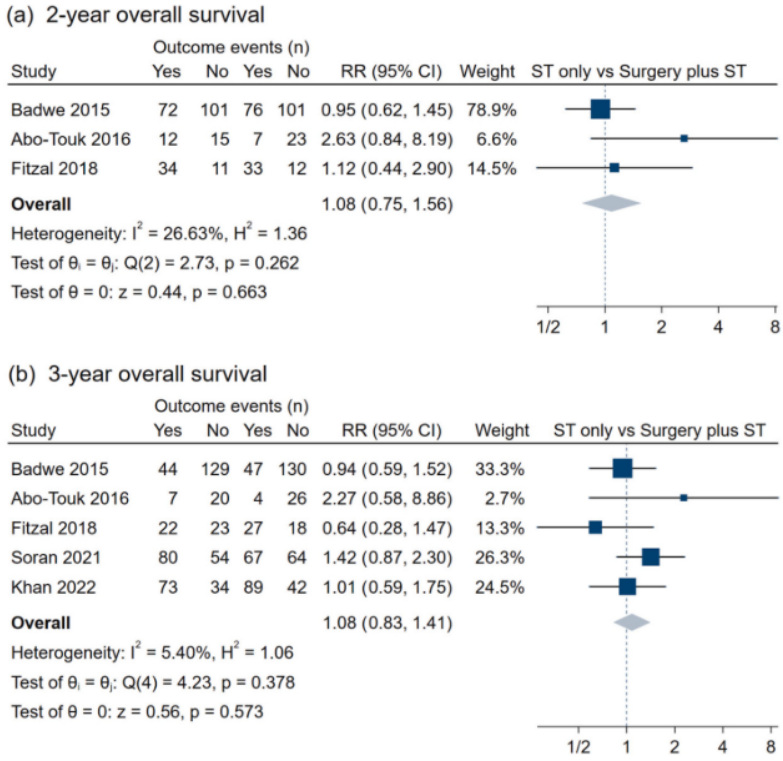


Fig. 2. Forest plot of two-year and three-year survival rates. Pooled overall survival of breast surgery plus systemic therapy versus systemic therapy only at different follow-up periods. 2-year overall survival (fixed effect model) (a); 3-year overall survival (fixed effect model) (b). RR relative risk; CI confidence interval.

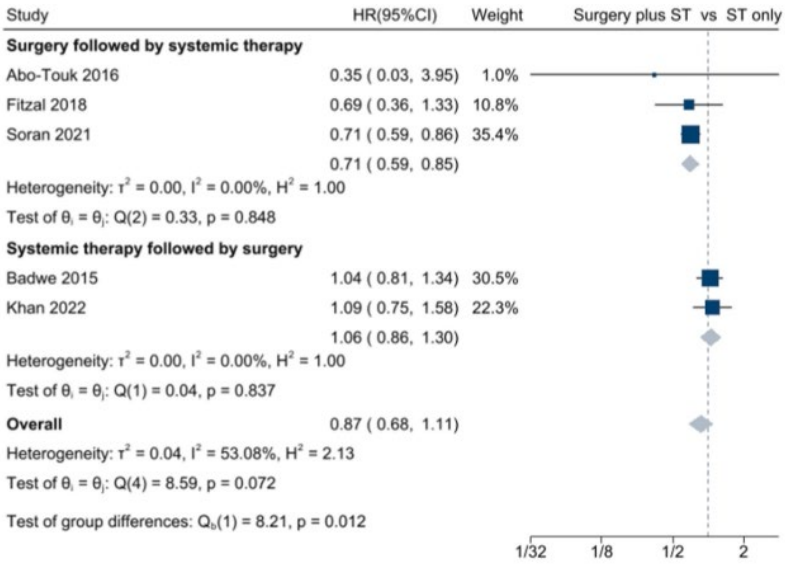


Fig. 3. Forest plot of the timing of surgery. Subgroup analysis of the timing of surgery (therapy schedule) for the overall survival in the comparison of breast surgery plus systemic therapy with systemic therapy only (fixed effect model). HR hazard ratio; CI confidence interval.

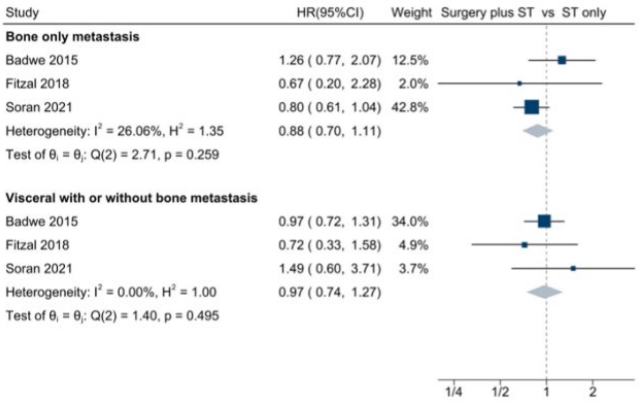


Fig. 4. Forest plot of initial metastatic sites. Subgroup analysis of metastatic sites for the overall survival in the comparison of breast surgery plus systemic therapy with systemic therapy only (fixed effect model). HR hazard ratio; CI confidence interval.

- The timing of breast surgery

  Across the five included studies, 2 of the studies randomization to breast surgery occurred after achieving clinical benefit from ST [25,28], while in 3 studies patients in surgery group were treated with an upfront surgery [24,26,29].Based on the different timing of the surgery, the pooled results show that breast surgery followed by ST versus ST alone resulted in significantly improved OS (HR = 0.71, 95 % CI 0.59–0.85, p < 0.001; Fig. 3); and ST followed by breast surgery was found to have no benefit compared with ST alone for dnMBC (HR = 1.06, 95 % CI 0.86–1.3, p = 0.610; Fig. 3).

- Bone metastasis and visceral metastasis

  In a subset of three studies with available data on bone only metastasis [25,26,29], breast surgery did not confer a survival benefit compared to ST alone (HR = 0.88, 95 % CI 0.70–1.11, p = 0.259; Fig. 4). In a subset of three studies with available data on visceral metastasis with or without bone metastasis [25,26,29], breast surgery did not improve survival compared with ST alone (HR = 0.97, 95 % CI 0.74–1.27, p = 0.495; Fig. 4). Notably,

one of the studies reported a beneficial outcome of breast surgery with regard to solitary bone metastasis [29].

- IHC subtypes

  Across the five included studies with available data on IHC subtypes, ER/PR negative data pooled by three trials (HR = 1.0,95 % CI 0.81–1.23,p = 0.825) [25,26,29],ER/PR positive data pooled by four trials (HR = 0.82, 95 % CI 0.63–1.05,p = 0.186) [25,26,28,29],HER2 negative data pooled by four trials (HR = 0.84, 95 % CI 0.65–1.08,p = 0.149) [25,26,28,29],HER2 positive data pooled by four trials (HR = 0.85, 95 % CI 0.62–1.17,p = 0.494) [25,26,28,29],and triple negative data pooled by three trials (HR = 1.36, 95 % CI 0.54–3.42,p = 0.087) [26,28,29] were analyzed respectively. The results showed that no significant survival advantage was found in breast surgery compared with ST alone for different IHC subtypes of dnMBC (Fig. 5).

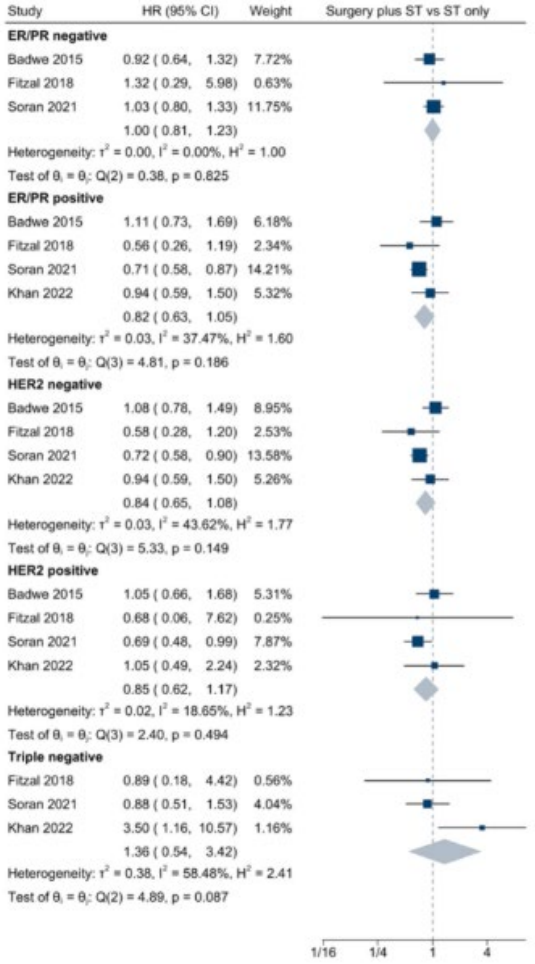


Fig. 5. Forest plot of molecular subtypes. Subgroup analysis of molecular subtypes for the overall survival in the comparison of breast surgery plus systemic therapy with systemic therapy only (fixed effect model). HR hazard ratio; CI confidence interval.

- QoL evaluation

  Of the seven included studies [24–26,28,29,54,55],three studies [28, 54,55], including 291 patients, performed quality-of-life analyses. In the POSYTIVE and E2108 trials [28,54], the results of QoL were prospectively assessed at multiple time points, extending to 24 months after randomization, whereas in the MF07-01Q study [55] only a single time point of 36 months were performed prospective assessment. Although the three studies reported QoL outcomes using different questionnaires, including the EORTC QLQ-C30, QLQ-BR23, SF-36 and FACT-B scores, the results were consistent that

breast surgery may not improve QoL. Here, QOL outcome data were pooled based on the three eligible studies [28,54,55]. Fig. 6 summarized effect size estimates (SMD and 95 % CIs) of the effects of breast surgery on QoL outcome. Pooled effect estimates showed that breast surgery had no significant impact on either QoL-global health status or QoL-mental-physical functionality, with effect size of 0.08 (95 % CI: 0.15 to 0.32, p = 0.478; 291 participants; 3 trials; low certainty) (Fig. 6a) and −0.15 (95 % CI: 0.50 to 0.13, p = 0.255; 160 participants; 2 trials; low certainty) (Fig. 6b). Of note, there was significant heterogeneity in the studies on QoL-global health status (p = 0.008), with an I2 value of 79.45 % (Fig. 6a).

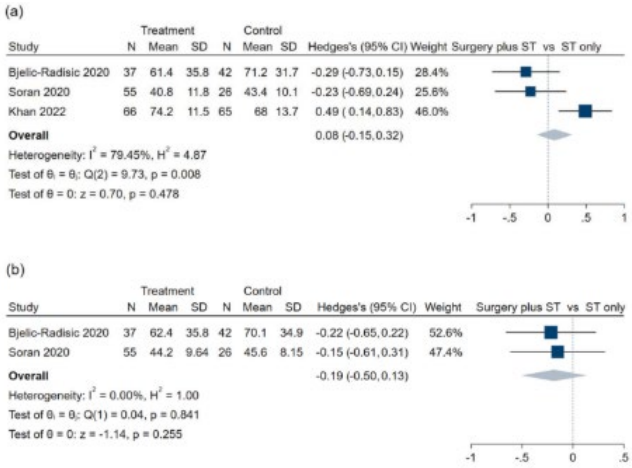


Fig. 6. Forest plot of quality of life. Meta-analysis results of breast surgery plus systemic therapy versus systemic therapy only on quality of life. QoL-global health status (fixed effect model) (a); QoL-mental-physical functionality (fixed effect model) (b). QoL quality of life; SMD standardised mean difference; SD standard deviation; CI confidence interval.

Anmerkung/Fazit der Autoren

The results of this meta-analysis suggest that breast surgery is not associated with improved survival and quality of life in patients with dnMBC, although it may be associated with improved locoregional control. Overall, the RCTs evidence does not establish that breast surgery provides survival and quality of life benefits for dnMBC patients, suggesting that it remains palliative for dnMBC population. Adequately powered prospective clinical trials, including quality of life analyses, are needed in the future to validate this finding.

Shao H et al., 2024 [17].

A network meta-analysis of efficacy and safety for first-line and second/further-line therapies in postmenopausal women with hormone receptor-positive, HER2-negative, advanced breast cancer

Fragestellung

Hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR + /HER2 −) advanced breast cancer is a prevalent subtype among postmenopausal women. Despite the growing number of randomized clinical trials (RCTs) exploring this topic, the efficacy and safety of first-line and second/further-line treatments remain uncertain. Accordingly, our aim was to conduct a comprehensive evaluation of the efficacy and safety of these therapies through network meta-analysis.

Methodik

Population:

- Women with HR + /HER2 − postmenopausal advanced breast cancer

Intervention:

- Single-agent chemotherapy, endocrine therapy monotherapy, targeted therapy, and combinations of endocrine therapy with targeted therapy were considered.

Komparator:

- Wie Intervention

Endpunkte:

- HRs of overall survival (OS), progression-free survival (PFS), and the objective response rate were examined. Adverse events (AEs) incidences were categorized into multiple groups: AEs of any grade, grade 3–5 AEs, AEs leading to discontinuation, and AEs leading to death.
- Attention was also given to the incidence rates of the three most common specific AEs, which included both hematologic and non-hematologic types, across any grade and specifically within grades 3–5.
- The presence of at least one Kaplan–Meier curve for either OS or PFS was a requirement. If specific data related to postmenopausal women were provided in any RCTs, those trials were included in this study.

Recherche/Suchzeitraum:

- PubMed, Embase, the European Society for Medical Oncology, the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium conference, and the Chinese Society of Clinical Oncology.
- published between November 2007 and November 2022

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Seventeen RCTs with 7062 patients were included in the first-line analysis, and 27 RCTs with 10,211 patients were included in the second/further-lines analysis (Additional file 1: Table S4-Table S5).

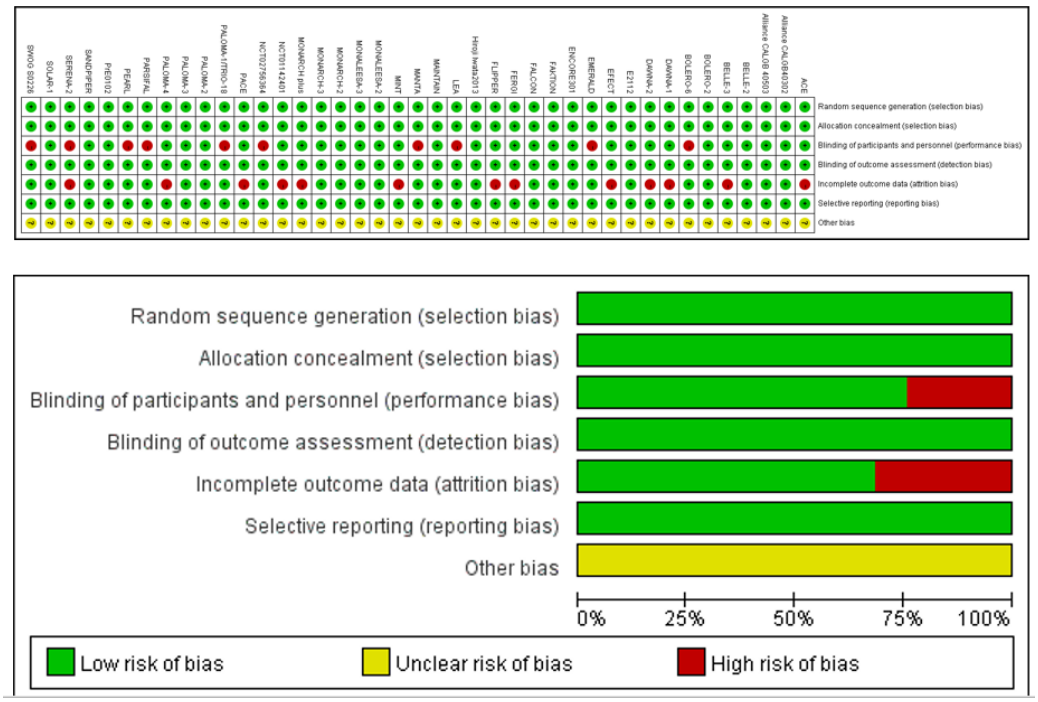
Charakteristika der Population/Studien:

- Nicht verfügbar

Qualität der Studien:

- Overall, the risk of bias was generally low across all RCTs. However, some included RCTs were open-label, elevating the risk of bias in participant and personnel blinding as well as allocation concealment.

Figure S1 Methodology quality of the included studies



GRADE:

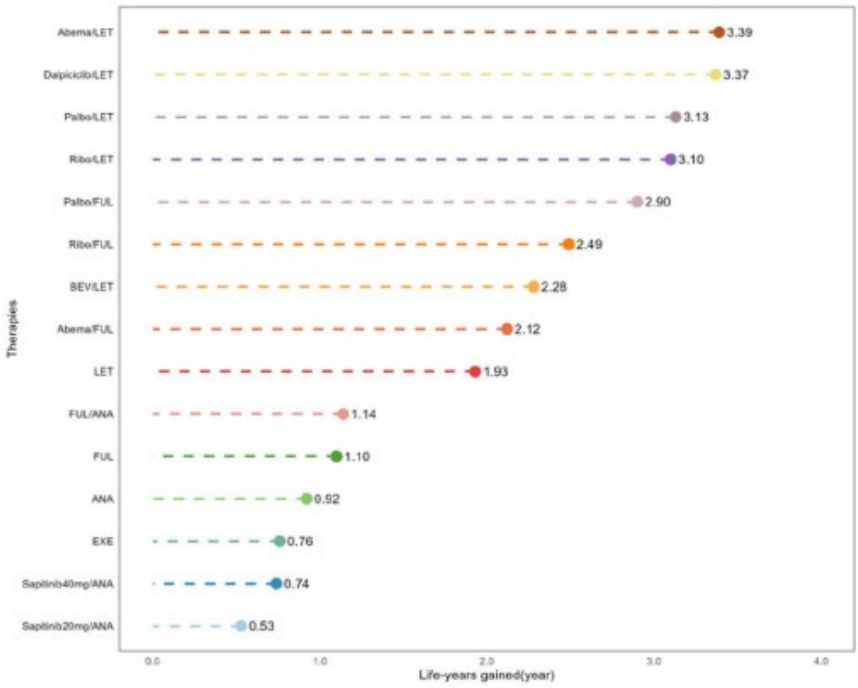
As mentioned above, none of the included RCTs was assessed as having a high risk of bias, and each comparison showed no inconsistency. In particular, all comparison groups had less than 10 studies, so publication bias was not detectable. Most comparisons were downgraded due to imprecision. Overall, it was judged as high or moderate certainty for most of the evidence of PFS and AE, and moderate or low certainty for most of the evidence of OS and ORR.

<u>Studienergebnisse:</u>

- Progression-free survival for first-line treatments

  The NMA encompassed 15 therapies and 7 mechanisms, respectively (Fig. 2A,B). The PH assumption was invalidated in this network, resulting in the selection of the FP model, which fit the data at power parameters = − 1 (Additional file 1: Table S7). In terms of 10-year PFS of the therapies (Fig. 3A and Additional file 2: Figure S3A), Abemaciclib/Letrozole demonstrated the best PFS benefit, providing a life-year gain over 10 years of 3.39 years. Dalpiciclib/Letrozole and Palbociclib/Letrozole were found to be comparable to Abemaciclib/Letrozole, with life-years gained over 10 years of 3.37 and 3.13 years, respectively. Bayesian NMA provided consistent treatment rankings for Cox-PH model (Additional file 1: Table S8). Concerning the 10-year PFS of the mechanisms (Fig. 5A and Fig. 5C), CDK4/6i in combination with ET performed the best, with CDK4/6i plus selective estrogen receptor degrader (SERD) (3.48 life years) slightly outperforming CDK4/6i plus aromatase inhibitor (AI) (3.30 life years). A similar trend was observed in the results from the Cox-PH model (Additional file 2: Figure S4).

