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: 2021-B-322-z Abemaciclib

Stand: Juli 2021

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

Abemaciclib
[zur Behandlung des HR-positiven/HER2-negativen, lokal fortgeschrittenen oder metastasierten Brustkrebs]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Grundsätzlich im Anwendungsgebiet in Betracht kommende nicht-medikamentöse Behandlungen: • Operative Resektion • Strahlentherapie • Ovariektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Abemaciclib (in Kombination mit Fulvestrant): Beschluss vom 2. Mai 2019 und 3. September 2020 • Abemaciclib (in Kombination mit einem Aromatasehemmer): Beschluss vom 2. Mai 2019 • Palbociclib: Beschluss vom 18. Mai 2017 und 22. März 2019 • Ribociclib (in Kombination mit Fulvestrant): Beschluss vom 4. Juli 2019 und 20. August 2020 • Ribociclib (in Kombination mit einem Aromatasehemmer): Beschluss vom 4. Juli 2019 und 20. August 2020 • Alpelisib (in Kombination mit Fulvestrant): Beschluss vom 18. Februar 2021
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Abemaciclib	<u>zugelassenes Anwendungsgebiet laut Beratungsanforderung:</u> 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.
Antiestrogene	
Tamoxifen L02BA01 Nolvadex®	• Adjuvante Therapie nach Primärbehandlung des Mammakarzinoms. • 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. -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
Aromataseinhibitoren (nicht-steroidal):	
Anastrozol L02BG03 Arimidex®	Arimidex® ist angezeigt für die: • Behandlung des hormonrezeptor-positiven fortgeschrittenen Brustkrebses bei postmenopausalen Frauen. • Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	• Adjuvante Behandlung des hormonrezeptor-positiven frühen invasiven Brustkrebses bei postmenopausalen Frauen, die bereits 2 bis 3 Jahre adjuvant Tamoxifen erhalten haben.
Letrozol L02BG04 Femara®	• Adjuvante Therapie postmenopausaler Frauen mit hormonrezeptor-positivem primärem Mammakarzinom. • Erweiterte adjuvante Therapie des hormonabhängigen primären Mammakarzinoms bei postmenopausalen Frauen nach vor-heriger adjuvanter Standardtherapie mit Tamoxifen über 5 Jahre. • 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. • Neoadjuvante Behandlung postmenopausaler Frauen mit hormonrezeptor-positivem, HER-2-negativem Mammakarzinom, bei denen eine Chemotherapie nicht in Betracht kommt und ein sofortiger chirurgischer Eingriff nicht indiziert ist.
Aromataseinhibitoren (steroidal):	
Exemestan L02BG06 Aromasin®	• adjuvante Behandlung eines Östrogenrezeptor-positiven, invasiven, frühen Mammakarzinoms bei postmenopausalen Frauen nach 2 – 3 Jahren adjuvanter Initialtherapie mit Tamoxifen. • 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
Medroxyprogesteronacetat 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:	
Everolimus L01XE10 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 L01XE33 IBRANCE®	IBRANCE ist angezeigt zur Behandlung von Hormonrezeptor (HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen lokal fortgeschrittenen oder metastasierten Brustkrebs: • in Kombination mit einem Aromatasehemmer • in Kombination mit Fulvestrant bei Frauen, die zuvor eine endokrine Therapie erhielten Bei prä- oder perimenopausalen Frauen sollte die endokrine Therapie mit einem LHRH-Agonisten (LHRH = Luteinizing Hormone-Releasing Hormone) kombiniert werden.
Ribociclib L01XE42 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.
Abemaciclib L01XE50 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.

PIK3-Inhibitor:	
Alpelisib L01XX65 Piqray®	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.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-322-z (Abemaciclib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	6. Juli 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

ABC	Advanced Breast Cancer
AE	Adverse Events
AI	Aromatase Inhibitor
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BC	Breast Cancer
CBR	Clinical Benefit Rate
CDK	Cyclin-Dependent Kinase
CR	Complete Response
ECRI	ECRI Guidelines Trust
ER	Estrogen Receptor
ET	Endokrine Therapie
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HER2-	Humaner epidermaler Wachstumsfaktor-Rezeptor-2(HER2)-negativ
HR	Hazard Ratio
HR+	Hormonrezeptor (HR)-positiv
ITC	Indirect Treatment Comparison
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LHRH	LHRH = Luteinising Hormone-Releasing Hormone
LoE	Level of Evidence
MBC	Metastatic Breast Cancer
mTOR	mechanistic Target of Rapamycin
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival
PgR	Progesterone Receptor
PFS	Progression Free Survival
PR	Partial Response
RR	Relatives Risiko

SIGN	Scottish Intercollegiate Guidelines Network
SUCRA	cumulative ranking area
TRIP	Turn Research into Practice Database
TTF	Time to Treatment Failure
TTP	Time To Progression
WHO	World Health Organization

1 Indikation

Behandlung von prä- und postmenopausalen Frauen sowie Männern mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die bereits eine endokrine Therapie erhalten haben und deren Krankheit fortschreitet

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Mammakarzinom* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 27.01.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 2795 Quellen. 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 Quellen 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. Nachträglich wurde die aktualisierte Leitlinie der Deutschen Krebsgesellschaft, Deutschen Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften (Leitlininprogramm Onkologie) von Juni 2021 identifiziert und in die Synopse aufgenommen. Basierend darauf, wurden insgesamt 26 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2020 [8].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V vom 20. August 2020 - Ribociclib (Neubewertung nach Fristablauf: Mammakarzinom, HR+, HER2-, Kombination mit Fulvestrant)

Anwendungsgebiet

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 endokrinbasierte 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.

Hinweis: Der Beschluss vom 20. August 2020 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Ribociclib in Kombination mit Fulvestrant in den Teilpopulationen: a1) postmenopausale Patientinnen, die noch keine initiale endokrine Therapie erhalten haben und b1) Postmenopausale Patientinnen mit vorangegangener endokriner Therapie

a1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

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

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ribociclib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Hinweis auf einen geringen Zusatznutzen

b1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

- eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:
  - Tamoxifen oder
  - Anastrozol oder
  - Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
  - Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder

- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung oder
- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nichtsteroidalen Aromataseinhibitor gekommen ist.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ribociclib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Anhaltspunkt für einen geringen Zusatznutzen.

G-BA, 2020 [5].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Abemaciclib (Neubewertung nach Fristablauf: Mammakarzinom, HR+, HER2-, Kombination mit Fulvestrant) Vom 3. September 2020.

Anwendungsgebiet

Der Beschluss vom 3. September 2020 bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant in den Teilpopulationen: a1) Postmenopausale Frauen, die noch keine initiale endokrine Therapie erhalten haben, b1) Postmenopausale Frauen mit vorangegangener endokriner Therapie und b2) Prä-/ perimenopausale Frauen mit vorangegangener endokriner Therapie.

Zweckmäßige Vergleichstherapie & Ausmaß und Wahrscheinlichkeit des Zusatznutzens:

<u>a1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben</u>

Zweckmäßige Vergleichstherapie:

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

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Ein Zusatznutzen ist nicht belegt

<u>b1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie</u>

Zweckmäßige Vergleichstherapie:

- eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:
  - Tamoxifen oder
  - Anastrozol oder
  - Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder

- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen Behandlung oder
- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung oder
- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant gegenüber Fulvestrant:

- Anhaltspunkt für einen geringen Zusatznutzen

b2) Prä-/perimenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie

Zweckmäßige Vergleichstherapie:

- eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligen Zulassung. Im vorliegenden Anwendungsgebiet sind Tamoxifen, Letrozol, Exemestan, Megestrolacetat und Medroxyprogesteronacetat zugelassen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

G-BA, 2020 [7].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Ribociclib (Neubewertung nach Fristablauf (Mammakarzinom, HR+, HER2-, Kombination mit einem Aromatasehemmer)) Vom 20. August 2020.

Anwendungsgebiet

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 endokrinbasierte 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.

Hinweis:

Die vorliegende Bewertung bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Ribociclib in Kombination mit einem Aromatasehemmer. Für die Bewertung des Zusatznutzens von Ribociclib mit Fulvestrant wird auf das separate Nutzenbewertungsverfahren für diese Kombinationstherapie verwiesen. Gegenstand des vorliegenden Nutzenbewertungsverfahrens ist die Patientengruppe „postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Mammakarzinoms, die noch keine initiale endokrine Therapie erhalten haben.

a1) postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

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

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Ribociclib in Kombination mit Letrozol gegenüber Letrozol:

Anhaltspunkt für einen geringen Zusatznutzen

G-BA, 2019 [9].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Mai 2019 - Abemaciclib (Mammakarzinom, HR+, HER2-, Kombination mit Aromatasehemmer)

Gültig bis: Patientengruppe a1) 31. Dezember 2022

Anwendungsgebiet

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.

Hinweis: Der vorliegende Beschluss bezieht sich ausschließlich auf die Bewertung des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer. Für die Bewertung des Zusatznutzens von Abemaciclib mit Fulvestrant wird auf das separate Nutzenbewertungsverfahren für diese Kombinationstherapie verwiesen.

a1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

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

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit Anastrozol oder Letrozol gegenüber Anastrozol oder Letrozol:

Ein Zusatznutzen ist nicht belegt

a2) Prä-/perimenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben:

Zweckmäßige Vergleichstherapie:

Tamoxifen in Kombination mit einer Ausschaltung der Ovarialfunktion.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b1) Postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

- eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:
  - Tamoxifen oder
  - Anastrozol oder
  - Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
  - Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung oder
  - Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung oder
  - Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b2) Prä-/perimenopausale Frauen mit Hormonrezeptor (HR)-positivem, HER2-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie:

Zweckmäßige Vergleichstherapie:

- eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligen Zulassung.

Im vorliegenden Anwendungsgebiet sind Tamoxifen, Letrozol, Exemestan, Megestrolacetat und Medroxyprogesteronacetat zugelassen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Abemaciclib in Kombination mit einem Aromatasehemmer gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

G-BA, 2021 [6].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Alpelisib in Kombination mit Fulvestrant (Mammakarzinom mit PIK3CA-Mutation, HR+, HER2-, Kombination mit Fulvestrant) vom 18. Februar 2021

Anwendungsgebiet

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.

a1) Postmenopausale Frauen mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom mit einer PIK3CA-Mutation nach Krankheitsprogression im Anschluss an eine endokrine Therapie als Monotherapie, welche in der (neo-) adjuvanten Therapiesituation erfolgte; Lungen- und/oder Lebermetastasen sind nicht vorhanden:

Zweckmäßige Vergleichstherapie:

- **Ribociclib** in Kombination mit einem nicht-steroidalen Aromatasehemmer
  oder
- Ribociclib in Kombination mit Fulvestrant
  oder
- Anastrozol
  oder
- Letrozol
  oder
- Fulvestrant
  oder
- ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alpelisib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Hinweis auf einen geringeren Nutzen.

a2) Postmenopausale Frauen mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom mit einer PIK3CA-Mutation nach Krankheitsprogression im Anschluss an eine endokrine Therapie als Monotherapie, welche in der (neo-) adjuvanten Therapiesituation erfolgte; Lungen- und/oder Lebermetastasen sind vorhanden:

Zweckmäßige Vergleichstherapie:

- Ribociclib in Kombination mit einem nicht-steroidalen Aromatasehemmer
  oder
- Ribociclib in Kombination mit Fulvestrant
  oder
- Anastrozol
  oder
- Letrozol
  oder
- Fulvestrant
  oder
- ggf. Tamoxifen, wenn Aromatasehemmer nicht geeignet sind

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alpelisib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Ein Zusatznutzen ist nicht belegt.

a3) Männer mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom mit einer PIK3CA-Mutation nach Krankheitsprogression im Anschluss an eine endokrine Therapie als Monotherapie, welche in der (neo-) adjuvanten Therapiesituation erfolgte:

Zweckmäßige Vergleichstherapie:

Therapie nach Maßgabe des Arztes

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alpelisib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

b1) Postmenopausale Frauen mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom mit einer PIK3CA-Mutation nach Krankheitsprogression im Anschluss an eine endokrine Therapie als Monotherapie, welche im lokal fortgeschrittenen oder metastasierten Stadium erfolgte:

Zweckmäßige Vergleichstherapie:

- Abemaciclib in Kombination mit Fulvestrant
  oder
- Ribociclib in Kombination mit Fulvestrant
  oder
- Tamoxifen
  oder
- Anastrozol
  oder
- Fulvestrant als Monotherapie; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung
  oder
- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung
  oder
- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung
  oder
- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alpelisib in Kombination mit Fulvestrant gegenüber Fulvestrant:

Hinweis auf einen geringeren Nutzen.

b2) Männer mit einem Hormonrezeptor(HR)-positiven, humanen epidermalen Wachstumsfaktor-Rezeptor-2(HER2)-negativen, lokal fortgeschrittenen oder metastasierten Mammakarzinom mit einer PIK3CA-Mutation nach Krankheitsprogression im Anschluss an eine endokrine Therapie als Monotherapie, welche im lokal fortgeschrittenen oder metastasierten Stadium erfolgte:

Zweckmäßige Vergleichstherapie:

Therapie nach Maßgabe des Arztes

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Alpelisib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

G-BA, 2019 [10].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Palbociclib (Brustkrebs; in Kombination mit Fulvestrant nach endokriner Therapie; Neubewertung nach Fristablauf) Vom 22. März 2019

Die in Anlage XII zu dem Wirkstoff Palbociclib enthaltenen Feststellungen in der Fassung des Beschlusses vom 18. Mai 2017 bleiben unter Aufhebung der Befristung für die Patientengruppen b1 und b2 nach Maßgabe der folgenden Änderungen Bestandteil der Arzneimittel-Richtlinie:

1. Die Angaben unter Palbociclib zu Datum und Inkrafttreten der Beschlüsse werden wie folgt gefasst:

„1. Beschluss vom: 18. Mai 2017 In Kraft getreten am: 18. Mai 2017 BAnz AT 16.06.2017 B2 2. Beschluss vom: 20. September 2018 In Kraft getreten am: 20. September 2018 BAnz AT 25.10.2018 B3 3. Beschluss vom: 22. März 2019 In Kraft getreten am: 22. März 2019 BAnz AT TT.MM.JJJJ Bx“

Anwendungsgebiet

2. Den Feststellungen unter „Zugelassenes Anwendungsgebiet (laut Zulassung vom 09. November 2016):“ werden folgende Feststellungen angefügt:

„Hinweis: Der Beschluss vom 22. März 2019 bezieht sich ausschließlich auf die Bewertung des

Zusatznutzens von Palbociclib in Kombination mit Fulvestrant in den Teilpopulationen: b1) Postmenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist und b2) Prä-/ perimenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist.“

3. Die Feststellungen unter „1. Zusatznutzen des Arzneimittels im Verhältnis zur zweckmäßigen Vergleichstherapie“ zu den Patientenpopulationen „b1)“ und „b2)“ werden wie folgt gefasst:

Zweckmäßige Vergleichstherapie

„b1) Postmenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist:

Zweckmäßige Vergleichstherapie:

Eine weitere endokrine Therapie in Abhängigkeit der Vortherapie mit:

- Tamoxifen

  oder
- Anastrozol

  oder
- Fulvestrant; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung,

  oder
- Letrozol; nur für Patientinnen mit Rezidiv oder Progress nach einer Antiöstrogen-Behandlung,

  oder
- Exemestan; nur für Patientinnen mit Progress nach einer Antiöstrogen-Behandlung,

  oder
- Everolimus in Kombination mit Exemestan; nur für Patientinnen ohne symptomatische viszerale Metastasierung, nachdem es zu einer Progression nach einem nicht-steroidalen Aromataseinhibitor gekommen ist.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Palbociclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt

b2) Prä-/perimenopausale Patientinnen, bei denen es nach endokriner Therapie zu einer Progression gekommen ist:

Zweckmäßige Vergleichstherapie:

- Eine endokrine Therapie nach Maßgabe des Arztes, unter Beachtung der jeweiligenZulassung.

Im vorliegenden Anwendungsgebiet sind Tamoxifen, Letrozol, Exemestan,

Megestrolacetat und Medroxyprogesteronacetat zugelassen.

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Palbociclib in Kombination mit Fulvestrant gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt“

3.2 Cochrane Reviews

Es wurden keine Cochrane Reviews identifiziert.

3.3 Systematische Reviews

Zheng J et al., 2020 [26].

Combination cyclin-dependent kinase 4/6 inhibitors and endocrine therapy versus endocrine monotherapy for hormonal receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: A systematic review and meta-analysis.

Fragestellung

This meta-analysis aimed to assess the efficacy and safety of cyclin-dependent kinase (CDK) 4/6 inhibitors plus endocrine therapy (ET) in hormonal receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (ABC).

Methodik

Population:

- adults with HR+, HER2- advanced breast cancer

Intervention:

- CDK 4/6 inhibitors plus ET

Komparator:

- single-agent ET

Endpunkte:

- progression-free survival (PFS), overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR), and adverse events (AEs)

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane, ClinicalTrials.gov., ASCO, ESMO and AACR databases from inception to October 10, 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration and PRISMA recommendations

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs with 5043 women

Charakteristika der Population:

Table 1. Characteristic of nine included trials.

Study	Year	Phase	Histology	region	Regimen	Dose	Patients	Median age (year)	Treatment strategy for ABC
PALOMA-1 NCT00721409	2017	II	Postmenopausal women; ER +/HER2-ABC	International	Palbociclib + Letrozole vs Letrozole	Palbociclib 125mg daily, 3 weeks on/ 1 week off; LTZ 2.5mg qd	165 (84/81)	63 64	First-line therapy
PALOMA-2 NCT01740427	2018	III	Postmenopausal women; ER +/HER2-ABC	International	Palbociclib + Letrozole vs Placebo+ Letrozole	Palbociclib 125mg daily, 3 weeks on/ 1 week off; LTZ 2.5mg qd	666 (444/ 222)	62 61	First-line therapy
PALOMA-3 NCT01942135	2018	III	Women; HR +/HER2- ABC	International	Palbociclib + Fulvestrant vs Placebo+ Fulvestrant	Palbociclib 125mg daily 3 weeks on/ 1 week off; Fulvestrant 500mg q4w (additional on d15 of cycle 1)	521 (347/ 174)	57 56	First-line or Subsequent-line ET; ≤1 line CT
MONALEESA-2 NCT01958021	2019	III	Postmenopausal women; HR +/HER2-ABC	International	Ribociclib+ Letrozole vs Placebo+ Letrozole	Ribociclib 600mg daily 3 weeks on/ 1 week off; LTZ 2.5mg qd	668 (334/ 334)	62 63	First-line therapy
MONALEESA-3 NCT02422615	2018	III	Postmenopausal women; HR +/HER2-ABC	International	Ribociclib + Fulvestrant vs Placebo+ Fulvestrant	Ribociclib 600mg daily 3 weeks on/ 1 week off; Fulvestrant 500mg q4w (additional on d15 of cycle 1)	726 (484/ 242)	63 63	First-line or Second-line ET; no CT
MONALEESA-7 NCT02278120	2019	III	Pre- or peri-menopausal Women; HR+/HER2- ABC	International	Ribociclib+ TAM/ NSAI + Goserelin vs Placebo + TAM/ NSAI + Goserelin	Ribociclib 600mg daily 3 weeks on/ 1 week off; 20mg qd; TAM 20mg qd OR LTZ 2.5mg qd OR Anastrozole 1mg qd; Goserelin 3.6mg q4w	672 (335/ 337)	43 45	First-line ET; ≤1 line CT
MONARCH-2 NCT02107703	2019	III	Women; HR +/HER2- ABC	International	Abemaciclib + Fulvestrant vs Placebo+ Fulvestrant	Abemaciclib 150mg bid; Fulvestrant 500mg q4w (additional on d15 of cycle 1)	669 (446/ 223)	59 62	First-line or Second-line ET; no CT
MONARCH-3 NCT02246621	2019	III	Postmenopausal women; HR +/HER2-ABC	International	Abemaciclib+ NSAI vs Placebo+ NSAI	Abemaciclib 150mg bid; LTZ 2.5mg qd OR Anastrozole 1mg qd;	493 (328/ 165)	63 63	First-line therapy
MONARCH plus NCT02763566	2019	III	Postmenopausal women; HR+/HER2-ABC	International	Abemaciclib+ NSAI vs Placebo+ NSAI Abemaciclib + Fulvestrant vs Placebo+ Fulvestrant	Abemaciclib 150mg bid; LTZ 2.5mg qd OR Anastrozole 1mg qd; Fulvestrant 500mg q4w (additional on d15 of cycle 1)	463 (207/99) (104/53)	- -	First-line therapy/ subsequent-line ET ≤1 line CT

ER+: Estrogen receptor positive; HR+: Hormonal receptor-positive; HER2-: Human epidermal growth factor receptor 2-negative; ABC: Advanced breast cancer; NSAI: Nonsteroidal aromatase inhibitor (letrozole or anastrozole); ET: endocrine therapy; CT: chemotherapy; LTZ: Letrozole; TAM: tamoxifen; NR: Not reached.

Qualität der Studien:

- all trials were at low risk of selection bias (random sequence generation and allocation concealment). Except for one trial was open-label trials, other RCTs were double-blind trials with low risk of performance bias. Most of the included randomized trials had a low risk of detection bias, reporting bias, and other bias. Eight of nine trials were at high risk of attrition bias because of more than 50% discontinued patients after randomization and receiving at least one dose of allocated intervention. However, objective progression or relapse caused approximately 50–80% of patients withdrew from the included RCTs. Such patients received other subsequent treatment with continuous follow-up. Therefore, the included studies had a low risk of incomplete outcome data. Indeed, the high attrition bias in the present study did not influence the result of this meta-analysis

Studienergebnisse:

- Compared with ET alone, CDK 4/6 inhibitors and ET combination improved in PFS (hazard ratio (HR) 0.54, 95% confidence interval (CI) 0.50–0.59, p< 0.00001) and OS (HR 0.77, 95% CI 0.69– 0.85, p< 0.00001), regardless of
  - ET strategies (HR 0.54, 95% CI 0.50–0.59 in PFS; HR 0.77, 95% CI 0.69–0.85 in OS),
  - treatment line of advanced disease (HR 0.52, 95% CI 0.46– 0.59 in PFS; HR 0.75, 95% CI 0.66–0.85 in OS) and
  - menopausal status (HR 0.54, 95% CI 0.50–0.58 in PFS; HR 0.76, 95% CI 0.68–0.84 in OS).

- Higher risk of grade 3/4 AEs (RR 2.66, 95% CI 2.44–2.90, p< 0.00001) were observed in the combination group than in the ET group.

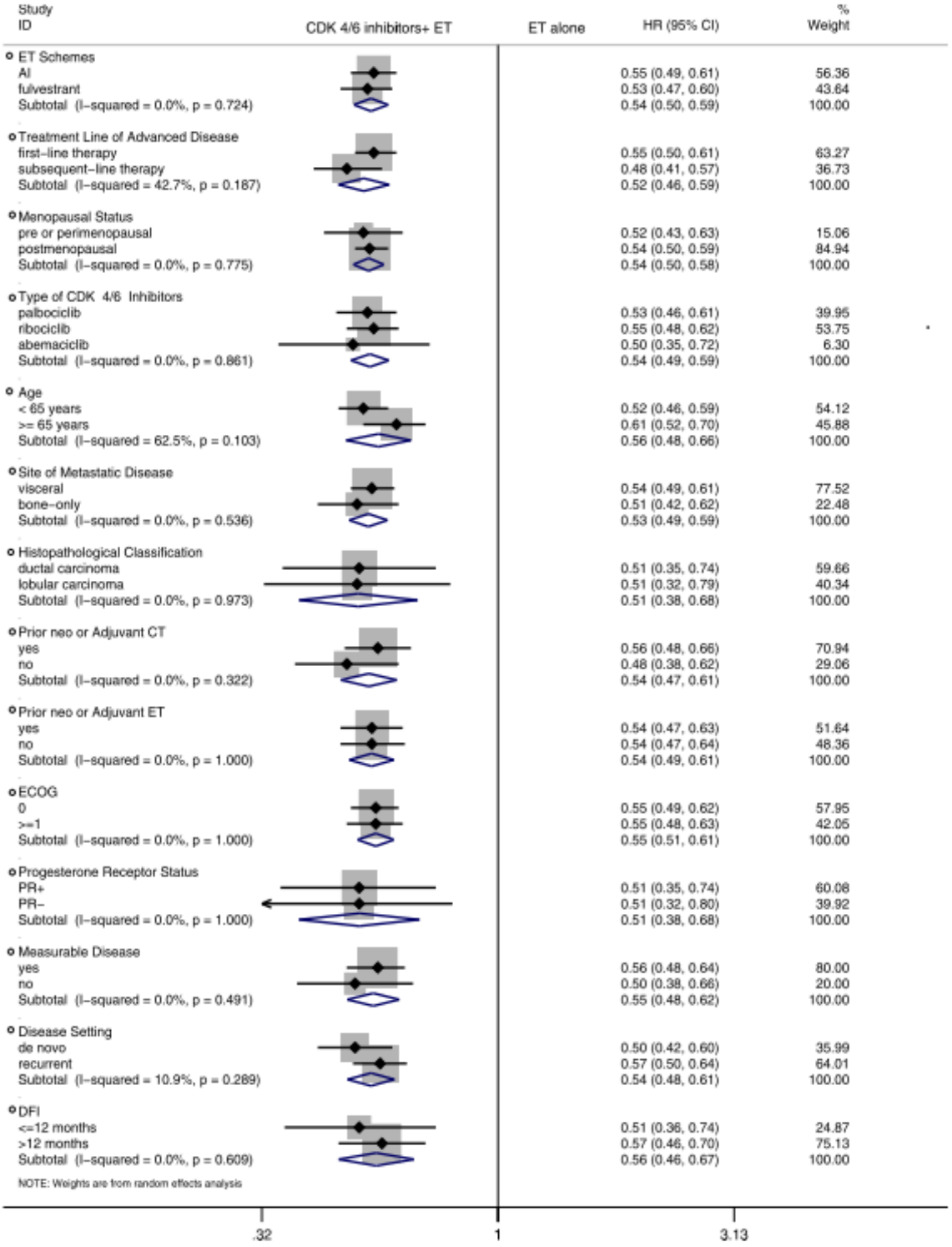

Fig 4. Forest plot of hazard ratio for progression-free survival (PFS) by subgroup analysis in CDK 4/6 inhibitors plus endocrine combination therapy and endocrine monotherapy. ET: endocrine therapy; AI: aromatase inhibitors; CT: chemotherapy; PR: progesterone receptor; DFI: disease-free interval.

Anmerkung/Fazit der Autoren

Combination therapy with CDK 4/6 inhibitors and ET prolongs survival in HR+/ HER2- ABC. This combination is a better therapeutic strategy than endocrine monotherapy in HR +/HER2- ABC, regardless of treatment line, menopausal status and other individual characteristics.

Xu L et al., 2018 [24].

A comparison of fulvestrant plus a targeted agent with fulvestrant alone in hormone receptor-positive advanced breast cancer that progressed on prior endocrine therapy: a meta-analysis.

Fragestellung

to evaluate the efficacy and safety of fulvestrant combined with a targeted agent compared with fulvestrant monotherapy in those hormone receptor-positive MBC patients progressed on prior endocrine therapy.

Methodik

Population:

- patients with hormone receptor-positive MBC progressed on previous endocrine therapy

Intervention:

- fulvestrant single agent

Komparator:

- fulvestrant plus targeted agents

Endpunkte:

- PFS, OS, overall response rate (ORR), clinical benefit rate (CBR), toxicity

Recherche/Suchzeitraum:

- From January 1, 1990 to December 10, 2017 from the PubMed, Cochrane library, and Embase. The ClinicalTrials.gov network

Qualitätsbewertung der Studien:

- Jadad scale

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 studies were included with 3,910-hour positive MBC patients progressed on prior endocrine therapy

Charakteristika der Population:

Table 1 Characteristics of 13 trials eligible for meta-analysis

Author	Year	Phase	Regimens	Dose of FUL	Pathways inhibited	Targeted agents	Jadad score
Sledge GW[14]	2017	III	FUL + abemaciclib/FUL	500 mg	CDK4/6	Abemaciclib	3
Zaman K[15]	2015	II	FUL + selumetinib/FUL	500 mg	MEK1/2	Selumetinib	3
Adelson K[23]	2016	II	FUL + bortezomib/FUL	500 mg	Proteasome	Bortezomib	3
Cristofanilli M[12]	2016	III	FUL + palbociclib/FUL	500 mg	CDK4/6	Palbociclib	3
Hyams DM[24]	2013	II	FUL + cediranib/FUL	250 mg	VEGF	Cediranib	3
Burstein HJ[16]	2014	III	FUL + lapatinib/FUL	250 mg	HER1, HER2	Lapatinib	3
Clemons MJ[17]	2014	II	FUL + vande/FUL	500 mg	VEGF, EGFR	Vandetanib	3
Musolino A[25]	2017	II	FUL + dovitinib/FUL	500 mg	FGFR	Dovitinib	3
Baselga J[13]	2017	III	FUL + buparlisib/FUL	500 mg	PI3K	Buparlisib	3
Kornblum NS[26]	2016	II	FUL + everolimus/FUL	500 mg	mTOR	Everolimus	3
Krop IE[27]	2016	II	FUL + pictilisib/FUL	500 mg	PI3K	Pictilisib	3
Di Leo A[28]	2017	III	FUL + buparlisib/FUL	500 mg	PI3K	Buparlisib	3
Robertson JF[29]	2013	II	FUL + ganitinib/FUL	500 mg	IGF-1/IGF-2	Ganitumab	3

Abbreviations: CDK4/6, cyclin-dependent kinase 4/6; FUL, fulvestrant; HER1, human epidermal growth factor receptor 1; HER2, human epidermal growth factor receptor 2.

Qualität der Studien:

- All studies had a Jadad score of 3.

Studienergebnisse:

Table 2 Patients characteristics and outcomes in this meta-analysis

Author	No of patients	Postmenopausal status (%)	HER2 status	ORR (doublet agents vs single agent)	Median PFS (months, doublet agents vs single agent)	Median OS (months, doublet agents vs single agent)
Sledge GW[14]	669	83	–	35% vs 16%	16.4 vs 9.3	–
Zaman K[15]	42	100	–	5% vs 15%	3.7 vs 5.6	22.9 vs 19.4
Adelson K[23]	116	100	–	–	2.73 vs 2.69	–
Cristofanilli M[12]	521	79	–	19% vs 9%	9.5 vs 4.6	–
Hyams DM[24]	62	100	NA	22% vs 8%	7.4 vs 3.7	–
Burstein HJ[16]	291	100	±18%	20% vs 9%	4.7 vs 3.8	30 vs 26.4
Clemons MJ[17]	129	100	±5%	0% vs 7%	5.8 vs 4.8	31 vs –
Musolino A[25]	97	100	–	28% vs 10%	5.5 vs 5.5	–
Baselga J[13]	1,147	100	–	12% vs 8%	6.9 vs 5.0	–
Kornblum NS[26]	130	100	–	–	10.4 vs 5.1	–
Krop IE[27]	168	100	–	8% vs 6%	6.6 vs 5.1	–
Di Leo A[28]	432	100	–	8% vs 2%	3.9 vs 1.8	–
Robertson JF[29]	156	100	±7%	–	3.7 vs 5.4	–

Abbreviations: HER2, human epidermal growth factor receptor 2; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; NA, not available.

- Improvements of doublet-agents group were proven in terms of PFS (HR 0.73, 95% CI =0.63–0.86, P=0.000) and ORR (RR 2.07, 95% CI =1.67–2.58, P=0.000).
- Further subgroup analysis also demonstrated that fulvestrant in combination with a cyclin-dependent kinase (CDK4/6) inhibitor or a PI3K/mTOR inhibitor was associated with a superior efficacy (RR 2.72, 95% CI =1.93–3.83, P=0.000 and RR 1.60, 95% CI =1.15–2.23, P=0.005, respectively).
- The efficacy was comparable between the other combination strategies and fulvestrant alone. With respect to the adverse effects, adding a targeted agent to fulvestrant also produced more frequent grade 3/4 toxicities (RR 3.86, 95% CI =2.66–5.61, P=0.000).