A



B

Abema /FUL									
0.78 (0.47, 1.30)	Abema /LET								
0.68 (0.41, 1.13)	0.88 (0.62, 1.25)	BEV/LET							
0.56 (0.31, 1.00)	0.72 (0.46, 1.13)	0.82 (0.53, 1.28)	EXE						
0.85 (0.64, 1.14)	1.09 (0.72, 1.67)	1.24 (0.82, 1.88)	1.52 (0.92, 2.50)	FUL					
0.73 (0.45, 1.17)	0.93 (0.68, 1.27)	1.06 (0.79, 1.43)	1.30 (0.86, 1.95)	0.85 (0.58, 1.25)	FUL/ANA				
0.60 (0.38, 0.93)	**0.76 (0.59, 0.99)**	0.87 (0.68, 1.11)	1.06 (0.73, 1.54)	**0.70 (0.50, 0.98)**	**0.82 (0.69, 0.98)**	LET			
0.65 (0.34, 1.17)	0.81 (0.49, 1.34)	0.92 (0.57, 1.51)	1.13 (0.64, 1.99)	0.74 (0.43, 1.28)	0.87 (0.55, 1.38)	1.06 (0.69, 1.63)	Palbo/FUL		
0.63 (0.39, 1.02)	0.81 (0.59, 1.11)	0.92 (0.68, 1.25)	1.13 (0.75, 1.70)	0.74 (0.51, 1.09)	0.87 (0.68, 1.12)	1.06 (0.89, 1.27)	1.00 (0.68, 1.48)	Palbo/LET	
1.33 (0.86, 2.05)	1.71 (1.00, 2.91)	1.94 (1.15, 3.29)	2.37 (1.31, 4.30)	1.56 (1.13, 2.16)	1.83 (1.11, 3.02)	2.23 (1.40, 3.56)	2.10 (1.11, 3.96)	2.10 (1.27, 3.47)	Ribo/FUL
0.78 (0.48, 1.27)	1.01 (0.73, 1.39)	1.14 (0.84, 1.56)	1.40 (0.92, 2.12)	0.92 (0.62, 1.36)	1.08 (0.83, 1.40)	1.32 (1.08, 1.60)	1.24 (0.77, 1.98)	1.24 (0.95, 1.62)	**0.59 (0.36, 0.98)**

Fig. 3 Summary results of efficacy outcomes for the first-line treatment. (A Life-year results within 10 years for first-line therapies' PFS. B Cox-PH model result for first-line therapies' OS). Abbreviations: Abema, Abemaciclib; ANA, Anastrozole; BEV, Bevacizumab; EXE, Exemestane; FUL, Fulvestrant; LET, Letrozole; Palbo, Palbociclib; Ribo, Ribociclib. Note: The direction of the reported relative effects in each cell is defined as treatment on the right vs. treatment on the left. Values < 1 favor the intervention on the right. Values in parenthesis are 95% credible intervals (95% CIs). Bold cells correspond to statistically significant relative effects for the respective treatment categories

- Overall survival for first-line treatments

  The NMA respectively incorporated 11 therapies and 6 mechanisms (Fig. 2C,D). The PH assumption was validated in this network, leading to the choice of the CoxPH model. The results of the Cox-PH model (Fig. 3B) showed that compared with the Letrozole, several treatments, including Abemaciclib/Fulvestrant (HR, 0.60 [95% CI, 0.38 ~ 0.93]), Abemaciclib/Letrozole (0.76 [0.59 ~ 0.99]), Fulvestrant (0.70 [0.50 ~ 0.98]), Ribociclib/Fulvestrant (0.45 [0.28 ~ 0.71]), Ribociclib/Letrozole (0.76 [0.63 ~ 0.92]), and Fulvestrant/Anastrozole (0.82 [0.69 ~ 0.98]) all significantly improved OS in first-line patients to varying extents. Additionally, for first-line mechanisms, whether considering

the Cox-PH model (Additional file 2: Figure S4) or the FP model (Fig. 5B,C), the results consistently indicated superior performance of CDK4/6i combined with SERD or AI.

- Progression-free survival for second/further-line treatments

  In the NMA of second/further-lines PFS, a total of 28 therapies and 14 mechanisms were incorporated (Fig. 2E,F). The PH assumption was invalidated in this network, leading to the selection of the FP model, which fit the data at power parameters = − 2 (Additional file 1: Table S7). Regarding to 10-year PFS for various therapies (Fig. 4 and Additional file 2: Figure S3B), the combination of Palbociclib, Fulvestrant, and Avelumab emerged as the most effective, contributing to a life-year gain of 2.58 years over a decade. Dalpiciclib/Fulvestrant and Everolimus/Exemestane followed closely, yielding life-year gains of 2.35 and 2.32 years respectively over the same period. Contrarily, results from the Cox-PH model (Additional file 1: Table S9) suggested that single-agent chemotherapy (Eribulin, Gemcitabine, or Capecitabine) outperformed others, with Everolimus/Exemestane ranking second. When examining 10-year PFS for different mechanisms (Fig. 5D and F), the combination of CDK4/6i, SERD, and ICI (2.76 life years) demonstrated the greatest benefit, followed by single-agent chemotherapy (2.49 life years). The Cox-PH model exhibited a similar trend (Additional file 2: Figure S5).

- Overall survival for second/further-line treatments

  In this portion, the NMA incorporated 16 therapies and 12 mechanisms (Fig. 2G,H). The PH assumption was not sustained in this network, prompting the use of the FP model with power parameters set at − 1 (Additional file 1: Table S7). In terms of 10-year OS for therapies (Fig. 4 and Additional file 2: Figure S3C), the combination of Palbociclib, Fulvestrant, and Avelumab exhibited the best OS benefit, contributing to a life-year gain of 4.84 years over a decade. This was followed by Ribociclib/Fulvestrant (3.58 life years) and Palbociclib/Fulvestrant (3.53 life years). However, the results derived from the Cox-PH model (Additional file 1: Table S9) suggested superior performance by Abemaciclib/Fulvestrant. For the mechanisms' 10-year OS (Fig. 5E,F), the combination of CDK4/6i, SERD, and ICI (5.20 life years) showed the best outcome, followed by CDK4/6i/SERD (3.58 life years), and single-agent chemotherapy (3.56 life years). The Cox-PH model displayed similar results (Additional file 2: Figure S5).

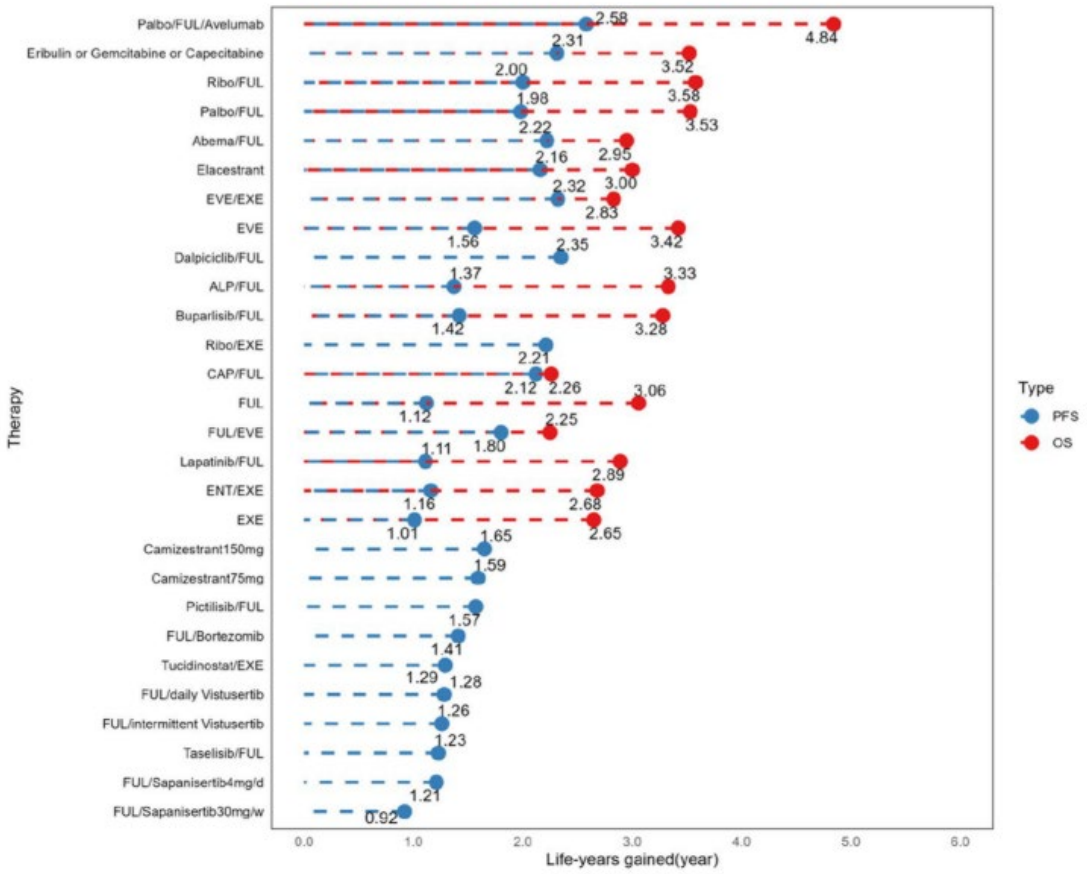


Fig. 4 Life-year results within 10 years for second/further-line therapies' PFS and OS. Abbreviations: Abema, Abemaciclib; ALP, Alpelisib; CAP, Capivasertib; ENT, Entinostat; EVE, Everolimus; EXE, Exemestane; FUL, Fulvestrant; Palbo, Palbociclib; Ribo, Ribociclib

- Safety outcomes

  Within the scope of first-line therapies, Letrozole consistently exhibits the lowest incidence rate for any grade AEs, grade 3–5 AEs, and AEs resulting in discontinuation. The only exception is the occurrence of AEs leading to death, where Fulvestrant has the lowest incidence rate. The highest incidence rates are observed with Palbociclib/Fulvestrant for any grade AEs, Sapitinib40mg/Anastrozole for grade 3–5 AEs, Ribociclib/Fulvestrant for AEs leading to discontinuation, and Bevacizumab/Letrozole for AEs leading to death. Additional detailed information is available in the Additional file 1: Table S10. Regarding the mechanisms of first-line treatment strategies, AI persistently displays the lowest incidence rates for any AEs, grade 3–5 AEs, AEs leading to treatment cessation, and AEs resulting in death. The highest incidence rates for any grade AEs, grade 3–5 AEs, and AEs resulting in discontinuation are associated with CDK4/6i/SERD. However, for AEs leading to death, the highest incidence rate was observed with the combination of anti-vascular endothelial growth factor and AI. Additional detailed information is available in Fig. 6. In terms of safety outcomes for second/further-line

  treatments, Everolimus presents the lowest incidence rate for any grade AEs, Fulvestrant exhibits the best performance in terms of grade 3–5 AEs, Palbociclib/Fulvestrant is optimal in minimizing AEs resulting in treatment discontinuation, and Exemestane shows the lowest rate of AEs leading to death. Conversely, Fulvestrant/ Sapanisertib 4mg/day manifests the worst performance in any

grade AEs, Buparlisib/Fulvestrant ranks highest in grade 3–5 AEs, Fulvestrant/Sapanisertib 30mg/week leads in AEs causing discontinuation, and Fulvestrant/ Everolimus has the highest incidence rate of AEs leading to death. Additional detailed information is available in the Additional file 1: Table S11. In the context of second/further-line mechanisms, SERD demonstrates the lowest incidence rates for any grade AEs, grade 3–5 AEs, and AEs leading to treatment discontinuation. AI is associated with the lowest rate of AEs leading to death. Conversely, a combination of SERD and mammalian target of rapamycin inhibitor (mTORi) demonstrated the highest incidence rate of any grade AEs. CDK4/6i/ SERD accounted for the highest occurrence of grade 3–5 AEs. Single-agent chemotherapy was most associated with AEs leading to treatment cessation, while mTORi presented the highest incidence of AEs that resulted in death. More information is available in Fig. 6. Additionally, it was observed that the incidence of both hematologic and non-hematologic AEs was relatively low with endocrine monotherapy. While most of CDK4/6 inhibitors were associated with an increased incidence of hematologic AEs such as neutropenia and leukopenia, our analysis indicates a more varied profile for non-hematologic AEs, such as Abemaciclib showing a notable increase in events like diarrhea (Additional file 1: Table S12).

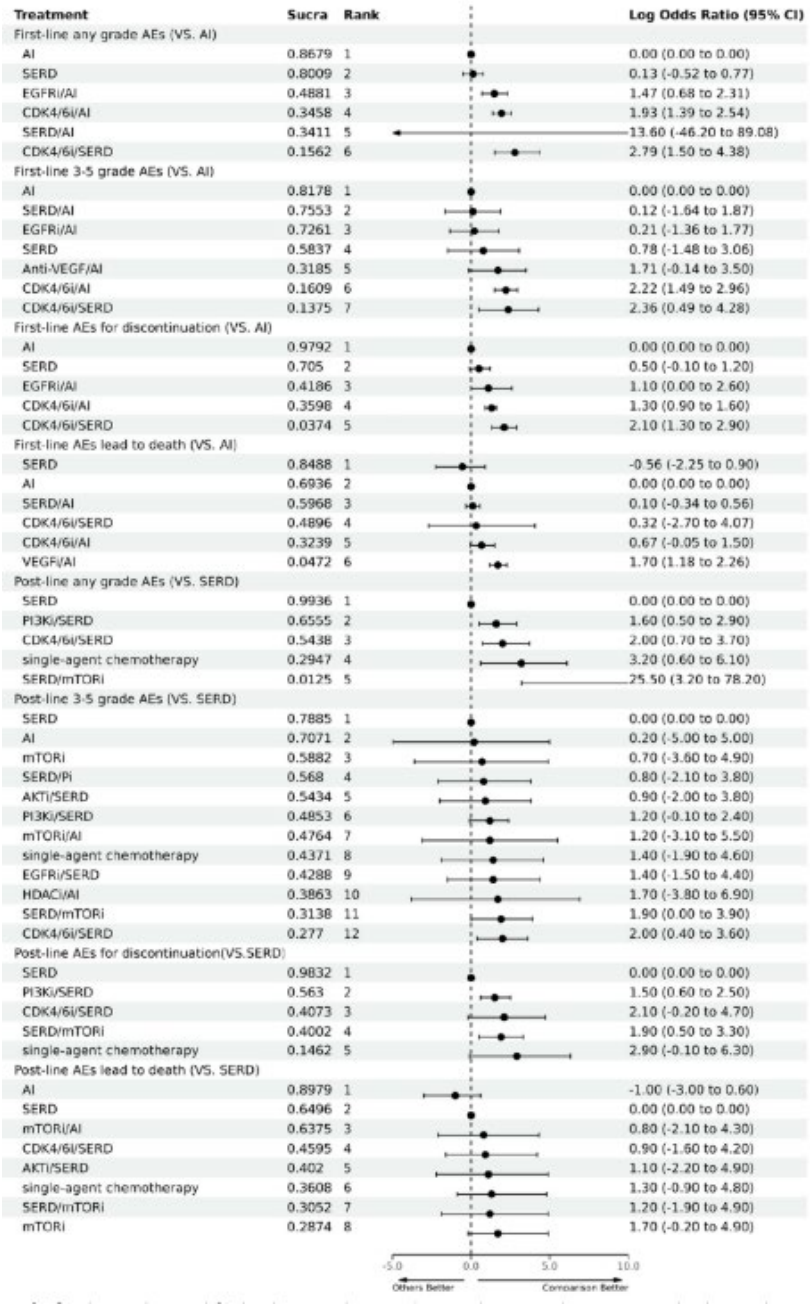


Fig. 6 Safety outcomes for first-line and second/further-lines mechanisms (any grade AEs; grade 3–5 AEs; AEs leading to discontinuation; AEs leading to death). Abbreviations: AI, Aromatase inhibitor; AKTi, AKT inhibitor; Anti-VEGF, Anti-vascular endothelial growth factor; CDK4/6i, Cyclin-dependent kinase 4 and 6 inhibitors; EGFRi: Epidermal growth factor receptor inhibitor; HDACi, Histone deacetylase inhibitor; ICI, Immune checkpoint inhibitor; mTORi, Mammalian target of rapamycin inhibitor; Pi, Protease inhibitor; PI3Ki, Phosphatidylinositol 3-kinase inhibitor; SERD, Selective estrogen receptor degrader

Anmerkung/Fazit der Autoren

In conclusion, our NMA demonstrated that the combination of CDK4/6i and ET exhibits superior efficacy in firstline treatment, albeit at the expense of increased adverse events. Notably, enhanced benefits were observed in patients under 65 and within the Asian demographic. The combination of CDK4/6i and SERD displayed remarkable efficacy in second/further-line treatment, and the addition of ICI might enhance this efficacy, notwithstanding discrepancies in the Cox-PH model results. Furthermore, while there are PFS benefits associated with drugs such as Sapanisertib and

Buparlisib, their development is hindered by toxicity. Noteworthy PFS improvements were observed in PIK3CA and ESR1 mutation patients treated with Capivasertib, Alpelisib, Camizestrant, and Elacestrant. Further research is necessary to determine the most effective treatment strategies in the HR + / HER2 − advanced breast cancer, and sequencing of these therapies is crucial. Additionally, more trials comparing these novel treatments are warranted to reduce uncertainty in these results.

Guo X et al., 2023 [5].

First-line CDK4/6 inhibitor-based combinations for HR+/HER2– advanced breast cancer: A Bayesian network meta-analysis

Fragestellung

International guidelines recommend cyclin-dependent kinase 4/6 inhibitor (CDK4/6i)-based first-line therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer (ABC). However, direct drug comparisons are lacking. We aimed to identify the most effective and safe therapy through network meta-analysis (NMA).

Methodik

Population:

- histologically confirmed HR+/HER2− ABC patients who receiving first-line endocrine therapy, including two eligibility criteria: those who had not received prior systematic therapy (except one line of cytotoxic chemotherapy) for advanced disease and those who had relapsed > 12 months after completing (neo) adjuvant endocrine therapy

Intervention:

- endocrine therapy included aromatase inhibitor, fulvestrant and tamoxifen and CDK4/6is included palbociclib, abemaciclib, ribociclib, and dalpiciclib

Komparator:

- at least one comparative group was endocrine therapy alone or in combination with CDK4/6i

Endpunkte:

- PFS, OS, ORR, or AE (PFS was defined as the time from random assignment to disease progression or death from any cause, OS was defined as the time from random assignment to death from any cause, and ORR represented the proportion of patients with complete response and partial response

Recherche/Suchzeitraum:

- PubMed, Embase,Web of Science, the Cochrane Central Register of Controlled Trials, and OpenGrey
- from database inception to September 30, 2023

Qualitätsbewertung der Studien:

- Cochrane’s RoB 2.0 tool
- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 eligible articles describing 13 randomized controlled studies were included in the final network meta-analyses (Figure 1).21–41 Characteristics of the 13 included trials are summarized in Table 1.

TABLE 1 Characteristics of included studies.

Trial identifier	Study	Mean age (year)	Number in Arm 1	Number in Arm 2	Treatment Arm 1	Treatment Arm 2	End points	HR (95% CrI) for PFS	HR (95% CrI) for OS	RR (95% CrI) for ORR	HR (95% CrI) for PFS with VM	RR (95% CrI) for grade 3/4 AE
SWOG NCT00075764	Mehta2012[21]	NA	266	270	Anastrozole+ fulvestrant	Anastrozole	PFS	0.81 (0.67–0.98)	NA	NA	NA	NA
PALOMA-1 NCT00721409	Finn 2015[22] Finn 2020[23]	Arm 1: 66 (56, 72) Arm 2: 64 (57, 70)	84	81	Palbociclib+ Letrozole	Letrozole	PFS, OS, ORR	0.49 (0.32, 0.75)	0.90 (0.62, 1.29)	1.29 (0.68, 2.42)	0.55 (0.32, 0.94)	3.65 (1.73, 7.70)
FALCON NCT01602380	Robertson 2016[24]	Arm 1: 64 (38, 87) Arm 2: 62 (36, 90)	230	232	Fulvestrant+ anastrozole placebo	Anastrozole+ fulvestrant placebo	PFS, OS, ORR	0.80 (0.64, 1.00)	0.88 (0.63, 1.22)	1.04 (0.72, 1.51)	0.99 (0.74, 1.33)	1.27 (0.80, 2.00)
PALOMA-2 NCT01740427	Finn 2016[25] Rugo 2019[26] Finn 2020[27] Finn 2022[28]	Arm 1: 62 (30, 89) Arm 2: 61 (28, 88)	444	222	Palbociclib+ letrozole	Placebo+ letrozole	PFS, OS, ORR	0.56 (0.46, 0.69)	0.96 (0.78, 1.18)	1.21 (0.87, 1.70)	0.61 (0.46, 0.80)	2.72 (1.87, 3.95)
MONALEESA-2 NCT01958021	Hortobagyi 2018[29] Yardley 2019[30] Hortobagyi 2022[31]	Arm 1: 62 (23, 91) Arm 2: 63 (29, 88)	334	334	Ribociclib+ letrozole	Placebo+ letrozole	PFS, OS, ORR	0.57 (0.46, 0.70)	0.76 (0.63, 0.93)	1.48 (1.07, 2.04)	0.54 (0.41, 0.71)	2.10 (1.40, 3.14)
MONARCH 3 NCT02246621	Johnston 2019[32] Goetz 2022[33]	Arm 1: 63 (38, 87) Arm 2: 63 (32, 88)	328	165	Abemaciclib+ anastrozole /letrozole	Placebo+ anastrozole /letrozole	PFS, OS, ORR	0.54 (0.42, 0.70)	0.75 (0.58, 0.97)	1.34 (0.92, 1.97)	0.57 (0.41, 0.79)	2.35 (1.55, 3.58)
MONALEESA-3 NCT02422615	Yardley 2019[30] Slamon 2020[34] Slamon 2021[35]	NA	237	128	Ribociclib+ fulvestrant	Placebo+ fulvestrant	PFS, OS, ORR	0.55 (0.42, 0.72)	0.64 (0.47, 0.88)	NA	0.61 (0.40, 0.93)	NA

(Continues)

TABLE 1 (Continued)

Trial identifier	Study	Mean age (year)	Number in Arm 1	Number in Arm 2	Treatment Arm 1	Treatment Arm 2	End points	HR (95% CrI) for PFS	HR (95% CrI) for OS	RR (95% CrI) for ORR	HR (95% CrI) for PFS with VM	RR (95% CrI) for grade 3/4 AE
MONARCH plus	Zhang 2020[36]	Arm 1: 54 (32, 83)	207	99	Abemaciclib+ anastrozole /letrozole	Placebo+ anastrozole /letrozole	PFS, ORR	0.50 (0.35, 0.72)	NA	1.85 (1.11, 3.08)	0.62 (0.40, 0.96)	2.54 (1.48, 4.37)
NCT02763566		Arm 2: 54 (27, 77)										
PALOMA-4	Xu 2022[37]	Arm 1: 53.8 (8.5)	169	171	Palbociclib+ letrozole	Placebo+ letrozole	PFS, ORR	0.68 (0.53, 0.87)	NA	1.18 (0.75, 1.85)	NA	4.11 (2.27, 7.46)
NCT02297438		Arm 2: 53.7 (9.1)										
PARSIFAL	Llombart 2021[38]	Arm 1: 64 (25, 88)	243	243	Palbociclib+ fulvestrant	Palbociclib+ letrozole	PFS, OS, ORR	1.13 (0.89, 1.45)	1.00 (0.68, 1.48)	0.93 (0.65, 1.32)	1.27 (0.91, 1.77)	1.03 (0.66, 1.61)
NCT02491983		Arm 2: 62 (35, 90)										
FLIPPER	Albanell 2022[39]	Arm 1: 64 (38, 81)	94	95	Palbociclib+ fulvestrant	Placebo+ fulvestrant	PFS, ORR	0.48 (0.32, 0.73)	NA	1.45 (0.80, 2.62)	0.45 (0.27, 0.76)	2.27 (1.07, 4.81)
NCT02690480		Arm 2: 64 (42, 82)										
DAWNA-2 NCT03966898	Zhang 2023[40]	Arm 1: 54 (47, 63)	303	153	Dalpiciclib+ anastrozole /letrozole	Placebo+ anastrozole /letrozole	PFS, ORR	0.51 (0.38, 0.69)	NA	1.20 (0.81, 1.78)	0.63 (0.43, 0.90)	7.63 (4.12, 14.13)
		Arm 2: 57(46, 632)										
FRIEND	Wang 2023[41]	NA	21	15	Fulvestrant	Exemestane	PFS	0.79 (0.34, 1.84)	NA	NA	NA	NA
NCT02646735												

PFS, progression-free survival; OS, overall survival; ORR, objective response rate; VM, visceral metastasis; AE, adverse event; HR, hazard ratio; RR, relative risk; CI, confidence interval.

<u>Qualität der Studien:</u>

Both measurement of outcome and selection of reported results were at low risk in all included studies. There were some concerns in the randomization process because of the insufficient reporting of allocation concealment. Four trials were open-label, leading to potential bias of deviations from intended interventions, whereas the remaining nine trials were free from bias in this regard. Overall, the included studies were of high quality.

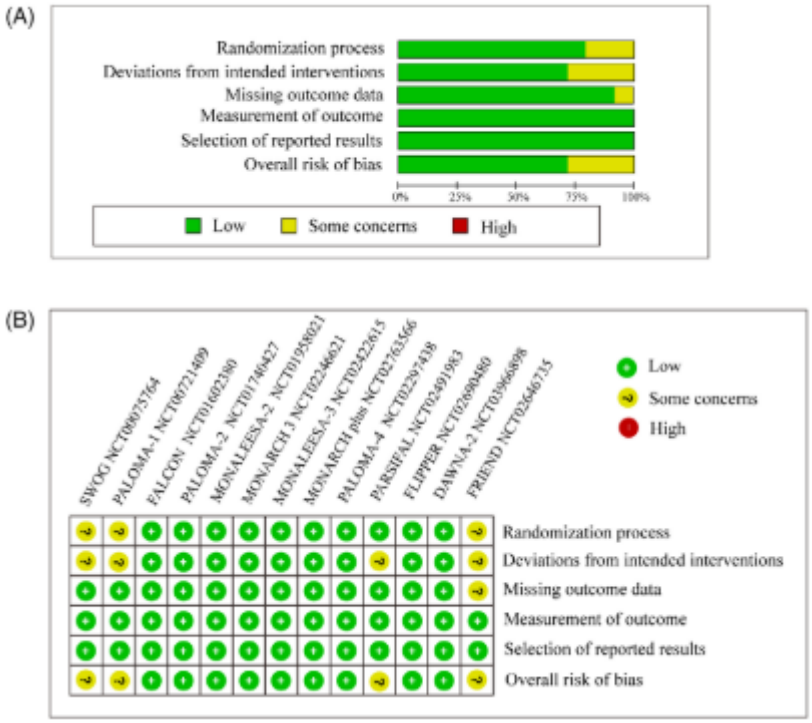


FIGURE 2 Quality assessment of included trials in the network meta-analysis. (A) Review authors' judgments about each methodological quality item presented as percentages across all included studies. (B) Risk of bias assessment detailed for each included study.

<u>Studienergebnisse:</u>

Bayesian network meta-analyses

- Progression-free survival

  Thirteen RCTs, involving ten regimens, reported PFS data.21,22,24,26,29,32,34,36–41 The network plot of all comparisons in these 13 studies is illustrated in Figure 3A. Compared with NSAI alone, the other seven regimens significantly improved PFS, including fulvestrant+NSAI (HR = 0.81, 95% CrI 0.67-0.98), palbociclib+NSAI (HR = 0.57, 95% CrI 0.49-0.65), ribociclib+NSAI (HR = 0.57, 95% CrI 0.46-0.70), abemaciclib+NSAI (HR = 0.53, 95% CrI 0.43-0.65), ribociclib+fulvestrant (HR = 0.48, 95% CrI 0.34-0.68), and palbociclib+fulvestrant (HR = 0.57, 95% CrI 0.45-0.73), dalpiciclib+NSAI (HR = 0.51, 95% CrI 0.38-0.69), whereas fulvestrant and exemestane indicated no statistically significant differences (Figure 3C and D). Besides, all six CDK4/6i-included treatments displayed a distinct improvement over fulvestrant and fulveatrant+NSAI (Figure 3D). Our results demonstrated no significant superiority of one drug over the other between the four CDK4/6is (Figure 3D). The SUCRA values and cumulative probability plots for all eight regimens are shown in Figure 3B, suggesting that ribociclib+fulvestrant ranked first with an SUCRA of 85.0%, followed by dalpiciclib+NSAI (SUCRA= 78.9%) and abemaciclib+NSAI (SUCRA = 76.0%). Moreover, a further subgroup analysis of patients with visceral metastasis indicated different rankings (eFigure 6). Ribociclib+NSAI, with an SUCRA of 78.9%, ranked first among all of the remedies, followed by palbociclib+NSAI (SUCRA = 75.0%) and abemaciclib+NSAI (SUCRA = 66.4%) (eFigure 6B). The estimated HRs and 95% CrIs for comparisons between any two rival interventions are presented in eFigure 6C and D.

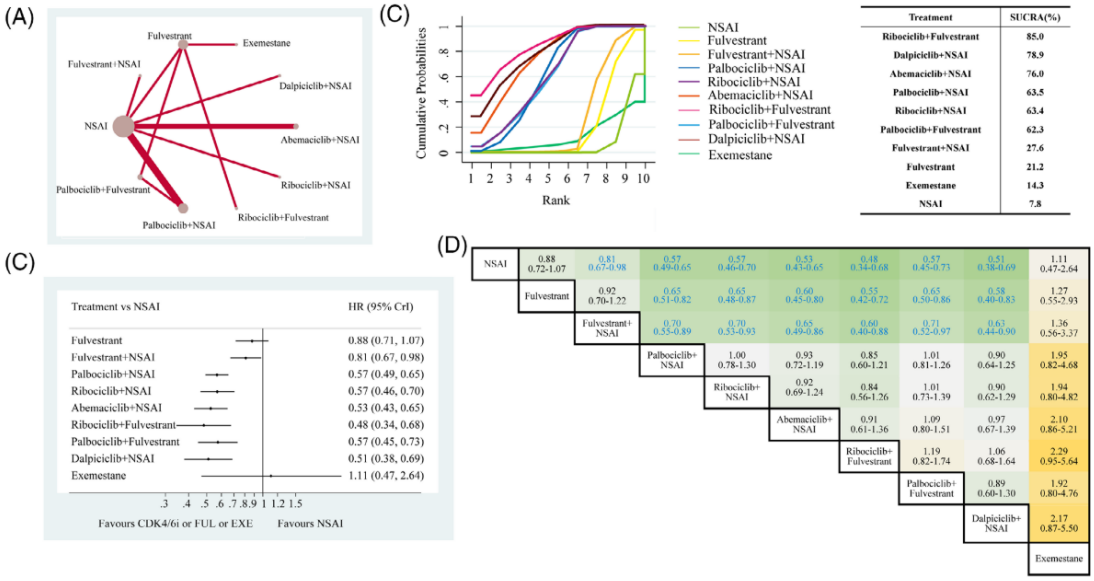


FIGURE 3 Network meta-analysis results of progression-free survival. (A) Network plot of the comparisons included in PFS network meta-analysis. (B) Cumulative probability plots and SUCRA values of all 10 treatments. (C) Forest plot of the estimated HR and 95%CrI for different regimens comparing with NSAI. (D) Estimated HR and 95%CrI between all treatments are shown in each cell. The column treatment is compared with the row treatment. HR< 1 (green squares) indicated patients in the column treatment group achieved better PFS than patients in the row treatment group, and the numberswere blue if the Bayesian p value < 0.05. HR> 1 (yellow squares) indicated patients in the column treatment group achieved worse PFS than patients in the row treatment group, and the numberswere red if the Bayesian p value < 0.05. Darker color represents larger difference. NSAI, nonsteroidal aromatase inhibitor; PFS, progression-free survival; HR, hazard ratio; CrI, credibility interval; SUCRA, surface under the cumulative ranking curve.

- Overall survival

  OS data were provided in seven studies covering seven therapies.23,24,28,31,33,35,38 The network plot of all direct comparisons is shown in Figure 4A. Ribociclib+NSAI (HR = 0.76, 95% CrI 0.63-0.92), ribociclib+fulvestrant (HR = 0.56, 95% CrI 0.35-0.90) and abemaciclib+NSAI (HR = 0.75, 95% CrI 0.58-0.97) improved OS significantly compared to NSAI (Figure 4C and D). Moreover, only ribociclib+fulvestrant displayed an increased OS compared to fulvestrant alone (HR = 0.64, 95% CrI 0.46-0.88) and palbociclib+NSAI (HR = 0.59, 95% CrI 0.36-0.97). There were no statistically significant differences between the other comparisons (Figure 4D). The ranking of competing therapies suggested that ribociclib+fulvestrant was the optimal intervention (SUCRA = 94.1%) with respect to OS (Figure 4B), which was consistent with the PFS results. Abemaciclib+NSAI (SUCRA = 69.9%) and ribociclib+NSAI (SUCRA = 68.5%) ranked second and third best, respectively (Figure 4B). Notably, palbociclib+fulvestrant (SUCRA = 32.2%) and palbociclib+NSAI (SUCRA= 29.0%) ranked behind fulvestrant alone.

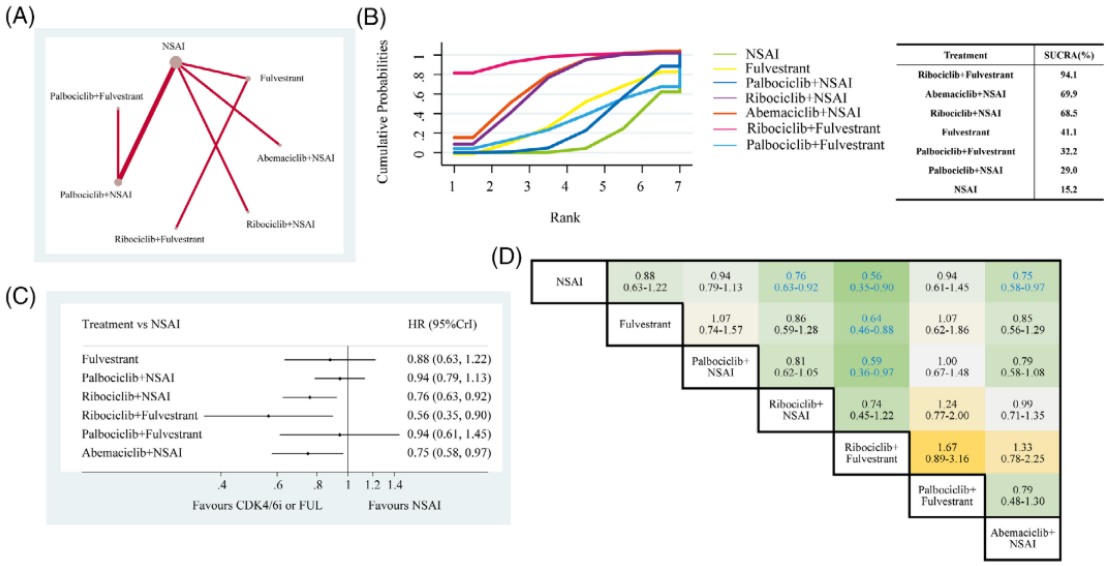


FIGURE 4 Network meta-analysis results of overall survival. (A) Network plot of the comparisons included in OS network meta-analysis. (B) Cumulative probability plots and SUCRA values of all seven treatments. (C) Forest plot of the estimated HR and 95% CrI for different regimens comparing with NSAI. (D) Estimated HR and 95% CrI between all treatments are shown in each cell. The column treatment is comparedwith the row treatment. HR< 1 (green squares) indicated patients in the column treatment group achieved better OS than patients in the row treatment group, and the numberswere blue if the Bayesian p value < 0.05. HR> 1 (yellow squares) indicated patients in the column treatment group achieved worseOS than patients in the row treatment group, and the numberswere red if the Bayesian p value < 0.05. Darker color represents larger difference. NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; HR, hazard ratio; CrI, credibility interval; SUCRA, surface under the cumulative ranking curve.

- Objective response rate

  Ten trials were selected for NMA of ORR, including seven competing treatments.22,24,25,29,32,36–40 The network graph of eligible comparisons for ORR is presented in Figure 5A. In terms of ORR, only ribociclib+NSAI (RR = 1.48, 95% CrI 1.082.05) and abemaciclib+NSAI (RR = 1.50, 95% CrI 1.11-2.04) had distinct advantages over NSAI (Figure 5C and D). Based on SUCRA values and cumulative probability plots, the top three ranked treatments were abemaciclib+NSAI (SUCRA = 82.3%), ribociclib+NSAI (SUCRA=80.0%), and palbociclib+NSAI(SUCRA=55.6%) (Figure5B).