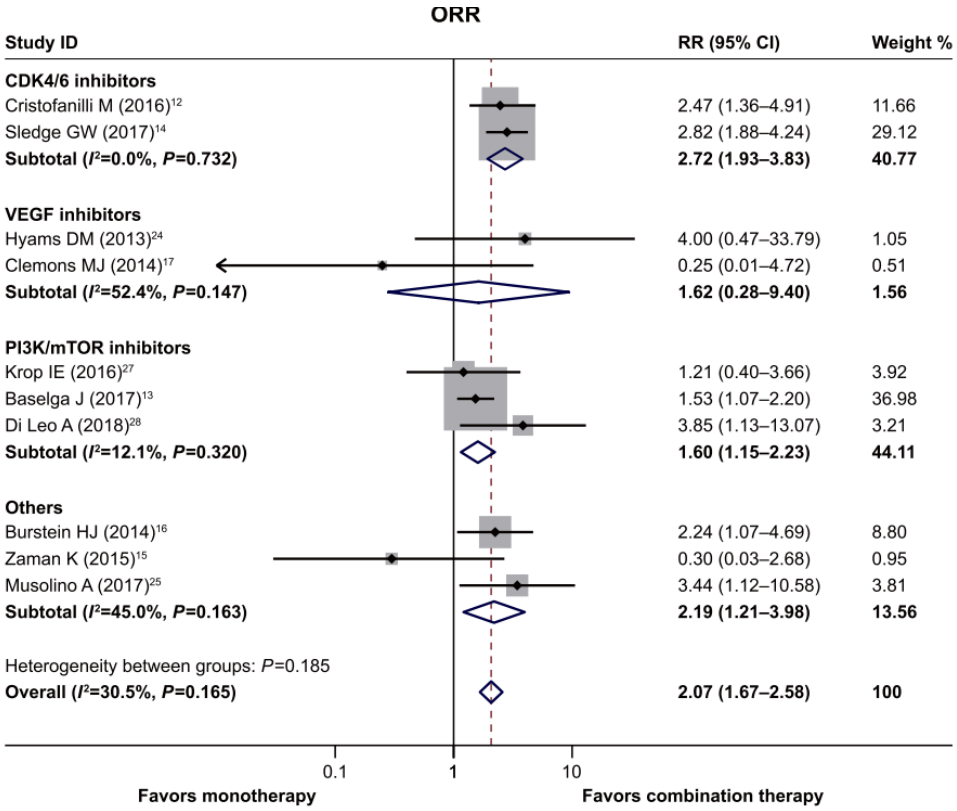

Figure 3 The pooled risk ratio (RR) and 95% CI for overall response rate.
Abbreviations: ORR, overall response rate; CDK4/6, cyclin-dependent kinase 4/6.

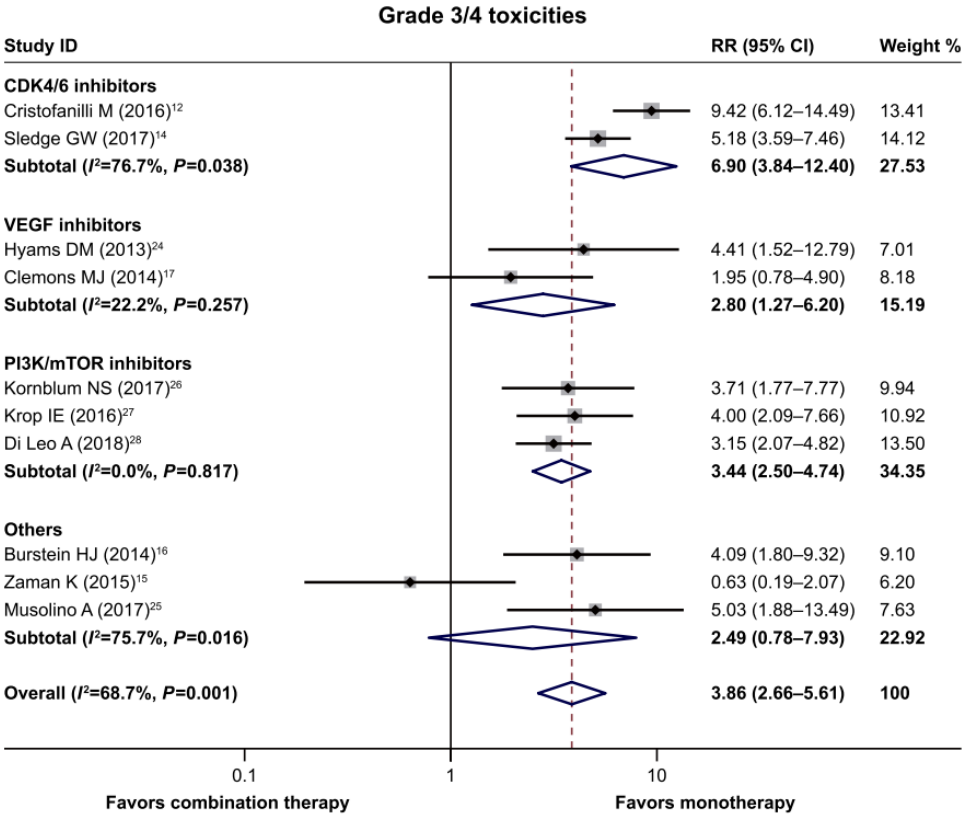

Figure 4 Forest plot of relative risk of treatment induced grade 3/4 toxicities.
Note: Weights are from random effects analysis.
Abbreviations: RR, risk ratio; CDK4/6, cyclin-dependent kinase 4/6.

Anmerkung/Fazit der Autoren

In conclusion, we validated the combination of a targeted agent with fulvestrant was associated with a superior benefit and more frequent AEs when compared with fulvestrant alone. This warrants that further studies focus on identification of those patients who will derive benefits from the combination strategy to aid treatment decisions.

Kommentare zum Review

- Einige Wirkstoffe (vgl. oben – Charakteristika der Population) in Deutschland nicht zugelassen

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Zhang T et al., 2018 [25].

Comparative efficacy of different targeted therapies plus fulvestrant for advanced breast cancer following progression on prior endocrine therapy: a network meta-analysis.

Fragestellung

a network meta-analysis of randomized controlled trials (RCTs) to indirectly compare the efficacy of different targeted agents with fulvestrant for patients with hormone-receptor-positive (HR+) and human epidermal growth factor receptor type 2-negative (HER2–) advanced breast cancer (ABC) following progression on prior endocrine therapy.

Methodik

Population:

- HR+/HER2– women with ABC who have progressed or recurrence after previous endocrine therapy or targeted therapy.

Intervention/Komparator:

- fulvestrant plus any of the following treatments: palbociclib, abemaciclib, buparlisib, dovitinib, ribociclib, vandetanib, and everolimus, pictilisib, bortezomib, selumetinib, and placebo

Endpunkte:

- PFS and ORR

Recherche/Suchzeitraum:

- PubMed, EMBASE, and the Cochrane Library databases from inception to June 5, 2018

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s tool

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 11 studies, including 4,178 patients

Charakteristika der Population:

Table 1 Characteristics of the 11 studies included in the network meta-analysis

Study (year)	Trial	Pathway inhibited	Disease stage	Intervention arm	Age (years)[a]	Sample size	Postmenopausal status (%)	HR+ status (%)	PET	ECOG PS (%) (0/1)	Median PFS (months)	Outcomes
Sledge et al (2017)[23]	MONARCH 2	CDK4/6	ABC	Abemaciclib + fulv Placebo + fulv	59 (32–91) 62 (32–87)	446 223	83.2% 80.7%	ER+: 100% PR+: 76.0% ER+: 100% PR+: 76.7%	AI	59.2/39.5 61.0/39.0	16.4 9.3	PFS/ORR
Musolino et al (2017)[27]	—	FGFR	LABC /MBC	Dovitinib + fulv Placebo + fulv	63 (44–82) 63 (38–82)	47 50	NR	ER+ and/or PR+: 100%	Tam and/ or AI	59.6/38.8 56.0/40.0	5.5	PFS/ORR
Kornblum et al (2018)[31]	PrECOG 0102	mTOR	MBC	Everolimus + fulv Placebo + fulv	61 (35–92)	66 65	NR	ER+ and/or PR+: 100%	AI	61/39 58/42	19.3	PFS/ORR
Baselga et al (2017)[25]	BELLE-2	PI3K	LABC /MBC/	Buparlisib + fulv Placebo + fulv	62 (55–69) 61 (54–68)	576 571	NR	ER+ and/or PR+: 100%	AI	58.0/40.0 60.0/37.0	6.9 5.0	PFS/ORR
Krop et al (2016)[28]	FERGI	PI3K–mTOR	LABC /MBC	Pictilisib + fulv Placebo + fulv	60 (36–90) 63 (40–82)	89 79	NR	ER+: 100% PR+: 65% ER+: 100% PR+: 73%	AI	NR	6.6 5.1	PFS/ORR
Cristofanilli et al (2016)[15]	PALOMA-3	CDK4/6	MBC	Palbociclib + fulv Placebo + fulv	57 (30–88) 56 (29–80)	347 174	79% 79%	ER+ and PR+: 43% ER+ and PR+: 40%	AI	59.0/41.0 67.0/33.0	9.5 4.6	PFS/ORR
Clemons et al (2014)[29]	OCOG ZAMBONEY	VEGF	MBC	Vandetanib + fulv Placebo + fulv	61.6 57.7	61 68	NR	ER+: 92% PR+: 77% ER+: 94% PR+: 69%	Tam and/ or AI	54.0/44.0 53.0/40.0	5.8 4.8	PFS
Adelson et al (2016)[30]	New York Cancer Consortium	—	LABC /MBC	Bortezomib + fulv Fulv	59 (31–80) 57 (31–83)	57 59	NR	ER+: 100% ER+: 100%	PET	65/33 64/34	2.73 2.69	PFS
Di Leo et al (2017)[24]	BELLE-3	PI3K	LABC /MBC	Buparlisib + fulv Placebo + fulv	60 (54–68) 62 (55–69)	289 143	NR	NR	PET	60/39 64/34	8.3 12.0	PFS/ORR
Slamon et al (2018)[22]	MONALEESA-3	CDK4/6	ABC	Ribociclib+ fulv Placebo + fulv	63 (31–89) 63 (34–86)	484 242	NR	ER+: 99.4% PR+: 72.9% ER+: 99.6% PR+: 69.0%	Tam and/ or AI	64.0/35.7 65.3/34.3	20.3 12.8	PFS
Zaman et al (2015)[26]	SAKK 21/08	SAKK 21/08	ABC	Selumetinib + fulv Placebo + fulv	66 (40–79) 69 (46–79)	22 20	NR	ER and/or PR ≥10%	Tam and/ or AI	73 65	3.7 5.6	PFS/ORR

Note: [a]Age data presented as median (range) or mean.
Abbreviations: ABC, advanced breast cancer; AI, aromatase inhibitor; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+, estrogen-receptor positive; FGFR, fibroblast growth factor receptor; fulv, fulvestrant; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; NR, not reported; ORR, objective response rate; PET, prior endocrine therapy; PI3K, phosphatidylinositol 3-kinase; PFS, progression-free survival; PR+, progesterone-receptor positive; Tam, tamoxifen.

Qualität der Studien:

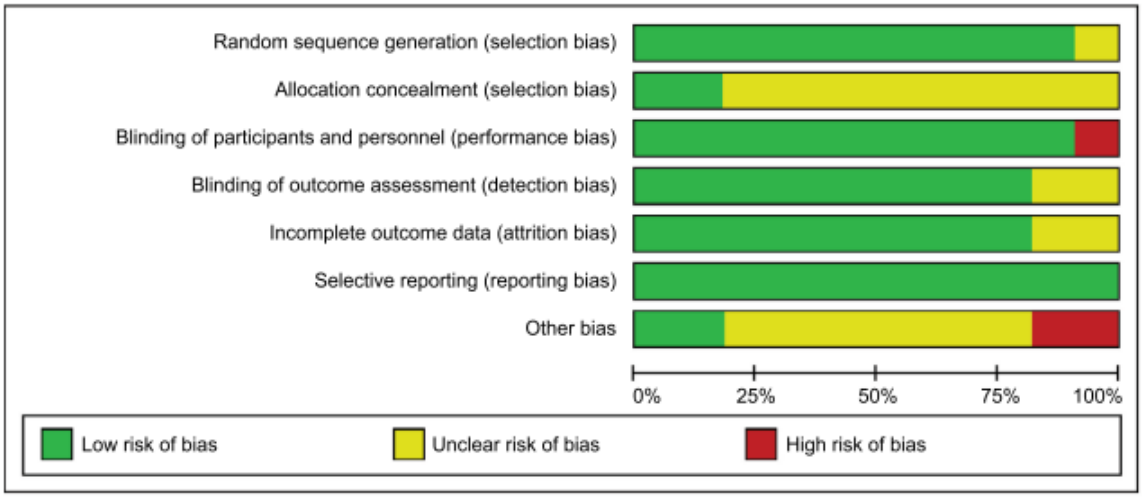

Figure 2 Cochrane risk of bias tool assessment (green: low risk of bias; red: high risk of bias; and yellow: unclear risk of bias).

Studienergebnisse:

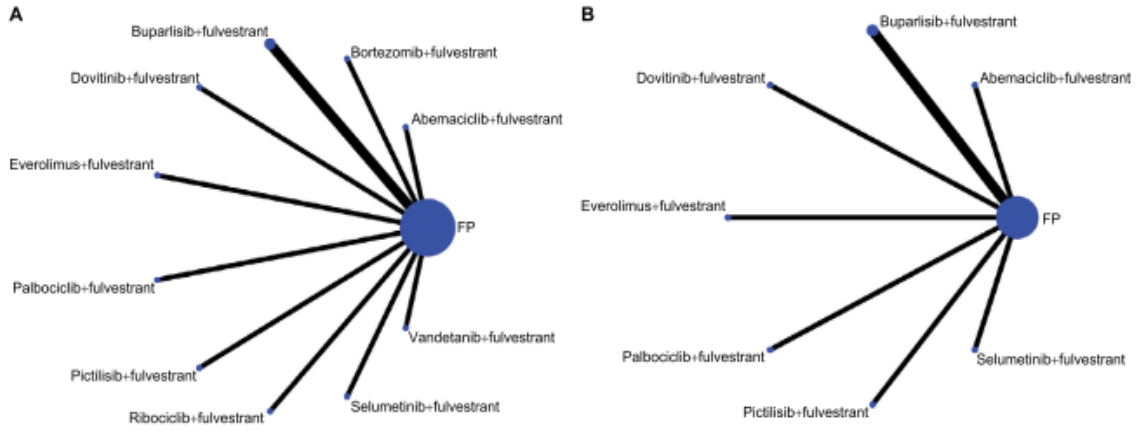

Figure 3 Network of eligible comparisons for network meta-analysis for PFS (**A**) and ORR (**B**).
Abbreviations: FP, placebo+fulvestrant; ORR, objective response rate; PFS, progression-free survival.

- In terms of the pooled hazard ratios (HRs) for PFS, palbociclib plus fulvestrant was superior to other target agents plus fulvestrant (HR=0.62, 95% credible interval [CrI]: 0.40–0.96; HR=0.62, 95% CrI: 0.47–0.96; for pictilisib plus fulvestrant and buparlisib plus fulvestrant, respectively).
- Ribociclib plus fulvestrant has no difference in abemaciclib plus fulvestrant and palbociclib plus fulvestrant (HR =1.02, 95% CrI =0.72–1.45; HR =1.22, 95% CrI =0.84–1.78).
- In terms of objective response rate, compared with placebo plus fulvestrant, abemaciclib plus fulvestrant, dovitinib plus fulvestrant, buparlisib plus fulvestrant, and palbociclib plus fulvestrant had a significant difference (odds ratio [OR] =2.84, 95% CrI =1.91– 4.31; OR =3.62, 95% CrI =1.21–12.48; OR =1.80, 95% CrI =1.25–2.60; and OR =2.52, 95% CrI =1.43– 4.72, respectively).

Anmerkung/Fazit der Autoren

The present study showed that palbociclib plus fulvestrant may be the optimal treatment for HR+/HER2– postmenopausal women with ABC after disease progression following endocrine therapy. However, direct comparisons are still needed to examine differences among different targeted agents plus fulvestrant.

Kommentare zum Review

- Einige Wirkstoffe (vgl. oben – Charakteristika der Population) in Deutschland nicht zugelassen

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Ding W et al., 2018 [4].

The CDK4/6 inhibitor in HR-positive advanced breast cancer: A systematic review and meta-analysis

Fragestellung

To explore whether CDK4/6 inhibitors had a significantly benefit to treating hormone receptor-positive (HR-positive)/human epidermal growth factor receptor 2 negative (HER2-negative) advanced breast cancer

Methodik

Population:

- patients with HR-positive/HER2-negative advanced breast cancer

Intervention:

- CDK4/6 inhibitors

Komparator:

- K.A. siehe ,,Charakteristika der Population''

Endpunkte:

- progression-free survival, response, and adverse events

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, and Cochrane Library from January 1980 to December 2017

Qualitätsbewertung der Studien:

- Cochrane Approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs (2x Palbociclib, 2x Ribociclib, 2 Abemaciclib) records containing 3182 patients

Charakteristika der Population:

Table 1

Characteristics of included studies and outcome events.

Trials	Finn 2014[9]	Finn 2016[10]	Hortobagyi 2016[11]	Cristofanilli 2016[13]	Sledge 2017[14]	Goetz 2017[15]
Information of the included trials						
Regions	50 sites in 12 countries	186 sites in 17 countries	223 sites in 29 countries	144 sites in 17 countries	142 sites in 19 countries	158 sites in 22 countries
Phases	I	II	II	II	III	II
Accrual dates	December 22, 2009, and May 12, 2012	February 2013 and July 2014	January 24, 2014, and March 24, 2015	October 7, 2013, and August 26, 2014	August 7, 2014, and December 29, 2015	November 18, 2014, and November 11, 2015
Inclusion criteria and study design						
Inclusion criteria	Postmenopausal; HR+, HER2− ABC; first-line	Postmenopausal; HR+, HER2− ABC; first-line	Postmenopausal; HR+, HER2− ABC; first-line	Any menopausal status; HR+, HER2− ABC; second-line	Any menopausal status, HR+, HER2− ABC; second-line	Postmenopausal; HR+, HER2− ABC; first-line
Study design	Palbociclib (125 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Palbociclib (125 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Ribociclib (600 mg daily for 21 d every 28 d) + letrozole (2.5 mg daily) vs placebo + letrozole (2.5 mg daily)	Palbociclib (125 mg daily for 21 d every 28 d) + fulvestrant (500 mg every 28 d) vs placebo + fulvestrant (500 mg every 28 d)	Abemaciclib (150 mg twice daily every 28 d) + fulvestrant (500 mg every 28 d) vs placebo + fulvestrant (500 mg every 28 d)	Abemaciclib (150 mg twice daily every 28 d) + anastrozole (1 mg daily) or letrozole (2.5 mg daily) vs placebo + anastrozole (1 mg daily) or letrozole (2.5 mg daily)
Patient demographic characteristic						
Age, y	T: 63 (54–71) C: 64 (56–70	T: 62 (30–89) C: 61 (28–88)	T: 62 (23–91) C: 63 (29–88)	T: 57 (30–88) C: 56 (29–80)	T: 59 (32–91) C: 63 (29–88)	T: 63 (38–87) C: 63 (32–88)
No. of patients	T: 84 C: 81	T: 444 C: 222	T: 334 C: 334	T: 347 C: 174	T: 446 C: 223	T: 328 C: 165
Outcomes assessment						
Primary end point	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival	Progression-free survival
Secondary end point	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response, the clinical benefit response	Objective response rate, the clinical benefit response	Objective response rate, the clinical benefit response

ABC = advanced breast cancer, C = control group, HER2− = human epidermal growth factor receptor 2 negative, HR+ = hormone receptor positive, T = treatment group (also known as CDK4/6 inhibitor group).

Qualität der Studien:

- For allocation concealment, the risk of bias was unclear in 3 RCTs with an allocation scheme which was not mentioned in the trials. For random sequence generation, the risk of bias was unclear in 2 RCT studies. For the performance bias and detection bias, the risk was high in one study and unclear in another one. Except these 3 outliers, no high or unclear risk of bias was observed in any other studies.

Studienergebnisse:

- The result showed the CDK4/6 inhibitor group had a longer progression-free survival (PFS) (hazard ratio=0.51; 95% confidence interval [CI], 0.46–0.57, P < .00001), a better

objective response (risk rate=1.53; 95% CI, 1.35–1.74, P < .00001), as well as a better clinical benefit response (risk rate=1.29; 95% CI, 1.13–1.47, P=.0001).

- Besides, subgroup analyses of PFS according to stratification factors and other baseline characteristics confirmed a great performance of CDK4/6 inhibitors across the all subgroups.
- As for neutropenia, all grades of it were substantially more frequent in the CDK4/6 inhibitor group (65%), compared with the control group (5%). Interestingly, grade 3 or 4 neutropenia was found among 43% of patients in the CDK4/6 inhibitor group and among 1% of patients in the control group. Meanwhile, leucopenia with all grades also appeared much more common in the CDK4/6 inhibitor group than in the control group (35% and 3% respectively), especially grade 3 or 4 leucopenia. Furthermore, infection, fatigue, nausea, anemia, thrombocytopenia, alopecia, nausea, rash, constipation, vomiting, and stomatitis were also more common in the CDK4/6 inhibitor group. Serious adverse events from any cause were occurred among 308 (19%) persons of 1974 patients in the CDK4/6 inhibitor group, and among 121 people (12%) of 1185 patients in the control group.

Subgroup sensitivity and analysis for progression-free survival

	HR (95% CI)	*P*	I^2, %
1. Subgroup analysis			
Age			
<65 y	0.50 (0.44–0.57)	<.00001	11
≥65 y	0.56 (0.47–0.67)	<.00001	0
Visceral metastasis			
Yes	0.57 (0.47–0.62)	<.00001	0
No	0.50 (0.42–0.59)	<.00001	23
Bone-only metastasis			
Yes	0.47 (0.34–0.65)	<.0001	17
No	0.56 (0.47–0.66)	<.00001	35
Race			
Asian	0.46 (0.36–0.59)	<.00001	0
Non-Asian	0.56 (0.49–0.64)	<.00001	24
Disease-free interval			
<12 mo	0.51 (0.38–0.68)	<.00001	20
≥12 mo	0.48 (0.37–0.61)	<.00001	0
Newly metastatic disease			
Yes	0.58 (0.43–0.79)	.0005	33
No	0.55 (0.45–0.67)	<.00001	0
Previous hormonal therapy			
Yes	0.48 (0.40–0.56)	<.00001	0
No	0.56 (0.48,0.66)	<.00001	0
Previous chemotherapy			
Yes	0.51 (0.43–0.61)	<.00001	0
No	0.51 (0.41–0.62)	<.00001	47
ECOG performance status			
0	0.55 (0.45–0.65)	<.00001	0
1 or 2	0.55 (0.46,0.67)	<.00001	0
Hormone-receptor status			
ER and PR-positive	0.55 (0.45–0.67)	<.0001	0%
Other	0.48 (0.36–0.64)	<.00001	0%
Palbociclib vs ribociclib vs abemaciclib			
Palbociclib	0.51 (0.43–0.60)	<.00001	37
Ribociclib	0.56 (0.43–0.72)	<.00001	—
Abemaciclib	0.49 (0.41,0.59)	<.00001	0
First-line vs second-line			
First-line	0.56 (0.48–0.65)	<.00001	0
Second-line	0.46 (0.39–0.55)	<.00001	—
2. Sensitivity analysis			
Excluding Finn 2014 trial	0.51 (0.46–0.58)	<.00001	3

Anmerkung/Fazit der Autoren

CDK4/6 inhibitors can significantly prolong the PFS and improve the objective response or clinical benefit response, which was confirmed in every subgroup of the meta-analysis we performed. Adverse events are reversible, and the rate of discontinuation due to adverse events is low. Further studies should focus on whether treating with CDK4/6 inhibitors can significantly prolong the overall survival of patients with advanced breast cancer.

And PALOMA-3 studied the combination of palbociclib and fulvestrant as a second-line treatment for premenopausal and postmenopausal patients with HR-positive/HER2-negative metastatic breast cancer and progression after prior endocrine therapy. Adding palbociclib to endocrine therapy with fulvestrant clinically led to a significant improvement in median PFS from 3.8 months (95% CI, 3.5–5.5) to 9.2 months (95% CI, 7.5 to not estimable). The difference in PFS rates between PALOMA2 and PALOMA-3 might be caused of the fact that different studies recruited different patient populations (endocrine-sensitive disease vs endocrine-resistant disease, first-line therapy vs second-line therapy).

Kommentare zum Review

- Eingeschlossene Studien umfassen first- oder secondline endocrine setting

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Messina C et al., 2018 [17].

CDK4/6 inhibitors in advanced hormone receptor-positive/HER2-negative breast cancer: a systematic review and meta-analysis of randomized trials

Fragestellung

We performed a meta-analysis of randomized clinical trials (RCTs) to better define the benefit and the risk of CDK4/6 inhibitors plus ET for endocrine-sensitive or endocrine-resistant population in metastatic HR+/HER2− breast cancer.

Methodik

Population:

- Patientes with metastatic HR+/HER2− breast cancer

Intervention:

- CDK4/6 inhibitors plus endocrine therapy (ET)

Komparator:

- ET

Endpunkte:

- PFS, ORR, Safety

Recherche/Suchzeitraum:

- Pubmed, Embase, and the Cochrane Library with no data restriction was carried out up to 30 June 2018

Qualitätsbewertung der Studien:

- Risk of Incomplete outcome data addressed bias assessment: Adequate sequence generation, Allocation concealment, Masking, Free of selective reporting

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs with 4.578 patients

Charakteristika der Population:

- 5 RCTs first-line
- 2 RCTs seconed-line
- 1 RCT first and seconed-line
- Five trials out of eight enrolled patients in endocrine-sensitive setting *(7–9, 12, 13; 12, 13)*, two were carried in endocrine-resistant setting *(10, 11)*, and only one trial included women ET naïve or who progressed to one prior line of ET *(14)*.

10. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im S-A, Masuda N, Colleoni M, DeMichele A, Loi S, Verma S, Iwata S, Harbeck N, Zhang K et al (2016) Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 17(4):425–439
11. Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llombart-Cussac A (2017) MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 35(25):2875–2884
14. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, Petrakova K, Bianchi GV, Esteva FJ, Martín M, Nusch A, Sonke GS, De la Cruz-Merino L, Beck JT, Pivot X, Vidam G, Wang Y, Rodriguez Lorenc K, Miller M, Taran T, Jerusalem G (2018) Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol https ://doi.org/10.1200/JCO.2018.78.9909

- Genaue Beschreibung der Studien siehe Anhang 1

Qualität der Studien:

Table 2 Risks of bias assessment of the randomized studies included in the present meta-analysis

Trial	Adequate sequence generation	Allocation concealment	Masking	Incomplete outcome data addressed	Free of selective reporting
MONALEESA-2 [9]	A computer-generated randomization schedule was used	Parallel assignment	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONARCH-2 [11]	A computer-generated randomization schedule was used	Web-based randomization scheme	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONARCH-3 [12]	A computer-generated randomization schedule was used	Centralized interactive Web response system	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
PALOMA-1 [7]	A computer-generated randomization schedule was used	Centralized interactive Web-based randomization system	Open label design	All randomized patients included in analyses	All outcome of interest reported
PALOMA-2 [8]	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
PALOMA-3 [10]	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONALEESA-3	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature
MONALEESA-7	A computer-generated randomization schedule was used	Randomization by interactive randomization technology	Blinding of participants and personnel	All randomized patients included in analyses	All outcome of interest reported. OS data are not mature

Studienergebnisse:

- PFS: A total of 2009 patients were enrolled in the CDKi plus ET arm and 1381 in the ET arm.
  - The addition of CDKi to ET was associated with a statistically significant PFS benefit (HR 0.55, 95% CI 0.50–0.62) for metastatic HR+/ HER2− breast cancer patients in endocrine-sensitive setting. Moreover, combination treatment improved PFS both in

women with visceral metastasis at presentation (HR 0.55, 95% CI 0.47–0.65) and in those with non-visceral metastasis (HR 0.56, 95% CI 0.46–0.68).

- Three phase III trials [10, 11] assessed the efficacy of CDKi plus ET versus ET alone and reported PFS HRs in endocrine-resistant setting: hence results were suitable for our meta-analysis (Fig. 2b). A total of 791 women were enrolled in the CDKi plus ET arm and 395 in the ET arm. All the women included in the two trials had been previously treated with ET. The addition of CDKi to ET was associated with a statistically significant PFS benefit (HR 0.51, 95% CI 0.43–0.61). The PFS advantage was significantly maintained both in patients with visceral metastasis (HR 0.47, 95% CI 0.38–0.58) and in those with non-visceral metastasis (HR 0.56, 95% CI 0.43–0.73).

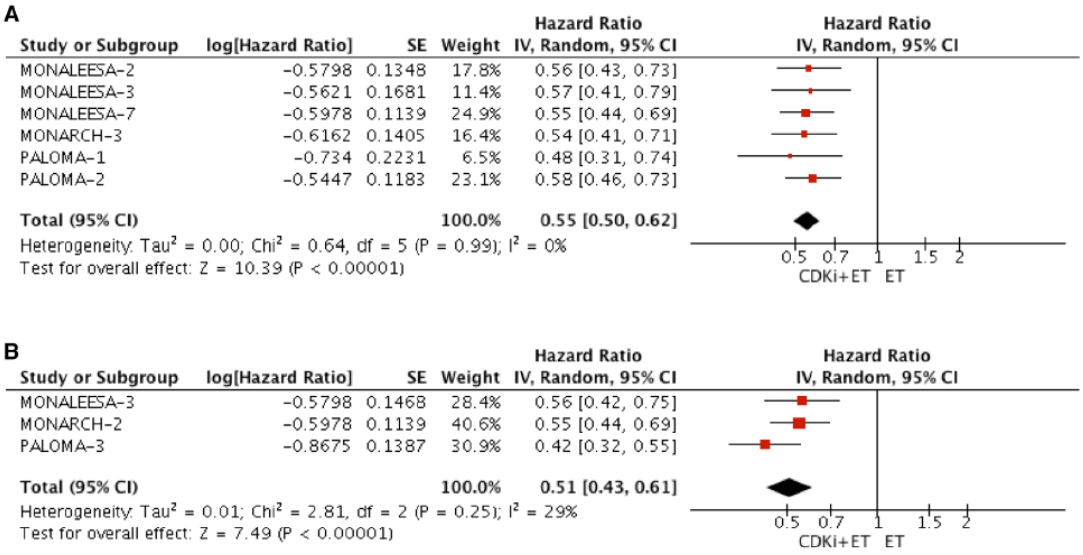


Fig. 2 Forest plot of hazard ratios (HRs) for progression-free survival (PFS) in eight randomized trials of CDK inhibitors plus endocrine therapy compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**) advanced HR+ HER2− breast cancer women. Pooling HRs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy

- Response: One phase II trial [7] and four phase III trials [8, 9, 12, 13] included in our systematic review reported on ORR events occurring in the CDKi plus ET arm and in the ET alone arm, respectively (Fig. 4). A total of 871 ORR events occurred among 1525 patients treated with CDKi plus ET, and 786 in the 1139 women receiving ET alone.
  - The combination of CDKi plus ET significantly improved the ORR compared to ET alone (ORs: 0.62, 95% CI 052–0.73) (Fig. 4a).
  - Two phase III trials reported the OR events occurring in the CDKi plus ET arm and in the ET alone arm, respectively, in endocrine-resistant setting: hence results were suitable for our meta-analysis (Fig. 4b). A total of 570 ORR events occurred among 793 patients treated with CDKi plus ET and 350 in the 397 women assigned to fulvestrant alone. The addition of CDKi–ET was associated with a statistically significant ORR benefit (ORs 0.33, 95% CI 0.24–0.47).