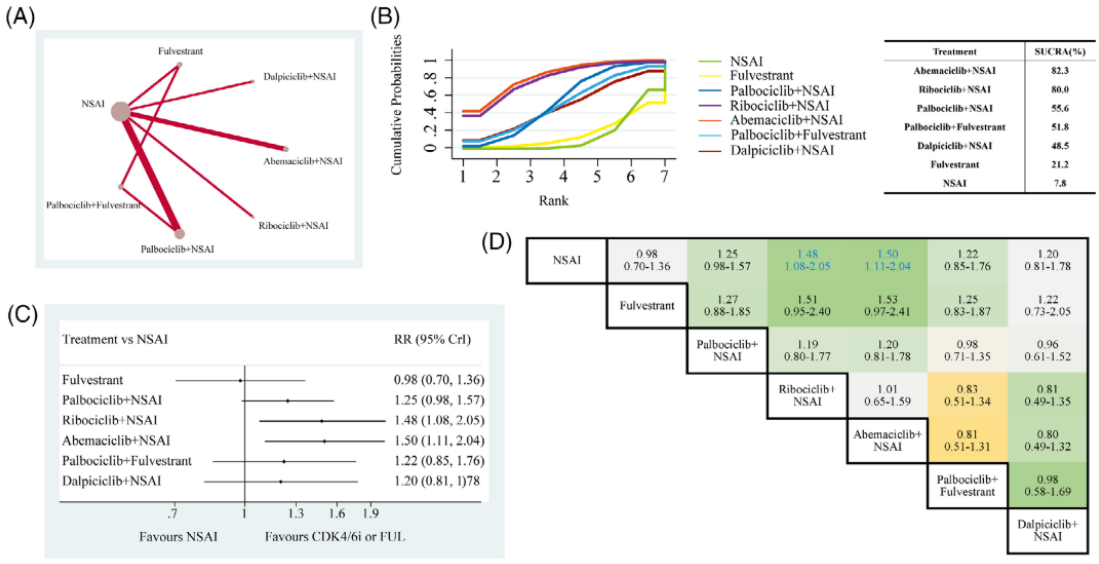


FIGURE 5 Network meta-analysis results of objective response rate. (A) Network plot of the comparisons included in ORR network meta-analysis. (B) Cumulative probability plots and SUCRA values of all seven

treatments. (C) Forest plot of the estimated RR and 95%CrI for different regimens comparing with NSAI. (D) Estimated RR and its 95% CrI between all treatments were shown in each cell. The column treatment is compared with the row treatment. HR> 1 (green squares) indicated patients in the column treatment group achieved better ORR than patients in the row treatment group, and the numberswere blue if the Bayesian p value < 0.05. HR< 1 (yellow squares) indicated patients in the column treatment group achieved worse ORR than patients in the row group, and the numberswere red if the Bayesian p value < 0.05. Darker color represents larger difference. NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; RR, relative risk; CrI, credibility interval; SUCRA, surface under the cumulative ranking curve.

- Safety

  Regarding all-cause grade 3/4 AEs, pooled results from 10 RCTs showed that single-agent NSAI (SUCRA = 98.2%) presented the lowest incidence between the seven concerned regimens, followed by fulvestrant (SUCRA = 84.2%) (Figure 6B).22,24,26,31,32,36–40 Adding CDK4/6i, including palbociclib, ribociclib, abemaciclib, and dalpiciclib, to endocrine therapy might increase the incidence of grade 3/4 AEs (Figure 6D). Out of all CDK4/6i-including regimens, ribociclib minimized grade 3/4 toxicity (Figure 6B), and dalpiciclib presented the highest grade 3/4 toxicity (Figure 6B). Based on data from CDK4/6i-related RCTs (PALOMA-2,26 MONALEESA-2,42 MONARCH-3,32 NCT02491983,38 and DAWNA240), the most common grade 3/4 AE was neutropenia in all CDK4/6i-containing treatment regimens (eTable 2). However, the most frequent all-grade AE reported in patients treated with abemaciclib-including therapies was diarrhea. As expected, of the four types of CDK4/6i, palbociclib and dalpiciclib resulted in more frequent neutropenia, and abemaciclib led to more frequent diarrhea and alanine aminotransferase increase, while clinically relevantQT interval prolongation was more likely reported with ribociclib administration.

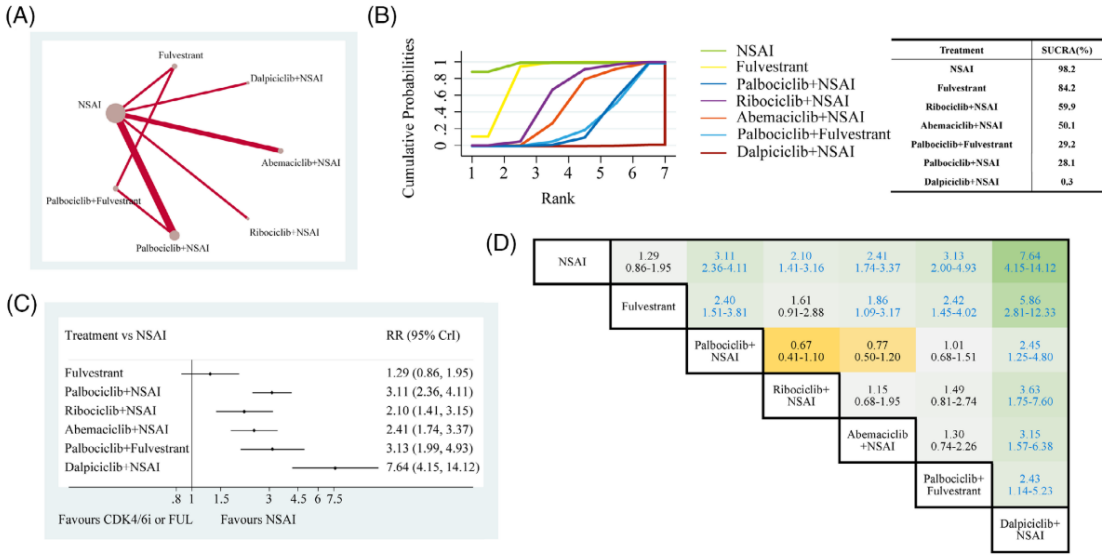


FIGURE 6 Network meta-analysis results of grade 3/4 adverse events. (A) Network plot of the comparisons included in AEs network meta-analysis. (B) Cumulative probability plots and SUCRA values of all seven treatments. (C) Forest plot of the estimated RR and 95%CrI for different regimens comparing with NSAI. (D) Estimated RR and its 95% CrI between all treatments were shown in each cell. The column treatment is compared with the row treatment. RR> 1 (green squares) indicated patients in the column treatment group had more grade 3/4 AEs than patients in the row treatment group, and the numberswere blue if the Bayesian p value < 0.05. RR< 1 (yellow squares) indicated patients in the column treatment group had less grade 3/4 AEs than patients in the row treatment group, and the numberswere red if the Bayesian p value < 0.05. Darker color represents larger difference. NSAI, nonsteroidal aromatase inhibitor; AE, adverse event; RR, relative risk; CrI, credibility interval; SUCRA, surface under the cumulative ranking curve.

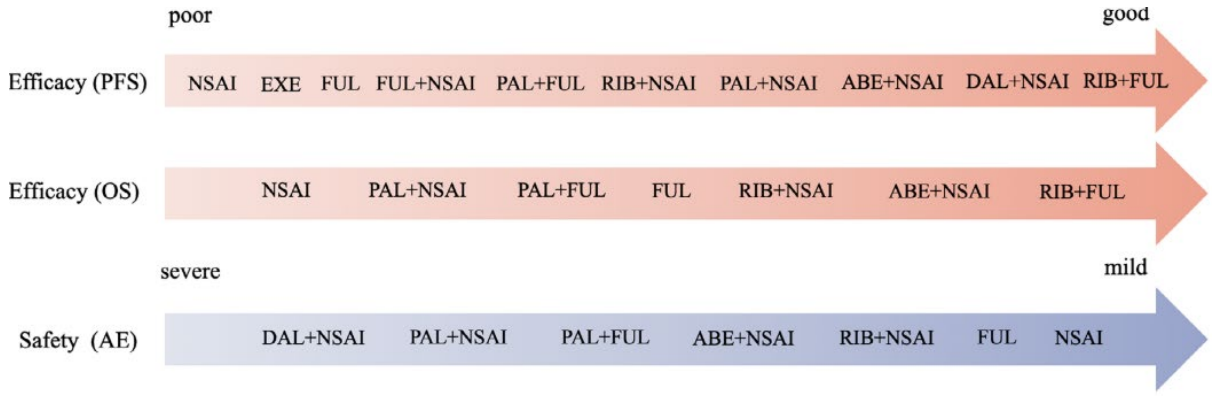


FIGURE 7 Rankings of included regimens in the analyses of progression-free survival, overall survival and adverse events. PFS, progression-free survival; OS, overall survival; AE, adverse event; NSAI, nonsteroidal aromatase inhibitor; FUL, fulvestrant; PAL, palbociclib;RIB, ribociclib; ABE, abemaciclib; DAL, dalpiciclib.

Anmerkung/Fazit der Autoren

Ribociclib+fulvestrant probably represents the best option in a firstline setting. When combined with NSAI, dalpiciclib likely showed the best efficacy

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National Institute for Health and Care Excellence (NICE), 2023 [14].

Early and locally advanced breast cancer: diagnosis and management.

NICE guideline NG101 Evidence reviews underpinning recommendations 1.10.13 to 1.10.16 and recommendations for research in the NICE guideline

Fragestellung

What is the effectiveness and cost-effectiveness of different hypofractionation radiotherapy regimens in patients with early-stage or locally advanced invasive breast cancer?

Methodik

Population:

- Adults (18 and over) with early and locally advanced breast cancer who have undergone any of the following alone or in combination:
  - breast-conserving surgery
  - mastectomy (which can include reconstruction)
  - axillary clearance
  - sentinel lymph node biopsy
  - axillary node sampling

Intervention:

- Radiotherapy hypofractionation with or without regional node radiotherapy:
  - Using greater than 2Gy per fraction for
  - whole breast radiotherapy
  - chest wall radiotherapy
  - partial breast radiotherapy

Komparator:

- Any other hypofractionation radiotherapy schedule

Endpunkte:

- Longest follow up available: Quality of life (using validated measures such as EORTC and BREAST-Q)
- Breast cancer mortality
- All-cause mortality
- Local Recurrence
- Distant recurrence (also referred as distant relapse)
- Normal tissue effects
- Treatment-related adverse events
- Cosmesis (including breast appearance, breast oedema, appearance of scar, breast size, shape, colour, nipple position, shape of areola in comparison with untreated breast)

Recherche/Suchzeitraum:

- The searches for the effectiveness evidence were run on 05 December 2022.
- The following databases were searched: Medline ALL (Ovid); Embase (Ovid); Emcare (Ovid); Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR) (Wiley).

Qualitätsbewertung der Studien:

- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- N=6

Charakteristika der Population/Studien:

Due to the variation in hypofractionation regimens reported, the studies were further categorised and presented within the following comparisons:

- Dose comparisons: studies using a different dose with the same number of fractions and over the same time period.
- FAST (Brunt et al. 2020a): 28.5 Gy in 5 fractions (5 weeks) vs 30 Gy in 5 fractions (5 weeks)
- Dose and fraction comparisons: studies using a different dose and different number of fractions over the same time period.
- START (Haviland et al. 2013): 39 Gy over 13 fractions (5 weeks) vs 41.6 Gy over 13 fractions (5 weeks)
- Dose, fraction and time period comparisons: studies using a different dose, number of fractions over a different time period.
- Aboziada et al. 2016: 42.4 Gy over 16 fractions (3 weeks) vs 25 Gy over 5 fractions (1 week)
- FAST-Forward (Brunt et al. 2020b): 40 Gy over 15 fractions (3 weeks) vs 26 Gy over 5 fractions (1 week) vs 27 Gy over 5 fractions (1 week)
- Ivanov et al. 2022: 40 Gy over 15 fractions (3 weeks) vs 26 Gy over 5 fractions (1 week)
- Shahid et al. 2009: 40 Gy over 15 fractions (3 weeks) vs 35 Gy over 10 fractions (2 weeks) vs 27 Gy over 5 fractions (1 week)

Qualität der Studien:

- The majority of the evidence ranged from high to very low quality with the main reasons for downgrading being due to imprecision and risk of bias from some of the trials. In some of the evidence, imprecision was rated serious or very serious with the 95% confidence intervals crossing one or two ends of the default minimally important difference (MIDs) thresholds. Some of the studies were downgraded for risk of bias due to lack of information on randomisation, allocation concealment and blinding. All studies were considered fully applicable to the review. There were a wide range of different hypofractionation regimens reported by different studies. This made it difficult for meta-analysis to be carried out, meaning that most of the evidence for the outcomes were based on the results from single studies.
- The studies used a range of hypofractionation regimens, some of which the committee considered less relevant to current practice. Some of the external beam hypofractionation regimens explored in the studies were higher than those that are used in current practice or had longer treatment periods than are used currently. The committee focused on the studies that were most in line with current practice (Brunt et al. 2020b, Ivanov et al. 2022, Shahid et al. 2009). These studies were conducted in Pakistan (Shahid et al. 2009), Serbia (Ivanov et al. 2022) and the United Kingdom (Brunt et al. 2020). Participants in each of these studies received whole breast hypofractionated radiotherapy and two of these studies (Brunt et al. 2020a and Shahid et al. 2009) randomised participants to receive 26 Gy in 5 fractions over 1 week compared with 40 Gy in 15 fractions over 3 weeks. The committee considered these two studies to be the most important for decision making, as these are the hypofractionation regimens that are used in current practice in the UK.
- The longest follow up in any of the studies that were most relevant to current practice was 5 years. While this is useful for decision making, the committee noted more longterm information about these outcomes is needed for informing clinical decisions.
- Longer term data will provide more information about the distant recurrence of tumours, disease free survival for people with breast cancer and the long-term adverse events associated with each treatment regimen. However, they were aware that longer-term data from the FAST-Forward trial (Brunt et al. 2020) would soon be available, and this would provide more information for clinicians when considering the most effective treatment options.
- Although the evidence considered a range of people who have breast cancer, there were some groups who were not included in the trials. Those excluded from the trials included people receiving regional lymph node irradiation. The committee were aware that a sub-study of the FAST-Forward trial (Brunt et al. 2020) included participants who received regional lymph node irradiation and has not yet reported results. The committee also noted that there is variation in radiotherapy practice for people who are offered autologous compared to implant-based breast reconstruction. Although the FAST-Forward trial included some people with breast reconstruction, they were a limited population and no further subgroup analyses were made. This made it difficult for the committee to be as confident in the effects of the different external beam hypofractionation regimens for these groups of people, as currently there is limited evidence. As such, the committee made 2 research recommendations (see Appendix K for more details) to further explore the effectiveness of the 26 Gy in 5 fractions regimen, one for people who have had breast reconstruction and another for people who are receiving nodal irradiation. The research recommendation for people who have had breast reconstruction included subgroups for people with autologous and implant-based reconstruction. Very few people who had either type of reconstruction were

included in the studies, but the committee were aware that long-term outcomes tend to be worse for people who have implant-based reconstruction.

Studienergebnisse:

Benefits and harms

The entire body of evidence could not differentiate between the effectiveness of all the included hypofractionation regimens compared to each other for the outcomes of mortality, local recurrence, or distant recurrence (defined as the location of a subsequent cancer in relation to the first episode that led to treatment). This indicates that regimens that require fewer fractions over fewer weeks may have a similar level of effectiveness, or are non-inferior, to those that require a higher number of fractions over a greater number of weeks. While some of the point estimates of effect favoured one treatment over another, most of the results had wide confidence intervals which crossed the line of no effect. Based on this, the committee could not differentiate between the effects of different hypofractionation regimens. For further information please see the summary of the effectiveness evidence tables.

The committee discussed how shorter regimens with fewer fractions may have benefits for people who are having radiotherapy, especially those in the groups identified in the equalities and health inequalities assessment (EHIA). Many of the issues that people face when they are having radiotherapy are associated with the time and costs relating to travel to multiple appointments. The time needed to attend multiple appointments can be a particular issue for people who need to arrange appointments around work or carer responsibilities, or for those who live far from their nearest treatment centre. As such, the committee highlighted that a shorter treatment duration time may make treatment more accessible for many people. However, the committee acknowledged that there are some people for whom potential adverse effects may make the shorter treatment duration less acceptable. For example, they discussed how, in their experience, some groups of people (for example, people with high BMI or fibromyalgia), may experience a greater number of adverse events such as skin reactions, breast oedema or pain. In these instances, treatment with a longer regimen may be more appropriate.

In addition to the benefits for people who are having radiotherapy, the committee highlighted how using fewer fractions has benefits for the centres that are providing radiotherapy. A hypofractionation regimen with fewer fractions over a shorter period of time means that centres can treat people more quickly compared to when radiotherapy takes place over a longer period of time, thereby reducing waiting lists.

The evidence could not differentiate between the number of adverse events when comparing radiotherapy with 26 Gy in 5 fractions and radiotherapy with 40 Gy in 15 fractions (please see Table 8). The committee noted that there were fewer clinician assessed adverse events, and higher quality of life measurements related to swollen breasts and harder or firmer breasts, for the 15 fraction regimen. However, the difference between the two regimens was not clinically meaningful for these outcomes and the committee did not think that this indicated any potential serious harms. In the committee's experience, these effects should also reduce over time as they are due to acute toxicity effects. The committee also discussed how, in their experience, many people who are given radiotherapy will favour higher doses per fraction in a shorter duration, than lower doses over a longer duration because they consider that the benefits of reduced number of appointments outweigh the risks of increased adverse events. For this reason, the committee made a recommendation in favour of offering a regimen over one week with fewer fractions (26 Gy in 5 fractions) for most people.

The committee discussed how the clinical evidence for the 26 Gy in 5 fractions was for people who were offered whole breast radiotherapy. They noted that there was no

evidence on the use of the 26 Gy in 5 fractions for people who are offered partial breast radiotherapy. However, people who are offered partial breast radiotherapy are considered at lower risk of disease recurrence than those offered whole breast radiotherapy. The committee therefore decided they could extrapolate the evidence from people in the higher risk group to those who have partial breast radiotherapy without any major concerns about differences in regimen effectiveness or safety. The committee also highlighted that current practice is already changing towards offering people who have partial breast radiotherapy the 26 Gy in 5 fractions regimen and that the decision between offering partial or whole breast radiotherapy can change based on clinical judgement and assessment during the radiotherapy planning process. As such, based on their clinical experience and judgement, the committee included people who have had partial breast radiotherapy in the recommendations, as they agreed that excluding it may disadvantage a large group of people and contradict current practice.

As discussed above in the quality of the evidence section, there was limited evidence on the use of the 26 Gy over 5 fractions regimen for people with conditions that increase sensitivity to radiotherapy or people who have received implant-based reconstruction. As such, the committee made a recommendation to consider the 40 Gy in 15 fractions regimen in these groups of people as there was no evidence which evaluated the benefits and harms of the lower fraction regimen for these people. The use of the 40 in 15 regimen for these groups is in line with current practice. They also recommended that the 15 fraction regimen should be considered for other people who have factors that may make 15 fractions more acceptable. The committee discussed examples of people who may prefer the 15 fraction regimen, such as those with a high BMI, increased breast separation (a measurement of breast size changes un breast cancer) or fibromyalgia who may experience greater acute adverse events, including breast oedema and pain with the 5 fraction regimen. This may also include people whose radiotherapy plans are outside the dosimetry used within the FAST-Forward trial. The committee thought that decisions on treatments for these groups should be based on discussions of the potential benefits and harms between a patient and a clinician, and included links to the NICE guidelines on patient experience and on shared decision making. This should ensure that information is provided in a way that is most useful for the patient, and that their individual circumstances are considered when choosing the most appropriate regimen.

As noted above under the quality of the evidence, people who were receiving regional lymph node radiotherapy were not represented in the evidence. The committee therefore thought it was important that this group continued to receive the 40 Gy in 15 fraction regimen until further evidence is available on the effectiveness of the 26 in 5 regimen. They also made a recommendation to highlight the need for research on this issue (see Appendix K for more details).

In addition to the number of fractions, the committee also discussed the dose per fraction. The committee noted that RCTs with long term follow up had already established the dose per fraction over a specified time period (for example, the FAST-Forward trial, Brunt et al. 2020 comparing doses over 5 weeks). They also noted that the FAST-Forward study did include a comparison between 26 Gy and 27 Gy per fraction, both over 5 fractions. The committee noted that the incidence of adverse events was lower in the 26 Gy group, with no clear difference in effectiveness. For example, there was a lower incidence of normal tissue effects, adverse events, swollen breasts and skin problems in the breast for people randomised to receive 26 Gy in 5 fractions compared to 27 Gy in 5 fractions. They agreed that this supported the use of this regimen in current practice.