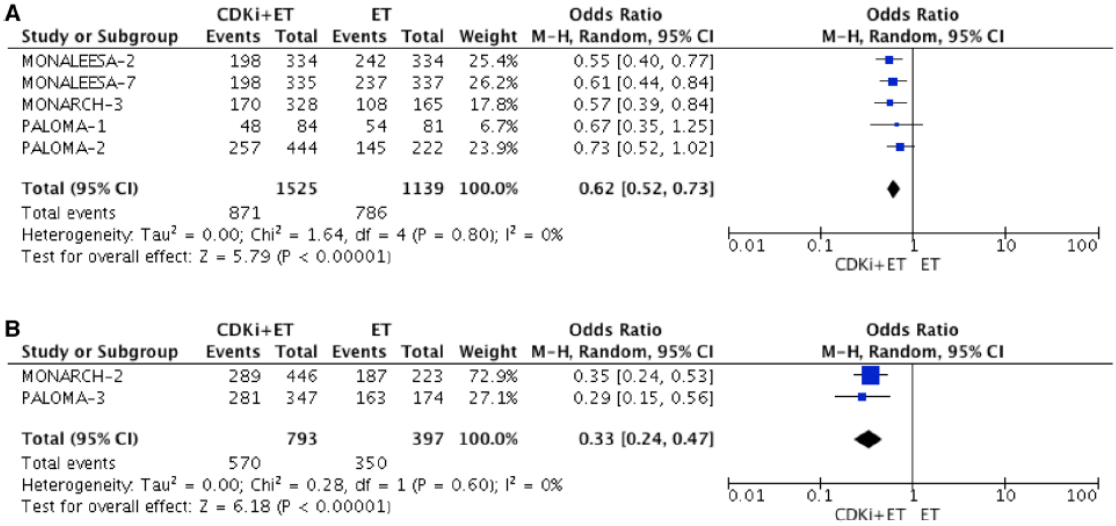


Fig. 4 Forest plot of Odds ratios (ORs) objective response rate (ORR) in seven randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive disease (**a**), endocrine-resistant disease (**b**) in advanced or metastatic HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* Odds ratios

- Toxicities: All the trials included in our systematic review reported G3–G4 AEs occurring in the CDKi plus ET arm and in the ET alone arm (Fig. 5a). A total of 1107 out of 1541 patients (71.8%) treated with CDKi plus ET developed G3–G4 AEs compared to 313 out of 1127 women (27.8%) assigned to treatment with ET alone in endocrine-sensitive setting. The pooled ORs was 7.51 (95% CI 5.52–10.21), indicating a much higher probability of developing ≥ G3–G4 AEs for patients treated with CDKi and ET (Fig. 5a); however, significant heterogeneity between the four studies emerged (I2 63%).
  - Two phase III trials [10, 11] included in our systematic review assessed the activity of CDKi plus ET vs ET alone in endocrine-resistant setting: hence again results were suitable for our meta-analysis. A total of 506 out of 791 patients (64%) treated with CDKi plus ET, and 82 out of 395 women (20.7%) assigned to ET alone developed G3–G4 AEs. The pooled ORs was 7.09 (95% CI 3.53–14.25), again indicating a much higher probability of developing G3–G4 AEs for patients treated with CDKi plus ET (Fig. 5b); however, significant heterogeneity between the two studies emerged (I2 83%).
  - Again, we pooled together the eight randomized trials to assess the global impact in terms of G3–G4 AEs of combining CDKi with ET compared to ET alone. A total of 2006 out of 2815 patients (71.2%) treated with CDKi plus ET and 411 out of 1763 women (23.3%) assigned to ET alone developed G3–G4 AEs. The pooled ORs was 9.64 (95% CI 6.00–15.49), indicating a much higher probability of developing G3–G4 AEs for patients treated with CDKi and ET (Fig. 5c); significant heterogeneity between the eight studies emerged (I2 90%). However, the increased chance of developing G3–G4 toxicities for patients treated with CDKi plus ET may be influenced mostly by the odds to develop G3–G4 neutropenia (OR 10.88, 95% CI 6.53–18.14; Fig. 6).

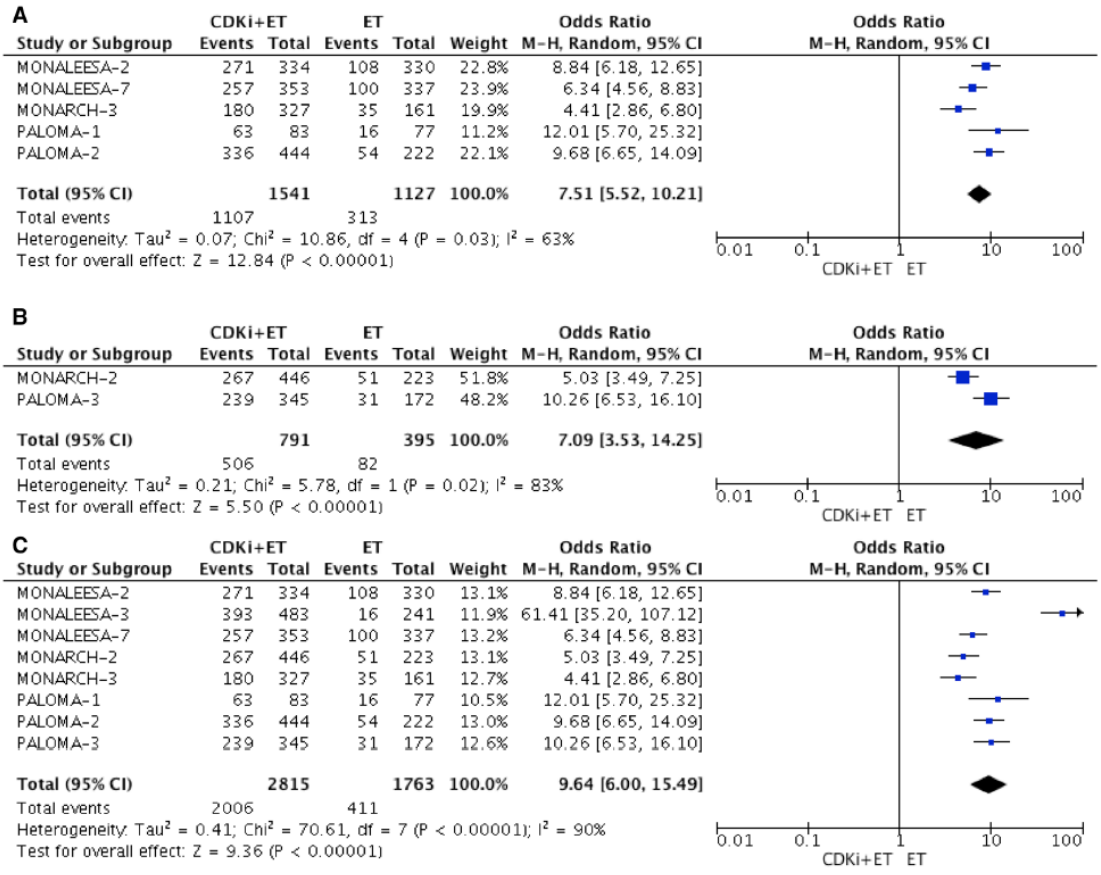


Fig. 5 Forest plot of odds ratios (ORs) for ≥G3–G4 AE in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population in advanced HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* odds ratios

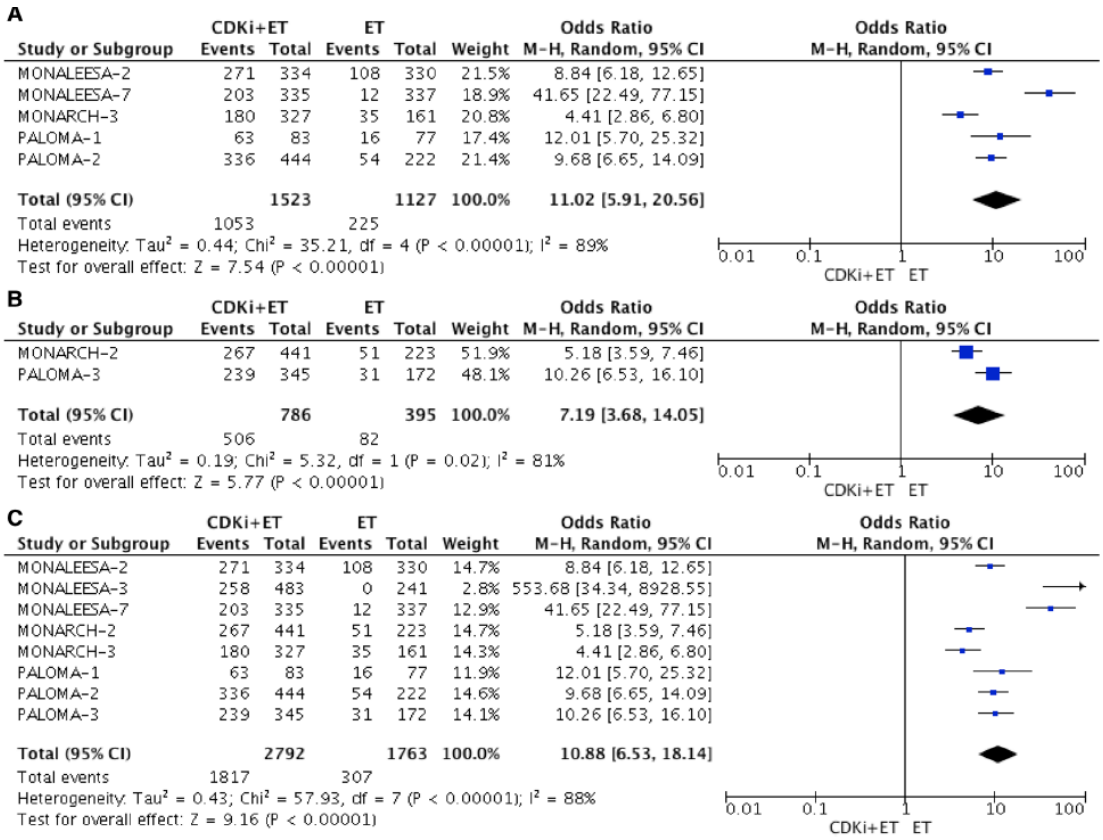


Fig. 6 Forest plot of odds ratios (ORs) for ≥G3–G4 neutropenia in eight randomized trials of CDK inhibitors plus endocrine therapy (ET) compared ET alone for endocrine-sensitive (**a**), endocrine-resistant (**b**), and overall population (**c**) in advanced HR+ HER2− breast cancer women. Pooling ORs were computed using random-effects models. The bars indicate 95% confidence intervals. *CDKi* cyclin-dependent kinase inhibitor, *ET* endocrine therapy, *ORs* odds ratios

Anmerkung/Fazit der Autoren

Emerging data provide a new standard treatment for advanced HR+/Her2− breast cancer, regardless of menopausal status, prior hormonal/chemotherapy treatments delivered, sites of metastasis. However, benefits should be balanced with longer treatment duration, toxicities, and costs. Mature OS data are awaited. Head-to-head trials are warranted to compare the efficacy of CDKi plus ET or chemotherapy especially for women with high tumour burden and visceral metastases in order to improve patient's selection and maximize the benefit from the combined approach.

Kommentare zum Review

- Eingeschlossene Studien umfassen firstline und/oder secondline endocrine therapy, Analysen getrennt nach setting, wobei in den Analyse unklar ist, inwiefern eine Endokrine-Therapie der 2. Linie voranging

Patterson-Lomba O et al., 2019 [19].

Systematic literature review of clinical trials of endocrine therapies for premenopausal women with metastatic HR+ HER2- breast cancer

Fragestellung

We conducted a systematic review and assessed the feasibility of an indirect treatment comparison (ITC) to characterize the comparative efficacy of endocrine-based therapies in this setting.

Methodik

Population:

- Premenopausal women with metastatic HR+ HER2- breast cancer

Intervention/Komparator:

The interventions will include at least one of the following therapies, either as monotherapy or as part of a combination therapy:

- Endocrine therapy: letrozole, anastrozole, exemestane, tamoxifen, fulvestrant
- Targeted therapy: palbociclib, ribociclib/LEE011, abemaciclib
- Chemotherapy: capecitabine, doxorubicin, paclitaxel, docetaxel, cyclophosphamide, eribulin

Endpunkte:

- At least one of the following outcomes is reported:
- Efficacy outcomes: Overall survival (OS), Progression-free survival (PFS), Time to progression (TTP) , Overall response rate (ORR)
- Safety outcomes: Adverse events (AEs), Serious AEs (SAEs), Discontinuation due to AE, All-cause discontinuation
- HRQOL outcomes: European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23), Functional assessment of cancer therapy for breast cancer (FACT-B), EQ-5D, Other QoL measures

Recherche/Suchzeitraum:

- MEDLINE (2007-December 26, 2017), MEDLINE (R) In-Process (2007-December 26, 2017), EMBASE (2007 week 1-2017 week 52), Cochrane Database of Systematic Reviews (CDSR) (2007-December 19 2017), Cochrane Central Register of Controlled Trials (CENTRAL) (2007-November 2017), and Database of Abstracts of Reviews of Effects (DARE) (2007-2017). The search also included several conference proceedings.

Qualitätsbewertung der Studien:

- adapted from the “Systematic reviews: CRD's guidance for undertaking reviews in health care”

TABLE 4 Quality assessment

Trial no. (acronym)	PALOMA-3	MONARCH-2	KCSG BR10-04	MONALEESA-7
Was randomization carried out appropriately?	Yes	Yes	Not clear	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	N/A[a]	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	Yes	N/A[a]	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	Yes	Not clear	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No
Did the analysis include an intention–to–treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data	Yes	Yes	Not clear	Yes

Abbreviation(s): N/A, not applicable.
[a]KCSG BR10-04 is an open label trial.

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs

Charakteristika der Population:

- The sample size per treatment arm of premenopausal women in the identified trials was relatively small (range, 36-72), except for the MONALEESA-7 trial (335-337)
- MONALEESA-7 trial is the only trial in the first-line treatment setting for metastatic disease, whereas the patient population in the other trials had progressed after prior ET either in the metastatic setting, and in the case of MONARCH 2, patients either progressed ≤12 months after adjuvant ET or while receiving ET for mBC.

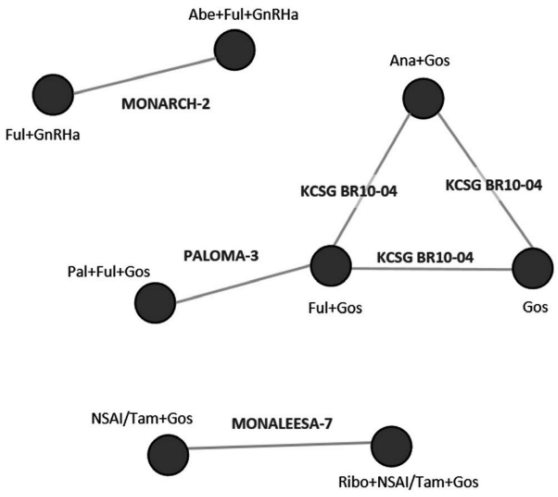


FIGURE 2 Evidence networks for PFS hazard ratio. Abbreviations: Abe, abemaciclib; Ana, anastrozole; ET, endocrine therapy; Ful, fulvestrant; GnRHa, gonadotropin-releasing hormone agonist (eg, goserelin); Gos, goserelin; NSAI, non-steroidal aromatase inhibitors; Pal, palbociclib; PFS, progression free survival; Ribo, ribociclib; Tam, tamoxifen

TABLE 2 Baseline characteristics

Characteristics[a]	PALOMA-3*		MONARCH-2		KCSG BR10-04*			MONALEESA-7*	
	Palbociclib + fulvestrant + goserelin	Placebo + fulvestrant + goserelin	Abemaciclib + fulvestrant + GnRHa	Placebo + fulvestrant + GnRHa	Fulvestrant + goserelin	Anastrozole + goserelin	Goserelin alone	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin
Trial phase	III		III		II			III	
Sample size, N	72	36	72	42	44	47	47	335	337
Age (y)									
Median (Range)	NR[b]	NR[b]	46 (32-57)	47 (32-66)	42.9 (28.0-53.0)	44.1 (23.0-53.0)	42.3 (32.0-55.0)	43 (25-58)	45 (29-58)
Race/Ethnicity, N (%)									
White	37 (51.4)	21 (58.3)	14 (19.4)[c]	16 (38.1)[c]	NR	NR	NR	187 (55.8)	201 (59.6)
Asian	31 (43.1)	13 (36.1)	51 (70.8)[c]	24 (57.1)[c]	NR	NR	NR	99 (29.6)	99 (29.4)
Black	NR[b]	NR[b]	NR[c]	NR[c]	NR	NR	NR	10 (3.0)	9 (2.7)
Native American	NR	NR	NR[c]	NR[c]	NR	NR	NR	3 (0.9)	3 (0.9)
Other	4 (5.6)[d]	2 (5.6)[d]	7 (9.7)[d]	2 (4.7)[d]	NR	NR	NR	16 (4.8)[d]	7 (2.1)[d]
Unknown	NR	NR	NR[c]	NR[c]	NR	NR	NR	20 (6.0)	18 (5.3)
Performance status, N (%)									
ECOG 0	NR	NR	NR	NR	27 (61.4)	26 (55.3)	31 (66.0)	245 (73.1)	255 (75.7)
ECOG 1	NR	NR	NR	NR	16 (36.4)	19 (40.4)	16 (34.0)	87 (26.0)	78 (23.1)
ECOG 2	NR	NR	0 (0.0)	0 (0.0)	1 (2.6)	2 (4.3)	0 (0.0)	0 (0.0)	1 (0.3)
ECOG >2	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	NR	NR	NR	NR	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.9)	3 (0.9)
Prior therapy, N (%)									
Endocrine therapy	72 (100.0)	36 (100.0)	72 (100)	42 (100)	NR	NR	NR	127 (37.9)[e]	141 (41.8)[e]
Chemotherapy	23 (31.9)[f]	12 (33.3)[f]	NR	NR	10 (22.7)	10 (21.3)	12 (25.5)	185 (55.2)[g]	185 (54.8)[g]
Cancer stage, N (%)			NR	NR					
Locally advanced	NR	NR	0 (0.0)[c]	0 (0.0)[c]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)
Metastatic	NR	NR	72 (100.0)[c]	42 (100.0)[c]	44 (100.0)	47 (100.0)	47 (100.0)	334 (99.7)	336 (99.7)

Abbreviation(s): ECOG, Eastern Cooperative Oncology Group; GnRHa, gonadotropin-releasing hormone agonist (eg, goserelin); NR, not reported; NSAI, nonsteroidal aromatase inhibitor.
[a]Baseline characteristics are for the entire trial population. Trials with * have 100% pre- or peri-menopausal population or report baseline characteristics for the pre- or peri-menopausal population.
[b]Age was reported as number and percentage for the following age groups: ≤40, 40-50, and >50 y old.
[c]The data has been extracted from the 2018 ASCO Annual Meeting Presentation.
[d]Other includes Black, Native American and etc when these categories have not been reported separately.
[e]Prior (neo) adjuvant endocrine therapy.
[f]Previous chemotherapy in metastatic setting. Subjects are counted for each treatment of metastatic disease (± neoadjuvant) received.
[g]Calculated as the sum of chemotherapy for (neo) adjuvant only and advanced disease.

Qualität der Studien:

- The included trials were all well-conducted and the risk of bias was low to moderate, with concealment of allocation (with the exception of KCSG BR10-04).

Studienergebnisse:

- PFS HR for the premenopausal population was reported in PALOMA-3 (palbociclib vs placebo arm: 0.50 [0.29-0.87]), MONARCH-2 (abemaciclib vs placebo arm: 0.45, [0.26-0.75]), KCSG BR 10-04 (fulvestrant + goserelin vs goserelin: 0.61 [0.37-1.00]; anastrozole + goserelin vs goserelin: 0.98 [0.62-1.55]) and MONALEESA-7 (ribociclib vs placebo arm: 0.55 [0.44-0.69]).
- PALOMA-3, MONARCH-2 and MONALEESA-7 reported median PFS, while KCSG BR 10-04 reported TTP. The median time to progression or death is longer in MONALEESA-7 compared to the other three trials, partly due to the former trial being in the first-line setting. Overall response rate (ORR) was larger in MONARCH-2 compared to MONALEESA-7 and PALOMA-3. Only MONALEESA-7 reported quality of life outcomes in the premenopausal population. Although there were differences between the PALOMA-3 and MONARCH-2 trials (eg, reference arms were slightly different [in MONARCH it was not specified that goserelin was the only GnRHa used], and patients had different prior treatment history [more patients in MONARCH-2 progressed within 12 months of adjuvant ET]), a naïve comparison of the PFS HR between these two trials indicates that abemaciclib + fulvestrant + GnRHa (HR = 0.45) is associated with a lower hazard of progression or death than palbociclib + fulvestrant + goserelin (HR = 0.50). However, due to the small sample size limitation, the confidence around these estimates are large and overlapping.

- No NMA conducted: disconnected network of the four identified trials corresponding to the PFS HR outcome (the only outcome reported for all trials): In order to form a fully connected network, strong clinical assumptions are needed, such as “pooling” endocrine-based therapies (ie, assume that the clinical efficacies of the comparator arms in PALOMA-3 [fulvestrant + goserelin], MONARCH-2 [fulvestrant + GnRHa] and MONALEESA-7 [NSAI/tamoxifen + goserelin] are all similar in terms of PFS). Moreover, MONALEESA 7 is in the first-line (ET-naïve) setting, while all other studies are in the ET-failure setting. Hence, to be able to compare the ribociclib arm with the rest of the therapies, it would have to be assumed that the PFS HRs are similar in the first-line and second line settings.

Anmerkung/Fazit der Autoren

To conclude, this systematic literature evaluation provides a comprehensive review of the available clinical trial evidence on the efficacy and safety of ET as treatments for premenopausal women with HR+/HER2− mBC. The search demonstrated the paucity of RCTs focusing on premenopausal HR+ HER2− mBC, with only four trials having reported relevant data in this setting. MONALEESA-7 is currently the only phase 3 trial focused on premenopausal HR+ HER2− mBC in the first-line setting. Efficacy results from the selected trials indicated that combining a CDK4/6 inhibitor with an endocrine monotherapy and a GnRHa led to improvements in PFS and ORR in premenopausal women with HR+/HER2− mBC in the first-line and ET-failure settings.

Kommentare zum Review

- Review umfasst Studien mit ET-naiven Patientinnen als auch Studien mit ET-vorbehandelten Patientinnen (MONALEESA 7 is in the first-line (ET-naïve) setting, while all other studies are in the ET-failure setting)
- Evidenz aus den Studien wird parallel berichtet (keine Meta-Analyse)

Bottcher TM et al., 2019 [1].

Treatment of advanced HR+/HER2- breast cancer with new targeted agents in combination with endocrine therapy: a review of efficacy and tolerability based on available randomized trials on everolimus, ribociclib, palbociclib and abemaciclib.

Fragestellung

To evaluate available randomized trials on the mammalian target of rapamycin (mTOR) inhibitor, everolimus, and the cyclin-dependent kinase (CDK) 4/6 inhibitors, ribociclib, palbociclib and abemaciclib in combination with endocrine therapy (ETs) in HR+/HER2- MBC regarding efficacy, tolerability and safety.

Methodik

Population:

- HR+/HER2- MBC

Intervention:/Komparator:

- everolimus, abemaciclib, ribociclib or palbociclib in combination with ET vs. ET

Endpunkte:

- OS, PFS, ORR, AE

Recherche/Suchzeitraum:

- A Pubmed search on the 2 November 2017

Qualitätsbewertung der Studien:

- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs
  - 4 Studies Patients received treatments as first-line metastatic treatment
  - 2 Studies previously treated for metastatic disease
  - 2 Studies: Mixed population

Charakteristika der Population:

Table 1. Study information and patient populations.

Studies	Bachelot et al. [25]	BOLERO-2 [26]	MONALEESA-2 [27]	PALOMA-1 [28]	PALOMA-2 [29]	PALOMA-3 [30]	MONARCH 2 [31]	MONARCH 3 [32]
Phase	II	III	III	II	III	III	III	III
Agent	EVE	EVE	RIB	PAL	PAL	PAL	ABE	ABE
ET combination	Tamoxifen	Exemestane	Letrozole	Letrozole	Letrozole	Fulvestrant	Fulvestrant	Letrozole 79.1% or anastrozole
No. of patients	111	724	668	165	666	521	669	493
Median age (yrs)	65	62	63	64	62	57	60	63
ECOG PS (%)								
0	50	60	61	55	52	62	60	60
1	41	36	39	45	47	38	39	40
2	6	3	0	0	1	0	0	0
Menopausal status (%)[a]								
Pre- or peri-menopausal	~	~	~	~	~	21	17	~
Postmenopausal	All	All	All	All	All	79	82.4	All
Prior ET (%)	All	All					All	
None	~	~	–	–	–	~	1	53
As neo-/adjuvant	41[b]	–	52	33	56	22	59	47
As metastatic	67[b]	–	~	~	~	78	38	~
First-line met. Treatment	~	21%	x	x	x	~	~	x
Prior met. Treatment	x	79%	~	~	~	x	38.20%	~
De novo metastatic disease	~	~	34	49	36	~	~	40
Site of metastases:								
Bone only (%)	27	–	22	18	22	–	27	22
Visceral (%)	53	56	59	49	49	60	56	53

When the sum does not equal 100%, it is due to missing patient information.
[a]pre- or peri-menopausal women received a gonadotropin-releasing hormone agonist.
[b]in Bachelot et al. previous ET only refers to aromatase inhibitor treatment.
~ refers to not relevant.
– refers to no data.
EVE: everolimus; RIB: ribociclib; PAL: palbociclib; ABE: abemaciclib; ET: endocrine therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; met: metastatic; mo: months; NR: Not Relevant.

Qualität der Studien:

	Risk of selection bias§: Randomization of patients	Risk of performance bias: Blinding	Loss to follow-up / risk of attrition bias: intervention group vs ET only group	ITT principle or PP analysis of results	Risk of detection bias: investigators of outcomes from tumor assessment (PFS etc.)	Other	Conclusion
Bachelot et al. [25]	Randomized, stratified Imbalance in PS 0; 59% vs 40%, favoring the everolimus group	Open label	0 (reported) lost to follow-up / 5.6% vs 3.5%	ITT and PP	Local (not blinded)		Serious limitations
BOLERO-2 [26]	Adequate, stratified	Double-blind	* No loss to follow-up was reported / Attrition: 8.5% vs. 2.5%	ITT	Both local and central results available		No serious limitations
MONALEESA-2 [27]	Adequate, stratified	Double-blind	* No loss to follow-up was reported / Attrition: 4.5% vs. 5.4%	ITT	Local results on PFS, only a HR was listed from the independent review committee	Stopped early	Serious limitations
PALOMA-1 [28]	Randomized, stratified. Imbalance of visceral metastases; 44% vs. 53% favoring the palbociclib group	Open label	No loss to follow-up was reported / Attrition: 7.1% vs 13.6%	ITT	Local only (not blinded)		Serious limitations
PALOMA-2 [29]	Randomized, stratified. Imbalance in PS 0; 57.9% vs 45.9% favoring the palbociclib group	Double-blind	*1 of 666 lost to follow-up / Attrition: 4.5% vs. 6.3%	ITT	Both local and blinded, independent central review results available		No serious limitations
PALOMA-3 [30]	Adequate, stratified	Double-blind	No loss to follow-up was reported / Attrition: 2.3% vs. 4.6%	ITT	Masked, independent central review		No serious limitations
MONARCH 2 [31]	Randomized, stratified.	Double-blind	Loss to follow-up: 6 of 446 vs 4 of 223 / Attrition: 2.5% vs. 1.8%	ITT	Both local and blinded, independent central review results available		No serious limitations
MONARCH 3 [32]	Randomized, stratified. Imbalance in treatment-free interval ≥ 36 months; 62.7% vs 50% favoring the abemaciclib group	Double-blind	Loss to follow-up: 3 of 328 vs. 1 of 165 / Attrition: 1.5% vs. 2.4%	ITT	Both local and blinded, independent central review results available		No serious limitations

The attrition was calculated as the sum of those who never received the study treatments, protocol deviators, loss to follow up, the withdrawn consent at any time and other, divided by the ITT group.
§: selection bias also includes allocation concealment, but the information was unclear from all eight studies. According to GRADE 4, blinded trials are very likely to be concealed, and thus only the two open-label trials have a risk of bias.
*indicates that data was found in the supplementary data of the articles.
Abbreviations: ITT=Intention to treat, PP=per protocol, PS=performance status, HR=hazard ratio, PFS=progression free survival, ET=endocrine therapy

Studienergebnisse:

- The efficacy results reported in the eight RCTs are listed in Table 2. In terms of first-line trials, the two palbociclib trials reported a median PFS of 20.2 months in the combination group versus 10.2 months in the ET only group (the corresponding hazard ratio (HR) for disease progression or death was 0.49; 95% CI 0.32–0.75; one-sided p<.0001), and 30.5 versus 19.3 months (HR 0.65; 95% CI 0.51–0.84; p=.001). It suggests an increase of the PFS of 10–11 months when adding palbociclib to ET. The PFSs were not reached in the first-line abemaciclib trial (HR 0.51 (0.36–0.72; p=.0001) [32], nor in the ribociclib group in MONALEESA-2, where the HR determined by blinded reviewers was 0.59 (95% CI 0.43–0.72; p=.002) [27], both suggesting a significant benefit from adding a CDK4/6 inhibitor.

Table 2. Efficacy outcomes of included clinical trials.

Studies	Bachelot et al. [25]		BOLERO-2 [26, 33]		MONALEESA-2 [27][a]		PALOMA-1 [28][a]		PALOMA-2 [29][a]		PALOMA-3 [30]		MONARCH2 [31]		MONARCH 3 [32][a]	
Study groups	EVE + ET	ET only	EVE + ET	P + ET	RIB + ET	P + ET	PAL + ET	ET only	PAL + ET	P + ET	PAL + ET	P + ET	ABE + ET	P + ET	ABE + ET	P + ET
Med. PFS (mo) (95% CI)	–	–	10.6[b] (9.5–NR)	4.1[b] (2.8–5.8)	NR (19.3–NR)	14.7 (13–16.5)	20.2 (13.8–27.5)	10.2 (5.7–12.6)	30.5[b] (24.7–NR)	19.3[b] (16.4–30.6)	9.5 (9.2–11)	4.6 (3.5–5.6)	22.4[b]	10.2[b]	NR[b]	19.2[b]
Med. TTP (mo) (95% CI)	8.6 (6 –14)	4.5 (3.6–8.7)	–	–	–	–	–	–	–	–	–	–	–	–	–	–
HR (95% CI; p-value)	0.54 (0.36–81; p = .0021)		0.36[b] (0.27–0.47; p < .001)		0.59[b] (0.43–0.72; p = .002)		0.49 (0.32–0.75; one–sided p < .0001)		0.65[b] (0.51–0.84; p = .001)		0.46 (0.36–0.59; p < .0001)		0.46[b] (0.36–0.58; p < .001)		0.51[b] (0.36–0.72; p = .000102)	
Med. OS (mo)	NR	32.9	31.0	26.6	NR	NR	37.5	33	NR	NR	NR	NR	NR	NR	NR	NR
HR (95% CI)	0.45 (0.24–0.81)		0.89 (0.73–1.10)		–		0.81 (0.49–1.35)		–		–		–		–	
Best overall response:																
ORR. ITT (%)	8.7	9.2	7 (4.9–9.7)	0.4 (0.0–2.3)	40.7 (35.4–46.0)	27.5 (22.8–32.3)	43 (32–54)	33 (23–45)	42.1 (37.5–46.9)	34.7 (28.4–41.3)	19 (15.0–23.6)	9 (4.9–13.8)	35.2 (30.8–39.6)	16.1 (11.3–21.0)	48.2 (42.8–53.6)	34.5 (27.3–41.8)
OR, p–value	–		–, p < .001		–, p < .001		–, p = .13		1.4, p = .06		2.47, p = .0019		2.82, p < .001		1.8, p = .002	
SD. ITT (%)	–	–	74.6	64.4	28.4	33.2	38	25	–	–	61	54	37.0	39.9	29.9	37.0
ORR. MD (%)	14	13	–	–	52.7	37.1	55	39	55.3	44.4	25	11	48.1	21.3	59.2	43.8
SD. MD (%)	–	–	–	–	37.1	45.3	31	33	–	–	53	47	25.2	30.5	20.2	25.4
CBR ITT (%) (95% CI)	61 (47–74)	42 (29–56)	–	–	79.6 (75–84)	72.8 (68–76)	81 (71–89)	58 (47–69)	84.9 (81–88)	70.3 (64–76)	67 (61–72)	40 (32–47)	72.2 (68–76.4)	56.1 (49.5–62.6)	78.0 (73.6–82.5)	71.5 (64.6–78.4)
p–value	–		–		.02		.0009		<.001		.0001		<.001		.101	

[a]Indicates the trials analyzing first-line treatment.
[b]Numbers were the ones assessed by blinded reviewers, when more was available. See Table A in supplementary material for more details on blinding.
EVE: everolimus; RIB: ribociclib; PAL: palbociclib; ABE: abemaciclib; P: placebo; med: median; PFS: progression free survival; TTP: time to progression; ET: endocrine therapy; MO: months; HR: Hazard ratio; OS: overall survival (defined as time from randomization to death); ORR: objective response rate (including complete and partial response); SD: stable disease (Note the definitions vary across studies); MD: for patients with measurable disease (as defined in the RECIST criteria; except for in BOLERO-2 and MONALEESA-2); CBR: clinical benefit rate for the ITT population defined as the sum of ORR and SD; NR: not reached.

- Adverse Events
- Everolismus: Bachelot et al. [25] and BOLERO-2 [26] the most common grade 3 and 4 adverse events (AEs) in the everolimus groups included stomatitis (8% and 11%), anemia (6% and 2%), pneumonitis (3% and 2%) and hyperglycemia (4%). These adverse events (AEs) only occurred in 0–1% of the ET only group. In BOLERO-2, serious AEs occurred in 23% of patients in the everolimus group and in only 12% in the ET only group [26]. In total, 19% discontinued everolimus treatment because of AEs (versus 4% in the placebo arm) in the BOLERO-2 study [26], and 11% (versus 4%) in the study by Bachelot et al. [25]. The death of 1.4% of patients was considered to be attributable to AEs caused by everolimus [26]. No deaths were reported by Bachelot et al. [25].
- CDK 4/6: The most common grade 3 and 4 AE of the CDK 4/6 inhibitors was neutropenia. The rates were highest in the ribociclib-; 59.3% [27] and palbociclib trials; 54%, 66.4% and 65% [28–30], compared to 26.5% and 21.1% in the abemaciclib trials [31,32]. The corresponding rates in all placebo groups were 1–2%. Other common grade 3 and 4 AEs were leukopenia (19%, 24.8% and 28%) and anemia (6%, 5.4% and 3%) in the palbociclib groups [28–30]; diarrhea (13.4% and 9.5%), leukopenia (8.8% and 7.6%), anemia (7.2% and 5.8%) and elevated alanine aminotransferase (ALT) level (4.1% and 6.1%) in the abemaciclib groups [31,32]; and for the ribociclib group: leukopenia (21%), lymphopenia (6.9%) and increased ALT- (9.3%) and aspartate aminotransferase (AST) level (5.7%) [27]. Serious AEs occurred in 21.3% (vs 11.8% in the placebo arm) in the ribociclib trial [27]; in 19.6% and 13% (versus 12.6% and 17%) in the palbociclib trials [29,30]; and in 22.4% and 27.5% (vs 10.8% and 14.9%) in the two abemaciclib trials [31,32]. Discontinuation of treatment due to AEs occurred in 7.5% (versus 2.1% in the placebo arm) of patients in the ribociclib study [27]; in 13%, 9.7% and 4% (versus 2%, 5.9% and 2%, respectively) in the palbociclib studies [28–30]; and in 15.2% and 19.6% (vs 3.1% and 2.5%) in the abemaciclib trials [31,32]. AEs led to the death of 2.4% and 2.0% of patients in the abemaciclib arms (vs 1.2% and 0.9% in the placebo arms) in MONARCH 2 and -3, respectively [31,32]. No deaths were directly linked to the toxic effect of palbociclib in any of the three trials [28–30]. In the ribociclib group, 2.7% experienced QTcF prolongation, leading to one death (among 334 patients) [27].

Anmerkung/Fazit der Autoren

The four new targeted agents are all associated with an improvement of the PFS and have an acceptable tolerability. Thus, they should be offered to women with advanced HR+/ HER2- breast cancer both as first-line therapy as well as among patients previously treated for metastatic disease. However, further data regarding the impact on overall survival are required to evaluate the full benefit. As the effect is comparable, price and differences in AEs could become substantial arguments for the individual choice of therapy.

Kommentare zum Review

- Einschluss von hinsichtlich des Therapielinien-Settings heterogenen Studien.

Li J et al., 2020 [16].

Cyclin-dependent kinase 4 and 6 inhibitors in hormone receptor-positive, human epidermal growth factor receptor-2 negative advanced breast cancer: a meta-analysis of randomized clinical trials.

Fragestellung

To further evaluate the efficacy and safety of CDK4/6 inhibitors for HR+ /HER2− ABC, and explore the prefer population through subgroup analysis.

Methodik

Population:

- Women of any menopausal status who were 18 years old or older with HR+/HER2− ABC

Intervention/ Komparator:

- CDK4/6 inhibitors plus standard ET in comparison to ET alone

Endpunkte:

- Primary outcome: progression-free survival (PFS)
- Secondary outcomes: clinical benefit rate (CBR, defined as a confirmed complete response, a partial response, or stable disease for 24 weeks), objective response rate (ORR, defined as a confirmed complete response or partial response), overall survival (OS, defined as the time from the date randomized to death during the study), and toxicity that recorded the occurrence of all grades of AEs and grade 3 or 4 AEs including three hematologic toxicities (neutropenia, leucopenia, and anemia) and four non-hematologic toxicities (diarrhea, fatigue, nausea, and arthralgia)

Recherche/Suchzeitraum:

- We searched the following databases from Jan 2008 up to April 2019: PUBMED, MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials.

Qualitätsbewertung der Studien:

- Cochrane‘s risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=14 (8 different RCTs (n=4580): 3 RCTs palbociclib (n=1352 patients), 3 RCTs ribociclib (n=2066 patients) and 2 RCTs abemaciclib (n=1162 patients)

Charakteristika der Population:

- Two trials enrolled patients receiving treatment in the first-line setting for advanced breast cancer, two trials was in the second-line setting and four trials both in the first-line and the second-line setting
- Five trials used AI as a combination treatment of CDK4/6 inhibitors, three trials used Fulvestrant as endocrine therapy

- Five studies enrolled only postmenopausal women, one study enrolled premenopausal and perimenopausal women, and two studies enrolled women with any menopausal status
- Two trials allowed previous chemotherapy for advanced breast cancer

Qualität der Studien:

Table 1 Risk of bias summary (review authors' judgement about each risk of bias item for each included study)

	Random sequence generation(selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (PFS)	Blinding of outcome assessment (CBR/ORR/toxicity)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
PALOMA-1 [23]	Low risk	Low risk	High risk	Unclear	Unclear	Low risk	Low risk
PALOMA-2 [24]	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
PALOMA-3 [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONALESSA-2 [26]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
MONALESSA-3 [27]	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Low risk
MONALESSA-7 [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONARCH-2 [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
MONARCH-3 [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Studienergebnisse:

- Progression-free Survival (PFS)
- The HRs significantly favored the CDK4/6 inhibitors containing groups over the endocrine therapy alone groups in first-line setting (HR 0.56, 95% CI 0.49–0.63, p < 0.00001, Fig. 3).

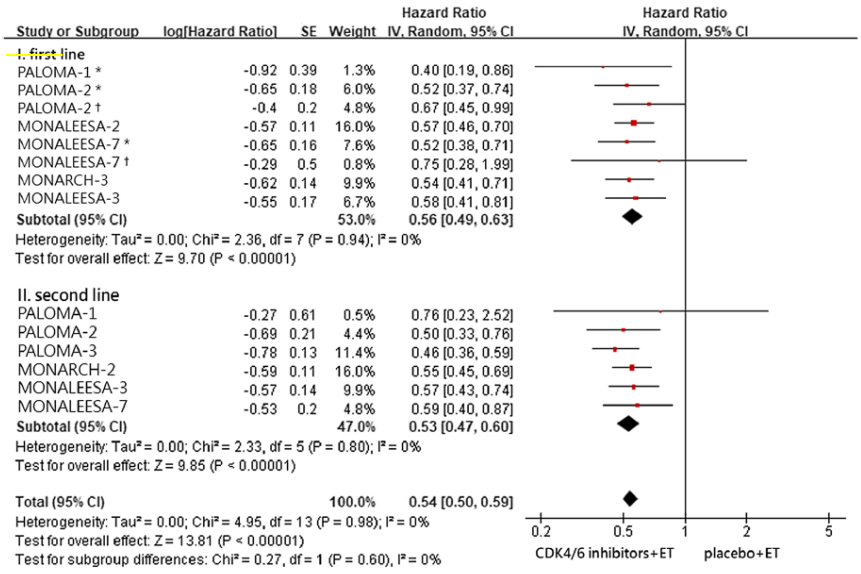
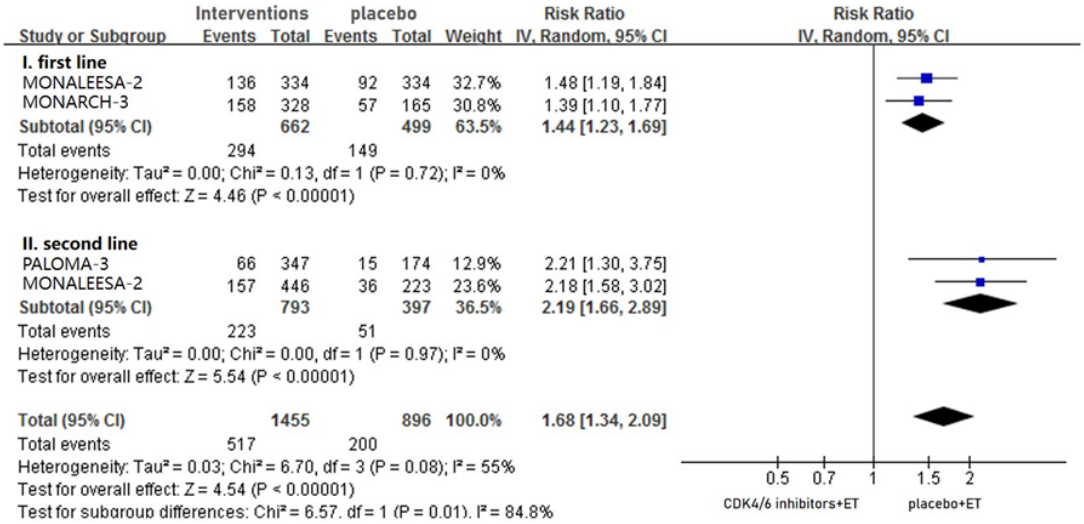


Fig. 3 PFS first line vs second line (*Patients with disease-free interval (the time from the end of adjuvant or neoadjuvant treatment to disease recurrence) > 12 months. †Patients with de novo metastatic breast cancer)

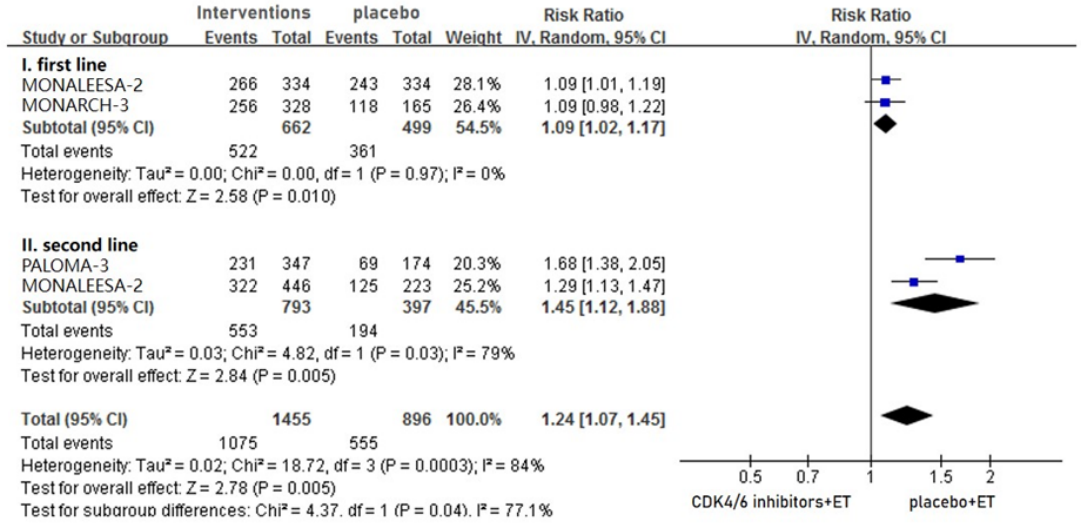
Overall survival (OS)

- Overall survival data were reported in three enrolled studies: Patients in the CDK4/6 inhibitors containing group were observed to have a significantly longer overall survival than those in the ET alone group with an HR = 0.79, 95% CI 0.67–0.93, and p = 0.004 (keine Angabe ob first oder secondline).
- Objective response rate (ORR) and Clinical benefit rate (CBR)
- In the first-line setting we found that the RR of ORR using CDK4/6 inhibitors was better than in the ET alone group, where RR = 1.44, 95% CI 1.23–1.69, and p < 0.00001.
- We also observed the improvements of CBR in both the first-line setting (RR = 1.09)

Supplemental Figure 5. ORR: first-line vs second-line therapy



Supplemental Figure 8. CBR: first-line vs second-line therapy



Toxicity

- All-grade neutropenia is the most commonly observed AEs in CDK4/6 intervention
- arms (RR 14.24, 95% CI 10.91–18.59)

- Similarly, all-grade leucopenia and anemia were recorded more in CDK4/6 inhibitor containing regiments
- For all-grade non-hematologic toxicity, the RR were 1.71 (95% CI 1.23–2.37) for diarrhea,
- 1.24 (95% CI 1.08–1.41) for fatigue, 1.63 (95% CI 1.44–1.84) for nausea, and 0.98 (95% CI 0.87–1.09) for arthralgia
- The grades 3 and 4 (G3-4) neutropenia were increased in intervention arms than control arms, the RR was 31.95 (95% CI 17.75–57.50) with substantial heterogeneity among different interventions (I^2 = 58.8%)
- In the subgroup analysis of different interventions, the incidence of G3-4 diarrhea was significantly higher in patients receiving abemaciclib (RR 12.62, 95% CI 3.48–45.82).

Anmerkung/Fazit der Autoren

The CDK4/6 inhibitors (including palbociclib, abemaciclib, and ribociclib) plus standard endocrine agents prolong PFS and OS and show benefit in ORR and CBR in HR+ /HER2− ABC irrespective of the prior therapy for advanced disease, menopausal status, the existence of visceral metastases, and different races. Though followed by the increasing occurrence of neutropenia, leucopenia, and diarrhea, most of the adverse events are reversible, manageable and acceptable. Given their superior efficacy and tolerable toxicity, the CDK4/6 inhibitors could be recommended as a preferred option for the majority of patients with HR+ /HER2− ABC.

Deng Y et al., 2018 [3].

CDK4/6 inhibitors in combination with hormonal therapy for HR+/HER2- advanced breast cancer: A systematic review and meta-analysis of randomized controlled trials.

Fragestellung

We conducted this meta-analysis based on available RCTs to evaluate the efficacy and safety of CDK4/6 inhibitors in combination with hormonal therapy for the treatment of HR+/HER2- advanced breast cancer, comparing with hormonal therapy alone.

Methodik

Population:

- HR+/HER2-advanced breast cancer

Intervention/Komparator:

- CDK4/6 inhibitors plus hormonal therapy versus hormonal therapy alone or with placebo

Endpunkte:

- progression free survival (PFS), the number of patients who experienced a partial response or complete response, all grade adverse events (AEs) and grade 3/4 AEs.

Recherche/Suchzeitraum:

- Electronic searches were conducted among varied databases including Cochrane Library (2018), PubMed, EMBASE (from 1946) (OvidSP) and Web of Science (from 1900) up till March 24th, 2018.

Qualitätsbewertung der Studien:

- Cochrane's risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs (n=3,854 patients)
- Among four of the included studies, CDK4/6 inhibitors were combined with letrozole or anastrozole in the experimental arms as first-line therapy for postmenopausal advanced disease
- Two studies used CDK4/6 inhibitors with fulvestrant as subsequent line therapy for patients that went progression from prior endocrine therapy without restriction on menopausal status.
- While the MONALEESA-7 study was conducted to assess the efficacy and safety of ribociclib in combination with hormonal therapy and ovarian function suppression therapy in pre- or perimenopausal patients

Charakteristika der Population:

Table 1: Characteristics of included studies.

Study (ClinicalTrials.gov Identifier)	Year	Phase	Participants	No. of patients	Median age (year)	Interventions	Treatment strategy	Median follow-up (months)	Outcomes	
									mPFS (months)	ORR
PALOMA-1 (NCT00721409)	2015	II	Postmenopausal women with ER+/HER-ABC	165	63(64)	Palbociclib +letrozole vs letrozole	First line therapy	29.6	20.2 vs 10.2	42.9% vs 33.3%
PALOMA-2 (NCT01740427)	2016	III	Postmenopausal women with ER+/HER-ABC	666	62(61)	Palbociclib +letrozole vs letrozole	First line therapy	23	24.8 vs 14.5	42.1% vs 34.7%
PALOMA-3 (NCT01942135)	2016	III	Women with HR+/HER-ABC	521	57(56)	Palbociclib + fulvestrant vs placebo + fulvestrant	Subsequent line therapy	8.9	9.5 vs 4.6	19% vs 9%
MONARCH-2 (NCT02107703)	2017	III	Women with HR+/HER-ABC	669	59(62)	Abemaciclib + fulvestrant vs placebo + fulvestrant	Subsequent line therapy	19.5	16.4 vs 9.3	35.2% vs 16.1%
MONARCH-3 (NCT02246621)	2017	III	Postmenopausal women with HR+/HER-ABC	493	63(63)	Abemaciclib + NSAI vs placebo + NSAI	First line therapy	17.8	NR vs 14.7	48.2% vs 34.5%
MONALEESA-2 (NCT01958021)	2016	III	Postmenopausal women with HR+/HER-ABC	668	62(63)	Ribociclib + letrozole vs placebo + letrozole	First line therapy	15.3	NR vs 14.7	40.7% vs 27.5%
MONALEESA-7 (NCT02278120)	2017	III	Pre- or peri-menopausal women with HR+/HER2- ABC	672		Ribociclib + ET(tamoxifen/NSAI + goserelin) vs placebo + ET	First line ET	19.2	23.8 vs 13.0	51.0% vs 36.0%*

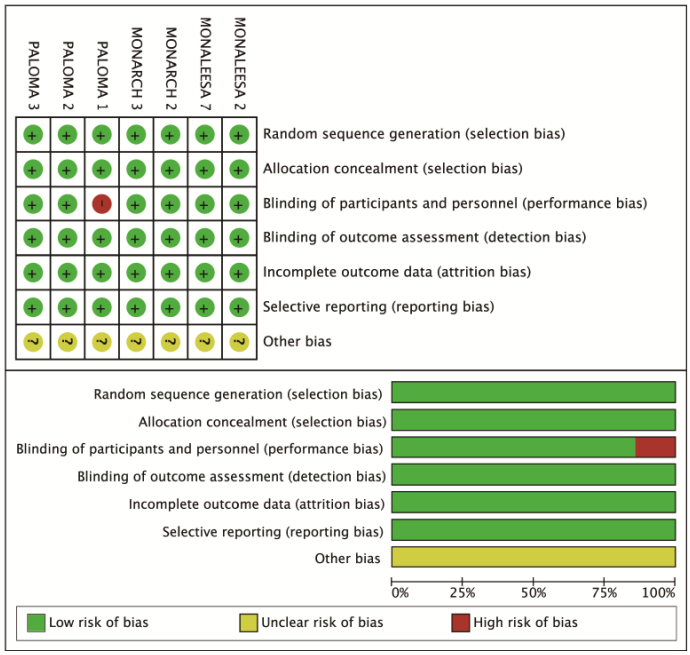
* ORR in patients with measurable disease.

ER+: Estrogen receptor positive; HR+: Hormonal receptor positive; HER2-: Human epidermal growth factor receptor 2 negative; ABC: Advanced breast cancer; mPFS: Median progression free survival; ORR: Objective response rate; NSAI: Nonsteroidal aromatase inhibitor (letrozole or anastrozole in MONARCH-3 and MONALEESA-7). ET: Endocrine therapy; NR: Not reached.

Palbociclib: 125mg per day orally for 3 weeks with 1 week off. Abemaciclib: 150mg twice daily orally and continuously. Ribociclib: 600mg per day orally for 3 weeks with 1 week off. Letrozole:1mg per day orally and continuously. Anastrozole: 2.5mg per day orally and continuously. Fulvestrant: 500mg intramuscularly on day 1 and 15 of the first cycle, then on day 1 of every 4 weeks. Tamoxifen: 20mg per day orally and continuously. Goserelin: 3.6mg subcutaneous injection every 28 days. All the drugs were administrated every 4 weeks a cycle.

Qualität der Studien:

Figure 6: Risk of bias for selected publications



Studienergebnisse:

- The HR for PFS for first line therapy was 0.56 (95% CI: 0.48-0.64; P<0.001, I^2=0)
- The pooled relative risk (RR) for objective response rate (ORR) for first line therapy was 1.35 (95% CI: 1.19-1.52; P<0.001, I^2=0)
- A higher rate of AEs in all grades as well as high grades (grade 3/4) were observed in the experimental arms where additional CDK4/6 inhibitors were added to regular hormonal therapy. And the pooled RR for all grade AEs was 1.07 (95% CI: 1.03-1.11; P=0.0002), the heterogeneity was significant (I^2=78%; P=0.0004) thus random effects model was adopted.
- For grade 3/4 AEs, the pooled RR was 2.81 (95% CI: 2.54-3.11; P<0.001) with slight heterogeneity (I2=17.7%; P=0.299). Hematological and gastrointestinal adverse events were the most common side effects of CDK4/6 inhibitors.

Figure 3: Subgroup analyses of pooled HRs for PFS

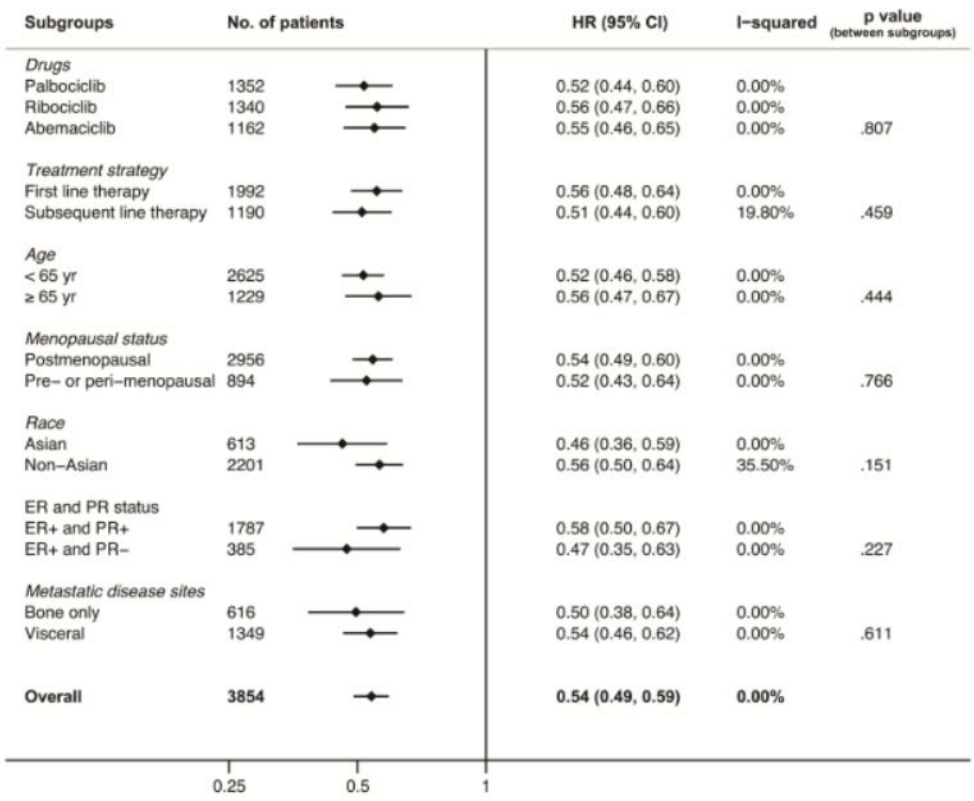
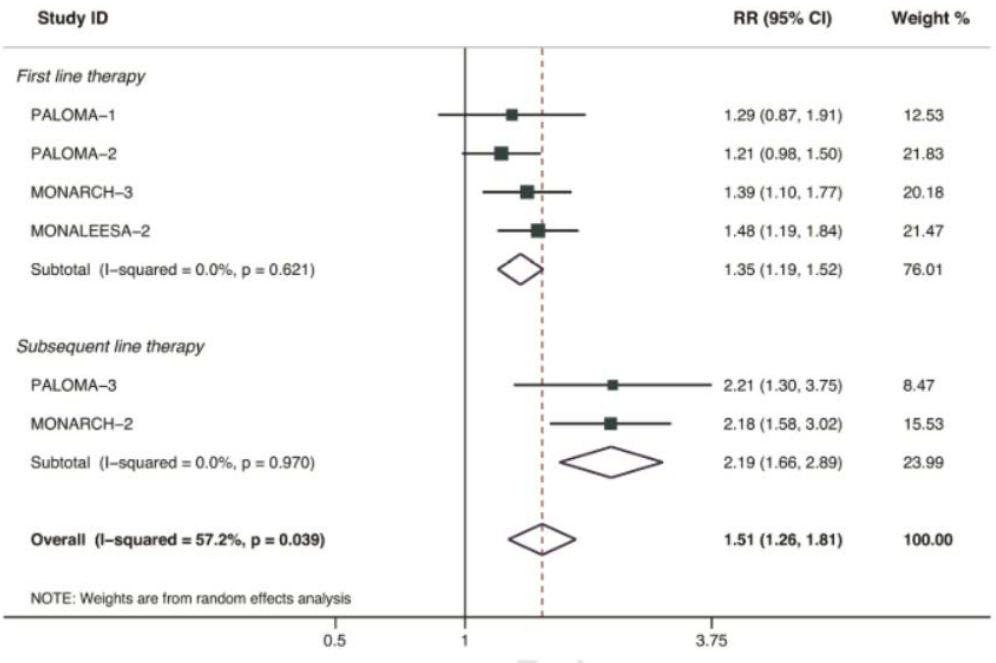


Figure 4: The pooled relative risk (RR) for objective response rate (ORR) among advanced breast cancer patients treated with CDK4/6 inhibitors



Anmerkung/Fazit der Autoren

Our meta-analysis demonstrated that additional use of CDK4/6 inhibitors can significantly prolong the PFS of patients with HR+/HER2- advanced breast cancer and improve the ORR with the basis of conventional hormonal therapy. Simultaneously, the combined regimen had higher rate of well-tolerated adverse events.

Huang H-W et al., 2019 [12].

CDK4/6 inhibition versus mTOR blockade as second-line strategy in postmenopausal patients with hormone receptor-positive advanced breast cancer

Fragestellung

The mTOR and CDK4/6 inhibitors added to the armory of second-line options in patients who developed resistance to initial endocrine therapy, but it challenged the optimal management regarding treatment sequence. Direct comparisons between these novel combinations are lacking. Therefore, we conducted a network meta-analysis to indirectly compare the efficacy and toxicity of CDK4/6 inhibitors plus fulvestrant versus everolimus plus exemestane.

Methodik

Population:

- patients with advanced breast cancer progression on prior aromatase inhibitors

Intervention:

- CDK4/6 inhibitors plus fulvestrant

Komparator:

- everolimus plus exemestane

Endpunkte:

- PFS or time to treatment progression

Recherche/Suchzeitraum:

- published between January 2000 and June 2018; PubMed, Embase; Abstracts: European Society of Medical Oncology and the American Society of Clinical Oncology between 2000 and 2017

Qualitätsbewertung der Studien:

- Jadad Score

Ergebnisse

Anzahl eingeschlossener Studien:

- Six trials comprising 4063 patients

Charakteristika der Population:

Table 1

Details of trials included in the network analysis.

	EFECT	CONFIRM	SoFEA	BOLERO-2	POLAMA-3	MONARCH-2
Year	2008	2011	2013	2012/2014	2015/2016	2017
Phase	III	III	III	III	III	III
Patient N	693	733	723	724	521	669
Prior endocrine therapy required	Metastatic setting: PD during therapy Adjuvant setting: progression during/ ≤6 mo after end of ET	Metastatic setting: ET for PD>12 mo after adjuvant ET or de novo disease Adjuvant setting: progression during/ ≤12 mo after end of ET	Metastatic setting: PD ≥6 mo on therapy Adjuvant setting: PD ≥12 mo on ET	Metastatic setting: PD during/≤1 mo after the end of therapy Adjuvant setting: progression during/ ≤12 mo after end of ET	Metastatic setting: PD during/≤1 mo after the end of therapy Adjuvant setting: progression during/≤12 mo after end of ET	Metastatic setting: PD during therapy Adjuvant setting: progression during/≤12 mo after end of ET
Prior AI (%)	100	43	100	100	85.8	69.5
Treatment arm 1	FUL 250mg/mo	FUL 500mg/mo	FUL 250mg/mo ANA 1mg/d	EVE 10mg/d EXE 25mg/d	PAL 125/d, 3wks on, 1wk off; FUL 500mg/mo	ABE 150mg/d FUL 500mg/mo
Treatment arm 2	EXE 25mg/d	FUL 250mg/mo	FUL 250mg/mo	EXE 25mg/d	FUL 500mg/mo	FUL 500mg/mo
Treatment arm 3	/	/	EXE 25mg/d	/	/	/

ABE = abemaciclib, AI = aromatase inhibitor, ANA = anastrozole, ET = endocrine therapy, EVE = everolimus, EXE = exemestane, FUL = fulvestrant, mo = month, PAL = palbociclib, PD = progression disease, wk = week.

Qualität der Studien:

- The quality was high in all included trials (Jadad score ≥3).

Studienergebnisse:

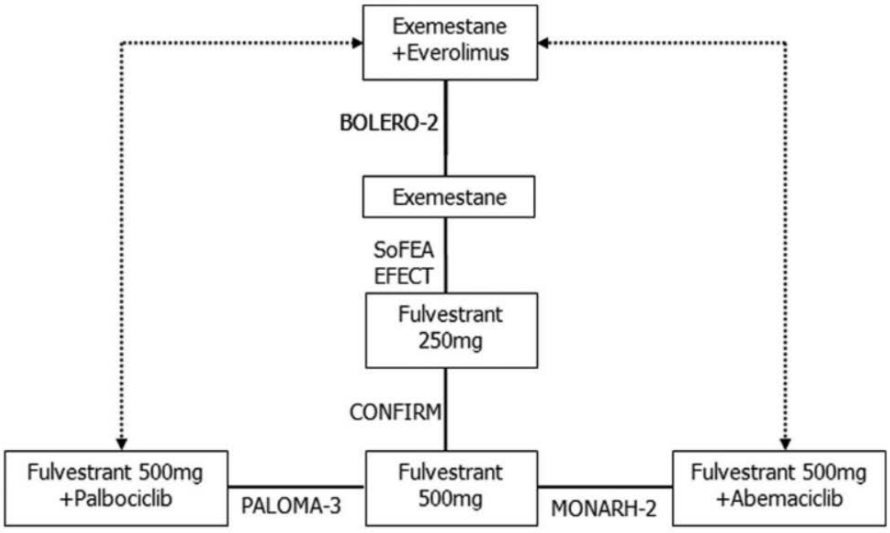


Figure 2. Network of the trials included in the analysis. The boxes denote therapies. Solid lines indicate direct comparisons, and dashed lines indicate indirect comparisons.

- As shown in Figure 2, a network was formed with the 5 comparisons to allow indirectly comparing the combination of palbociclib or abemaciclib plus fulvestrant and the combination of everolimus plus exemestane. Details of the included studies, patient characteristics, and main study outcomes are summarized in Tables 1 and 2. No significant heterogeneity or inconsistencies were found for the whole network (Q=0.01, P=.92); therefore, a fixed-effect method was used for the meta-analysis. Network meta-analysis results for the PFS and response rates are summarized in Figures 3 and 4, respectively. The P-scores for each treatment are presented in Table 3.

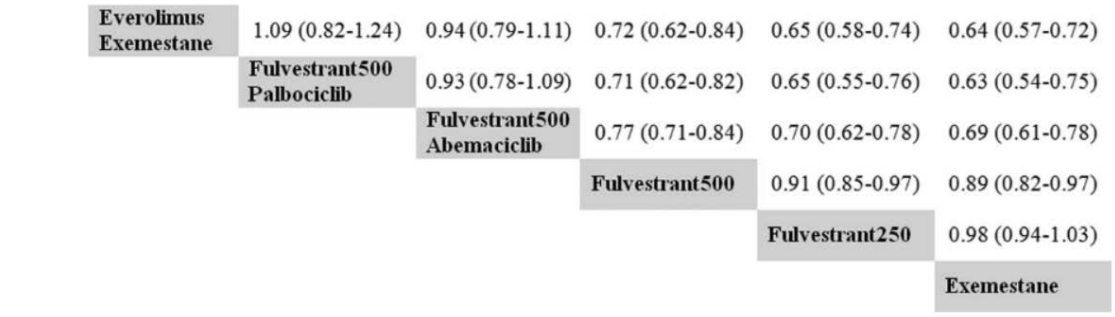


Figure 3. Pooled hazard ratios for disease progression. Treatments in the columns are compared with those in the rows.