Table 5 Hypofractionation regimen: 28.5 Gy in 5 fractions over 5 weeks (whole breast) compared to 30 Gy in 5 fractions over 5 weeks (whole-breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 30Gy/5 fractions	Risk difference with 28.5Gy/5 fractions (95% CI)	
All-cause mortality [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	RR 1.01 (0.64 to 1.59)	108 per 1000	1 more per 1000 (from 39 fewer to 64 more)	Could not differentiate (low quality evidence)
Breast cancer-related mortality [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	RR 1.26 (0.51 to 3.16)	33 per 1000	9 more per 1000 (from 16 fewer to 71 more)	Could not differentiate (low quality evidence)
Local relapse [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	RR 1.01 (0.21 to 4.96)	10 per 1000	0 more per 1000 (from 8 fewer to 39 more)	Could not differentiate (low quality evidence)
Loco-regional relapse [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	RR 7.07 (0.37 to 136.27)	10 per 1000	60 more per 1000 (from 6 fewer to 1000 more)	Could not differentiate (low quality evidence)
Distant relapse [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	RR 1.01 (0.50 to 2.03)	49 per 1000	0 more per 1000 (from 25 fewer to 51 more)	Could not differentiate (low quality evidence)
Adverse events [MID +/- 0.8 to 1.25]	613 (1 study[3]) 10 years	RR 0.50 (0.13 to 2.00)	10 per 1000	5 fewer per 1000 (from 9 fewer to 10 more)	Could not differentiate (low quality evidence)
Normal tissue effects in breasts (G1-G4) - None [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	RR 1.09 (0.87 to 1.37)	508 per 1000	46 more per 1000 (from 66 fewer to 188 more)	Could not differentiate (moderate quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 30Gy/5 fractions	Risk difference with 28.5Gy/5 fractions (95% CI)	
Normal tissue effects in breast (G1-G4) – Mild [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	RR 0.98 (0.67 to 1.41)	308 per 1000	6 fewer per 1000 (from 102 fewer to 126 more)	Could not differentiate (low quality evidence)
Normal tissue effects in breast (G1-G4) – Moderate [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	RR 0.94 (0.51 to 1.75)	138 per 1000	8 fewer per 1000 (from 68 fewer to 104 more)	Could not differentiate (low quality evidence)
Normal tissue effects in breast (G1-G4) – Marked [MID +/- 0.8 to 1.25]	260 (1 study[3]) 10 years	RR 0.33 (0.07 to 1.62)	46 per 1000	31 fewer per 1000 (from 43 fewer to 29 more)	Could not differentiate (low quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[2] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[3] FAST trial (Brunt et al. 2020a)

Dose and fraction comparisons (studies using different doses, different number of fractions over the same time period)

Table 6 Hypofractionation regimen: 39 Gy in 13 fractions over 5 weeks (whole breast) compared to 41.6 Gy in 13 fractions over 5 weeks (whole-breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect
			Risk with 41.6Gy/13 fractions	Risk difference with 39Gy/13 fractions (95% CI)	
All-cause mortality [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 1.03 (0.83 to 1.29)	171 per 1000	5 more per 1000 (from 29 fewer to 49 more)	Could not differentiate (moderate quality evidence)
Local relapse [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 1.29 (0.85 to 1.96)	49 per 1000	14 more per 1000 (from 7 fewer to 47 more)	Could not differentiate (moderate quality evidence)
Loco-regional relapse [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 1.26 (0.85 to 1.87)	56 per 1000	15 more per 1000 (from 8 fewer to 49 more)	Could not differentiate (moderate quality evidence)
Distant relapse [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 1.12 (0.88 to 1.42)	147 per 1000	18 more per 1000 (from 18 fewer to 62 more)	Could not differentiate (moderate quality evidence)
Normal tissue effects: breast shrinkage [MID +/- 0.8 to 1.25]	1244 (1 study[1]) 10 years	RR 0.85 (0.7 to 1.03)	268 per 1000	40 fewer per 1000 (from 80 fewer to 8 more)	Could not differentiate (moderate quality evidence)
Normal tissue effects: breast induration (tumour bed) [MID +/- 0.8 to 1.25]	1244 (1 study[1]) 10 years	RR 0.75 (0.6 to 0.93)	239 per 1000	60 fewer per 1000 (from 17 fewer to 96 fewer)	Favours 39 Gy in 13 fractions (moderate quality evidence)
Normal tissue effects: telangiectasia [MID +/- 0.8 to 1.25]	1456 (1 study[1]) 10 years	RR 0.42 (0.25 to 0.73)	59 per 1000	34 fewer per 1000 (from 16 fewer to 44 fewer)	Favours 39 Gy in 13 fractions (low quality evidence)
Normal tissue effects: breast oedema [MID +/- 0.8 to 1.25]	1244 (1 study[1]) 10 years	RR 0.65 (0.45 to 0.94)	107 per 1000	37 fewer per 1000 (from 6 fewer to 59 fewer)	Favours 39 Gy in 13 fractions (moderate quality evidence)
Normal tissue effects: shoulder stiffness [MID +/- 0.8 to 1.25]	187 (1 study[1]) 10 years	RR 0.83 (0.34 to 2)	105 per 1000	18 fewer per 1000 (from 69 fewer to 105 more)	Could not differentiate (low quality evidence)
Normal tissue effects: arm oedema [MID +/- 0.8 to 1.25]	187 (1 study[1]) 10 years	RR 0.39 (0.16 to 0.95)	168 per 1000	103 fewer per 1000 (from 8 fewer to 141 fewer)	Favours 39 Gy in 13 fractions (moderate quality evidence)
Normal tissue effects: other [MID +/- 0.8 to 1.25]	1457 (1 study[1]) 10 years	RR 1.21 (0.68 to 2.18)	27 per 1000	6 more per 1000 (from 9 fewer to 32 more)	Could not differentiate (low quality evidence)
Adverse events: symptomatic rib fracture [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 3.05 (0.12 to 74.82)	0 per 1000	-	Could not differentiate (low quality evidence)
Adverse events: symptomatic lung fibrosis [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 0.51 (0.05 to 5.6)	3 per 1000	1 fewer per 1000 (from 3 fewer to 12 more)	Could not differentiate (low quality evidence)
Adverse events: ischaemic heart disease [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 1.22 (0.37 to 3.98)	7 per 1000	1 more per 1000 (from 4 fewer to 20 more)	Could not differentiate (low quality evidence)
Adverse events: brachial plexopathy [MID +/- 0.8 to 1.25]	1487 (1 study[1]) 10 years	RR 0.34 (0.01 to 8.31)	1 per 1000	1 fewer per 1000 (from 1 fewer to 10 more)	Could not differentiate (low quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] START (Haviland et al. 2013)
[2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.

Dose, fraction and time period comparisons (studies using different doses, different number of fractions over different time periods)

Table 7 Hypofractionation regimen: 39 Gy in 13 fractions over 2.6 weeks (whole breast) compared to 42.4 Gy in 16 fractions over 3.3 weeks (whole breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 39Gy/13 fractions	Risk difference with 42.4Gy/16 fractions (95% CI)	
Radiation dermatitis – Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 0.59 (0.4 to 0.87)	680 per 1000	279 fewer per 1000 (from 88 fewer to 408 fewer)	Favours 42.4 Gy in 16 fractions (very low quality evidence)
Radiation dermatitis - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 0.43 (0.12 to 1.56)	140 per 1000	80 fewer per 1000 (from 123 fewer to 78 more)	Could not differentiate (very low quality evidence)
Acute pneumonitis - Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 0.17 (0.02 to 1.33)	120 per 1000	100 fewer per 1000 (from 118 fewer to 40 more)	Could not differentiate (very low quality evidence)
Acute pneumonitis - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 4 (0.46 to 34.54)	20 per 1000	60 more per 1000 (from 11 fewer to 671 more)	Could not differentiate (very low quality evidence)
Subcutaneous fibrosis - Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 1.75 (0.55 to 5.61)	80 per 1000	60 more per 1000 (from 36 fewer to 369 more)	Could not differentiate (very low quality evidence)
Subcutaneous fibrosis - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 0.2 (0.05 to 0.87)	200 per 1000	160 fewer per 1000 (from 26 fewer to 190 fewer)	Favours 42.4 Gy in 16 fractions (very low quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 39Gy/13 fractions	Risk difference with 42.4Gy/16 fractions (95% CI)	
Incidence of lymphoedema - Grade 1 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 1 (0.35 to 2.89)	120 per 1000	0 fewer per 1000 (from 78 fewer to 227 more)	Could not differentiate (very low quality evidence)
Incidence of lymphoedema - Grade 2 [MID +/- 0.8 to 1.25]	100 (1 study[1]) 2 years	RR 0.38 (0.15 to 1)	260 per 1000	161 fewer per 1000 (from 221 fewer to 0 more)	Could not differentiate (very low quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Aboziada et al. 2016
[2] Study at high risk of bias. Quality of the outcome downgraded twice.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[4] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.

Table 8 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 26 Gy in 5 fractions over 1 week (whole breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	
All-cause mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.03 (0.78 to 1.36)	66 per 1000	2 more per 1000 (from 14 fewer to 24 more)	Could not differentiate (low quality evidence)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 0.89 (0.61 to 1.31)	39 per 1000	4 fewer per 1000 (from 15 fewer to 12 more)	Could not differentiate (low quality evidence)
Local relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.48 (0.86 to 2.57)	15 per 1000	7 more per 1000 (from 2 fewer to 24 more)	Could not differentiate (moderate quality evidence)
Loco-regional relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.49 (0.94 to 2.37)	21 per 1000	10 more per 1000 (from 1 fewer to 29 more)	Could not differentiate (moderate quality evidence)
Distant relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 0.78 (0.56 to 1.09)	56 per 1000	12 fewer per 1000 (from 24 fewer to 5 more)	Could not differentiate (moderate quality evidence)
Acute skin toxicity - 1 point [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	RR 1.39 (0.86 to 2.22)	455 per 1000	177 more per 1000 (from 64 fewer to 555 more)	Could not differentiate (moderate quality evidence)
Acute skin toxicity - 2 points [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	RR 6.11 (0.76 to 49.21)	30 per 1000	155 more per 1000 (from 7 fewer to 1000 more)	Could not differentiate (very low quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	
Late skin toxicity [MID +/- 0.8 to 1.25] RESS-RTOG/EORTC	60 (1 study[3]) 18 months	RR 0.55 (0.22 to 1.34)	333 per 1000	150 fewer per 1000 (from 260 fewer to 113 more)	Could not differentiate (very low quality evidence)
Subcutaneous tissue toxicity - 1 point [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	RR 0.94 (0.39 to 2.25)	259 per 1000	16 fewer per 1000 (from 158 fewer to 324 more)	Could not differentiate (very low quality evidence)
Subcutaneous tissue toxicity - 2 points [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	RR 0.07 (0 to 1.3)	185 per 1000	172 fewer per 1000 (from 185 fewer to 56 more)	Could not differentiate (very low quality evidence)
Cosmetic results - 1 point [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	RR 1.29 (0.83 to 1.99)	519 per 1000	150 more per 1000 (from 88 fewer to 513 more)	Could not differentiate (low quality evidence)
Cosmetic results - 2 points [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	RR 0.69 (0.37 to 1.29)	481 per 1000	149 fewer per 1000 (from 303 fewer to 140 more)	Could not differentiate (very low quality evidence)
Adverse events (clinician assessed) [MID +/- 0.8 to 1.25]	12448 (1 study[1]) 5 years	RR 0.87 (0.79 to 0.96)	122 per 1000	16 fewer per 1000 (from 5 fewer to 26 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5136 (1 study[1]) 5 years	RR 0.9 (0.8 to 1.02)	175 per 1000	18 fewer per 1000 (from 35 fewer to 4 more)	No meaningful difference (high quality evidence)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5128 (1 study[1]) 5 years	RR 0.83 (0.64 to 1.08)	48 per 1000	8 fewer per 1000 (from 17 fewer to 4 more)	Could not differentiate (moderate quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25]	5129 (1 study[1]) 5 years	RR 0.93 (0.76 to 1.14)	72 per 1000	5 fewer per 1000 (from 17 fewer to 10 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25]	5135 (1 study[1]) 5 years	RR 0.83 (0.73 to 0.95)	161 per 1000	27 fewer per 1000 (from 8 fewer to 43 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25]	5137 (1 study[1]) 5 years	RR 0.65 (0.52 to 0.81)	74 per 1000	26 fewer per 1000 (from 14 fewer to 35 fewer)	Favours 40 Gy in 15 fractions (moderate quality evidence)
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25]	5115 (1 study[1]) 5 years	RR 0.91 (0.78 to 1.06)	123 per 1000	11 fewer per 1000 (from 27 fewer to 7 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25]	5131 (1 study[1]) 5 years	RR 0.97 (0.79 to 1.2)	63 per 1000	2 fewer per 1000 (from 13 fewer to 13 more)	Could not differentiate (moderate quality evidence)
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25]	5043 (1 study[1]) 5 years	RR 1.04 (0.96 to 1.13)	300 per 1000	12 more per 1000 (from 12 fewer to 39 more)	No meaningful difference (high quality evidence)
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25]	4987 (1 study[1]) 5 years	RR 1.18 (1.06 to 1.31)	203 per 1000	36 more per 1000 (from 12 more to 63 more)	Favours 26 Gy in 5 fractions but is less than the defined MID (moderate quality evidence)
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25]	4980 (1 study[1]) 5 years	RR 0.83 (0.74 to 0.92)	247 per 1000	42 fewer per 1000 (from 20 fewer to 64 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25]	5081 (1 study[1]) 5 years	RR 1.05 (0.91 to 1.21)	131 per 1000	7 more per 1000 (from 12 fewer to 28 more)	No meaningful difference (high quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **CTCAE:** Common terminology criteria for adverse events scale; **EORTC-QLQ BR23:** European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Breast Cancer; **RESS:** Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer Scoring Schema; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] FAST-Forward (Brunt et al. 2020b)
[2] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[3] Ivanov et al. 2022
[4] Study at moderate risk of bias. Quality of the outcome downgraded once.
[5] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.

Table 9 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole-breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects Risk with 27Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	Interpretation of effect (quality)
All-cause mortality [MID +/- 0.8 to 1.25]	2928 (2 studies[1,2])	RR 0.92 (0.72 to 1.18)	83 per 1000	7 fewer per 1000 (from 23 fewer to 15 more)	Could not differentiate (moderate quality evidence)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2728 (1 study[1]) 5 years	RR 1.05 (0.82 to 1.34)	83 per 1000	4 more per 1000 (from 15 fewer to 28 more)	Could not differentiate (moderate quality evidence)
Locoregional relapse [MID +/- 0.8 to 1.25]	2928 (2 studies[1,2])	RR 1.16 (0.79 to 1.7)	31 per 1000	5 more per 1000 (from 7 fewer to 22 more)	Could not differentiate (low quality evidence)
Metastatic disease [MID +/- 0.8 to 1.25]	2928 (2 studies[1,2])	RR 0.92 (0.7 to 1.21)	65 per 1000	5 fewer per 1000 (from 19 fewer to 14 more)	Could not differentiate (moderate quality evidence)
Overall survival [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	RR 0.94 (0.84 to 1.06)	870 per 1000	52 fewer per 1000 (from 139 fewer to 52 more)	No meaningful difference (moderate quality evidence)
Disease free survival [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	RR 1 (0.84 to 1.19)	710 per 1000	0 fewer per 1000 (from 114 fewer to 135 more)	No meaningful difference (moderate quality evidence)
Adverse events - Any adverse event [MID +/- 0.8 to 1.25]	12424 (1 study[1]) 5 years	RR 0.67 (0.61 to 0.73)	159 per 1000	53 fewer per 1000 (from 43 fewer to 62 fewer)	Favours 40 Gy in 15 fractions (low quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects Risk with 27Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	Interpretation of effect (quality)
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	RR 1.25 (0.35 to 4.52)	40 per 1000	10 more per 1000 (from 26 fewer to 141 more)	Could not differentiate (very low quality evidence)
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	RR 0.83 (0.45 to 1.56)	180 per 1000	31 fewer per 1000 (from 99 fewer to 101 more)	Could not differentiate (very low quality evidence)
Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	RR 1.17 (0.82 to 1.67)	350 per 1000	59 more per 1000 (from 63 fewer to 234 more)	Could not differentiate (low quality evidence)
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25]	200 (1 study[2]) 6 months	RR 1 (0.98 to 1.02)	1000 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)	No meaningful difference (moderate quality evidence)
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5138 (1 study[1]) 5 years	RR 0.93 (0.82 to 1.05)	170 per 1000	12 fewer per 1000 (from 31 fewer to 8 more)	No meaningful difference (high quality evidence)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5136 (1 study[1]) 5 years	RR 1.01 (0.77 to 1.32)	40 per 1000	0 more per 1000 (from 9 fewer to 13 more)	Could not differentiate (low quality evidence)
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25]	5132 (1 study[1]) 5 years	RR 0.84 (0.69 to 1.02)	80 per 1000	13 fewer per 1000 (from 25 fewer to 2 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25]	5139 (1 study[1]) 5 years	RR 0.81 (0.71 to 0.92)	165 per 1000	31 fewer per 1000 (from 13 fewer to 48 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects Risk with 27Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	Interpretation of effect (quality)
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25]	5135 (1 study[1]) 5 years	RR 0.53 (0.43 to 0.65)	91 per 1000	43 fewer per 1000 (from 32 fewer to 52 fewer)	Favours 40 Gy in 15 fractions (low quality evidence)
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25]	5124 (1 study[1]) 5 years	RR 0.87 (0.75 to 1.01)	129 per 1000	17 fewer per 1000 (from 32 fewer to 1 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25]	5135 (1 study[1]) 5 years	RR 0.76 (0.62 to 0.93)	81 per 1000	19 fewer per 1000 (from 6 fewer to 31 fewer)	Favours 40 Gy in 15 fractions (moderate quality evidence)
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25]	5030 (1 study[1]) 5 years	RR 0.86 (0.8 to 0.93)	364 per 1000	51 fewer per 1000 (from 26 fewer to 73 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (high quality evidence)
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25]	4965 (1 study[1]) 5 years	RR 0.99 (0.9 to 1.1)	240 per 1000	2 fewer per 1000 (from 24 fewer to 24 more)	No meaningful difference (high quality evidence)
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25]	4958 (1 study[1]) 5 years	RR 0.74 (0.67 to 0.82)	275 per 1000	71 fewer per 1000 (from 49 fewer to 91 fewer)	Favours 40 Gy in 15 fractions (moderate quality evidence)
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25]	5076 (1 study[1]) 5 years	RR 0.89 (0.78 to 1.02)	152 per 1000	17 fewer per 1000 (from 34 fewer to 3 more)	Could not differentiate (moderate quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **EORTC-QLQ BR23:** European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Breast Cancer; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] FAST-Forward (Brunt et al. 2020b)
[2] Shahid et al. 2009
[3] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[4] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[6] Study at moderate risk of bias. Quality of the outcome downgraded once.

Table 10 Hypofractionation regimen: 26 Gy in 5 fractions over 1 week (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects Risk with 27Gy/5 fractions	Risk difference with 26Gy/5 fractions (95% CI)	Interpretation of effect (quality)
All-cause mortality [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	RR 0.86 (0.65 to 1.12)	77 per 1000	11 fewer per 1000 (from 27 fewer to 9 more)	Could not differentiate (moderate quality evidence)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	RR 1 (0.78 to 1.28)	83 per 1000	0 fewer per 1000 (from 18 fewer to 23 more)	Could not differentiate (low quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 27Gy/5 fractions	Risk difference with 26Gy/5 fractions (95% CI)	
Local relapse [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	RR 0.78 (0.44 to 1.37)	77 per 1000	17 fewer per 1000 (from 43 fewer to 28 more)	Could not differentiate (low quality evidence)
Loco-regional relapse [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	RR 0.83 (0.51 to 1.35)	26 per 1000	4 fewer per 1000 (from 13 fewer to 9 more)	Could not differentiate (low quality evidence)
Metastatic disease [MID +/- 0.8 to 1.25]	2735 (1 study[1]) 5 years	RR 1.10 (0.80 to 1.51)	50 per 1000	5 more per 1000 (from 10 fewer to 26 more)	Could not differentiate (moderate quality evidence)
Normal tissue effects - Breast appearance changed [MID +/- 0.8 to 1.25]	5113 (1 study[1]) 5 years	RR 0.82 (0.76 to 0.89)	364 per 1000	66 fewer per 1000 (from 40 fewer to 87 fewer)	Favours 26 Gy in 5 fractions but is less than the defined MID (moderate quality evidence)
Normal tissue effects - Breast smaller [MID +/- 0.8 to 1.25]	5062 (1 study[1]) 5 years	RR 0.84 (0.76 to 0.93)	240 per 1000	38 fewer per 1000 (from 17 fewer to 58 fewer)	Favours 26 Gy in 5 fractions but is less than the defined MID (moderate quality evidence)
Normal tissue effects - Breast harder or firmer [MID +/- 0.8 to 1.25]	5046 (1 study[1]) 5 years	RR 0.9 (0.82 to 0.99)	275 per 1000	27 fewer per 1000 (from 3 fewer to 49 fewer)	Favours 26 Gy in 5 fractions but is less than the defined MID (high quality evidence)
Normal tissue effects - Skin appearance changed [MID +/- 0.8 to 1.25]	5147 (1 study[1]) 5 years	RR 0.86 (0.75 to 0.98)	152 per 1000	21 fewer per 1000 (from 3 fewer to 38 fewer)	Favours 26 Gy in 5 fractions but is less than the defined MID (moderate quality evidence)
Adverse events - Any adverse event [MID +/- 0.8 to 1.25]	12630 (1 study[1]) 5 years	RR 0.77 (0.7 to 0.84)	159 per 1000	37 fewer per 1000 (from 25 fewer to 48 fewer)	Favours 26 Gy in 5 fractions (moderate quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 27Gy/5 fractions	Risk difference with 26Gy/5 fractions (95% CI)	
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5200 (1 study[1]) 5 years	RR 1.03 (0.92 to 1.16)	170 per 1000	5 more per 1000 (from 14 fewer to 27 more)	Could not differentiate (high quality evidence)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5192 (1 study[1]) 5 years	RR 1.21 (0.94 to 1.56)	40 per 1000	8 more per 1000 (from 2 fewer to 22 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Difficulty raising arm [MID +/- 0.8 to 1.25]	5195 (1 study[1]) 5 years	RR 0.9 (0.75 to 1.09)	80 per 1000	8 fewer per 1000 (from 20 fewer to 7 more)	Could not differentiate (moderate quality evidence)
EORTC QLQ-BR23 - Breast pain [MID +/- 0.8 to 1.25]	5198 (1 study[1]) 5 years	RR 0.98 (0.86 to 1.1)	165 per 1000	3 fewer per 1000 (from 23 fewer to 16 more)	Could not differentiate (high quality evidence)
EORTC QLQ-BR23 - Breast swollen [MID +/- 0.8 to 1.25]	5196 (1 study[1]) 5 years	RR 0.81 (0.68 to 0.98)	91 per 1000	17 fewer per 1000 (from 2 fewer to 29 fewer)	Favours 26 Gy in 5 fractions but is less than the defined MID (moderate quality evidence)
EORTC QLQ-BR23 - Breast oversensitive [MID +/- 0.8 to 1.25]	5183 (1 study) 5 years	RR 0.96 (0.83 to 1.11)	129 per 1000	5 fewer per 1000 (from 22 fewer to 14 more)	Could not differentiate (high quality evidence)
EORTC QLQ-BR23 - Skin problems in breast [MID +/- 0.8 to 1.25]	5188 (1 study[1]) 5 years	RR 0.79 (0.65 to 0.96)	81 per 1000	17 fewer per 1000 (from 3 fewer to 28 fewer)	Favours 26 Gy in 5 fractions (moderate quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **EORTC-QLQ BR23:** European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Breast Cancer; **RR:** Risk ratio
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.
[1] FAST-Forward (Brunt et al. 2020b) [2] 95% interval crosses one end of a defined MID interval. Quality of the outcome downgraded once [3] 95% interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice

Table 11 Hypofractionation regimen: 35 Gy in 10 fractions over 2 weeks (whole breast) compared to 27 Gy in 5 fractions over 1 week (whole breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 27Gy/5 fractions	Risk difference with 35Gy/10 fractions (95% CI)	
All-cause mortality [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 1.06 (0.58 to 1.93)	170 per 1000	10 more per 1000 (from 71 fewer to 158 more)	Could not differentiate (very low quality evidence)
Locoregional relapse [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 1.09 (0.51 to 2.36)	110 per 1000	10 more per 1000 (from 54 fewer to 150 more)	Could not differentiate (very low quality evidence)
Metastatic disease [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 0.92 (0.57 to 1.49)	260 per 1000	21 fewer per 1000 (from 112 fewer to 127 more)	Could not differentiate (very low quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 27Gy/5 fractions	Risk difference with 35Gy/10 fractions (95% CI)	
Overall survival [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 0.95 (0.85 to 1.07)	870 per 1000	44 fewer per 1000 (from 130 fewer to 61 more)	No meaningful difference (moderate quality evidence)
Disease free survival [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 1.01 (0.85 to 1.21)	710 per 1000	7 more per 1000 (from 106 fewer to 149 more)	No meaningful difference (moderate quality evidence)
Adverse events - Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 0.97 (0.66 to 1.42)	350 per 1000	10 fewer per 1000 (from 119 fewer to 147 more)	Could not differentiate (very low quality evidence)
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 1.25 (0.35 to 4.52)	40 per 1000	10 more per 1000 (from 26 fewer to 141 more)	Could not differentiate (very low quality evidence)
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 1.11 (0.63 to 1.97)	180 per 1000	20 more per 1000 (from 67 fewer to 175 more)	Could not differentiate (very low quality evidence)
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25]	200 (1 study[4]) 6 months	RR 1 (0.98 to 1.02)	1000 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)	No meaningful difference (moderate quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio;
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.
[2] Study at moderate risk of bias. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[4] Shahid et al. 2009

Table 12 Hypofractionation regimen: 40 Gy in 15 fractions over 3 weeks (whole breast) compared to 35 Gy in 10 fractions over 2 weeks (whole breast)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		
			Risk with 35Gy/10 fractions	Risk difference with 40Gy/15 fractions (95% CI)	Interpretation of effect (quality)
All-cause mortality [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 1.11 (0.63 to 1.97)	180 per 1000	20 more per 1000 (from 67 fewer to 175 more)	Could not differentiate (very low quality evidence)
Locoregional relapse [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 0.83 (0.38 to 1.84)	120 per 1000	20 fewer per 1000 (from 74 fewer to 101 more)	Could not differentiate (very low quality evidence)
Metastatic disease [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 1.17 (0.73 to 1.87)	240 per 1000	41 more per 1000 (from 65 fewer to 209 more)	Could not differentiate (very low quality evidence)
Overall survival [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 0.99 (0.87 to 1.12)	830 per 1000	8 fewer per 1000 (from 108 fewer to 100 more)	No meaningful difference (moderate quality evidence)
Disease free survival [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 0.99 (0.83 to 1.17)	720 per 1000	7 fewer per 1000 (from 122 fewer to 122 more)	No meaningful difference (moderate quality evidence)

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		
			Risk with 35Gy/10 fractions	Risk difference with 40Gy/15 fractions (95% CI)	Interpretation of effect (quality)
Adverse events - Incidence of lymphoedema (G1-G3) [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 1.21 (0.84 to 1.73)	340 per 1000	71 more per 1000 (from 54 fewer to 248 more)	Could not differentiate (low quality evidence)
Adverse events - Radiation pneumonitis [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 1 (0.3 to 3.35)	50 per 1000	0 fewer per 1000 (from 35 fewer to 117 more)	Could not differentiate (very low quality evidence)
Adverse events - Sore throat & dysphagia [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 0.75 (0.41 to 1.38)	200 per 1000	50 fewer per 1000 (from 118 fewer to 76 more)	Could not differentiate (very low quality evidence)
Adverse events - Skin reactions (G1-G4) [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 1 (0.98 to 1.02)	1000 per 1000	0 fewer per 1000 (from 20 fewer to 20 more)	No meaningful difference (moderate quality evidence)
Adverse events - Cardiac toxicity >10% LVEF reduction [MID +/- 0.8 to 1.25]	200 (1 study[1]) 6 months	RR 0.83 (0.26 to 2.64)	60 per 1000	10 fewer per 1000 (from 44 fewer to 98 more)	Could not differentiate (very low quality evidence)

*The basis for the **assumed risk** (e.g., the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Shahid et al. 2009
[2] Study at moderate risk of bias. Quality of the outcome downgraded once.
[3] 95% confidence interval crosses both ends of a defined MID interval. Quality of the outcome downgraded twice.
[5] 95% confidence interval crosses one end of a defined MID interval. Quality of the outcome downgraded once.

Anmerkung/Fazit der Autoren

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.13 to 1.10.16

3.3 Leitlinien

Burstein HJ et al. [2,3,13]

ASCO (American Society of Clinical Oncology)

- Burstein HJ et al., 2021: Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO Guideline Update
- Moy MD et al., 2022: 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

[*Methodikeranmerkung: Die beiden ASCO Updates (und das Rapid Update) werden vorliegend gemeinsam dargestellt. Die Empfehlungen werden Update-gebunden nacheinander aufgeführt.]*

Zielsetzung/Fragestellung

- Burstein HJ et al., 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 practice changing data to support substantive revisions (Table 1). The evidence supporting these unchanged recommendations is reviewed in the previous guideline publication."
- Moy MD et al., 2022: "[…] (2) What are the indications for chemotherapy versus endocrine therapy in endocrine-pretreated ER positive metastatic breast cancer? (3) Is there an optimal sequence of nonendocrine agents for patients with hormone receptor–positive but HER2-negative metastatic breast cancer who are no longer benefiting from endocrine therapy (with or without BRCA1 or BRCA2 germline mutations)? […] Note that although this guideline provides recommendations for chemotherapy and targeted therapy for patients with HER2-negative MBC that is either endocrine-pretreated or HR-negative, a companion guideline [Burstein HJ et al., 2021] provides endocrine therapy (ET) and targeted therapy recommendations, including cyclin-dependent kinase (CDK) 4/6 and PI3 kinase inhibition, for HR-positive MBC patients."

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
- Moy MD et al., 2022:
  - RCT und Meta-Analysen: January 1, 2014-February 29, 2020; updated with a targeted search in April 2021
- 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 aus Burstein HJ et al., 2022 [3]

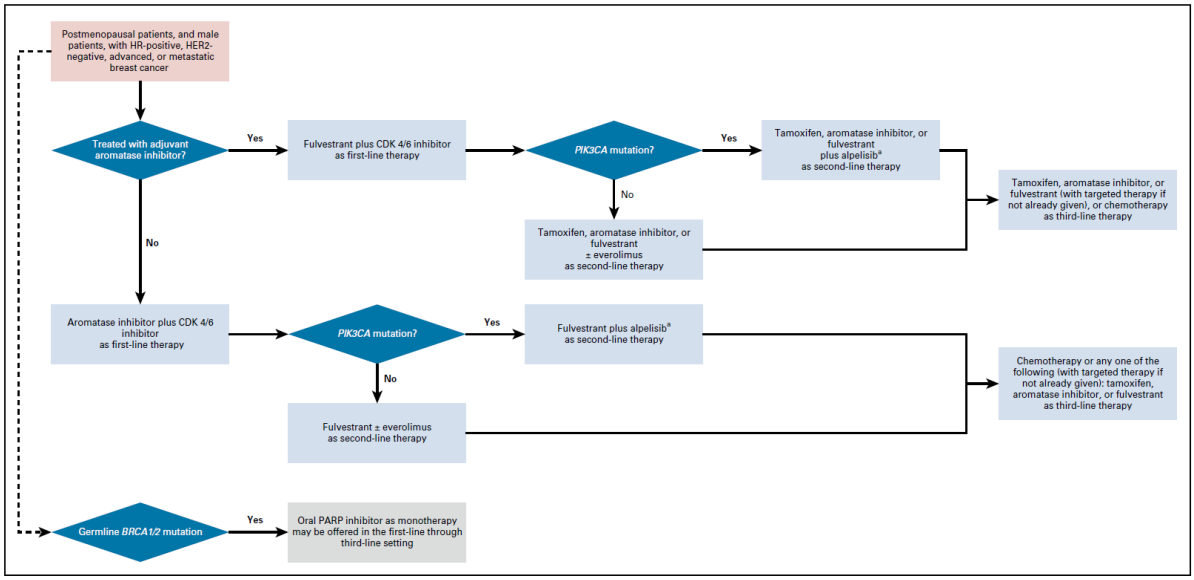

FIG 1. Algorithm for endocrine treatment and targeted therapy for HR-positive, HER2-negative MBC. [a]Patients receiving alpelisib should have laboratory and symptom monitoring weekly for the first 4 weeks of therapy to avoid serious toxicity. CDK, cyclin-dependent kinase; HER2, human epidermal growth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

TABLE 1. Complete List of Recommendations From 2016 ASCO Guideline and From the ASCO 2021 Focused Guideline Update

New Recommendations from 2021 Focused Guideline Update

Recommendation	Evidence Rating
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 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
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
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 ctDNA with *ESR1* mutations	Type: informal consensus Evidence quality: insufficient Strength of recommendation: moderate
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 third-line setting rather than chemotherapy *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 be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown*	Type: evidence-based, benefits outweigh harms Evidence quality: intermediate Strength of recommendation: strong
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
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	Type: evidence-based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong

Recommendations Unchanged From 2016 Guideline

Postmenopausal women with metastatic, HR-positive breast cancer should be offered AIs as first-line ET
Combination hormone therapy with fulvestrant with a loading dose followed by 500 mg every 28 days combined with a nonsteroidal AI may be offered for patients with MBC without prior exposure to adjuvant ET
Premenopausal women with metastatic HR-positive breast cancer should be offered ovarian suppression or ablation in combination with hormonal therapy. Ovarian suppression with either GnRH agonists or ablation with oophorectomy appears to achieve similar results in MBC. For most patients, clinicians should use guidelines for postmenopausal women to guide the choice of hormone treatment, although sequential therapy can also be considered. Patients without exposure to prior hormone therapy can also be treated with tamoxifen or ovarian suppression or ablation alone, although combination therapy is preferred. Treatment should be based on the biology of the tumor and the menopausal status of the patient with careful attention paid to production of ovarian estrogen
Treatment should take into account the biology of the tumor and the menopausal status of the patient with careful attention paid to ovarian production of estrogen
The choice of second-line hormonal therapy should take into account prior treatment exposure and response to previous ET
Sequential hormonal therapy should be offered to patients with endocrine responsive disease
Fulvestrant should be administered using the 500 mg dose and with a loading schedule
Exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC progressing on prior treatment with nonsteroidal AIs, either before or after treatment with fulvestrant, as PFS but not OS is improved compared with exemestane alone. This combination should not be offered as first-line therapy for patients who relapse more than 12 months from prior nonsteroidal AI therapy or for those who are naïve to hormonal therapy
Hormonal therapy should be offered to patients whose tumors express any level of estrogen and/or progesterone receptors
Treatment recommendations should be offered based on the type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence. A specific hormone agent may be used again if recurrence occurs > 12 months from last treatment
ET should be recommended as initial treatment for patients with HR-positive MBC, except in patients with immediately life-threatening disease or in those with rapid visceral recurrence on adjuvant ET
The use of combined ET and chemotherapy is not recommended
Treatment should be given until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. Tumor markers or circulating tumor cells should not be used as the sole criteria for determining progression
The addition of HER2-targeted therapy to first-line AIs should be offered to patients with HR-positive, HER2-positive MBC in whom chemotherapy is not immediately indicated. The addition of HER2-targeted therapy to first-line AIs improves PFS without a demonstrated improvement in OS. HER2-targeted therapy combined with chemotherapy has resulted in improvement in OS and is the preferred first-line approach in most cases
Patients should be encouraged to consider enrolling in clinical trials, including those receiving treatment in the first-line setting. Multiple clinical trials are ongoing or planned, with a focus on improving response to hormonal therapy in metastatic disease

Abbreviations: AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ctDNA, circulating tumor DNA; ET, endocrine therapy; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; OS, overall survival; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

Methodikeranmerkung: Die zugrundeliegende Evidenz kann der Original-LL aus dem Jahr 2016 entnommen werden: Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016;34(25):3069-3103. 10.1200/JCO.2016.67.1487

Update: Burstein HJ et al., 2021 [3].

Clinical Question 1: Should alpelisib be given to postmenopausal women, and to male patients, with HRpositive, 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 HRpositive, HER2-negative, PIK3CA-mutated, ABC, or MBC following prior ET including an 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).

Literature review and analysis. The systematic review identified two articles reporting on one randomized trial that inform the use of alpelisib in combination with ET. […].3,23

Patients who received alpelisib-fulvestrant had significantly prolonged progression-free survival (PFS), the primary study end point (11.0 months v 5.7 months, P , .001). This benefit was not observed in the group of patients without PIK3CA-mutated breast cancer who received alpelisib-fulvestrant. In safety analyses, the most frequent AEs observed in the overall population were hyperglycemia and rash. Grade 3 hyperglycemia occurred in 36.6% of patients in the alpelisib-fulvestrant group and in 0.7% of patients in the placebo-

fulvestrant group; rash occurred in 9.9% of patients in the alpelisib-fulvestrant group and 0.3% of patients in the placebo-fulvestrant group. Grade 3 diarrhea occurred in 6.7% of patients who received alpelisib-fulvestrant versus 0.3% of patients who received placebo-fulvestrant.

In the final overall survival (OS) results from the SOLAR-1 trial, the authors that reported no statistically significant differences in OS were detected between treatment groups. There was an improvement of 7.9 months in OS in the PIK3CA-mutated breast cancer cohort who received alpelisib-fulvestrant (39.3 months; 95% CI, 34.1 to 44.9) compared with patients who received placebo-fulvestrant (31.4 months; 95% CI, 26.8 to 41.3). However, the OS results did not cross the prespecified efficacy boundary. No new safety signals were seen in this follow-up analysis.

[…]

Global Health Status/QoL scores and functioning and symptom scale scores were similar between the alpelisib and the placebo arms at baseline; and, over time, there was no overall change from baseline in either arm. […] In the alpelisib arm, there was a larger deterioration in Social functioning (treatment difference, 24.98; 95% CI, 28.86 to 21.09; P = .012), but there were no other differences between arms in overall adjusted mean changes from baseline in other EORTC QLQ-C30 functioning scale scores.