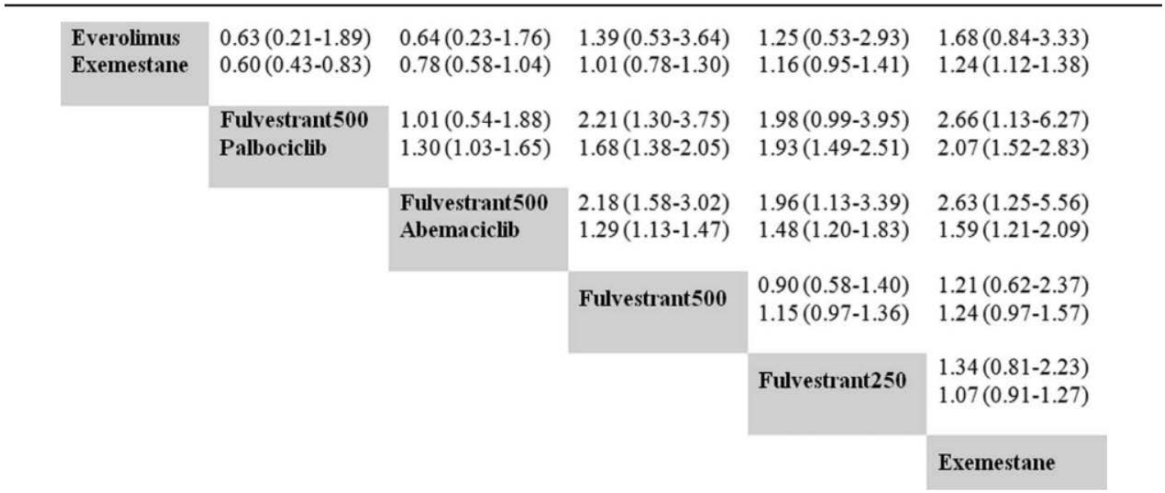


Figure 4. Pooled ORs for response. Treatments in the columns are compared with those in the rows. The first line shows the ORs for overall response rate, and the second line shows the ORs for clinical benefit rates. ORs = odds ratios.

Table 3

P-scores of treatments in the network meta-analysis.

Treatments	PFS	ORR	CBR
Fulvestrant500 + Palbociclib	0.87	0.85	0.99
Everolimus + Exemestane	0.84	0.55	0.49
Fulvestrant500 + Abemaciclib	0.68	0.85	0.79
Fulvestrant500	0.39	0.25	0.47
Fulvestrant250	0.16	0.37	0.18
Exemestane	0.03	0.10	0.04

CBR = clinical benefit rate, ORR = objective response rate, PFS = progression-free survival.

Table 4

Toxicity profile of treatments in each included trial.

	Common grade≥3 AEs with at least 5% incidence	Drug related SAE (%)	Withdrawal rate (%)
EFECT			
Fulvestrant250	Injection-site pain 9.8%, hot flashes 8.8%, nausea 6.8%, fatigue 6.3%	1.1	2
Exemestane	Hot flashes 11.5%, fatigue 10%, nausea 7.5%, arthralgia 5.6%	0.6	2.6
CONFIRM			
Fulvestrant250	—	7.2	2.2
Fulvestrant500	—	9.7	1.6
SoFEA			
Fulvestrant250 + Anastrozole	—	14.8	2.8
Fulvestrant250	Fatigue 5%	22	3.4
Exemestane	Fatigue 5%	29	3.6
BOLERO-2			
Exemestane + Everolimus	Stomatitis 8%, anemia 6%,	13.1	29
Exemestane	—	1.7	5
POLAMA-3			
Fulvestrant500 + Palbociclib	Neutropenia 62%	9.6*	4
Fulvestrant500	—	14.4*	2
MONARCH-2			
Fulvestrant500 + Abemaciclib	Diarrhea 13.3%, neutropenia 26.5%, anemia 7.2%	8.8	15.9
Fulvestrant500	—	1.3	3.1

* AEs of any cause.

- Regarding PFS, the 2 CDK4/6-based combinations showed similar efficacies compared with everolimus plus exemestane. The corresponding P-scores were .87, .84, and .68 for palbociclib plus fulvestrant, abemaciclib plus fulvestrant, and everolimus plus exemestane, respectively. No differences were found in objective response rate (ORR) among the 2 CDK4/6-based combinations and everolimus plus exemestane. For CBR, only palbociclib plus fulvestrant showed improvement compared with everolimus plus exemestane. When excluding either the SoFEA or EFECT studies to form the alternative network, the sensitivity analysis results were generally consistent with those of the original network. The most common grade 3 or 4 adverse events from the treatments in each trial as well as withdrawal due to toxicity are summarized in Table 4. Regarding severe adverse events, compared with everolimus plus exemestane in the network, both CDK4/6-based combinations showed a nonsignificant increasing trend. The ORs were 1.57 (95% CI, 0.57–4.34) and 1.59 (95% CI, 0.53–4.77) for palbociclib plus fulvestrant and abemaciclib plus fulvestrant, respectively.

Anmerkung/Fazit der Autoren

Compared with everolimus plus exemestane, the combinations of palbociclib or abemaciclib with fulvestrant showed similar efficacies in PFS and no differences in ORR. For the CBR, palbociclib demonstrated improvement, while abemaciclib did not. Incidences of severe adverse events did not significantly differ. A total of 29%, 15.9%, and 4% of patients discontinued everolimus, abemaciclib, and palbociclib, respectively, due to toxicity.

These results suggest similar efficacies between CDK4/6 inhibition and mTOR blockade; however, CDK4/6 inhibitors were associated with favorable toxicity profiles.

Kommentar zum Review:

HR und HER-Status nicht dargelegt/ thematisiert

Lee C-H et al., 2020 [13].

Endocrine therapies in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative, pretreated, advanced breast cancer: A network meta-analysis

Fragestellung

Recently, many endocrine therapies have become available for hormone receptor-positive, human epidermal growth factor receptor 2-negative, pretreated, advanced breast cancer. Direct comparisons of these novel treatments to assess their added value, however, are lacking.

Our aim was to synthesize available evidence to compare all current endocrine treatments for hormone receptor-positive / human epidermal growth factor receptor 2-negative advanced breast cancer. We performed a systematic review to identify available randomized controlled trial evidence.

Methodik

Population:

- postmenopausal patients with HR+(or ER +)/HER2 and local ABC or MBC whose diseases had received prior endocrine treatment

Intervention:

- endocrine therapies (endocrine mono-therapies or combined with biological/ target agents, including all available endocrine therapies)

Komparator:

- nicht präspezifiziert

Endpunkte:

- (1) PFS/time to progression (TTP) (2) Clinical benefit rate (CBR). (3) Objective response rate (ORR) (4) Grade 3/4 adverse events (AEs) (per the Common Terminology Criteria of Adverse Events v4.03., (5) Treatment discontinuation rate.

Recherche/Suchzeitraum:

- The latest searching date was on October 19, 2018. Embase, MEDLINE, and the Cochrane Central Register of Controlled Clinical Trials; protocols from clinicaltrial.gov to establish the eligibility of available evidence. Furthermore, specific online websites (FDA website; ASCO; American Association for Cancer Research, including the San Antonio Breast Cancer Symposium; and European Society for Medical Oncology)

Qualitätsbewertung der Studien:

- methodology and categories described in the Cochrane Collaboration Handbook

Ergebnisse

Anzahl eingeschlossener Studien:

- 32 trials and 12,726 patients

Charakteristika der Population:

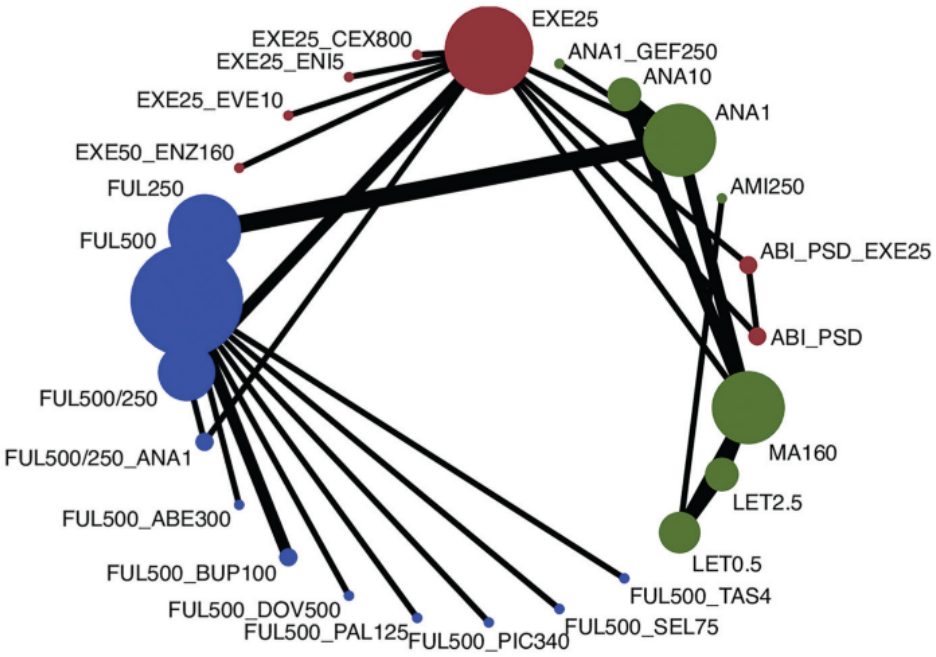
- *Siehe Anhang*
- Single agents
- Anastrozole 1mg; anastrozole 10mg; letrozole 0.5mg; letrozole 2.5mg; exemestane 25mg; fulvestrant 250mg; fulvestrant 500 mg; fulvestrant 500mg followed by 250mg; aminoglutethimide 250mg; megestrol acetate 160mg.
- Aromatase inhibitor-based therapies

- Anastrozole 1mg + gefitinib 500mg; anastrozole 1mg + fulvestrant 250mg; anastrozole 1mg + fulvestrant 500mg/250 mg; exemestane 25mg + entinostat 5mg; exemestane 25mg + abiraterone acetate + prednisone; exemestane 25mg + celecoxib 800mg; exemestane 25mg + everolimus 10mg; exemestane 50 mg + enzalutamide 160mg.
- Selective ER degraders-based therapies
- Fulvestrant 500mg + palbociclib 125mg; fulvestrant 500mg + abemaciclib 300mg; fulvestrant 500mg + ribociclib 600mg; fulvestrant 500mg + selumetinib 75mg; fulvestrant 500mg + pictilisib 340mg; fulvestrant 500mg + taselisib 4mg; fulvestrant 500mg + dovitinib 500mg; fulvestrant 500mg + buparlisib 100mg.

Qualität der Studien:
Daten nicht genannt

Studienergebnisse:

- Figure 2. A Network Graph of evidence used in network meta-analysis. (Directly comparable treatments are linked with a line. Green squares means conventional endocrine therapies; Khaki squares means comparisons of Exemestane; Orange squares means comparisons of Fulvestrant).
- FUL500_PAL125 = Fulvestrant (500 mg) + Palbociclib (125mg); EXE25_ENI5 = Exemestane (25mg) + Entinostat (5mg); EXE25_EVE10 = Exemestane (25mg) + Everolimus (10mg); FUL500_ABE300 = Fulvestrant (500mg) + Abemaciclib (300mg); FUL500_TAS4 = Fulvestrant (500mg) + Taselisib (4mg); FUL500_RIB600 = Fulvestrant (500mg) + Ribociclib (600 mg); FUL500_SEL75 = Fulvestrant (500mg) + Selumetinib (75mg); FUL500_BUP100 = Fulvestrant (500mg) + Buparlisib (100mg); EXE25_CEX800= Exemestane (25mg) + Celecoxib (800mg); ABI_PSD = Abiraterone acetate + Prednisone; EXE25 = Exemestane (25mg); LET0.5 = Letrozole (0.5 mg); FUL500/250== Loading Fulvestrant (500mg) and follow by Fulvestrant (250mg); ABI_PSD_EXE25 = Abiraterone acetate + Prednisone + Exemestane (25mg); FUL500_PIC340 = Fulvestrant (500mg) + Pictilisib (340mg); FUL500_DOV500=Fulvestrant (500mg) + Dovitinib (500mg); FUL500/250_ANA1 = Loading Fulvestrant (500mg) and follow by Fulvestrant (250mg) + Anastrozole (1mg); FUL500 = Fulvestrant (500mg); ANA10 = Anastrozole (10mg); LET2.5 = Letrozole (2.5 mg); FUL250 = Fulvestrant (250mg); EXE50_ENZ160 = Exemestane (50mg) + Enzalutamide (160mg); ANA1_GEF250 = Anastrozole (1mg) + Gefitinib (250mg); MA160 = Megestrol acetate (160mg); ANA1 = Anastrozole (1mg); AMI250 = Aminoglutethimide (250mg).

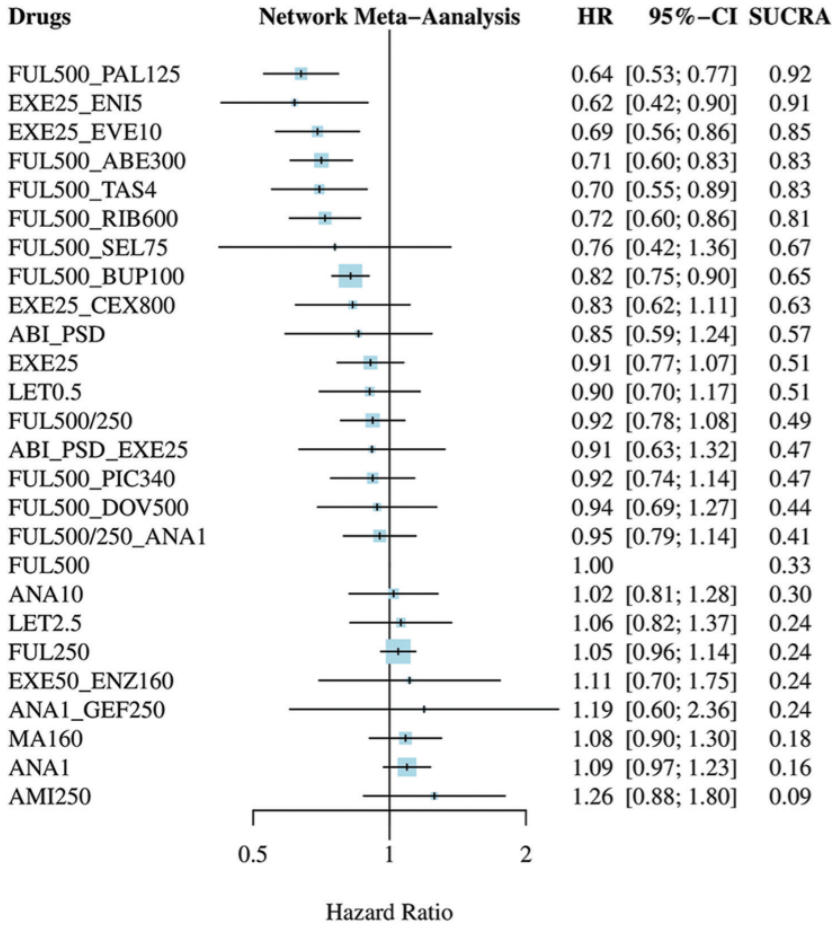


- PFS
- Figure 3A presents the NMA results of PFS from a total of 32 studies (27 arms, 12,726 cases), in which fulvestrant 500mg was the reference. All treatments were sorted on the basis of their ranking along with their HR and 95% CI in comparison with that of fulvestrant 500mg. The probability scores for being the most effective treatment were also listed. A total of 7 combination therapies had significantly prolonged PFS with HRs ranging from 0.62 to 0.82 compared with intramuscular fulvestrant 500mg alone (Fig. 3A). Among the significant findings, 2 therapies were based on exemestane 25mg. For 1, exemestane 25mg combined with entinostat 5mg had a lower HR than fulvestrant 500mg (HR: 0.62, 95% CI: 0.42–0.90, SUCRA: 91%). For another, exemestane 25mg combined with everolimus 10mg also resulted in a better PFS than fulvestrant 500mg (HR: 0.69, 95% CI: 0.56– 0.86, SUCRA: 85%). The other 5 significant findings were 5 fulvestrant-based therapies. The first one was fulvestrant 500mg combined with palbociclib 125mg (HR: 0.64, 95% CI: 0.53– 0.77, SUCRA: 92%), the second was fulvestrant 500mg combined with abemaciclib 300mg (HR: 0.71, 95% CI: 0.60– 0.83, SUCRA: 83%), the third was fulvestrant 500mg combined with taselisib 4mg (HR: 0.70, 95% CI: 0.55–0.89, SUCRA: 83%), the fourth was fulvestrant 500mg combined with ribociclib 600mg (HR: 0.72, 95% CI: 0.60–0.86, SUCRA: 81%), and the fifth was fulvestrant 500mg combined with buparlisib 100mg (HR: 0.82, 95% CI: 0.75–0.90, SUCRA: 65%). Briefly, the top 3 therapies for PFS among ABC/MBC were fulvestrant 500mg plus palbociclib 125mg, exemestane 25 mg plus entinostat 5mg, and exemestane 25mg plus everolimus 10mg. The inconsistency was not serious in the NMA of PFS although
- the design-by-treatment interaction model reached statistical significance. The design-by-treatment interaction model reflected inconsistency between designs (Q: 11.15, p: 0.025) though there was no significance in within designs (Q: 9.85, p: 0.454) (…). We followed significant findings to check the inconsistency contributors. Then, we found similar trends between network estimates and direct estimates (…).

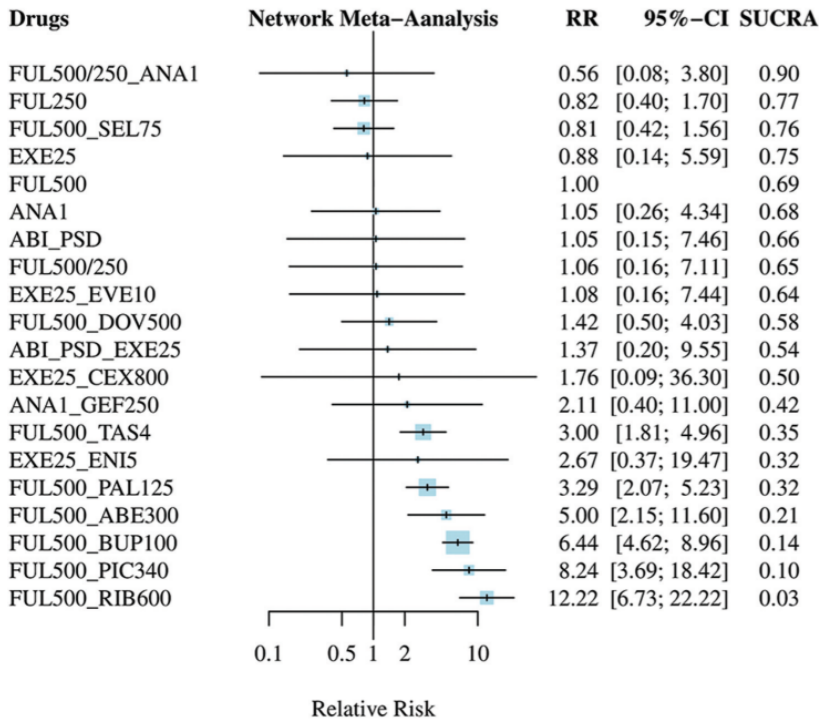
Figure 3. The network meta-meta-analyses results (presented as hazard ratio).
(A) Forest plot of progression free survival (Cumulative ranking).
(B) Forest plot of adverse events (Cumulative ranking).
FUL500_PAL125 = Fulvestrant (500mg) + Palbociclib (125mg); EXE25_ENI5 = Exemestane (25mg) + Entinostat (5mg); EXE25_EVE10 = Exemestane (25mg) + Everolimus (10mg); FUL500_ABE300 = Fulvestrant

(500mg) + Abemaciclib (300mg); FUL500_TAS4 = Fulvestrant (500 mg) + Taselisib (4mg); FUL500_RIB600 = Fulvestrant (500mg) + Ribociclib (600mg); FUL500_SEL75 = Fulvestrant (500mg) + Selumetinib (75mg); FUL500_BUP100 = Fulvestrant (500mg) + Buparlisib (100mg); EXE25_CEX800 = Exemestane (25mg) + Celecoxib (800mg); ABI_PSD = Abiraterone acetate + Prednisone; EXE25 = Exemestane (25mg); LET0.5 = Letrozole (0.5 mg); FUL500/250 = Loading Fulvestrant (500mg) and follow by Fulvestrant (250mg); ABI_PSD_EXE25 = Abiraterone acetate + Prednisone + Exemestane (25mg); FUL500_PIC340 = Fulvestrant (500mg) + Pictilisib (340mg); FUL500_DOV500 = Fulvestrant (500mg) + Dovitinib (500mg); FUL500/250_ANA1 = Loading Fulvestrant (500mg) and follow by Fulvestrant (250mg) + Anastrozole (1mg); FUL500 = Fulvestrant (500mg); ANA10 = Anastrozole (10mg); LET2.5 = Letrozole (2.5 mg); FUL250 = Fulvestrant (250mg); EXE50_ENZ160 = Exemestane (50mg) + Enzalutamide (160mg); ANA1_GEF250 = Anastrozole (1mg) + Gefitinib (250mg); MA160 = Megestrol acetate (160mg); ANA1 = Anastrozole (1mg); AMI250 = Aminoglutethimide (250mg). CI=confidence interval, HR=hazard ratio, RR=risk ratio, SUCRA=surface under the cumulative ranking curve.

A)

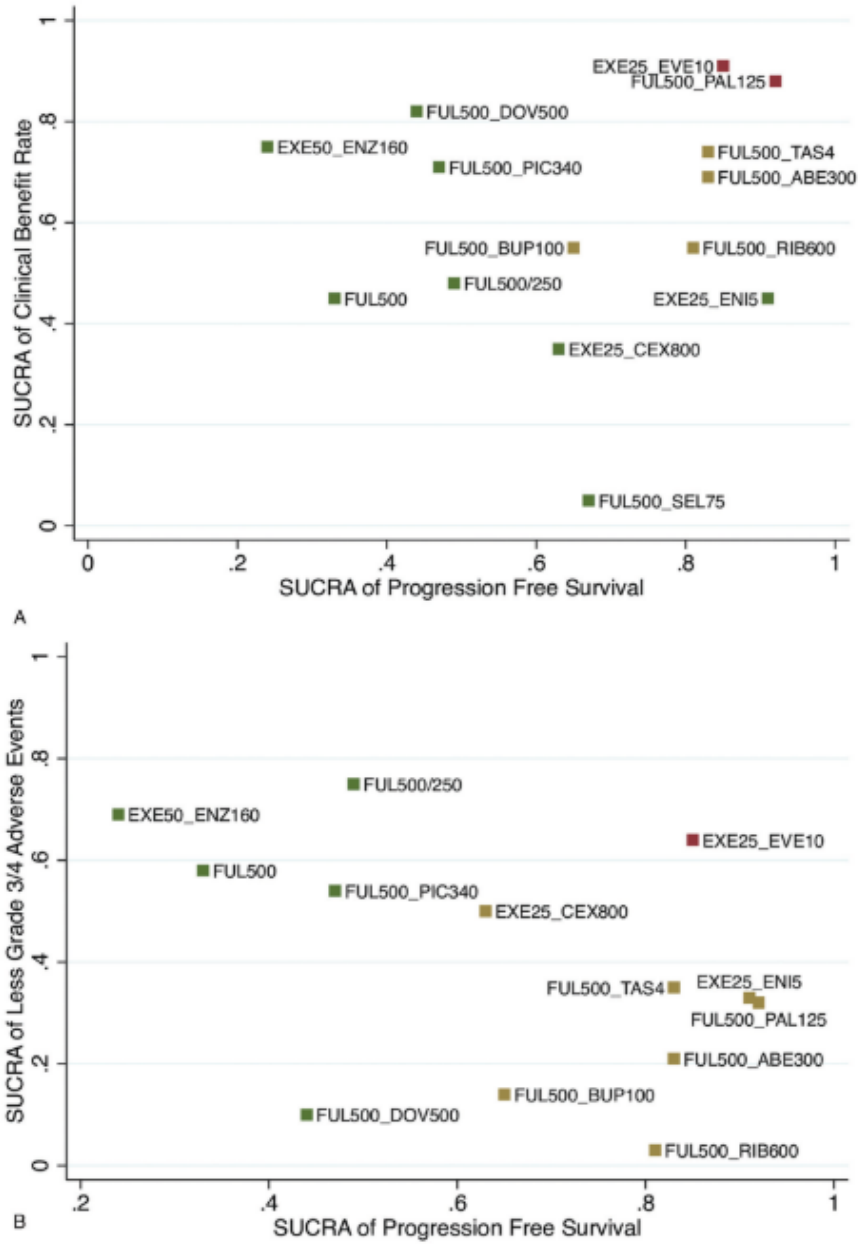


B)



- CBR and overall response rate (ORR)
- We further explored the results of CRB and ORR (…).Exemestane 25mg plus everolimus 10mg was found to be the best meaningful therapy both in CBR (risk ratio: 1.84, 95% CI: 1.21–2.80, SUCRA: 91%) and ORR (risk ratio: 6.05, 95% CI: 1.75–20.87, SUCRA: 97%). Fulvestrant 500mg combined with palbociclib 125mg, or abemaciclib 300mg, or taselisib 4mg, or dovitinib 500mg all revealed both better efficacies in CBR and ORR than fulvestrant 500mg alone. However, the difference in CBR or ORR between the combination of exemestane 25mg plus entinostat 5mg with fulvestrant 500mg alone were not significantly different (see Table, Supplemental Digital Content 7, http://links.lww.com/MD/D987, which illustrates the Summary of clinical benefit rate and overall response rate, Supplemental Digital Content 8, http://links.lww.com/MD/D988, which illustrates the NMA of secondary outcomes).
- Grade 3/4 and treatment discontinuation
- In the safety evaluation, 6 fulvestrant 500-mg-based therapies combined with either CDK 4/6 or PIK3 inhibitors all showed statistically significant increases in the risk of grade 3/4 AEs. Fulvestrant 500-mg-based therapies combined with palbociclib 125mg, abemaciclib 300mg, taselisib 4mg, ribociclib 600mg, pictilisib 340mg, or buparlisib 100mg increased the risk of grade 3/4 AEs more than 3 times as they were compared with fulvestrant 500mg alone, the risk ratios ranged from 3.00 to 12.22 (…).
- We generated 2 scatter plots: one combined PFS with CBR to distinguish the true clinical efficacy, and the other put PFS and grade 3/4 AEs together to consider efficacy and safety together. When assessing the effect of CRB and PFS together, fulvestrant 500mg plus palbociclib 125mg and exemestane 25mg plus everolimus 10mg were the top 2 choices for postmenopausal pretreated ABC/MBC patients (Fig. 4A). If safety was the top priority, exemestane 25mg plus everolimus 10mg was the optimal therapy (Fig. 4B).

Figure 4. Scatter plots of network meta-analyses, presenting with cumulative SCRUA values (the closer to 1.0, the better).
(A) Association of progression free survival (X-axis) and clinical benefit rate (Y-axis).
(B) Association of progression free survival (X-axis) and grade 3/4 adverse events (Y-axis).
FUL500_PAL125 = Fulvestrant (500mg) + Palbociclib (125mg); EXE25_ENI5 = Exemestane (25mg) + Entinostat (5mg); EXE25_EVE10 = Exemestane (25mg) + Everolimus (10mg); FUL500_ABE300 = Fulvestrant (500mg) + Abemaciclib (300mg); FUL500_TAS4 = Fulvestrant (500mg) + Taselisib (4mg); FUL500_RIB600 = Fulvestrant (500mg) + Ribociclib (600mg); FUL500_SEL75 = Fulvestrant (500mg) + Selumetinib (75mg); FUL500_BUP100 = Fulvestrant (500mg) + Buparlisib (100mg); EXE25_CEX800 = Exemestane (25mg) + Celecoxib (800mg); ABI_PSD = Abiraterone acetate + Prednisone; EXE25 = Exemestane (25mg); LET0.5 = Letrozole (0.5 mg); FUL500/250 == Loading Fulvestrant (500mg) and follow by Fulvestrant (250mg); ABI_PSD_EXE25 = Abiraterone acetate + Prednisone + Exemestane (25mg); FUL500_PIC340 = Fulvestrant (500mg) + Pictilisib (340mg); FUL500_DOV500 = Fulvestrant (500mg) + Dovitinib (500mg); FUL500/250_ANA1 = Loading Fulvestrant (500mg) and follow by Fulvestrant (250mg) + Anastrozole (1mg); FUL500 = Fulvestrant (500mg); ANA10 = Anastrozole (10mg); LET2.5 = Letrozole (2.5 mg); FUL250 = Fulvestrant (250mg); EXE50_ENZ160 = Exemestane (50mg) + Enzalutamide (160mg); ANA1_GEF250 = Anastrozole (1mg) + Gefitinib (250 mg); MA160 = Megestrol acetate (160mg); ANA1 = Anastrozole (1mg); AMI250 = Aminoglutethimide (250mg).



Anmerkung/Fazit der Autoren

On the basis of this analysis, the 2 combinations of exemestane plus everolimus and fulvestrant plus palbociclib were the best treatment options.

Piezzo M et al., 2020 [20].

Progression-Free Survival and Overall Survival of CDK 4/6 Inhibitors Plus Endocrine Therapy in Metastatic Breast Cancer: A Systematic Review and Meta-Analysis

Fragestellung

The introduction ofCDK4/6 inhibitors in combination with endocrine therapy (ET) represents the most relevant advance in the management of hormone receptor (HR) positive, HER2-negative metastatic breast cancer over the last few years. This meta-analysis of randomized controlled trials (RCTs) is aimed to better characterize the efficacy of CDK4/6 inhibitors in some relevant subgroups and to test heterogeneity between different compounds with a particular focus on their ability to improve overall survival (OS).

Methodik

Population:

- Patients with HR-positive/HER2-negative advanced or metastatic BC

Intervention:

- selective inhibitor of CDK4/6 (palbociclib, ribociclib or abemaciclib)

Komparator:

- standard of care (SOC) treatment ± placebo)
- standard of care (SOC) treatment included ET only, such as aromatase inhibitors (i.e., anastrozole, letrozole, exemestane), oestrogen receptor modulators (i.e., tamoxifen) or selective oestrogen receptor downregulators (i.e., fulvestrant)

Endpunkte:

- primary outcome of interest (PFS/TTP reported in terms of HR and related CIs)

Recherche/Suchzeitraum:

- MEDLINE via PubMed and the Cochrane databases; Research was restricted from January 2010 until June 30, 2019, but two additional results, relevant to assess overall survival, were added: MONALEESA-3 and MONARCH-2, presented at the European Society for Medical Oncology Meeting (ESMO) in September 2019
- A computerized search was also run in order to identify abstracts and presentations of relevant unpublished studies, reported at the Annual Meetings of the American Society of Clinical Oncology (ASCO), at the San Antonio Breast Cancer Symposium (SABC), and at ESMO meetings over the last three years. Additional studies were hand-searched on Clinicaltrials.gov.

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCTs; 4580 patients

Charakteristika der Population:

Table 1. Characteristics of included studies.