Several differences were observed between treatment arms in overall mean changes from baseline in symptoms scores. Patients who received alpelisib experienced worsening scores from baseline in appetite loss (10.96 v 1.83; P < .001), diarrhea (13.39 v 1.63; P < .001), nausea or vomiting (6.97 v 4.14; P = .019), and fatigue (9.85 v 3.34; P = .014); however, the onstipation score (28.54 v 23.61; P = .004) improved from baseline among patients in the alpelisib arm.

Clinical interpretation. Patients with estrogen receptor–positive (ER1) ABC have multiple hormonal therapy options and, increasingly, have targeted therapy options, to improve important outcomes. Based on the multiple randomized trials of CDK4/6 inhibitors (see section 3, below) showing substantial improvements in PFS and in some instances OS, and the tolerability profile of CDK4/6 inhibitors, patients should receive ET plus a CDK4/6 inhibitor before initiation of PIK3CA- or mammalian target of rapamycin (mTOR)-targeted therapy.

In the SOLAR-1 trial, adding alpelisib yielded improvement in PFS, a trend for improved OS in patients with visceral metastases, and an 8.5-month delay in time to chemotherapy.

However, use of alpelisib is associated with significant toxicities that must be carefully monitored and managed. In SOLAR-1, the deterioration in Global Health Status and Quality of Life were similar between the placebo and alpelisib arms, with improvement in Worst Pain Score with alpelisib.48 However, symptom subscales favored placebo for the common side effects seen with alpelisib, diarrhea, appetite loss, nausea or vomiting, and fatigue.

All patients who are being considered for treatment with alpelisib should have a baseline hemoglobin A1c and fasting glucose. SOLAR-1 eligibility was modified part-way through the trial to better manage toxicity, including only patients with baseline hemoglobin A1c , 6.5% (compared with , 8% at study start). Patients with uncontrolled diabetes should not receive alpelisib, although patients with well-controlled type 2 diabetes can be treated. Risk factors such as an elevated baseline hemoglobin A1c and obesity should be considered. The median time to onset of.grade 3 hyperglycemia and rash in SOLAR-1 was 15 and 13 days, respectively. This is critical information, as patients receiving alpelisib should have laboratory and symptom monitoring weekly for the first 4 weeks of therapy to avoid serious toxicity. Interestingly, diarrhea is a later toxicity, with grade 3 events occurring at a median of 139 days.

The majority of patients in SOLAR-1 received metformin alone or in combination with other hypoglycemic agents. Preventive agents appeared to reduce the incidence of higher-grade rash; the most commonly used agents were nonsedating antihistamines or steroids. Preventive agents for rash should be considered in patients who are planned to start alpelisib. In addition to the medications noted above, and antipropulsive agents for diarrhea, dose delays and reductions were commonly used to manage toxicity. In SOLAR-1, using detailed side-effect management guidelines resulted in a decrease in discontinuations for higher-grade AEs.

The SOLAR-1 trial was conducted before CDK4/6 inhibitors were routinely used in combination with ET as treatment for metastatic, HR-positive and HER2-negative breast cancer.

Therefore, only 5.9% of patients with PIK3CA-mutated disease enrolled in SOLAR-1 had received prior CDK4/6 inhibitors. Additional data on outcomes with alpelisib after prior treatment with a CDK4/6 inhibitor are available from the nonrandomized BYLIEVE trial, which enrolled 3 cohorts of patients with known PIK3CA-mutated MBC.53 Patients receiving alpelisib and fulvestrant after an AI and a CDK4/6 inhibitor had a median PFS of 7.3 months and 50.4% were alive without disease progression at 6 months (n = 121).

These data provide some support for the sequential use of alpelisib after CDK4/6 inhibitors. Based on tolerability and efficacy, the Expert Panel strongly recommends that patients receive CDK4/6 inhibitors in combination with ET before the line of therapy including alpelisib or everolimus.

In the previous guideline,1 the Expert Panel considered the role of the mTOR inhibitor, everolimus, in the management of ER-positive ABC, and recommended that exemestane and everolimus may be offered to postmenopausal women with HR-positive MBC who experience progression during treatment with nonsteroidal AIs, either before or after treatment with fulvestrant, because PFS but not OS was improved compared with exemestane alone. That recommendation is unchanged.

There are limited data for the use of everolimus after CDK4/ 6 inhibitors. Following CDK4/6 inhibitor therapy, the duration of treatment with everolimus paired with ongoing ET is diminished compared with that seen among patients without prior CDK4/6 inhibitor treatment, with clinical evidence for 4 to 5 months' treatment duration.54 Thus, everolimus may be an option in second or subsequent lines of endocrine-based therapy, although the clinical benefits in contemporary practice in patients treated with CDK4/6 inhibitors are not well defined.

It is not known how the efficacy of everolimus-based therapy compares to that seen with alpelisib; in particular, there are no data for use of everolimus in direct comparison to alpelisib. These targeted agents broadly affect similar PI3K/mTOR pathways in the tumor cell, with overlapping toxicity profiles. If PIK3CA status is not or cannot be determined, if PIK3CA is wild-type, or if the tolerability profile of everolimus in a given patient may be preferable to that of alpelisib, everolimus may be offered as a clinical option. There are no data for the use of alpelisib after everolimus, or vice versa, to guide clinical recommendations.

3. Andre F, Ciruelos E, Rubovszky G, et al: Alpelisib for PIK3CA-mutated, hormone receptor-positive advanced breast cancer. N Engl J Med 380:1929-1940, 2019

23. Andre F, Ciruelos EM, Juric D, et al: Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: Final overall survival results from SOLAR-1. Ann Oncol 32:208-217, 2021

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51. Aaronson NK, Ahmedzai S, Bergman B, et al: The European Organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365-376, 1993
52. Cleeland CS, Ryan KM: Pain assessment: Global use of the Brief pain Inventory. Ann Acad Med Singap 23:129-138, 1994
53. Rugo HS, Lerebours F, Ciruelos E, et al: Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): One cohort of a phase 2, multicentre, open-label, non-comparative study. Lancet Oncol 22:489-498, 2021
54. Rozenblit M, Mun S, Soulos P, et al: Patterns of treatment with everolimus exemestane in hormone receptor-positive HER2-negative metastatic breast cancer in the era of targeted therapy. Breast Cancer Res 23:14, 2021

Clinical Question 2: What is the role of biomarkers in treatment selection for patients with HR-positive MBC?

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 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).

Literature review and analysis

The systematic literature review identified two RCTs that bear on the question of the role of testing BRCA1/2 testing to guide the use of PARP inhibitors in the treatment of patients with HER2-negative MBC. In an open-label, phase III RCT (OlympiAD), Robson et al43 compared the efficacy and safety of the PARP inhibitor, olaparib (n = 205), with the efficacy and safety of standard therapy with single-agent chemotherapy (capecitabine, eribulin mesylate, or vinorelbine; n = 91) in women with HER2-negative MBC and a germline BRCA mutation. The primary end point, median PFS, was significantly longer in the group that received olaparib monotherapy than in the group that received standard chemotherapy (7.0 months v 4.2 months; hazard ratio for disease progression or death, 0.58; 95% CI, 0.43 to 0.80). The risk of disease progression or death in the olaparib group was 42% lower than in the standard therapy group, and the response rate was almost two times the response rate in the standard therapy group (59.9% v 28.8%). The rate of grade 3 or higher AEs in patients who received olaparib was 36.6%; it was 50.5% in the group that received standard chemotherapy. HRQoL measures were also superior with olaparib than with chemotherapy: treatment with olaparib lead to improvements in the functioning, symptoms, and HRQoL. One exception was the nausea or vomiting symptom score, which was worse among patients who received olaparib.49

[…]

Clinical interpretation

PARP inhibitors are generally well tolerated oral agents compared with most chemotherapeutic agents and are an important addition to treatment options for patients with germline mutations in BRCA1 or BRCA2. For patients with HR-positive disease, the optimal sequencing is unknown, and the combination of PARP inhibition and ET has not been evaluated. In general, the combination of ET with a CDK4/6 inhibitor is the preferred first-line treatment in most patients with HR-positive metastatic disease. Treatment decisions should take into account potential toxicities and goals of therapy.

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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-naive HR-positive MBC (type: evidence-based, benefits outweigh harms; evidence quality: high; strength of recommendation: strong).

Literature review and analysis.

Use of a nonsteroidal AI and a CDK4/6 inhibitor in postmenopausal women with treatment-naive HR-positive MBC. The systematic literature review identified 16 articles reporting the results of distinct analyses of data from one of four large-scale phase III RCTs—PALOMA-2, MONALEESA-2, MONALLESA-7, or MONARCH-3—that inform the recommendation on the use of a nonsteroidal AI and a CDK4/6 inhibitor in postmenopausal women with treatment-naive HR-positive MBC. In what follows, the results of the relevant RCTs are summarized by broad trial end point—PFS and OS; AEs; and PROs, most frequently HRQoL. The detailed efficacy and PRO results from the individual studies are presented in the Data Supplement; data on the incidence of AEs (grade ≥ 3) from reports of the major RCTs are provided in the Data Supplement.

[…]

Clinical interpretation. The efficacy and overall tolerability of CDK4/6 inhibitors in combination with ET have changed treatment options for patients with HR-positive MBC. Marked PFS benefits in the first-line setting in postmenopausal as well as premenopausal and perimenopausal women receiving AIs and all three CDK4/6 inhibitors, including patients with visceral disease and high risk features, as well as OS benefit in premenopausal and perimenopausal women receiving AIs and CDK4/6 inhibitors, suggest that in most patients, these combinations are the preferred first-line treatment. Survival data from the majority of first-line studies evaluating AIs in combination with CDK4/6 inhibitors are still awaited, but crossover to CDK4/6 inhibitors from placebo following disease progression may affect these results.

The MONALEESA-3 trial also evaluated fulvestrant in the first-line setting in a combined study including patients with early relapse or in the second-line setting (see full results below). However, given the efficacy data of fulvestrant in the second-line setting, the difficulty separating patients treated in the first-line setting, and the convenience of oral therapy with AIs, the Panel recommends that first-line therapy in patients either na¨ıve to prior ET, or with recurrent disease at least 1 year fromprior exposure to an AI, include an AI as the endocrine partner with CDK4/6 inhibition.

The large number of randomized trials of ET1/2 CDK4/6 inhibitor therapy has allowed the US FDA to do pooled analyses of subsets of patients. The efficacy benefits of adding CDK4/6 inhibitor therapy were similar in younger (< 70 years) and older (> 70 years) women, including women > 75 years.41 However, in the analysis of older patients (≥ 75 years), there was more toxicity among women age ≥ 75 years, including greater risks of fatigue, diarrhea, neutropenia, and hepatotoxicity. Older patients were more likely to have dose reductions or treatment interruptions because of side effects. Patients > 75 years were also more likely to have decreased quality of life, with less mobility, self-care, and activity, while on CDK4/6 inhibitors than were younger patients. Clinicians and patients should be aware of the greater toxicity experience and greater risk of adverse impact on quality of life in older patients receiving CDK4/6 inhibitors, and factor that into decision making along with the

documented improvement in PFS seen with this class of drugs among elderly patients with breast cancer.

Although the majority of patients appear to benefit from combination therapy, there are postmenopausal women for whom endocrine monotherapy may be the best choice for first-line therapy. This decision should be influenced by limited disease burden, long disease-free interval, patient age, patient choice, and other factors such as treatment tolerance. In this case, it is recommended that CDK4/6 inhibitors be combined with second-line ET. Optimal sequencing is an ongoing research question.

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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).

Literature review and analysis. […]

The systematic literature review identified 11 articles reporting the results of analyses of data from one of three large-scale phase III RCTs—PALOMA-3, MONALEESA-3, or MONARCH-2—that inform the recommendation concerning the use of fulvestrant and a CDK4/6 inhibitor in patients with progressive disease during treatment with AIs, or who develop a recurrence within 1 year of adjuvant AI therapy, either with or without one line of prior chemotherapy for metastatic disease or as first-line therapy. The results of the relevant RCTs are summarized by broad trial end point—PFS and OS; AEs; and PROs, most frequently HRQoL. The efficacy and PRO results from the individual studies are presented in the Data Supplement; data on the incidence of AEs (grade ≥ 3) from reports of the major RCTs are provided in the Data Supplement.

[…]

Clinical interpretation. The survival benefits seen with the addition of CDK4/6 inhibitors to fulvestrant in the chemotherapy naive second-line setting are impressive, and along with tolerability and maintained or improved quality of life, have further solidified the role of these targeted agents in the treatment of metastatic HR-positive breast cancer. For the majority of patients, treatment with CDK4/6 inhibitors in the first-line setting is preferable, but combinations with fulvestrant may be optimal for those intolerant to AIs; for those who have developed recurrent disease within 1 year of last adjuvant AI therapy; or for those for whom single-agent ET is the preferred first-line treatment. We learned inadvertently from these trials that prior chemotherapy affects PFS and OS in response to subsequent ET. In PALOMA-3, approximately one third of patients had received prior chemotherapy, compared with none in MONARCH-2 and MONALEESA-3. Interestingly, the PFS to fulvestrant alone was shorter in PALOMA-3 compared with the other two trials, although the impact of adding the CDK4/6 inhibitor was similar by hazard ratios across all three trials. A subset analysis also suggests that the survival impact in PALOMA-3 was limited to those patients who had not received prior chemotherapy. These data serve to further emphasize the importance of sequential ET before use of chemotherapy for the treatment of HR-positive MBC, except in situations with primary endocrine resistance or immediately life-threatening visceral disease.

Given the extensive efficacy data, there has been interest in the use of CDK4/6 inhibitors following progression on the same or different CDK4/6 inhibitor, given either alone or in combination with the same or sequential ET. To date, retrospective data suggest potential efficacy confounded by the nature of the analyses, but support future study. Several prospective randomized phase II trials are evaluating this question.

A new question is likely to arise in the near future. Recent preliminary data have demonstrated potential efficacy of the CDK4/6 inhibitor, abemaciclib, in the adjuvant high-risk setting in combination with ET.62 If these data are confirmed with longer follow-up, we will need to understand the efficacy of CDK4/6 inhibitors in the metastatic setting in patients who received adjuvant CDK4/6 inhibition, and what the optimal time from last exposure is to see efficacy in the metastatic setting. At the moment, there are no data to inform this question, and there is no current approved indication for CDK4/6 inhibitors in early-stage disease.

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Update: Moy MD et al., 2022 [13]

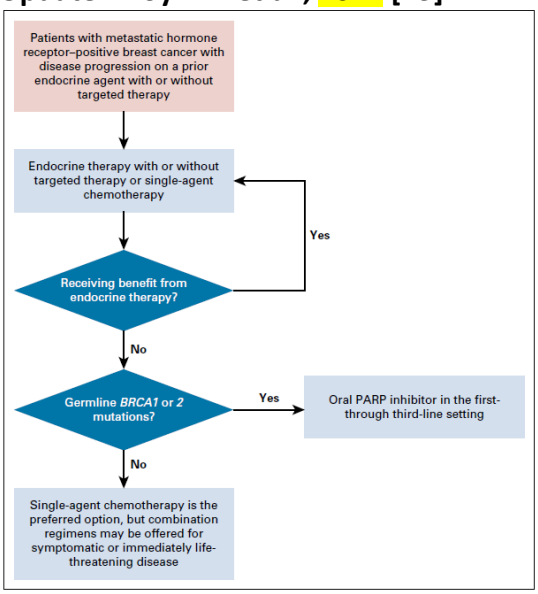

FIG 2. Treatment algorithm for chemotherapy and targeted therapy for patients with HER2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor–negative. HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death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

Recommendations

Clinical Question 2: What are the indications for chemotherapy versus endocrine therapy in endocrine-pretreated ER-positive metastatic breast cancer?

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 for details) or single-agent chemotherapy (Type: evidence based; benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

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. […]

Clinical interpretation: The treatment choice between ET with targeted agents such as CDK 4/6 inhibitors, everolimus, 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 response 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.

Clinical Question 3: Is there an optimal sequence of nonendocrine agents for patients with HR-positive but HER2-negative MBC that are no longer benefiting from ET (with or without BRCA1 or BRCA2 germline mutations)?

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).

Literature update and analysis: […] the OlympiAD trial[11] […] the EMBRACA trial[12] […]

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.

Clinical interpretation: Given the lower toxicity of PARP inhibitors compared with chemotherapy, after 1-2 prior lines of ET, PARP inhibition is preferable to chemotherapy, although it should be noted that neither of these trials involved comparisons with taxanes or with platinums. Therefore, it is not known whether PARP inhibitors are superior to platinum or taxane chemotherapy in the metastatic setting.

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).

Literature update and analysis. As described previously in Recommendation 2.2, the phase III CALGB 40502/NCCTG N063H[7] trial evaluated optimal first-line chemotherapy for patients with MBC. This trial randomly assigned 799 patients to receive paclitaxel versus nab-paclitaxel versus ixabepilone. All patients also received bevacizumab as part of the treatment protocol. The ixabepilone arm was closed at the first interim analysis for futility. The median PFS for paclitaxel was 11 months, and at 7.4 months, ixabepilone was inferior to paclitaxel (hazard ratio, 1.59; 95% CI, 1.31 to 1.93; P < .001). Nab-paclitaxel was also not superior to paclitaxel (PFS, 9.3 months; hazard ratio, 1.20; 95%CI, 1.00 to 1.45; P = .054). Also, as described previously in Recommendation 2.2, NCCN[17] issued a guideline update

that recommends first line chemotherapy with a taxane (paclitaxel is the preferred agent) or an anthracycline, if not previously used in the neoadjuvant or adjuvant setting. It endorses sequential single-agent chemotherapy as the preferred approach.

Referenzen

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Update: Burstein HJ et al., 2024 [2]

UPDATED RECOMMENDATIONS

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. Secondand third-line therapies reflect targeted options based on tumor genomics. Combining ET with the AKT pathway inhibitor capivasertib is appropriate for tumors harbouring 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.

BACKGROUND

Patients with hormone receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC) have emerging therapeutic options including novel endocrine1 and targeted agents, with treatment informed by genomic biomarker testing.2 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.1,2

EVIDENCE REVIEW

CAPItello-291 randomly assigned 708 premenopausal, perimenopausal, or postmenopausal women or men with hormone receptor–positive, HER2-negative locally advanced or metastatic breast cancer to either capivasertib 1 fulvestrant (n 5 355) or placebo 1 fulvestrant (n 5 353).3 Patients had experienced disease progression or relapse during previous aromatase inhibitor therapy, with or without a CDK4/6 inhibitor. Capivasertib was administered on a unique schedule of 400 mg orally twice a day for 4 days, then 3 days off, each week. All patients had tumor tissue submitted for next-generation sequencing. Activating mutations in PIK3CA and AKT1 and inactivating alterations in PTEN genes were determined centrally with the FoundationOneCDx assay in all countries except China (which used OncoScreen Plus). Analyses were stratified by prior CDK4/6 exposure. Progression-free survival (PFS) in all patients (N 5 477) and in patients with PIK3CA/AKT1/PTEN-altered tumors (n 5 289) were the dual primary end points. The median PFS in the overall population was 7.2 months with capivasertib 1 fulvestrant and 3.6 months for placebo 1 fulvestrant (hazard ratio [HR], 0.60; P < .001). The median PFS in the PIK3CA/AKT1/PTEN-altered tumor population was 7.3 months with capivasertib 1 fulvestrant and 3.1monthswith placebo1fulvestrant (HR, 0.50; P < .001). Among those whose tumors were AKT pathway nonaltered, the median PFS was 5.3 months and 3.7 months for capivasertib-treated and placebo-treated patients, respectively (HR, 0.79; P 5 nonsignificant), suggesting greatest benefit when tumors harbored AKT pathway mutations. Capivasertib 1 fulvestrant improved PFS regardless of prior CDK4/6 exposure.

Patient-reported outcome measures of quality of life showed consistent overall global health status (GHS) for both groups from baseline and no clinically meaningful changes in functional or symptom scores apart from worse diarrhea in the capivasertib 1 fulvestrant arm. Time to deterioration of GHS was longer with capivasertib and numerically longer in functional and symptomdomains apart fromdiarrhea.4 Physicianreported grade ≥3 adverse events (AEs) were more frequent in the capivasertib 1 fulvestrant group, including rash (12.1% v 0.3% with placebo-fulvestrant), diarrhea (9.3% v 0.3%), and hyperglycemia (2.3% v 0.3%), and AEs more frequently led to treatment discontinuation (13% v 2.3%).

To our knowledge, to date, no survival benefit has been demonstrated. Appraisal of the trial report using the GRADE5 instrument was performed as per ASCO's methodology and found a high certainty of the evidence.

The similar FAKTION study,6 a randomized phase II comparison of fulvestrant with either capivasertib or placebo, showed qualitatively similar results as CAPItello-291 with benefit restricted to tumors harboring PIK3CA/AKT1/PTEN alterations.

Hasset MJ et al., 2020 [6].

ASCO (American Society of Clinical Oncology)

Management of Male Breast Cancer: ASCO Guideline

Zielsetzung/Fragestellung

To develop recommendations concerning the management of male

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

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- PubMed: January 1, 1998 - September 20, 2019

LoE

Strength of Total Body of Evidence

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

GoR

Type of Recommendation	Definition
Evidence-based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in an online data supplement.
Informal Consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No Recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

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

Sonstige methodische Hinweise

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

Empfehlungen

CLINICAL QUESTION 4: Which endocrine therapies should be offered to men with advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer?

- Recommendation 4.1 Men with advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer should be offered endocrine therapy as first-line therapy except in cases of visceral crisis or rapidly progressive disease. Options include tamoxifen, an AI with a GnRH agent, and fulvestrant. CDK 4/6 inhibitors can be used in men as they are used in women (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).
- Recommendation 4.2 Men who develop recurrent metastatic, hormone receptor–positive, HER2-negative breast cancer while receiving adjuvant endocrine therapy should be offered an alternative endocrine therapy except in cases of visceral crisis or rapidly progressive disease (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong).
- Recommendation 4.3 Endocrine therapy for men with advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer may be sequenced as in women (Type: formal consensus; Evidence quality: low; Strength of recommendation: moderate)

  Literature review and analysis:

  Metastatic breast cancer in men is treated with the same endocrine therapies used to treat metastatic breast cancer in women. Endocrine treatment options include tamoxifen, an AI with a GnRH agent, and fulvestrant. There is no evidence from clinical trials in men with advanced or metastatic breast cancer to inform clinical questions regarding the optimal sequencing of endocrine therapies. In general, the Expert Panel recommends using the therapies in the order listed above. The recommendations offered here reflect the best clinical opinion of the Expert Panel members based on their personal clinical experience managing male breast cancer, and based on extrapolation from studies of endocrine therapy conducted in women with advanced breast cancer.[35] As with women, men experiencing visceral crisis and/or rapidly progressive disease should consider chemotherapy as an initial treatment option. Available data from case reports

and small case series do not support strong conclusions about the use of monotherapy versus combination endocrine therapy in men with metastatic breast cancer, but some studies[7,8] have reported greater responses when an AI is combined with a GnRH analog. Based on this information, the Expert Panel suggests combining AIs with GnRH analogs but acknowledges that single-agent AIs may be reasonable for patients unlikely to tolerate combined therapy who have unmeasurable estrogen levels. A pooled analysis of case reports and case series conducted by Zagouri et al[15]suggests a promising role for fulvestrant.

Among women with hormone receptor–positive metastatic breast cancer, endocrine therapy is often combined with CDK inhibitor therapy, because multiple studies have demonstrated that this treatment increases the response rate and prolongs progression-free survival.[36,37] Data regarding the benefits and adverse effects of CDK4/6 inhibitors in men with metastatic breast cancer are sparse, but selected trials of these targeted agents have included men and small case series have been reported. Consequently, the FDA granted approval for the use of one CDK4/6 inhibitor in men with metastatic hormone receptor–positive breast cancer (https://www.ascopost.com/News/59909). The Expert Panel suggests that it would be reasonable to use CDK4/6 inhibitors in men as they are used in women.

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CLINICAL QUESTION 5

What is the role of targeted therapy in the treatment of men with advanced or metastatic breast cancer? Note that “targeted therapy” refers to treatments that target HER2- positive tumors, PD-L1–positive tumors, and patients carrying pathogenic germline BRCA 1/2 mutations; endocrine therapies are addressed elsewhere in the guideline.

- Recommendation 5: Targeted therapy guided by hormone receptor (HR), HER2, programmed death ligand 1 (PDL-1), PIK3CA, and germline BRCA mutation status may be used in the treatment of advanced or metastatic male breast cancer using the same indications and combinations that are offered to women (Type: formal consensus; Evidence quality: low; Strength of recommendation: strong). (Targeted therapy based on hormone receptor status is addressed in Recommendations 4.1 to 4.3.)

[*Methodikeranmerkung: Hintergrundinformationen zu dieser Empfehlung können der LL entnommen werden und sind vorliegend nicht extrahiert.]*

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 07 of 12, July 2024) am 31.07.2024

#	Suchfrage
1	[mh ^"Breast Neoplasms"]
2	(breast*):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 Jul 2019 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 31.07.2024

#	Suchfrage
1	breast neoplasms/TH[majr]
2	breast[tiab]
3	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]
4	advance*[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR relaps*[tiab] OR progression*[tiab] OR progressive*[tiab] OR neoplasm metastasis/TH OR neoplasm recurrence, local/TH
5	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
6	#2 AND #3 AND #4 AND #5
7	#1 AND #4
8	#6 OR #7
9	(#8) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti]))

#	Suchfrage
	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[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
10	((#9) AND ("2019/07/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
11	(#10) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in Medline (PubMed) am 31.07.2024

#	Suchfrage
1	breast neoplasms[majr]
2	(breast[ti]) AND (cancer*[ti] OR tumour*[ti] OR tumor[ti] OR tumors[ti] OR carcinom*[ti] OR neoplas*[ti] OR malignan*[ti])
3	(#1 OR #2) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
4	(((#3) AND ("2019/07/01"[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]))
5	(#4) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 01.08.2024

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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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.: 2024-B-043

Verfasser	
Name der Institution	Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Bundesärztekammer, Dezernat 6 – Wissenschaft, Forschung und Ethik, Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de)
Namen aller beteiligten Sachverständigen	
Datum der Erstellung	12. März 2024

(Bei mehreren beteiligten Fachgesellschaften bitte mit entsprechenden Angaben.)

Indikation

Szenario 1

zur Behandlung von erwachsenen Patienten mit einem Hormonrezeptor(HR)-positiven, HER2-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom nach Rezidiv oder Progression der Erkrankung während oder nach einer endokrinen Therapie

Zweckmäßige Vergleichstherapie:

CDK 4/6-Inhibitor kombiniert mit endokriner Therapie:

- Ribociclib kombiniert mit nichtsteroidalem Aromatasehemmer oder
- Ribociclib kombiniert mit Fulvestrant oder
- Abemaciclib kombiniert mit nichtsteroidalem Aromatasehemmer oder Fulvestrant oder
- Palbociclib kombiniert mit nichtsteroidalem Aromatasehemmer

oder

endokrine Monotherapie:

- Anastrozol oder
- Letrozol oder
- Fulvestrant oder
- ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind

Anmerkungen:

- Bei prä- oder postmenopausalen Patientinnen erfolgt die endokrine Mono- oder Kombinationstherapie unter Ausschaltung der Ovarialfunktion.
- Bei unmittelbar bedrohender viszeraler Krise besteht die Indikation zu einer zytostatischen Chemotherapie.

Begründung:

Die aktuelle S3-Leitlinie (1) empfiehlt bei fernmetastasierter Erkrankung:

- für prä- und perimenopausale Patientinnen:
  endokrine Therapie mit einem nicht steroidalen Aromatasehemmer (Anastrozol oder Letrozol) oder mit Fulvestrant entweder in Kombination mit einem CDK4/6-Inhibitor (vor allem bei Notwendigkeit des Erreichens einer schnellen Remission) oder als endokrine Monotherapie (jeweils unter Ausschaltung der Ovarialfunktion).
- für postmenopausale Patientinnen:
  endokrine Therapie ggf. kombiniert mit einer zielgerichteten Therapie. Bei Notwendigkeit des Erreichens einer schnellen Remission gilt eine endokrine Monotherapie als nicht indiziert.

Die CDK-4/6-Inhibitoren Ribociclib, Palbociclib und Abemaciclib sind als sogenannte „zielgerichtete Therapie“ in Kombination mit endokriner Therapie für diese Indikationen zugelassen. Die robusteste Evidenz besteht dabei für Ribociclib:

- Für Ribociclib in Kombination mit Letrozol wurde bei postmenopausalen Patientinnen in der ITT-Population gegenüber Letrozol eine signifikante Verlängerung des OS und des PFS gezeigt (MONALEESA-2 Studie (2)).
- Für Ribociclib in Kombination mit Anastrotol oder Letrozol oder Tamoxifen wurde für prä/perimenopausale Patientinnen gegenüber Placebo plus Anastrozol oder Letrozol oder Tamoxifen eine signifikante Verlängerung des OS und des PFS gezeigt (MONALEESA-7-Studie (3).
- Für Palbociclib und für Abemaciclib jeweils in Kombination mit endokriner Therapie wurde bisher in keiner Einzelstudie eine signifikane Überlebenszeitverlängerung gegenüber alleiniger endokriner Therapie nachgewiesen. Für Abemaciclib zeigten allerdings gepoolte Ergebnisse der MONARCH-3-Studie und der MONARCH plus-Studie bei postmenopausalen Patientinnen eine signifikante Überlebenszeitverlängerung (siehe GBA-Beschluss vom 13.10.2023 (4)).

Szenario 2 (Biomarker-basiert):

Behandlung von erwachsenen Patienten mit einem PIK3CA/AKT1/PTEN-mutierten, Hormonrezeptor(HR)-positiven, HER2-negativen lokal fortgeschrittenen oder metastasierten Mammakarzinom nach Rezidiv oder Progression der Erkrankung während oder nach einer endokrinen Therapie

Wie bei Szenario 1: Obige Einschätzung der ZVT gilt aktuell auch für Patientinnen mit einem PIK3CA/AKT1/PTEN-mutierten, Hormonrezeptor(HR)-positiven, HER2-negativen lokal fortgeschrittenen oder metastasierten Mammakarzinom.

Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Siehe oben.

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? *(Bitte begründen Sie Ihre Ausführungen; geben Sie ggf. zitierte Quellen in einer Referenzliste an.)*
Siehe oben.

Referenzliste:

1. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms. AWMF-Register Nr. 032/045OL; Langversion 4.4; Juni 2021. Verfügbar unter: https://www.leitlinienprogramm-onkologie.de/leitlinien/mammakarzinom/.
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Gemeinsamer Bundesausschuss

Expertengespräch zur Fragestellung: „Unterschiede zwischen prä- und postmenopausalen Patientinnen mit einem HR-positiven Mammakarzinom sowie einer natürlichen und einer induzierten Menopause“

Diskussionsthemen

Für das Expertengespräch wurde den geladenen Experten vorab ein Fragenkatalog für die Vorbereitung übermittelt, der zugleich für die Struktur des Expertengespräches verwendet wurde. Nachfolgend ist eine Zusammenfassung der im Rahmen des Expertengesprächs am 2. Juli 2024 in der AG 35a-Sitzung diskutierten Inhalte dargestellt:

Themenkomplex 1: Menopausenstatus als Prognosefaktor für Gesamtüberleben

1. Die klinischen Experten führen aus, dass sich aus den bekannten Daten hinsichtlich des Alters ein Unterschied hinsichtlich der Mortalität feststellen lässt: junge Frauen, unter 35 Jahre und ältere Frauen über 75 Jahre. Ein weiterer Unterschied besteht hinsichtlich der Therapieadhärenz für die antiöstrogene Therapie (häufigeres Absetzen bei jungen Frauen) und erhöhten Östrogenspiegeln in bestimmten Situationen wie Schwangerschaft und Stillzeit bei jungen Frauen mit Auswirkungen auf die Tumorbiologie.
2. Hinsichtlich der Anteile führen die klinischen Experten aus, dass circa 20% der Patientinnen ein prämenopausales Mammakarzinom haben. Der Anteil sehr junger Frauen (< 35 Jahre) wird als eher gering eingestuft.
3. Die klinischen Experten führen aus, dass, basierend auf der aktuellen Evidenz, der Menopausenstatus grundsätzlich keinen gesicherten unabhängigen prognostischen Faktor darstellt.
4. Die klinischen Experten weisen darauf hin, dass eine adäquate endokrine Therapie insbesondere bei prämenopausalen Patientinnen essentiell sei. Diesbezüglich sei es in Bezug auf relevante Studien beim frühen Brustkrebs jedoch oftmals unklar, inwieweit

eine adäquate endokrine Therapie durchgeführt worden ist, was sich potentiell auf Effektunterschiede auswirken kann.

5. Es wird von den klinischen Experten bestätigt, dass der Menopausenstatus eindeutig einen Prädiktionsfaktor für die Therapie darstellt bzw. die Wahl der endokrinen Therapie in Abhängigkeit von dem Menopausenstatus erfolgt.

Themenkomplex 2:
Menopausenstatus und Biologie des Tumors

1. Basierend auf bisherigen Erkenntnissen wird ausgeführt, dass postmenopausale Patientinnen eher höhere Werte der Hormonrezeptorexpression aufweisen. Unterschiede bestehen im Detail in erster Linie zwischen sehr jungen, unter 35-Jährigen vs. diejenigen, die über 50 Jahre alt sind.
2. Die 45- bis 50-Jährigen und die über 50-jährigen Patientinnen scheinen vergleichbar zu sein hinsichtlich der Tumorbiologie.
3. Basierend auf den vorliegenden Daten geben die klinischen Experten keine abschließenden Einschätzungen hinsichtlich weiterer biologischer Faktoren und deren Bedeutung für die Tumorbiologie.

Themenkomplex 3:
Induktion der Menopause - ovarielle Suppression

1. Die klinischen Experten halten fest, dass in der metastasierten Situation die ovarielle Suppression, unabhängig von der Art, den absoluten Standard in der Prämenopause darstellt. Dies stellt die Grundlage jeder Therapie in der Prämenopause bei metastasiertem Mammakarzinom dar. Die Art der ovariellen Suppression (verschiedene Formen der Suppression) hat laut klinischer Experten keinen Einfluss auf die Therapieentscheidung.
2. Basierend auf Studiendaten zeigen ca. 10 - 20% der Patientinnen keine adäquate medikamentös induzierte ovarielle Suppression mit Aromatasehemmern und GnRH-Analoga. Aus diesen Daten geht kein abschließender Hinweis auf eine Korrelation mit einem bestimmten Alter hervor.
3. Für die adjuvante Situation der Frauen ohne vorherige Chemotherapie wird von den klinischen Experten mit Verweis auf die NCCN-Leitlinien vor dem Hintergrund des Flare-up-Phänomens empfohlen, jedes Mal, wenn eine endokrine Therapie begonnen wird, selbst wenn Aromatasehemmer geplant sind, die ersten beiden Monate Tamoxifen zu geben.
4. Eine Ovariektomie wird in Deutschland eher selten durchgeführt (Einschätzung eines klinischen Experten: ca. maximal 10%). Es wird erläutert, dass gerade in der metastasierten Situation versucht wird, in der klinischen Versorgung die Anzahl der operativen Eingriffe möglichst gering zu halten. Es wird ergänzt, dass die frühere

zusätzlich therapeutische Ovariektomie aufgrund von Metastasierung des Mammakarzinoms in die Ovarien aus heutiger Sicht irrelevant ist.

5. Die klinischen Experten bestätigen, dass Unterschiede hinsichtlich der Rate von Ovariektomien zwischen den Ländern vorliegen, die sich auch in internationalen Studien widerspiegeln. Die klinischen Experten leiten daraus keine Konsequenz ab.

Themenkomplex 4: Menopausenstatus in Leitlinien und Zulassung

1. Es wird festgehalten, dass eine prämenopausale Patientin, die eine ovarielle Suppression hat, im therapeutischen Sinne wie eine postmenopausale Patientin zu werten sei, wie es auch in Leitlinien international vorliegt. Dies wird von den klinischen Experten auch hinsichtlich der Wahl der Therapieoptionen ausgeführt. Auf die Frage, warum in der S3-Leitlinie dennoch zwischen prä- und postmenopausalen Patientinnen kategorisch unterschieden wird, äußert sich ein klinischer Experte dahingehend, dass Daten aus Studien mit prämenopausalen Patientinnen im Vergleich zu Studien, in denen prämenopausale Patientinnen gar nicht eingeschlossen waren, zu unterschiedlichen Schlussfolgerungen in den Leitlinien führen könnten. Eine kategorische Unterscheidung zwischen prä- und postmenopausalen Patientinnen in Bezug auf die Therapieempfehlungen ließe sich aus biologischen Gründen jedenfalls nicht ableiten.
2. Aus den unterschiedlichen Anteilen prämenopausaler Patientinnen in klinischen Studien bzw. deren Berücksichtigung durch Ein- und Ausschlusskriterien ziehen die klinischen Experten keine Schlussfolgerungen, weisen jedoch auf die unter Umständen breitere Datenlage für den Einsatz von unterschiedlichen Medikamenten bei jüngeren Patientinnen hin.
3. Die Teilnehmerin des BfArM führt aus, dass die Formulierung der Indikation zum Teil die Einschlusskriterien der Studien widerspiegelt. Die Entscheidung für eine Weiterfassung der Indikation ist eine Frage der Antragstellung des pharmazeutischen Unternehmers, der Bewertung und Diskussion der Zulassungsbehörden, die mehrere Beteiligte umfasst. Die Teilnehmerin des BfArM weist auf ein FDA Guidance Papier von 2021 hin, das dazu auffordert, prämenopausale Frauen in Studien mit HR+-Mammakarzinom einzuschließen[1]. Dem schlösse sich das BfArM in wissenschaftlichen Beratungen an. Zusätzlich würde vom BfArM in der Regel um Stratifizierung hinsichtlich des Menopausenstatus gebeten, um eine Bewertung der Daten von prämenopausalen Frauen durchzuführen.
4. Bei Studien mit sowohl primär postmenopausalen Frauen als auch primär prämenopausalen Frauen mit ovarieller Suppression würde das BfArM konkret nach Ergebnissen der Subgruppen fragen und diese diskutieren. Die Teilnehmerin des BfArM kann nicht für andere Zulassungsbehörden sprechen. Spontane Nachfragen zum konkreten Umgang mit den vorgelegten Daten in früheren Zulassungen - konkret

[1] "Premenopausal Women with Breast Cancer: Developing Drugs for Treatment Guidance for Industry" U.S. Department of Health and Human Services, Food and Drug Administration, Oncology Center of Excellence (OCE) Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), June 2021 https://www.fda.gov/media/142638/download

nachgefragt wurde zur initialen Zulassung von Abemaciclib - können von der Teilnehmerin des BfArM spontan nicht kommentiert werden.