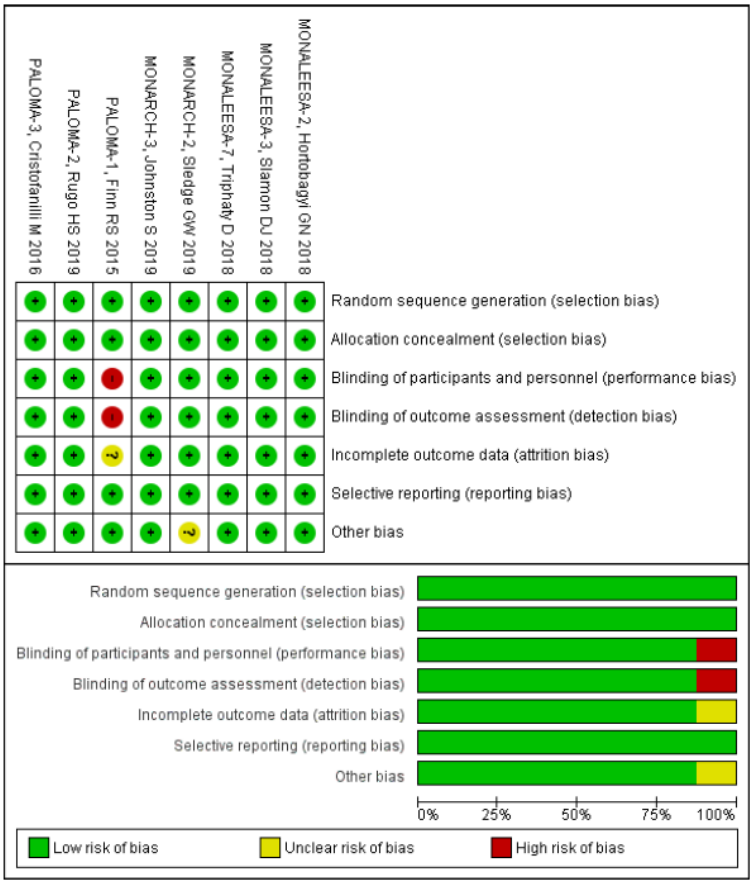
First Author, Year (Study Name)	Phase	Population	Experimental Arm (n)	Control Arm (n)	Endocrine Status	Median PFS Exp Arm	Median PFS Ctrl Arm	HR (95% CI)
Hortobagyi GN, 2018 (MONALEESA-2)	III	Post-menopausal AI-sensitive	Ribociclib + Letrozole (334)	Letrozole + Placebo (334)	Sensitive	25.3 (23.0–30.3)	16 (13.4–18.2)	0.568 (0.457–0.704)
Slamon DJ, 2018 (MONALEESA-3)	III	Post-menopausal AI-sensitive/resistant	Ribociclib + Fulvestrant (484)	Fulvestrant + Placebo (242)	Mixed	20.5 (18.5–23.5)	12.8 (10.9–16.3)	0.593 (0.480–0.732)
Tripathy D, 2018 (MONALEESA-7)	III	Pre-menopausal AI-sensitive	Ribociclib + Tamoxifene or NSAI (335)	Placebo + Tamoxifene or NSAI (337)	Mixed	23.8 (19.2–NR *)	13.3 (11.0–16.4)	0.553 (0.441–0.694)
Sledge GW, 2019 (MONARCH-2)	III	Pre/Post-menopausal AI-resistant	Abemaciclib + Fulvestrant (446)	Fulvestrant + Placebo (223)	Resistant	16.4 (not reported)	9.3 (not reported)	0.553 (0.449–0.681)
Johnston S, 2019 (MONARCH-3)	III	Pre/Post-menopausal AI-sensitive	Abemaciclib + NSAI (328)	Placebo + NSAI (165)	Sensitive	28.1 (not reported)	14.7 (not reported)	0.540 (0.418–0.698)
Finn RS, 2015 (PALOMA-1)	II	Pre/Post-menopausal AI-sensitive	Palbociclib + Letrozole (84)	Letrozole (81)	Sensitive	20.2 (13.8–27.5)	10.2 (5.7–12.6)	0.488 (0.319–0.748)
Rugo HS, 2019 (PALOMA-2)	III	Pre/Post-menopausal AI-sensitive	Palbociclib + Letrozole (444)	Letrozole (222)	Sensitive	27.6 (22.4–30.3)	14.5 (12.3–17·1)	0.563 (0.461–0.687)
Cristofanilli M, 2016 (PALOMA-3)	III	Pre/Post-menopausal AI-resistant	Palbociclib + Fulvestrant (521)	Fulvestrant + Placebo (347)	Resistant	9.5 (9.2–11.0)	4.6 (3.5–5.6)	0.46 (0.36–0.59)

* NR, not reached.

Qualität der Studien:

- Overall, the risk of selection, performance, attrition, detection, and reporting bias was very low because all trials were double blind, with the exception of the PALOMA-1 study that was a phase II, open-label study.

Figure S2. Risk of bias for selected studies: review authors' judgements about each risk of bias item for each included study



Studienergebnisse:

- PFS
- PFS hazard ratios were directly available for all included studies. Single study HRs ranged from 0.46 to 0.59 and were all statistically significant. Pooled analysis showed a statistically significant improvement in PFS for patients treated with the CDK4/6 inhibitor in combination with ET versus patients treated with ET alone (HR 0.547 [95% CI 0.504, 0.594], p-value < 0.0001). Both a fixed-effect model and a random-effect model were implemented, as initially planned if no heterogeneity between studies was detected (Iˆ2 0%; chiˆ2 2.95, p 0.89) or publication bias (Egger test, p 0.09).
- AI Sensitivity and Treatment-Free Interval (TFI) Based on the aforementioned definitions, we pooled PFS estimates for AI-sensitive patients and AI-resistant patients among all trials included in this analysis. Patients with de novo disease were considered a separate group. A total of 5329 patients were included in this group, of which 2852 were AI-sensitive, 1536 were AI-resistant, and 941 patients had de novo disease. MONALEESA-2, MONALEESA-7, MONARCH-3, PALOMA-1, and PALOMA-2 studies enrolled exclusively AI-sensitive patients while MONARCH-2 and PALOMA-3 enrolled AI-resistant patients only; MONALEESA-3 enrolled both sensitive and resistant patients. It also enrolled ‘de novo’ patients (19% of the total), but separate estimates for these patients are not available. ‘De novo’ patients of the MONALEESA-3 trial were therefore included in the AI-sensitive group for the purpose of this meta-analysis. No between-group difference was observed (Iˆ2 0%; chiˆ2 4.92, p-value 0.960). The pooled HRs were very similar in AI-sensitive and ‘de novo’ AI-resistant patients. The treatment-free interval (TFI) was defined as the time from the end of the adjuvant therapy
- to randomization. TFI was analyzed at four time points: ≤24 months, >24 months, ≤36 months, and >36 months. Overall, 1391 patients were included in this analysis, of which 199 had a TFI ≤ 24 months, 686 had a TFI > 24 months, 244 had a TFI ≤ 36 months, and 262 had a TFI > 36 months. No significant heterogeneity was observed (Iˆ2 0%; chiˆ2 6.22, p-value 0.622). The pooled analysis confirms the beneficial effect of adding theCDK4/6 inhibitor to standardET regardless the treatment-free interval. The estimated pooled HRs according the AI-sensitivity and TFI are shown in Figure 1.

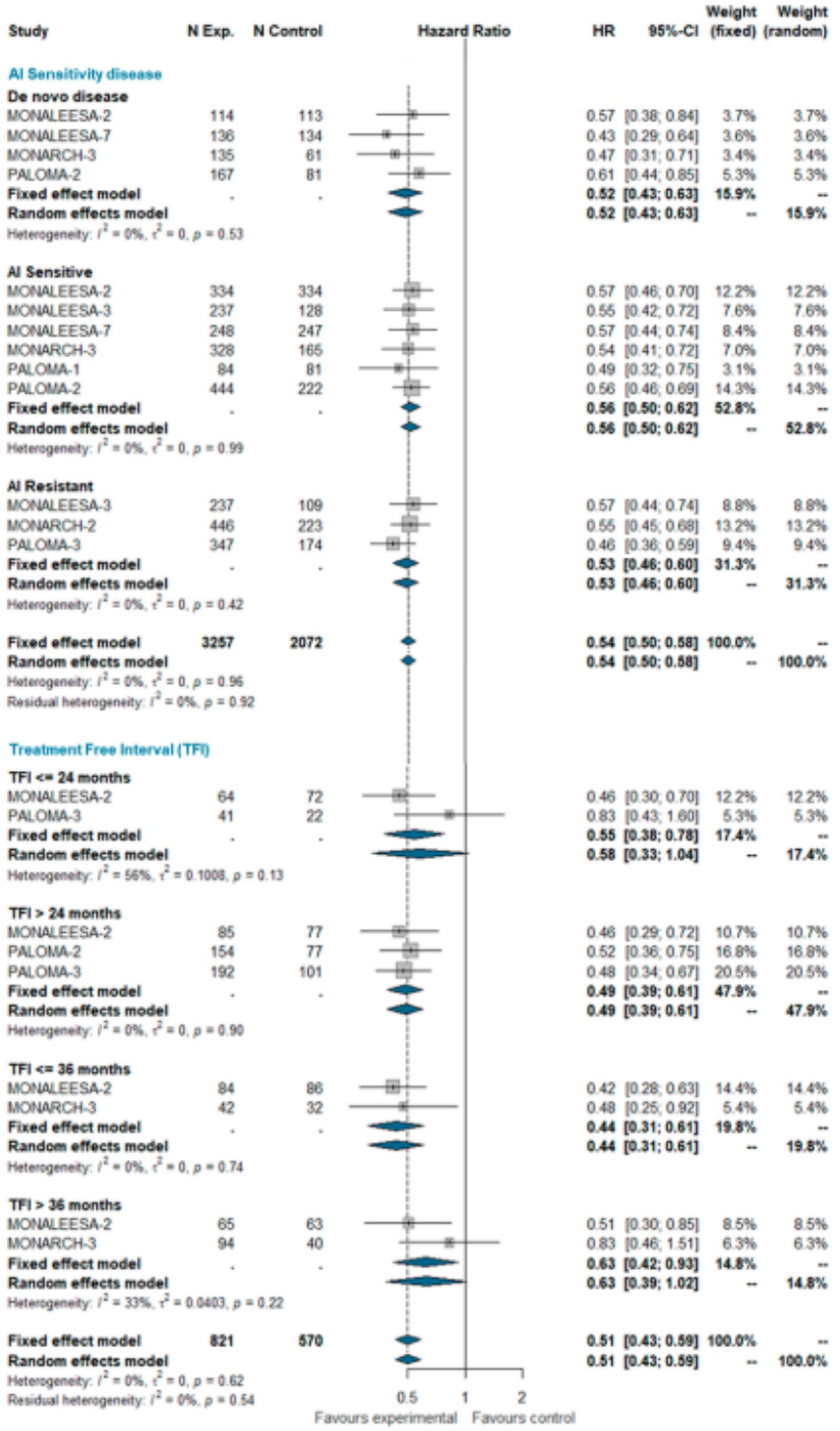
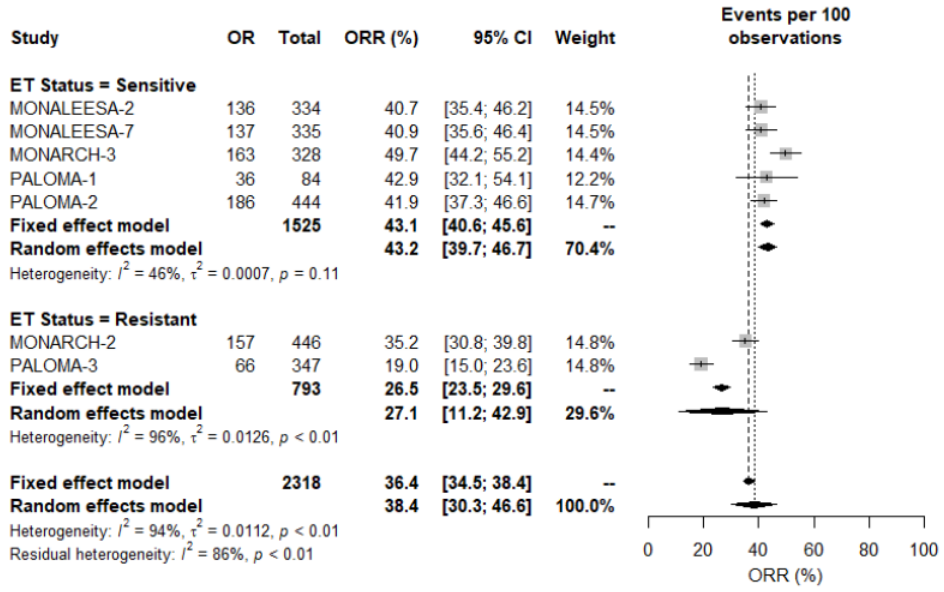


Figure 1. Pooled comparison of PFS according endocrine sensitivity (de novo disease, AI sensitive, AI resistant) and treatment-free interval (TFI <= 24 months, TFI > 24 months, TFI <= 36 months, TFI > 36 months). Abbreviations: PFS: progression free survival; N exp: number of patients randomized in experimental arm; N control: number of patients randomized in control arm; HR: hazard ratio; CI: confidence interval; AI: aromatase inhibitors; TFI: treatment free interval).

- Objective Response
- ORR data were available for all studies. Pooled estimates of ORR were summarized as bar plots; forest plots are available as Supplemental Data. Figure 3 shows the bar plot of

pooled ORR in all randomly assigned patients and in patients with measurable disease according to AI sensitivity. Overall, 2318 patients treated with the CDK 4/6 inhibitor plus ET and 1536 patients treated with ET alone were included in this analysis, while 1781 patients had measurable disease (1195 treated with the CDK 4/6 inhibitor + ET and 586 treated with ET alone). The meta-analysis shows an increased ORR in patients treated with CDK 4/6 inhibitors, both in AI-sensitive (pooled ORR = 43.3% for CDK4/6 inhibitor-treated patients) and AI-resistant groups (pooled ORR = 26.5% for CDK4/6 inhibitor-treated patients). Patients treated with the CDK 4/6 inhibitor reached a pooled ORR of 55% in the AI-sensitive group and 35.6% in the AI-resistant group.

Figure S6. Meta-analysis of objective response rate (ORR) in patients treated with CDK 4/6 inhibitor plus endocrine therapy according AI-sensititvity



A meta-analysis of single proportions was carried out to obtain the pooled estimate of ORR in patients treated with CDK 4/6 inhibitor plus endocrine therapy according their AI-sensititvity.

- Overall Survival
- Overall survival (OS) data were available only for MONALEESA-2, MONALEESA-3, MONALEESA-7, MONARCH-2, PALOMA-1, and PALOMA-3 trials [24,27,28,35–37]. This analysis included a total of 3421 patients, of which 2030 were treated with CDK 4/6 inhibitors and 1391 were treated with ET alone. The pooled HR indicates a statistically significant reduction in the risk of dying for patients receiving the CDK4/6 inhibitor (HR 0.763 [95% CI 0.683; 0.852], p-value < 0.0001); this effect is independent of whether patients were AI sensitive or not. When grouped by CDK4/6 inhibitor, a statically significant reduction in the hazard of dying was apparent for ribociclib and abemaciclib only, but not for palbociclib (Figure 4). However, the test for heterogeneity (Iˆ2 0%; chiˆ2 1.44, p-value 0.919) suggests that discrepant OS results among different CDK4/6 inhibitors may be explained by chance.

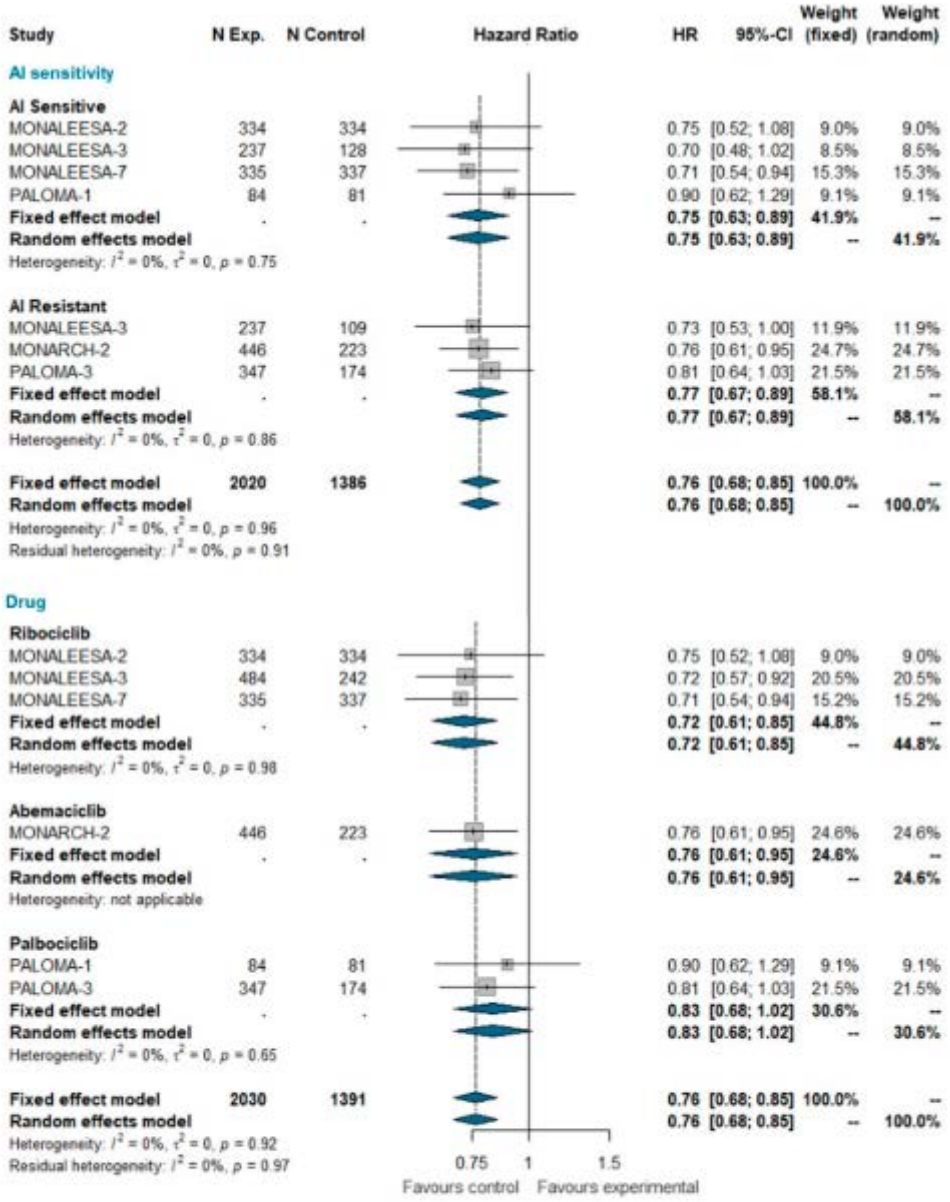


Figure 4. Meta-analysis of overall survival grouped by AI sensitivity (AI sensitive versus AI resistant) and CDK 4/6 inhibitor (Ribociclib, Abemaciclib, Palbociclib). Abbreviations: OS: overall survival; N exp: number of patients randomized in experimental arm; N control: number of patients randomized in control arm; HR: hazard ratio; CI: confidence interval; AI: aromatase inhibitors).

Anmerkung/Fazit der Autoren

Adding a CDK4/6 inhibitor to ET is beneficial in terms of PFS, irrespective of the presence or not of visceral metastases, the number of metastatic sites, and the length of the treatment-free interval (TFI). The addition of CDK4/6 inhibitors produces a significant OS improvement, both in aromatase inhibitor (AI)-sensitive (HR 0.75, 95% CI) and AI-resistant patients (HR 0.77, 95% CI [0.67–0.89]). Pooled data from each single drug show that palbociclib remains the only class member not showing a statistically significant HR for OS (HR 0.83, 95% CI [0.68–1.02]).

Schettini F et al., 2020 [22].

Overall Survival of CDK4/6-Inhibitor–Based Treatments in Clinically Relevant Subgroups of Metastatic Breast Cancer: Systematic Review and Meta-Analysis

Fragestellung

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors þ endocrine therapy (ET) prolonged progression-free survival as first- or second-line therapy for hormone receptor-positive (HRþ)/HER2-negative metastatic breast cancer prognosis. Given the recent publication of overall survival (OS) data for the 3 CDK4/6-inhibitors, we performed ameta-analysis to identify amore precise and reliable benefit from such treatments in specific clinical subgroups.

Methodik

Population:

- hormone receptor-positive (HRþ)/HER2-negative metastatic breast cancer
- Subgroups of interest were the following: visceral disease (yes vs no), bone-only disease (yes vs no), number of metastatic sites (<3 sites vs >=3), endocrine sensitivity and resistance (yes vs no), previous CT for the metastatic setting (yes vs no), age (<65 vs >= 65 years), and menopausal status (pre-perimenopausal vs postmenopausal). Endocrine resistance and sensitivity were defined according to ESO-ESMO International Consensus Guidelines

Intervention/ Komparator:

- cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors + endocrine therapy (ET)

Endpunkte:

- overall survival (OS)

Recherche/Suchzeitraum:

- PubMed at the end of October 2019; European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology meetings' and San Antonio Breast Cancer Symposium' online databases were also consulted.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's "Risk of Bias" tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Six studies (3421 patients)

Charakteristika der Population:

- Three out of 6 (50.0%) studies were set in first line, while the remaining (50.0%) were set in first or second line.

Table 1. Characteristics and results of published randomized phase II or III trials of CDK4/6-inhibitors combined with ET in HR+/HER2-negative MBC

	Published randomized Phase II or III trials								
Features	PALOMA 1	PALOMA 2	PALOMA 3	MONALEESA 2	MONALEESA 7	MONALEESA 3	MONARCH 3	MONARCH 2	MONARCH plus
Phase	II	III	III	III	III	III	III	III	III
No. of patients	165	666	521	668	672	726	493	669	463
Treatment	Palbociclib + letrozole vs letrozole	Palbociclib + letrozole vs letrozole -	Palbociclib + fulvestrant vs fulvestrant (+ GnRHa in pre/peri pts)	Ribociclib + letrozole vs letrozole	Ribociclib + tamoxifen or AI + GnRHa vs tamoxifen or AI + GnRHa	Ribociclib + fulvestrant vs fulvestrant	Abemaciclib + NSAI vs NSAI	Abemaciclib + fulvestrant vs fulvestrant (+ GnRHa in pre/peri pts)	Abemaciclib + NSAI or fulvestrant vs NSAI or fulvestrant
Menopausal status at moment of trial enrollment	Post	Post	Pre/post	Post	Pre	Post	Post	Pre/post	Post
Setting	1st line HR+ HER2− MBC	1st line HR+ HER2− MBC	≥1st line HR+ HER2− MBC	1st line HR+ HER2− MBC	1st line HR+ HER2− MBC	≥1st line HR+ HER2− MBC	1st line HR+ HER2− MBC	≥1st line HR+ HER2− MBC	≥1st line HR+ HER2− MBC
Median PFS, mo	20.2 vs 10.2	24.8 vs 14.5	9.5 vs 4.6	25.3 vs 16.0	23.8 vs 13.0	20.5 vs 12.8	NR vs 14.7	16.4 vs 9.3	NR and 11.5 vs 14.7 and 5.6
PFS HR (95% CI)	0.49 (0.32 to 0.75)	0.58 (0.46 to 0.72)	0.46 (0.36 to 0.59)	0.57 (0.46 to 0.70)	0.55 (0.44 to 0.69)	0.59 (0.48 to 0.73)	0.54 (0.41 to 0.72)	0.55 (0.45 to 0.68)	0.50 (0.35 to 0.72) and 0.38 (0.24 to 0.59)
ORR[a]	43% vs 33%	42% vs 35%	25% vs 11%	43% vs 29%	51% vs 36%	41% vs 9%	59% vs 44%	48% vs 21%	56% and 39% vs 30% and 8%
Median OS, mo	37.5 vs 33.3	NM	35.0 vs 28.0	NR	NR vs 40.9	NR vs 40.0	NM	46.7 vs 37.3	NM
OS HR (95% CI)	0.81 (0.49 to 1.35)	NM	0.81 (0.64 to 1.03)	0.75 (0.52 to 1.08)	0.71 (0.54 to 0.95)	0.72 (0.57 to 0.92)	NM	0.76 (0.61 to 0.95)	NM
Journal/Congress[b]	Lancet Oncol/J Clin Oncol	N Engl J Med	New Engl J Med	Ann Oncol	New Engl J Med	N Engl J Med	J Clin Oncol	JAMA Oncol	Ann Oncol
First author[b]	Finn RS	Finn RS	Turner NC	Hortobagyi G	Im S-A	Slamon DJ	Goetz MP	Sledge GW	Jiang Z
Year[b]	2014/2017	2016	2018	2018	2019	2019	2017	2019	2019

[a]Values are rounded. AI = aromatase inhibitor; CI = confidence interval; ET = endocrine therapy; GnRHa = gonadotropin-releasing hormone agonist; HER2- = human epidermal growth factor receptor 2 negative; HR = hazard ratio; HR+ = hormone receptor positive; MBC = metastatic breast cancer; NM = not mature; NR = not reached; NSAI = nonsteroidal aromatase inhibitor; ORR = overall response rate; OS = overall survival; peri = perimenopausal; PFS = progression-free survival; post = postmenopausal; pre = premenopausal; ESMO = European Society for Medical Oncology; ASCO = American Society of Clinical Oncology.
[b]The citations refer to manuscripts with available OS results unless they have not been published yet.

Qualität der Studien:

- The studies included in our analyses did not show any relevant risk of bias within the 7 domains considered.

Studienergebnisse:

- A clear OS benefit was observed in patients without (hazard ratio [HR] = 0.68, 95% confidence interval [CI] = 0.54 to 0.85, I2 = 0.0%) and with visceral involvement (HR = 0.76, 95% CI = 0.65 to 0.89, I2 = 0.0%), with at least 3 metastatic sites (HR = 0.75, 95% CI =0.60 to 0.94, I2 = 11.6%), in an endocrine-resistant (HR = 0.79, 95% CI = 0.67 to 0.93, I2 = 0.0%) and sensitive subset (HR =0.73, 95% CI = 0.61 to 0.88, I2 = 0.0%), for younger than 65 years (HR = 0.80, 95% CI = 0.67 to 0.95, I2 = 0.0%) and 65 years or older (HR = 0.71, 95% CI = 0.53 to 0.95, I2 = 44.4%), in postmenopausal (HR = 0.76, 95% CI = 0.67 to 0.86, I2 = 0.0%) and pre- or perimenopausal setting (HR = 0.76, 95% CI = 0.60 to 0.96, I2 = 0.0%) as well as in chemotherapy-naı¨ve patients (HR = 0.72, 95% CI = 0.55 to 0.93, I2 = 0.0%).

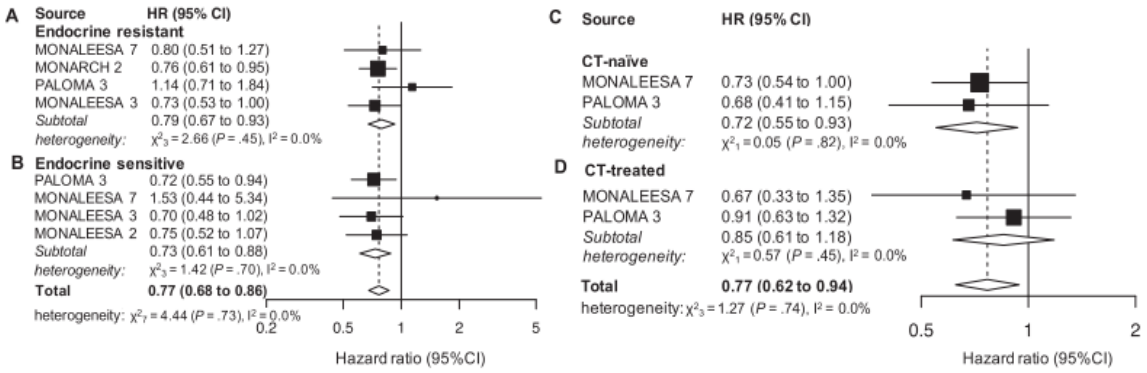
Table 2. Full subgroup analyses results[a]

Variables	No. of Pts	No. of studies	Pooled HR (95% CI)	I^2, %	P_{pooled}	P_H	$P_{sub.\ diff.}$
Age, y	1916	3	0.77 (0.66 to 0.88)	12.0	<.001	.34	.49
<65	1203	3	0.80 (0.67 to 0.95)	0.0	.01	.45	
≥65	713	3	0.71 (0.53 to 0.95)	44.4	.003	.17	
Menopausal status	3417	6	0.75 (0.67 to 0.84)	0.0	<.001	.95	.99
Pre- or perimenopausal	894	3	0.76 (0.60 to 0.96)	0.0	.02	.41	
Postmenopausal	2523	5	0.76 (0.67 to 0.86)	0.0	<.001	.89	
Bone-only disease	1577	3	0.74 (0.62 to 0.89)	0.0	<.001	.61	.47
Yes	492	3	0.82 (0.60 to 1.13)	0.0	.23	.45	
No	1085	2	0.71 (0.58 to 0.88)	0.0	.002	.47	
Metastatic sites	1600	3	0.77 (0.65 to 0.91)	0.0	.002	.63	.74
<3	891	2	0.79 (0.62 to 1.01)	0.0	.06	.63	
≥3	709	3	0.75 (0.60 to 0.94)	11.6	.02	.32	
Previous CT in metastatic setting	979	2	0.77 (0.62 to 0.94)	0.0	.01	.74	.42
Yes	271	2	0.85 (0.61 to 1.18)	0.0	.34	.45	
No	708	2	0.72 (0.55 to 0.93)	0.0	.01	.82	
Visceral involvement	2291	4	0.73 (0.65 to 0.83)	0.0	<.001	.89	.91
No	901	3	0.68 (0.54 to 0.85)	0.0	<.001	.96	
Yes	1390	4	0.76 (0.65 to 0.89)	0.0	<.001	.69	
Endocrine sensitivity status	2834	5	0.77 (0.68 to 0.86)	0.0	<.001	.73	.55
Resistance	1331	4	0.79 (0.67 to 0.93)	0.0	.004	.45	
Sensitive	1503	4	0.73 (0.61 to 0.88)	0.0	.001	.70	

[a]CI = confidence interval; CT = chemotherapy; HR = hazard ratio; P_H = P value for heterogeneity test; P_{pooled} = P value for the pooled analysis; $P_{sub.diff.}$ = P value for subgroup differences; Pts = patients.

- Endocrine Sensitivity Status
- Four studies provided results for the endocrine resistant subset (1331 patients). The effect in the subgroup was statistically significant (HR = 0.79, 95% CI = 0.67 to 0.93, P=.004, I2 = 0.0%; Figure 2A). Four studies (1503 patients) reported results for the endocrine sensitive subset, which was statistically significant as well (HR ¼ 0.73, 95% CI = 0.61 to 0.88, P=.001, I2 = 0.0%; Figure 2B). The overall effect in the joint analysis of the 2 subgroups was also statistically significant (HR = 0.77, 95% CI = 0.68 to 0.86, P<.001, I2 = 0.0%; Figure 2), whereas the between-group difference for the endocrine resistance and sensitive setting was not (P=.55).
- Previous CT for Metastatic Disease
- Two studies reported results for CT-naı¨ve (708) and CTpretreated (271) patients in a metastatic setting. A statistically significant cumulative effect was demonstrated for the first (HR = 0.72, 95% CI = 0.55 to 0.93, P=01, I2 = 0.0%; Figure 2C) but not for the latter group (HR = 0.85, 95% CI = 0.61 to 1.18, P=.34, I2 = 0.0%; Figure 2D). The joint analysis of the 2 subpopulations was statistically significant (HR = 0.77, 95% CI ¼ 0.62 to 0.94, P=.01, I2 = 0.0%; Figure 2), and there was no statistically significant difference between the 2 groups (P=.42).

Figure 2. Pooled overall survival (OS) according to endocrine resistance status and previous chemotherapy (CT). Pooled OS in patients younger than 65 years (A), 65 years or older (B), postmenopause (C) and pre- or perimenopause (D). CI ¼ confidence interval; HR ¼ hazard ratio.



Anmerkung/Fazit der Autoren

In conclusion, CDK4/6-inhibitors plus ET combinations are substantially effective in improving OS in HRþ/HER2-negative MBC as first- or second-line treatment in young or adult (<65 years) as well as in older patients independently from visceral involvement, endocrine sensitivity, and menopausal status. Ribociclib-based combinations might be preferred for the premenopausal setting, because the major contribution on the overall positive subgroup analysis result came from the ribociclib-based MONALEESA 7 trial, which specifically enrolled pre- and perimenopausal patients (a total of 672), whereas the other studies included only contributed with relatively small subgroups of the overall patients enrolled (108 and 114 for PALOMA 3 and MONARCH 3, respectively). On the other hand, abemaciclib-based combinations might be preferred for endocrine-resistant tumors, being the only CDK4/6inhibitor clearly providing a statistically significant effect in this subset. However, it must be considered that this is only speculative, because no currently published data support the superiority of 1 of the 3 molecules, or the same CDK4/6inhibitor with a different ET companion (AI, fulvestrant or tamoxifen), over the others (10,31). Furthermore, the degree of benefit shown across pivotal trials for the intention-to-treat populations is quite similar (3–9).

Thein KZ et al., 2020 [23].

Venous thromboembolism risk in patients with hormone receptor-positive HER2-negative metastatic breast cancer treated with combined CDK 4/6 inhibitors plus endocrine therapy versus endocrine therapy alone: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

The primary objective of our analysis was to determine the risk of VTE with the use of CDKIs plus ET versus ET alone in patients with MBC. Subgroup analyses for RRs for VTE risk were conducted based on different CDKIs; types of ET, or whether CDKIs containing regimen were used as firstline or secondline treatment, in the HR-positive, HER2-negative MBC.

Methodik

<u>Population:</u>

- hormone receptor positive, HER-2 negative, metastatic BC

Intervention:

- CDKIs-based regimen

Komparator:

- nicht eingeschränkt

Endpunkte:

- venous thromboembolism (VTE) as adverse effects

Recherche/Suchzeitraum:

- literature search in MEDLINE and EMBASE databases, from inception until 31 August 2019
- hand searched major oncology conferences, especially the American Society of Clinical Oncology and the European Society of Medical Oncology

Qualitätsbewertung der Studien:

- Risk of bias for each study was evaluated by Cochrane RevMan 5.3 software

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCT

Charakteristika der Population:

Table 1 Characteristics of the studies included in the meta-analysis

Study	Author (year)	Study type	Study phase	Type of cancer	Line of treatment	Number of patients		Treatments rendered		Number of VTE events	
						CDK 4/6 inhibitor	Control			CDK 4/6 inhibitor	Control
PALOMA 1 [19]	Finn (2015)	Open label, randomized	Phase 2	ER + ve, HER2-ve advanced breast cancer	First line	83	77	Palbociclib + letrozole	Letrozole	4	0
PALOMA 2 [20]	Finn (2016)	Randomized, multicenter, double-blind	Phase 3	ER + ve, HER2-ve advanced breast cancer	First line	444	222	Palbociclib + letrozole	Letrozole	4	3
PALOMA 3 [26]	Cristofanilli (2016)	Multicenter, randomized, double-blind, placebo-controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	Second line	345	172	Palbociclib + fulvestrant	+ fulvestrant	6	0
MONARCH 2 [21]	Sledge (2017)	Randomized, Double-Blind, Placebo-Controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	Second line	441	223	Abemaciclib + fulvestrant	+ fulvestrant	9	1
MONARCH 3 [22, 27]	Goetz (2017)	Randomized, double blind	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line	327	161	Abemaciclib + Aromatase Inhibitor[a]		20	1
MONALEESA 2 [23]	Hortobagyi (2016)	Randomized double-blind, placebo-controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line	334	330	Ribociclib + letrozole	+ letrozole	2	0
MONALESSA 3 [24]	Slamon (2018)	Randomized double-blind, placebo-controlled	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line or Second line	484	242	Ribociclib + fulvestrant	Fulvestrant	1	1
MONALESSA 7 [25, 28]	Tripathy (2018)	Randomized, double blind	Phase 3	HR + ve, HER2-ve advanced breast cancer	First line	335	337	Ribociclib + hormone therapy[b]	Hormone therapy[b]	10	4

HR + ve, hormone receptor positive; HER2 − ve, HER2 negative; CDK 4/6 inhibitor, cyclin dependent kinase 4 and 6 inhibitor; VTE, venous thromboembolism

[a]Includes a nonsteroidal aromatase inhibitor: anastrozole or letrozole

[b]Includes goserelin and either a nonsteroidal aromatase inhibitor or tamoxifen

Qualität der Studien:

Table 2 Risk of bias summary

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Free of selective reporting (reporting bias)
PALOMA 1 (Finn et al., 2015)	+	+	–	+	+	+
PALOMA 2 (Finn et al., 2016)	+	+	+	+	+	+
PALOMA 3 (Cristofanilli et al., 2016)	+	+	+	+	+	+
MONARCH 2 (Sledge et al., 2017)	+	+	+	+	+	+
MONARCH 3 (Goetz et al., 2017)	+	+	+	+	+	+
MONALEESA 2 (Hortobagyi et al., 2016)	+	+	+	+	+	+
MONALEESA 3 (Slamon et al., 2018)	+	+	+	+	+	+
MONALEESA 7 (Tripathy et al., 2018)	+	+	+	+	+	+

Abbreviations: +, low risk of bias; –, high risk of bias; ?, unclear risk of bias

All studies used computer-generated randomization schedule and only PALOMA 2 study lacked blinding between investigators and participants. Other biases remain uncertain since they are pharmaceutical sponsored studies.

Studienergebnisse:

- The total number of VTE events occurred in 56 (2%) in the CDKIs group compared to 10 (0.5%) in the control group. The pooled RR for VTE was 2.62 (95% CI 1.21–5.65; P = 0.01) and the absolute RD was 0.01 (95% CI 0.00–0.03; P = 0.02) (Figs. 2, 3). Over a median follow-up of up to 36 months, the pooled RR of VTE was 3.18 (95% CI 1.22–8.24; P = 0.02) and RD was 0.03 (95% CI 0.01–0.06, P = 0.008).
- first-line: RR = 2.75 (95% CI 0.98–7.75, P = 0.06); I^2=0%; CDKI-arm: Events/number of patients=40/1523; control arm: Events/number of patients=8/1127
- second-line: RR = 5.14 (95% CI 0.96–27.38, P = 0.06); I^2=34%; CDKI-arm: Events/number of patients=15/786; control arm: Events/number of patients=1/395

Anmerkung/Fazit der Autoren

Our meta-analyses clearly demonstrated that the addition of CDKIs to endocrine therapies in patients with HR-positive HER 2- negative MBC contribute to a higher incidence of VTE, compared to ET alone. VTE remains the second leading cause of death in cancer patients

receiving antineoplastic therapy in general. BC patients account for the vast majority of cancer patients in the world. Future well designed randomized controlled trials are required to define the actual relation and definitive incidence of VTE with different CDKIs, and their risk factors.

3.4 Leitlinien

Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlich Medizinischen Fachgesellschaften), 2021 [14] & [15].

Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Interdisziplinäre S3-Leitlinie, Langversion 4.4.

Fragestellung

Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms.

Methodik

Grundlage der Leitlinie

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

LoE

- Evidenzgraduierung nach Klassifikation des Oxford Centre for Evidence-based Medicine (Version 2009)

Formulierung der Empfehlungen und formale Konsensusfindung

- Entwurferstellung und Diskussion der Empfehlungen durch Arbeitsgruppen (nach Regeln des nominalen Gruppenprozesses)
- Konsentierung der Empfehlungen und der dazu gehörigen Empfehlungsgrade durch Leitliniengruppe im moderierten, formalen Konsensusverfahren (Nominaler Gruppenprozess).

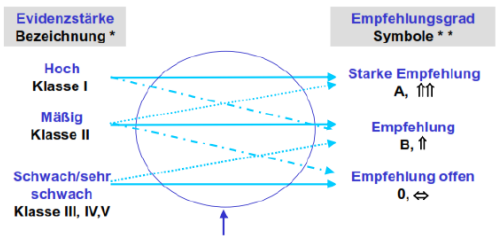
GoR:

Tabelle 9: verwendete Empfehlungsgrade

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

- Empfehlungen, welche nicht durch Leitlinienadaptation oder durch Primärrecherche generiert wurden, sind als Expertenkonsens (EK) ausgewiesen. Der Empfehlungsgrad ergibt sich lediglich anhand der Ausdrucksweise (soll/sollte/kann) und wird nicht explizit mit A/B/0 gekennzeichnet.

Festlegung des Empfehlungsgrades



*: blau = Evidenzstärke nach GRADE bzgl. des gesamten ‚body of evidence', schwarz = Evidenzklassifikation bzgl. Einzelstudien, z.B. nach Oxford;
**: Empfehlungsgraduierung im Programm für Nationale Versorgungsleitlinien. Die Empfehlungen werden nach Möglichkeit analog formuliert: Starke Empfehlung: „soll"; (abgeschwächte) Empfehlung: „sollte"; Negativ-Empfehlungen werden entweder rein sprachlich ausgedrückt („nicht" / „kann verzichtet werden") bei gleichen Symbolen oder sprachlich mit zusätzlich nach unten gerichteten Pfeilen; Offene Empfehlungen drücken eine Handlungsoption in Unsicherheit aus („kann erwogen werden" / „kann verzichtet werden").

Quelle: modifiziert AWMF-Regelwerk [29]

Abbildung 2: Schema zur Darstellung der kriteriengestützen Entscheidungsprozesse bei der Wahl des Empfehlungsgrades.

Tabelle 10: Festlegungen hinsichtlich der Konsensstärke

Konsensstärke	Prozentuale Zustimmung
Starker Konsens	> 95% der Stimmberechtigten
Konsens	>75 – 95% der Stimmberechtigten
Mehrheitliche Zustimmung	>50 – 75% der Stimmberechtigten
Dissens	≤50% der Stimmberechtigten

Sonstige methodische Hinweise

- Version 4.4 (Mai 2021) in Form eines Amendments: Es erfolgte eine Überarbeitung der Kapitel:
  - 5.4.1. Systemische Therapie bei prä- und perimenopausalen Patientinnen und positivem Hormonrezeptorstatus und negativem HER2-Status
  - 5.4.2. Systemische Therapie bei postmenopausalen Patientinnen und positivem Hormonrezeptorstatus und negativem HER2-Status

  Die Aktualisierung im Rahmen eines Amendments erfolgte aufgrund der Zulassung mehrerer CDK4/6-Inhibitoren.

Empfehlungen

4.7.2. Endokrine Therapie

4.108.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Patientinnen mit östrogen- und/oder progesteronrezeptor-positiven (°) invasiven Tumoren sollen eine endokrine Therapie erhalten. ° (>/=10% progesteronrezeptor-positive Tumorzellkerne)
Level of Evidence **1a**	Quellen: [29, 726-729]
	Starker Konsens

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

4.110.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A/B**	Nach 5 Jahren Tamoxifen soll für jede Patientin mit einem ER+-Mammakarzinom die Indikation zu einer erweiterten endokrinen Therapie geprüft werden. Die Indikationsstellung sollte in der Abwägung des Rückfallrisikos und den therapieassoziierten Nebenwirkungen (Toxizität, verminderte Adhärenz) erfolgen (Empfehlungsgrad B). Bei der Wahl der endokrinen Therapie soll der aktuelle Menopausenstatus der Patientin berücksichtigt werden.
Level of Evidence **1a**	Leitlinienadaptation: [737]
	Starker Konsens

4.111.	Evidenzbasierte Empfehlung
Empfehlungsgrad **A**	Bei prämenopausalen Patientinnen soll eine Tamoxifentherapie für mindestens 5 Jahre durchgeführt werden. Die antiöstrogene Therapie mit Tamoxifen 20 mg pro Tag soll in Abhängigkeit des Rezidivrisikos über eine Zeitdauer von 5 – 10 Jahren bzw. bis zum Rezidiv erfolgen. Die Indikation der erweiterten Therapie ist vom Rezidivrisiko und Wunsch der Patientin abhängig.
Level of Evidence **1a**	Quellen: [726, 727, 738, 739, 741]
	Starker Konsens

4.112.	Konsensbasierte Empfehlung
EK	Für Patientinnen mit einem ER+-Mammakarzinom und erhöhtem Risiko, die nach abgeschlossener Chemotherapie noch prämenopausal sind, kann unter Ausschaltung der Ovarfunktion ein Aromatasehemmer eingesetzt werden.
	Konsens

4.113.	Evidenzbasierte Empfehlung
Empfehlungsgrad 0	Die alleinige Ovarialsuppression kann entweder durch Gabe eines GnRHa oder durch eine bilaterale Ovarektomie für prämenopausale Frauen mit einem ER+-Mammakarzinom erwogen werden, die kein Tamoxifen erhalten können oder wollen.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

4.114.	Evidenzbasierte Empfehlung
Empfehlungsgrad A	Die Ovarialsuppression (GnRHa oder bilaterale Ovarektomie) zusätzlich zu Tamoxifen oder einem Aromatasehemmer soll nur bei hohem Rezidivrisiko und prämenopausaler Situation nach adjuvanter Chemotherapie erwogen werden. Bei Einsatz eines Aromatasehemmers soll eine Ovarialsuppression obligat erfolgen.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

Therapie bei postmenopausalen Patientinnen

4.115.	Evidenzbasierte Empfehlung
Empfehlungsgrad B	Die adjuvante endokrine Therapie für postmenopausale Patientinnen mit einem ER+ Mammakarzinom sollte einen Aromatasehemmer enthalten.
Level of Evidence 1b	Leitlinienadaptation: [730]
	Starker Konsens

4.7.4. Neoadjuvante Therapie

Neoadjuvante systemische Therapie

4.122.	Konsensbasiertes Statement
EK	Eine neoadjuvante (primäre, präoperative) systemische Therapie wird als Standardbehandlung bei Patientinnen mit lokal fortgeschrittenen, primär inoperablen oder inflammatorischen Mammakarzinomen im Rahmen eines multimodalen Therapiekonzeptes angesehen.
	Starker Konsens

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

Neoadjuvante oder adjuvante Chemotherapie

4.124.	Evidenzbasierte Empfehlung
Empfehlungsgrad 0	Ist eine Chemotherapie indiziert, kann diese vor der Operation (neoadjuvant) oder danach (adjuvant) durchgeführt werden. Beide Verfahren sind hinsichtlich des Gesamtüberlebens gleichwertig. Die neoadjuvante Therapie kann zu einer höheren Rate an brusterhaltenden Therapien führen.
Level of Evidence 1a	Quellen: [558, 560, 793]
	Starker Konsens

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

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

Primäre Hormontherapie bei postmenopausalen Patientinnen

4.127.	Konsensbasierte Empfehlung
EK	Bei postmenopausalen Patientinnen mit endokrin sensitivem Mammakarzinom kann, wenn eine Operation oder Chemotherapie nicht möglich oder nicht gewünscht sind, eine primäre endokrine Therapie durchgeführt werden.
	Starker Konsens

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

Neoadjuvante Chemotherapiekombination

4.129.	Konsensbasierte Empfehlung
EK	Wenn eine neoadjuvante Chemotherapiekombination zum Einsatz kommt, sollte diese ein Anthrazyklin und ein Taxan enthalten. Die Dauer der präoperativen Therapie sollte 18–24 Wochen betragen. Bei HER2-positiven Tumoren und Indikation zur neoadjuvanten Chemotherapie sollte eine Therapie mit Trastuzumab erfolgen. Bei HER2-Positivität und High-risk Situation (klinisch/sonographisch oder stanzbioptisch N+, Tumorgröße > 2cm) sollte die Therapie durch Pertuzumab ergänzt werden.
	Starker Konsens

4.130.	Konsensbasiertes Statement
EK	Platinsalze erhöhen beim triple-negativen Mammakarzinom (TNBC) unabhängig vom BRCA-Status die Komplettremissions-Rate (pCR-Rate). Der Vorteil auf das progressionsfreie Überleben (PFS) und das Gesamtüberleben ist nicht abschließend geklärt. Die Toxizität ist höher.
	Starker Konsens

Postneoadjuvante Behandlung

4.131.	Konsensbasierte Empfehlung
EK	Bei adäquater Anthrazyklin-Taxan-haltiger neoadjuvanter Chemotherapie ist bei Tumorresiduen in der Brust und/oder in den Lymphknoten keine zusätzliche adjuvante Chemotherapie zu empfehlen. Eine postneoadjuvante Chemotherapiebehandlung sollte nur im Rahmen von Studien durchgeführt werden.
	Starker Konsens

5.4.1. Systemische Therapie bei prä- und perimenopausalen Patientinnen und positivem Hormonrezeptorstatus und negativem HER2-Status

5.26.	Evidenzbasierte Empfehlung	Modifiziert 2020
Empfehlungsgrad **A**	Bei prä- und perimenopausalen Patientinnen soll bei positivem Hormonrezeptorstatus und negativem HER2-Status eine endokrine Therapie, ggf. kombiniert mit einer zielgerichteten Therapie angeboten werden. Die rein endokrine Monotherapie ist nicht indiziert bei Patientinnen, bei denen die Notwendigkeit des Erreichens einer schnellen Remission zur Abwendung von ausgeprägten Symptomen des betroffenen Organs besteht.	
Level of Evidence **1b**	Quellen: [985-991]	
	Starker Konsens	

5.27.	Evidenzbasierte Empfehlung	Geprüft 2020
Empfehlungsgrad **A**	Eine kombinierte chemo-endokrine Therapie wird nicht empfohlen. Sie kann zwar die Remissionsraten erhöhen, führt aber auch zu gesteigerter Toxizität ohne Verlängerung des progressionsfreien Intervalls oder des Gesamtüberlebens.	
Level of Evidence **1a**	Quelle: [992, 993]	
	Starker Konsens	

5.28.	Evidenzbasierte Empfehlung	Neu 2020
Empfehlungsgrad **B**	Bei prämenopausalen Patientinnen sollte die endokrin-basierte Therapie mit einem CDK4/6-Inhibitor unter Ausschaltung der Ovarialfunktion und in Kombination mit einem Aromatasehemmer oder mit Fulvestrant erfolgen (in Abhängigkeit von der Vortherapie).	
Level of Evidence **1b**	Quellen: [994-1002]	
	Starker Konsens	

5.29.	Evidenzbasierte Empfehlung	Modifiziert 2020
Empfehlungsgrad **O**	Bei prämenopausalen Patientinnen kann die Ausschaltung der Ovarialfunktion (GnRH-Analoga, Ovarektomie) in Kombination mit Tamoxifen durchgeführt werden, wenn die Therapie mit Tamoxifen vor mehr als 12 Monaten beendet wurde.	
Level of Evidence **1b**	Quellen: [988, 989, 1003, 1004]	
	Starker Konsens	

5.30.	Evidenzbasierte Empfehlung	Modifiziert 2020
Empfehlungsgrad **B**	Bei sequenziellen endokrinen Therapien sollten die verschiedenen endokrinen Substanzen in Abhängigkeit von vorhergehenden Therapien, Ansprechen, sowie Tumor- und Patientencharakteristika ausgewählt werden.	
Level of Evidence **1b**	Quellen: [989, 1005, 1006]	
	Starker Konsens	

5.31.	Evidenzbasierte Empfehlung	Modifiziert 2020
Empfehlungsgrad **0**	Die Therapie kann somit unter Beibehaltung der ovariellen Suppression in Analogie zu der Behandlung postmenopausaler Patientinnen durchgeführt werden. Als Optionen kann in Kombination mit einem GNRH-Analogon in Abhängigkeit der Vortherapie eingesetzt werden: - Aromatasehemmer - Fulvestrant - Tamoxifen	
Level of Evidence **1b**	Quellen: [988, 989, 1003, 1004]	
	Starker Konsens	

Hintergrund 5.26.

Eine endokrine Therapie ist weniger toxisch als eine Chemotherapie und sollte daher grundsätzlich als Erstlinientherapie eingesetzt werden. Insbesondere diejenigen Patientinnen, die ein langes krankheitsfreies Intervall hatten, die auf vorherige antihormonelle Therapiemaßnahmen angesprochen haben und die nicht zu der kleinen Gruppe von Patientinnen gehören, bei denen ein sehr rascher Wirkeintritt von Nöten ist (z.B. bei Luftnot bei diffuser Lungenmetastasierung oder drohendem Leberversagen bei Lebermetastasierung oder möglichem Ileus bei Peritonealkarzinose), profitieren von einer endokrinen Therapie. Bei positivem Hormonrezeptorstatus ist eine Remission bei 60% der Patientinnen zu erwarten, bei negativem Hormonrezeptorstatus bei weniger als 10%. Bei den seltenen Fällen mit unbekanntem Hormonrezeptorstatus kann die Indikation zur endokrinen Therapie allerdings auch in Abhängigkeit vom klinischen Verlauf gestellt werden.

Spricht eine Patientin auf eine endokrine Therapie an, wird diese bis zur Progression durchgeführt. Bei Progression ist der Einsatz alternativer endokriner Substanzen indiziert und gerechtfertigt. Erst nach Ausschöpfung aller endokrinen Behandlungsmaßnahmen oder bei Nichtansprechen auf die endokrine Therapie sollte eher auf eine zytostatische Therapie umgestellt werden.
Bei Vorliegen einer HER2-Überexpression ist mit einem schlechteren Therapieansprechen einer endokrinen Therapie zu rechnen. Studien zur Kombination endokriner Therapie mit HER2-gerichteter Therapie konnten keinen Überlebensvorteil durch die zusätzliche HER2-gerichtete Therapie zeigen. Deshalb wird bei Patientinnen mit Hormonrezeptor-positiven, HER2-positiven Tumoren bevorzugt eine Chemotherapie in Kombination mit HER2-gerichteter Therapie empfohlen, siehe hierzu den Abschnitt Fernmetastasen – Chemotherapie [988, 1007-1018].

Hintergrund 5.27.
In einer Metaanalyse von 26 Studien mit 3.606 Patientinnen mit fortgeschrittenem Mammakarzinom konnten Fossati et al [985] zeigen, dass die Kombination aus Chemotherapie und endokriner Therapie im Vergleich zu alleiniger Chemotherapie zwar zu einer erhöhten Remissionsrate, nicht aber zu einem verlängerten Überleben führte. Unter der kombinierten Chemoendokrinen Therapie waren unerwünschte Wirkungen wie Ödemneigung und kardiovaskuläre Komplikationen signifikant gesteigert.

Hintergrund 5.28.
Zur Therapie mit CDK4/6-Inhibitoren zusätzlich zu einer endokrinen Therapie bei prä- oder perimenopausalen Patientinnen liegen Daten aus AMNOG- Nutzenbewertungen zu insgesamt drei randomisierten kontrollierten Studien (MONARCH-2 [189], PALOMA-3 [197] und MONALEESA-7 [200]) zu drei Substanzen (Abemaciclib, Palbociclib und Ribociclib) vor. Bei diesen Studien handelt es sich um randomisierte, kontrollierte und verblindete klinische Studien (ausführliche Details zur Studienbewertung siehe Leitlinienreport). In PALOMA-3 und MONARCH-2 wurden dabei Patientinnen mit Versagen einer vorherigen Therapielinie unabhängig vom Menopausalstatus eingeschlossen, während MONALEESA-7 lediglich prä- und perimenopausale Patientinnen betraf. Eine Stratifizierung nach Menopausalstatus erfolgte für PALOMA-3 und MONARCH-3 post hoc, um den Anforderungen der Nutzenbewertung für den G-BA zu entsprechen. Die im Folgenden aufgeführten Daten zu Abemaciclib und Palbociclib sind daher Resultate von Subgruppenanalysen. Diese verfügen bei nicht signifikanten Effektschätzern nicht über eine ausreichende Teststärke, um eine statistisch abgesicherte Interpretation zu ermöglichen und sind daher als explorative Ergebnisse zu sehen.
Die nachfolgenden Ergebnisse wurden den zugehörigen Nutzenbewertungsverfahren entnommen, dort jeweils aus den Modulen 4 und/oder den betreffenden Publikationen. Zum Zeitpunkt des Admendments befinden sich die Wirkstoffe Abemaciclib und Ribociclib noch in zusätzlichen, laufenden Nutzenbewertungsverfahren ohne Entscheidungen über den Zusatznutzen durch den G-BA. Der Verfahrensstand kann auf den Seiten des G-BA eingesehen werden5.

Gesamtüberleben

Hinsichtlich des Gesamtüberlebens zeigten sich keine konsistenten Vorteile der Behandlung mit CDK4/6-Inhibitoren für die Gruppe der prä- oder perimenopausalen Patientinnen. Unter der Behandlung mit Abemaciclib oder Palbociclib bestand kein signifikanter Überlebensvorteil gegenüber Placebo (Abemaciclib HR: 0,69 [0,38; 1,25], Palbociclib HR: 1,07 [0,61; 1,86]) [994, 997]. Unter der Behandlung mit Ribociclib ergab sich ein signifikanter Überlebensvorteil für prä- oder perimenopausale Patientinnen (HR: 0,71 [0,54; 0,95]), es zeigten sich aber auch deutliche Effektunterschiede bezüglich der Ethnie, Therapielinie und des Alters: Patientinnen mit Alter <40 Jahre: HR 0,79 [0,48; 1,30] vs. Alter ≥40 Jahre: HR 0,68 [0,48; 0,98]. Asiatische Patientinnen: HR 0,40 [0,22; 0,72]) vs. nicht-asiatische Patientinnen: HR 0,91 [0,64; 1,30]) [1000]. Nach Therapielinie getrennt ergaben sich für die Erstlinie ein HR von 0,68 [0,45; 1,00] und für die Zweit- und Folgelinie ein HR von 0,78 [0,50; 1,21] [1019].

Progressionsfreies Überleben

In allen drei Studien zeigte sich ein deutlicher Vorteil unter der Therapie mit CDK4/6-Inhibitoren vs. Placebo hinsichtlich des progressionsfreien Überlebens: HR 0,41 [0,25; 0,70] unter Abemaciclib (Zweit- und Folgelinie) [995], HR 0,44 [0,23; 0,83] unter Palbociclib (Zweit- und Folgelinie) [998] und HR 0,52 [0,38; 0,70] unter Ribociclib in der Erstlinie bzw. HR 0,62 [0,44; 0,89] in der Zweit- und Folgelinie [1001]. Es zeichneten sich für keine der drei Substanzen persistente Effektmodifikationen in Subgruppen ab [995, 998, 1001, 1020-1022], d. h. der Vorteil der CDK4/6-Inhibitoren zeigte sich auch in den untersuchten Subgruppenstrata.

Gesundheitsbezogene Lebensqualität

Eine generalisierende Aussage zum Effekt der CDK4/6-Inhibitoren auf die gesundheitsbezogene Lebensqualität wurde für alle Studien anhand des Fragebogens „European Organization for Research and Treatment of Cancer Quality of Life Questionnaire“ (EORTC QLQ-C30) und der Skala „globaler Gesundheitszustand“ getroffen. Dazu wurde eine minimale klinisch relevante Differenz von 10 Punkten angenommen [1023, 1024]. Für die Patientinnen unter der Behandlung mit Abemaciclib zeigte sich keine signifikante, klinisch relevante Verbesserung (HR: 0,63 [0,33; 1,20]) [996]. Unter Palbociclib bestanden ebenfalls keine statistisch signifikanten Unterschiede gegenüber Placebo (HR: 0,81 [0,47; 1,41]) [999]. Unter Ribociclib in der Zweit- und Folgelinie wurden jedoch klinisch relevante Vorteile bezüglich des globalen Gesundheitszustandes gegenüber Placebo ermittelt (HR: 0,70 [0,53; 0,92] [1002]. Aufgrund der heterogenen Ergebnisse für die bewerteten CDK4/6-Inhibitoren lassen sich für diese keine belastbaren Hinweise auf eine Verbesserung der Lebensqualität ableiten.

Unerwünschte Ereignisse

Die Behandlung mit CDK4/6-Inhibitoren war grundsätzlich mit einer signifikant höheren Inzidenz unerwünschter Ereignisse assoziiert. Ausgedrückt als Hazard Ratio für das Eintreten unerwünschter Ereignisse mit Common Terminology Criteria for Adverse Events (CTCAE)-Grad ≥3 wurden für alle Wirkstoffe vergleichbare Effektschätzer ermittelt: HR 5,64 [2,54; 12,55] unter Abemaciclib, HR 5,90 [2,91; 11,95] unter Palbociclib sowie HR 4,14 [3,28; 5,23] unter Ribociclib [996, 999, 1002]. Unter allen Wirkstoffen brachen Patienten die Behandlung signifikant häufiger ab als unter Placebo: RR 4,18 [0,22; 79,00] unter Abemaciclib, RR 3,60 [0,19; 67,81] unter Palbociclib und HR 1,66 [0,82; 3,38] unter Ribociclib [996, 999, 1002].

Insgesamt spricht die Evidenz insbesondere für einen Vorteil der Behandlung prä- und perimenopausaler Patientinnen in der Zweit- und Folgelinientherapie mit CDK4/6-Inhibitoren in Form von signifikanten Effekten für das progressionsfreie Überleben. Die Ergebnisse zur Verträglichkeit der CDK4/6-Inhibitoren waren für alle analysierten Patientenkollektive vergleichbar und deuteten auf signifikant höhere Ereignisraten gegenüber Placebo hin. Unerwünschte Ereignisse können durch ein sorgfältiges Therapiemanagement auf ein Minimum reduziert werden [1025].

Fazit prä- und perimenopausale Patientinnen

CDK4/6-Inhibitoren in der Frühen Nutzenbewertung Für Palbociclib, Ribociclib und Abemaciclib liegen zum Zeitpunkt der Leitlinienerstellung (letzte Sichtung: Februar 2020) Ergebnisse der Frühen Nutzenbewertung gemäß § 35a SGB vor. Das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) sowie der Gemeinsame Bundesausschuss (G-BA) kommen zu dem Schluss, dass es für Palbociclib, Ribociclib und Abemaciclib für keine Therapieline und keine Patientengruppe Hinweise auf einen medizinischen Zusatznutzen gegenüber der jeweiligen zweckmäßigen Vergleichstherapie gibt [1026-1031]. Dieses Fazit beruhte im Wesentlichen auf dem beobachteten ungünstigen Nebenwirkungsprofil bei gleichzeitigem Fehlen von Belegen für Vorteile bzgl. des Gesamtüberlebens oder der Lebensqualität. Effekte auf das progressionsfreie Überleben (PFS) werden im Rahmen der Frühen Nutzenbewertung nur berücksichtigt, wenn Analysen vorliegen, die das PFS als validen Surrogatendpunkt für das Gesamtüberleben zeigen. Diese lagen laut IQWiG nicht vor. Somit lässt sich die Diskrepanz zwischen den Ergebnissen der Frühen Nutzenbewertung und der Leitlinienempfehlung auf Daten zum Gesamtüberleben, die zum Zeitpunkt der Frühen Nutzenbewertung nicht vorlagen, und der Berücksichtigung des progressionsfreien Überlebens als Nutzenparameter erklären. Für Abemaciclib und Riboclicib laufen zum Zeitpunkt des Admendments jedoch weitere Nutzendossiers, deren letztendliche Bewertungen noch ausstehen6.

Die aufgezeigten Nebenwirkungen wurden grundsätzlich im Vergleich zu der vom G-BA definierten zweckmäßigen Vergleichstherapie Placebo bzw. alleiniger endokriner Therapie erhoben. In der klinischen Praxis ist jedoch ein Vergleich zu einer mit deutlich schwerwiegenderen Nebenwirkungen assoziierten Chemotherapie angebracht. Es ist damit zu rechnen, dass CDK4/6-Inhibitoren gegenüber den verfügbaren Chemotherapeutika ein deutlich verträglicheres Nebenwirkungsprofil zeigen als gegenüber Placebo. Darüber hinaus sind die Nebenwirkungen mit etablierten supportiven Maßnahmen sehr gut zu behandeln [1025]. Eine tabellarische Übersicht in Form von Evidenztabellen über die aufgeführten Effektschätzer befindet sich im Evidenzbericht zu dieser Leitlinie.

5.4.2. Systemische Therapie bei postmenopausalen Patientinnen und positivem Hormonrezeptorstatus und negativem HER2-Status

5.32.	Evidenzbasierte Empfehlung	Neu 2020
Empfehlungsgrad A	Bei postmenopausalen Patientinnen soll bei positivem Hormonrezeptorstatus und negativem HER2-Status eine endokrine Therapie, ggf. kombiniert mit einer zielgerichteten Therapie angeboten werden. Die endokrine Therapie ist nicht indiziert bei Patientinnen, bei denen die Notwendigkeit des Erreichens einer schnellen Remission zur Abwendung von ausgeprägten Symptomen des betroffenen Organs besteht.	
Level of Evidence 1b	Quellen: [985-991]	
	S	

5.33.	Evidenzbasierte Empfehlung	Geprüft 2020
Empfehlungsgrad A	Eine kombinierte chemo-endokrine Therapie wird nicht empfohlen. Sie kann zwar die Remissionsraten erhöhen, führt aber auch zu gesteigerter Toxizität ohne Verlängerung des progressionsfreien Intervalls oder des Gesamtüberlebens.	
Level of Evidence 1a	Quelle: [992, 993]	
	Starker Konsens	

5.4.2.1. Erstlinientherapie

5.34.	Evidenzbasierte Empfehlung	Neu 2020
Empfehlungsgrad B	Die Kombinationstherapien eines Aromatasehemmers oder Fulvestrant mit CDK 4/6-Inhibitoren sollte durchgeführt werden, sofern diese Substanzgruppe noch nicht eingesetzt wurde.	
Level of Evidence 1b	Quellen: [1021, 1037-1042]	
	Starker Konsens	

5.35.	Konsensbasierte Empfehlung	Modifiziert 2020
EK	ine Behandlung mit Fulvestrant sollte insbesondere nach Vorbehandlung mit einem Aromatasehemmer erfolgen, kann aber auch als erste Therapielinie eingesetzt werden, insbesondere bei noch nicht endokrin vorbehandelten Patientinnen.	
	Starker Konsens	

5.4.2.2. Zweit- und Folgelinientherapie

5.36.	Konsensbasierte Empfehlung	Modifiziert 2020
Empfehlungsgrad **B**	Sofern in der Erstlinie noch kein CDK4/6-Inhibitor eingesetzt worden war, sollte er in weiteren endokrinbasierten Therapielinien eingesetzt werden.	
Level of Evidence **1b**	Quellen: [994, 997, 1040].	
	Starker Konsens	

5.37.	Konsensbasierte Empfehlung	Modifiziert 2020
EK	Nach antihormoneller Vortherapie mit einem nicht-steroidalen Aromatasehemmer sowie CDK4/6-Inhibitoren kann eine Folgetherapie mit Exemestan und dem mTOR-Inhibitor Everolimus durchgeführt werden.	
	Starker Konsens	

5.38.	Konsensbasierte Empfehlung	Neu 2020
EK	Weitere Schritte in der endokrinen Behandlungssequenz bei postmenopausalen Patientinnen stellen je nach Vorbehandlung der Einsatz von Alpelisib (bei Nachweis einer entsprechenden PI3KA Mutation) bzw. Antiöstrogenen, Östrogenrezeptor-Antagonisten, der Wechsel des Aromatasehemmers von einem steroidalen auf einen nicht-steroidalen Aromatasehemmer oder vice versa dar.	
	Starker Konsens	

9. Mammakarzinom des Mannes

9.1.	Konsensbasierte Empfehlung
EK	Eine frühzeitige ärztliche Konsultation soll durch Information von Männern über die Erkrankung, insbesondere über Symptome und Veränderungen der Brust und durch die Aufforderung zur Selbstbeobachtung, gefördert werden.
	Starker Konsens

9.2.	Konsensbasierte Empfehlung
EK	Die Basisdiagnostik soll bei Verdacht auf maligne Befunde durch Anamnese, klinische Untersuchung, Mammographie sowie Ultraschalldiagnostik der Brust und der Lymphabflussregionen erfolgen. Zum diagnostischen Einsatz der KM-MRT liegen keine Daten vor.
	Starker Konsens

9.3.	Konsensbasierte Empfehlung
EK	Die weiterführende Diagnostik und das Staging/ Ausbreitungsdiagnostik soll bei Brust- und Axillabefunden entsprechend der Empfehlung für Frauen erfolgen, wobei zum diagnostischen Einsatz von KM-MRT keine Daten vorliegen.
	Starker Konsens

9.4.	Konsensbasierte Empfehlung
EK	Die Operation hat die vollständige Tumorentfernung zum Ziel und sollte als Mastektomie durchgeführt werden. Bei günstigem Größenverhältnis zwischen Tumor und Brust sollte die Brusterhaltung erwogen werden.
	Starker Konsens

9.5.	Konsensbasierte Empfehlung
EK	Bei klinisch unauffälliger Axilla (cN0) soll eine Sentinel-Lymphknotenentfernung nach den gleichen Regeln wie bei der Frau vorgenommen werden.
	Starker Konsens

9.6.	Konsensbasierte Empfehlung
EK	Bei größeren Tumoren (≥ 2cm), bei axillärem Lymphkotenbefall und bei negativem Hormonrezeptor soll eine adjuvante Radiotherapie der Brustwand und ggf. der Lymphabflusswege (Indikation wie bei der Frau) unabhängig vom Operationsverfahren erfolgen.
	Starker Konsens

9.7.	Konsensbasierte Empfehlung
EK	Die adjuvante Chemotherapie sowie die Antikörpertherapie (Anti-HER2) soll nach den gleichen Regeln wie bei der Frau indiziert und durchgeführt werden.
	Konsens

9.8.	Konsensbasierte Empfehlung
EK	Patienten mit einem Hormonrezeptor-positiven Mammakarzinom sollen eine adjuvante endokrine Therapie mit Tamoxifen in der Regel über 5 Jahre erhalten. Für eine Behandlung über 5 Jahre hinaus liegen keine Daten vor. Analog zum weiblichen Mammakarzinom kann diese in Einzelfällen erwogen werden.
	Starker Konsens

9.9.	Konsensbasierte Empfehlung
EK	a.) Die Therapie bei metastasierter Erkrankung sollte nach den gleichen Regeln wie bei der Frau erfolgen. b.) Es ist unklar, ob Aromatasehemmer ohne Suppression der testikulären Funktion beim Mann ausreichend wirksam sind. Daher sollten Aromatasehemmer in Kombination mit einer Suppression der testikulären Funktion gegeben werden.
	Starker Konsens

9.10.	Konsensbasierte Empfehlung
EK	Die Teilnahme an Studien/Registern sollte Männern mit Brustkrebs angeboten und ermöglicht werden.
	Konsens

9.11.	Konsensbasierte Empfehlung
EK	Eine genetische Beratung soll allen Männern mit Brustkrebs empfohlen werden.
	Konsens

9.12.	Konsensbasierte Empfehlung
EK	Die Ausgestaltung der Nachsorge einschließlich der bildgebenden Diagnostik soll in Analogie zum Vorgehen der Frauen erfolgen.
	Starker Konsens

9.13.	Konsensbasierte Empfehlung
EK	Qualifizierte und sachdienliche genderspezifische Informationen (Print und Internet) sollten dem Patienten von dem behandelnden Fachpersonal zur Verfügung gestellt werden und der Zugang zum speziellen Angebot der Selbsthilfegruppen ermöglicht werden.
	Starker Konsens

NICE, 2009 [18].

Advanced breast cancer (update) Diagnosis and treatment; Issued: February 2009, last modified: August 2017. NICE (CG81)

Leitlinienorganisation/Fragestellung

What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer?

Methodik

Grundlage der Leitlinie

- systematische Evidenzaufbereitung (Formulierung von PICO-Fragen; Systematische Literaturrecherche in mehreren Datenbanken; Datenextraktion, Qualitätsbewertung der gefundenen Literatur auf Basis der SIGN Kriterien für systematische Reviews/Meta-analysen und RCTs)
- Formulierung der Empfehlung basierend auf klinischer und ökonomischer Evidenz in Konsensusprozessen; bei schwacher Evidenz basierend auf informellen Konsens

Recherche/Suchzeitraum:

- Literaturrecherche der LL-Version 2009: bis 30.06.2008. Future guideline updates will consider evidence published after this cut-off date.

LoE

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs) or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

Table A Levels of evidence for intervention studies. Data source: 'NICE guidelines manual' (NICE 2007).

GoR

- Anwendung von GRADE - GoR finden sich in den Formulierungen wieder: "To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations."

Sonstige methodische Hinweise

- Regelmäßige Überprüfung der Aktualität der Empfehlungen: letzter Surveillance Report vom Januar 2018: Es wurden in Bezug auf die Therapieempfehlungen keine neue Evidenz identifiziert, die zu einer Änderung dieser Empfehlungen führen würde

Aktualisierungen:

- Update 2014: review of the evidence on exercise for people with or at risk of lymphoedema and addition of 2 recommendations to section 1.5
- Update 2017: Review of the evidence and update of recommendations in section 1.1 on assessing oestrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) status on disease recurrence.

Empfehlungen

Systemic disease-modifying therapy

Recommendations

1.3.1 Offer endocrine therapy as first-line treatment for the majority of patients with ER positive advanced breast cancer. [2009]

1.3.2 Offer chemotherapy as first-line treatment for patients with ER-positive advanced breast cancer whose disease is imminently life-threatening or requires early relief of symptoms because of significant visceral organ involvement, providing they understand and are prepared to accept the toxicity. [2009]

1.3.3 For patients with ER-positive advanced breast cancer who have been treated with chemotherapy as their first line treatment, offer endocrine therapy following the completion of chemotherapy. [2009]

Qualifying statement: These recommendations are based on one systematic review and GDG consensus
Clinical Evidence: Only one paper was appraised for this topic. A high quality systematic review (Wilcken et al. 2006) examined ten RCTs of chemotherapy vs endocrine therapy, the most recent of which was published in 1995 (even though Cochrane databases were searched as recently as October 2006).
Neither chemotherapy nor endocrine therapy demonstrated an advantage in overall survival and tumour response was variable between studies. No data were presented for quality of life (QOL) or adverse events but, in narrative form, the reviewers stated that in the majority of studies chemotherapy had resulted in higher levels of toxicity (predominantly nausea, vomiting and alopecia) but that it was not clear in which direction QOL had been affected as the results were conflicting.

Endocrine Therapy

Recommendation

1.3.4 Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy
- postmenopausal women with ER-positive breast cancer previously treated with tamoxifen. [2009]

Qualifying statement: These recommendations are based on high quality evidence of clinical and cost effectiveness. There is no evidence directly comparing these agents so it is not possible to recommend any particular aromatase inhibitor. All aromatase inhibitors appear to be equally effective in terms of primary outcome (overall survival).

1.3.5 Offer tamoxifen and ovarian suppression as first-line treatment to premenopausal and perimenopausal women with ER-positive advanced breast cancer not previously treated with tamoxifen. [2009]

1.3.6 Offer ovarian suppression to premenopausal and perimenopausal women who have previously been treated with tamoxifen and then experience disease progression. [2009]

Qualifying statement: These recommendations are based on 1 moderate quality RCT report showing a survival benefit for combination therapy over single agents in pre-menopausal patients. There is also evidence of clinical effectiveness from one high-quality systematic review of randomised trials in pre-menopausal women. There was GDG consensus that perimenopausal women should be treated in the same manner. The GDG has made no recommendation on the optimal endocrine management of patients with ER-positive disease who relapse whilst on adjuvant tamoxifen as there is no data in this area. Current UK practice varies, with the use of either ovarian suppression or ovarian suppression in combination with aromatase inhibitors being used.
Clinical Evidence: The evidence base for this topic comprises one guideline (Eisen et al. 2004), five systematic reviews (Mauri et al. 2006; Gibson et al. 2007; Ferretti et al. 2006; Klijn et al. 2001 and Crump et al. 1997), five RCTs (Chia et al. 2008; Mouridsen et al. 2007; Taylor et al. 1998; Klijn et al. 2000 and Goss et al. 2007) a pooled analysis of RCT data (Howell et al. 2005) and a small, low quality comparative study (Catania et al. 2007a). The number of study participants exceeded 30,500 women, the majority of whom were post-menopausal with metastatic breast cancer. Most of the papers were of moderate to high quality, although the guideline did review non-published abstracts.

Mauri D, et al. (2006) Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. J Natl Cancer Inst 98(18): 1285–1291.
Chia S, et al. (2008) Double-blind, Randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptorpositive, advanced breast cancer: Results from EFECT. J Clin Oncol 26: 1664–1670.
Mouridsen HT (2007) Letrozole in advanced breast cancer: the PO25 trial. Breast Cancer Res Treat 105(1): 19–29.
Catania C, et al. (2007a) Fulvestrant in heavily pre-treated patients with advanced breast cancer: results from a single compassionate use programme centre. Breast Cancer Res Treat 106: 97–103.

Pre-menopausal women with metastatic breast cancer experienced no significant difference in tumour response or survival between ovarian ablation and tamoxifen as first-line therapy. Atamestane and toremifine as first-line combination therapy resulted in similar tumour response and survival compared with letrozole alone.
Fulvestrant and exemestane showed equal clinical benefit for women that had previously received non-steroidal AIs for the treatment of advanced breast cancer. Limited evidence also suggested that fulvestrant conferred short term benefit to heavily pre-treated women with metastatic disease by postponing the requirement for chemotherapy. An equivalence analysis of pooled data (Howell et al. 2005) from two trials showed that fulvestrant and anastrozole were not significantly different from one another in their effects on overall survival. Study participants given fulvestrant reported fewer incidences of joint pain.

Howell A, et al. (2005) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. Cancer 104: 236–239 –nicht systematisch erstellt, Dosierung von 250mg/Monat Fulvestrant nicht zulassungskonform, identisch mit Robertson, et al. 2003 (siehe oben)

Good evidence showed that there was significant clinical benefit, increased progression-free survival and ~13% reduction in the risk of death with third generation AIs compared with standard endocrine therapy (the analyses included all treatment lines). No individual AI was better than another in this regard. Very limited evidence suggested that there was no significant difference between the AIs and standard therapy in patient reported quality of life. However, more gastro-intestinal symptoms and hot flushes were associated with AI therapy compared to standard endocrine therapy but there were fewer reports of blood clots and vaginal bleeding.
A moderate quality systematic review (Klijn et al. 2001) and meta-analysis of data from four RCTs (one unpublished) concluded that combination therapy with LHRH agonists, buserelin or goserelin, combined with tamoxifen produced significant improvements in tumour response, reduction in the risk of death (~22%) and disease progression (~30%) than LHRH agonist monotherapy. Lack of methodological detail suggests caution in the interpretation of these results.
One RCT (Klijn et al. 2000) compared buserelin alone versus tamoxifen alone versus the two agents combined. Tumour response was not significantly different between combined and monotherapies unless data from patients with stable disease for > 6 months was included. The re-analysis showed a superior response for the combined therapy compared with tamoxifen but not LHRH. Combined therapy significantly improved actuarial survival at 5 and 7 years, together with overall urvival and progression-free survival compared with monotherapy with either buserelin or tamoxifen.
A second RCT (Taylor et al. 1998) compared goserelin with surgical ovarian ablation (ovariectomy). The authors found that the outcomes for tumour response, overall survival and failure free survival were not significantly different between treatments and concluded that either treatment could reasonably be offered to patients and their physicians. The study was terminated prematurely due to poor accrual, believed to be because of the unwillingness of patients to be randomised to the surgical arm.

1.3.7 Offer tamoxifen as first-line treatment to men with ER-positive advanced breast cancer. [2009]

Rugo HS et al., 2016 [21].

Endocrine therapy for women with hormone receptor (HR) –positive metastatic breast cancer (MBC).

Leitlinienorganisation/Fragestellung

- American Society of Clinical Oncology (ASCO) Clinical Practice Guideline
- Guideline Questions:

1. Is there an optimal (defined throughout this guideline as treatments with demonstrated benefits in both treatment-related and quality-of-life outcomes) first-line endocrine therapy regimen for hormone receptor (HR) –positive metastatic breast cancer (MBC)?

1.1 For postmenopausal women: What are the optimal sequence and duration?

1.2 Should hormone therapy be administered in combination with other hormonal agents or chemotherapy?

1.3 For premenopausal women: What is the optimal timing of ovarian suppression or ablation? Should all patients have their ovaries suppressed? What is the best partner hormonal agent in this setting?

1.4 Are there demonstrated differences between pre- and postmenopausal patients?

2. Is there an optimal second- or later-line endocrine therapy for HR-positive MBC?

2.1 Should other treatment or disease-free interval play a role in treatment selection?

2.2 Which hormone therapy should be offered?

2.3 What are the optimal timing, dose, and schedule of treatment?

3. How or should endocrine therapies be used in combination or sequence with:

3.1 Mammalian target of rapamycin inhibitors (everolimus)?

3.2 Cyclin-dependent kinase 4/6 inhibitors (palbociclib)?

4. Does estrogen or progesterone expression (high v low expression) affect hormone therapy considerations and modify recommendations for hormone therapy—either the recommended agents or dosing details—among pre-, peri-, and postmenopausal women?

5. How does adjuvant treatment affect recommendations for treatment in the metastatic or advanced setting?

6. In which patients or settings is hormone therapy recommended over chemotherapy?

6.1 Is there a role for combined cytotoxic and endocrine therapies?

6.2 What is the optimal duration of treatment with hormonal therapy?

7. Is there a role for additional biomarkers in the selection of treatment for patients with HR-positive disease?

7.1 What is the role of genomic profiling or intrinsic subtypes in this population?

8. How does human epidermal growth factor receptor 2 (HER2) positivity affect treatment of patients with HR-positive MBC?

9. What are the future directions for treatment in this patient population?

Methodik

<u>Grundlage der Leitlinie</u>

- multidisciplinary Expert Panel (medical oncology, radiation oncology, psycho-oncology, patient advocacy, and guideline methodology).
- All members of the panel completed ASCO's disclosure form, which requires disclosure of financial and other interests... In accordance with the Policy, the majority of the members of the panel did not disclose any relationships constituting a conflict under the Policy.
- ASCO guidelines are based on systematic reviews of evidence from 2008 through 2015:
  - A protocol for each guideline defines the parameters for a targeted literature search, including relevant study designs, literature sources, types of reports, and prespecified study selection criteria for literature identified
  - Formal assessment of Study Quality (siehe Anhang Detaillierte Informationen + Bewertungsergebnisse)
- The co-chairs determine the need for guideline updates or revisions on the basis of periodic review and consideration of the literature. If new and compelling data are identified, the Expert Panel or an update committee is reconvened to discuss revisions to the document.

Recherche/Suchzeitraum:

- Literature search: in Medline to 4/2014; Cochrane Library databases to Issue 3 of March 2013; Antonio Breast Cancer Symposium (2011 to 2014) and ASCO abstracts (2012 to 2014); targeted literature search update: in June 2015

LoE/ GoR

- Definitions for Types + Strengths of recommendation, Strengths of evidence: → Anhang 2
- Recommendations reflect high, moderate or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “must not,” “should,” and “should not” indicate that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases.

Sonstige methodische Hinweise

- Evidenzgrundlage im Anhang abgebildet

Empfehlungen

ASCO Key Guideline Recommendations for HR-positive MBC

Hormone therapy should be offered to patients whose tumors express any level of estrogen and/or progesterone receptors. (*Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Treatment recommendations should be offered on the basis of type of adjuvant treatment, disease-free interval, and extent of disease at the time of recurrence. A specific hormonal agent may be used again if recurrence occurs >12 months from last treatment. (*Type: evidence and consensus based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong*).

Endocrine therapy should be recommended as initial treatment for patients with HR-positive MBC, except for patients with immediately life-threatening disease or for those experiencing rapid visceral recurrence during adjuvant endocrine therapy. (*Type: Evidence-based; benefits outweigh harms, Evidence quality: Intermediate; Strength of Recommendation: Strong*)

Treatment should be administered until there is unequivocal evidence of disease progression as documented by imaging, clinical examination, or disease-related symptoms. *(Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)*

The use of combined endocrine therapy and chemotherapy is not recommended. *(Type: Evidence-based; benefits outweigh harms; Evidence quality: High; Strength of Recommendation: Strong)*

Second-Line Therapy

- Sequential hormone therapy should be offered to patients with endocrine-responsive disease, except in the case of rapid progression with organ dysfunction; no specific order of agents is recommended.
- When fulvestrant is administered, it should be administered using the 500-mg dose and with a loading schedule (treatment start, day 15, day 28, then once per month).

Targeted Therapy

A nonsteroidal AI and palbociclib may be offered to postmenopausal women with treatment-naıve HR-positive MBC, because PFS but not OS was improved compared with

the nonsteroidal AI letrozole alone. Palbociclib may also be offered in combination with fulvestrant in patients exposed to prior hormone therapy and up to one line of chemotherapy, on the basis of data from the phase III PALOMA-3 trial. PFS was improved compared with fulvestrant alone; OS data are immature (*Type: evidence based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: intermediate*).
Postmenopausal women

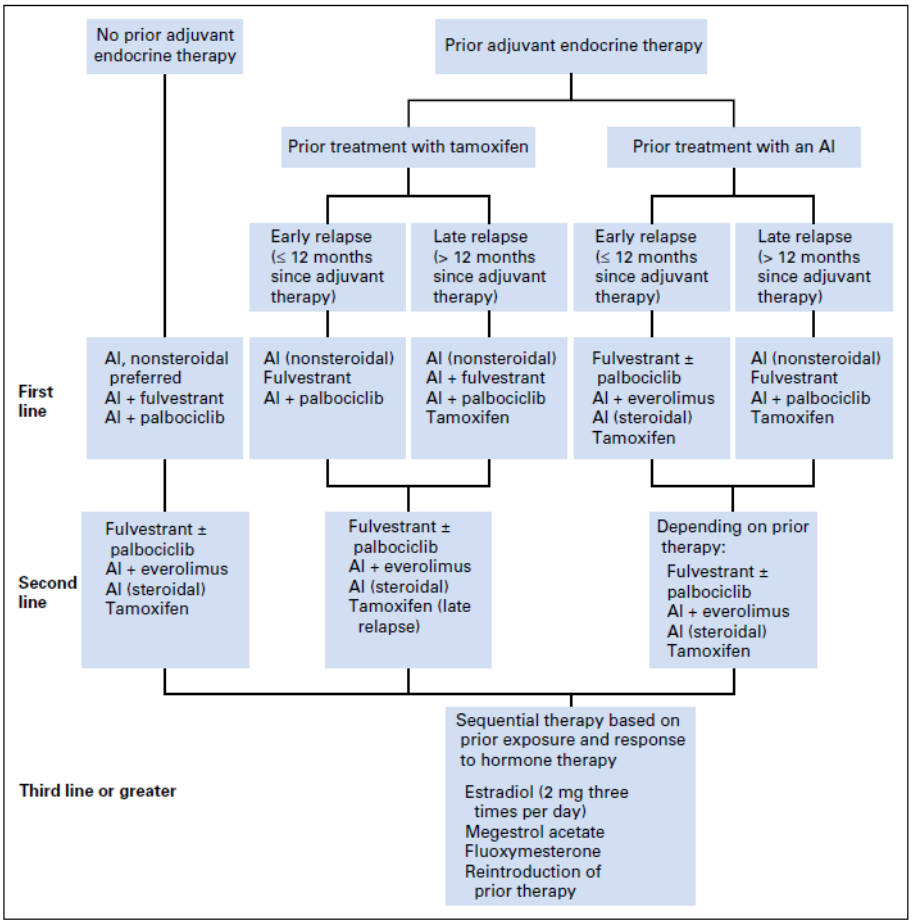


Fig 1. Hormone therapy for postmenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then once per month as an intramuscular injection. Withdrawal of tamoxifen or progestinswas reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates anastrozole or letrozole. AI, aromatase inhibitor

Premenopausal women

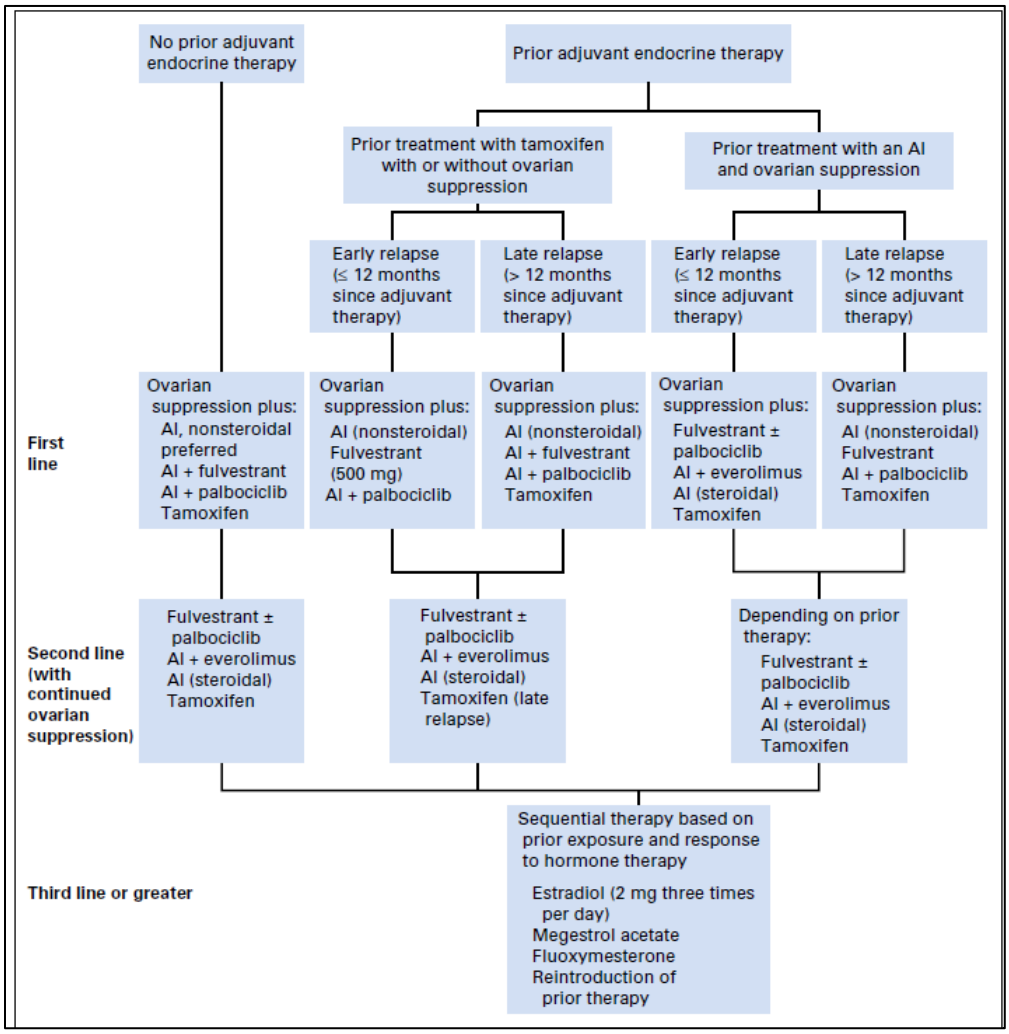


Fig 2. Hormone therapy for premenopausal women with hormone receptor–positive metastatic breast cancer by line of therapy and adjuvant treatment. NOTE. Use of palbociclib should be reserved for patients without prior exposure to cyclin-dependent kinase 4/6 inhibitors. Fulvestrant should be administered at 500 mg every 2 weeks for three cycles, then monthly as an intramuscular injection. Withdrawal of tamoxifen or progestins was reported to result in short-term disease responses in older literature. Steroidal indicates exemestane; nonsteroidal indicates anastrozole or letrozole.

Hasset MJ et al., 2020 [11].

ASCO

Management of Male Breast Cancer: ASCO Guideline

Zielsetzung/Fragestellung

To develop recommendations concerning the management of male

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.

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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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2021) am 27.01.2021

#	Suchfrage
1	[mh ^“Breast Neoplasms”]
2	(breast OR mamma*):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
4	(advanced OR metastat* OR metastas* OR recurren* OR relaps* OR progression*):ti,ab,kw
5	(#1 OR (#2 AND #3)) AND #4
6	#5 with Cochrane Library publication date from Jan 2016 to present

Systematic Reviews in Medline (PubMed) am 27.01.2021

#	Suchfrage
1	breast neoplasms/TH[majr]
2	((breast[ti]) OR mamma*[ti]) AND (neoplasm metastasis/TH OR neoplasm recurrence, local/TH)
3	(#1) OR #2
4	(breast[ti]) OR mamma*[ti]
5	(#4) AND ((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab])
6	(#5) AND ((((((((advanced[tiab]) OR metastat*[tiab]) OR metastas*[tiab]) OR recurren*[tiab]) OR relaps*[tiab]) OR progression*[tiab]) OR progressive*[tiab]) OR disseminat*[tiab])
7	(#6) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
8	#3 OR #7
9	(#8) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence

#	Suchfrage
	based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
10	((#9) AND ("2016/01/01"[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])

Leitlinien in Medline (PubMed) am 27.01.2021

#	Suchfrage
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	cancer*[ti] OR tumour*[ti] OR tumor[ti] OR tumors[ti] OR carcinom*[ti] OR neoplas*[ti] OR malignan*[ti]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[Title] OR recommendation*[Title]) NOT (letter[ptyp] OR comment[ptyp])))

#	Suchfrage
7	(((#6) AND ("2016/01/01"[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]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Messina C et al., 2018 [17].

Tabelle 1: Characteristics of RCTs included in the meta-analysis

Table 1 Main characteristics of the randomized studies included in the present meta-analysis

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS	PFS bone+	PFS viscera+	ORR	Toxicity G3/G4 (≥ 2%)
Paloma 1 [7]	Open label, randomized, phase II, palbociclib + letrozole versus letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.49 (95% CI 0.32–0.75)	HR 0.29 (95% CI 0.09–0.94)	HR 0.55 (95% CI 0.32–0.94)	43% (95% CI 32–54) in the palbociclib + letrozole arm vs 33% (95% CI 23–45) *P* = 0·13 in the letrozole arm	54% neutropenia, 19% leukopenia, 6% anaemia, 5% fatigue, 4% diarrhoea, 2% nausea, 2% thrombocytopenia, 2% nausea, 2% dyspnoea, 2% back pain
Paloma 2 [8]	Double blind, randomized (2:1), phase III, palbociclib + letrozole versus placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.58 (95% CI 0.46–0.72)	HR 0.36 (95% CI 0.22–0.59)	HR 0.63 (95% CI 0.47–0.85)	42.1% (95% CI 37.5–46.9) in the palbociclib + letrozole arm versus 34.7% (95% CI 28.4–41.3) in the placebo + letrozole arm	66% neutropenia, 25% leukopenia, 5% anaemia, 2% febrile neutropenia, 2% fatigue, 2% asthenia, 2% thrombocytopenia
Monaleesa 2 [9]	Double blind, randomized (1:1), phase III trial, ribociclib + letrozole vs placebo + letrozole	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.56 (95% CI 0.43–0.72)	HR 0.69 (CI 95% 0.38–1.25)	NA	40.7% in the ribociclib + letrozole arm vs 27.5% in the placebo + letrozole arm	59% neutropenia, 21% leukopenia, 9% increased alanine aminotransferase (ALT), 6% increased aspartate aminotransferase (AST), 4% infections, 4% vomiting, 2% fatigue, 2% nausea
Monarch 3 [12]	Double blind, randomized (2:1), phase III, abemaciclib + AI (letrozole or anastrozole) versus abemaciclib + AI	HR+ HER2−, postmenopausal pts, ET in neoadjuvant or adjuvant setting allowed if completed > 12 months	1° line	PFS	HR 0.54 (95% CI 0.41–0.72)	HR 0.58 (CI 95% 0.27–1.25)	HR 0.61 (95% CI 0.42–0.87)	48.2% in the abemaciclib + AI arm vs 24.5% in the placebo + AI arm	20% neutropenia, 9.5% diarrhoea, 8% leukopenia, 6% anaemia, 6% increased ALT, 5% infections, 2% fatigue, 2% increased blood creatinine

Table 1 (continued)

Trial	Design	Population characteristics	Setting	Primary endpoint	PFS	PFS bone+	PFS viscera+	ORR	Toxicity G3/G4 (≥ 2%)
Paloma 3 [10]	Double blind, randomized (2:1), phase III, palbo + ful vs palbo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.42 (95% CI 0.32–0.56)	HR 0.36 (95% CI 0.22–0.60)	HR 0.45 (95% CI 0.32–0.63)	10.4% (95% CI 7.4–14.1) in the palbociclib + fulvestrant arm vs 6.3% (95% CI 3.2–11.0) in the placebo + fulvestrant arm (P = 0.16)	62% neutropenia, 25% leukopenia, 3% anaemia, 2% fatigue, 2% thrombocytopenia
Monarch 2 [11]	Double blind, randomized (2:1), phase III, abemaciclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts or pre-peri menopausal, pts progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	2° line	PFS	HR 0.55 (95% CI 0.45–0.68)	HR 0.54 (95% CI 0.35–0.83)	HR 0.48 (95% CI 0.37–0.63)	35.2% (95% CI 30.8% − 39.6%) in the abemaciclib + fulvestrant arm vs 16.1% (95% CI 11.3% − 21.0%) in the placebo + fulvestrant arm (P = 0.001)	26.5% neutropenia, 13% diarrhoea, 9% leukopenia, 7% anaemia, 4% increased ALT, 3% fatigue, 3% nausea, 3% thrombocytopenia, 3% dyspnoea, 2.5% abdominal pain, 2% increased AST
Monaleesa 3 [14]	Double blind, randomized (2:1), phase III, ribociclib + fulvestrant versus placebo + fulvestrant	HR+ HER2−, postmenopausal pts, newly diagnosed or relapse > 12 months from (neo)-adjuvant ET, or progressed after one line of ET	1°and 2°line	PFS	HR 0.59 (95% CI 0.48–0.73)	HR 0.37 (95% CI 0.23–0.61)	HR 0.64 (95% CI 0.48–0.86)	32.4% (95% CI 28.3–36.6%) in the ribociclib + fulvestrant versus 21.5% (95% CI 16.3–26.7%) in placebo + fulvestrant (P = < 0.001)	46.6% neutropenia,13.5% leukopenia, 6.6% increased ALT, 45.3% nausea, 31.5% fatigue
Monaleesa 7 [13]	Double blind, randomized (1:1), phase III, ribociclib + tamoxifen or AI versus placebo + tamoxifen or AI	HR+ HER2−, premenopausal or perimenopausal pts, progressed during ET (adjuvant or 1° line) or DFS from adjuvant ET ≤ 12 months	1° line	PFS	HR 0.55 (95% CI 0.44–0.69)	HR 0.70 (95% CI 0.41–1.19)	HR 0.50 (95% CI 0.38–0.68)	35.1% (95% CI 30.1–40.6) in the ribociclib + tamoxifen or AI versus 24.6% (95% CI 20.2–29.6%)	61% neutropenia, 14% leukopenia, 5% increased ALT, 31% nausea, 22% fatigue

ET endocrine therapy, *HR+* hormone receptor positive, *ORR* overall response rates, *PFS* progression-free survival, *pts* patients

Brandao M et al., 2020 [2].

Patientenmerkmale der eingeschlossenen Studien

Table 1 Characteristics of the randomised controlled trials included in the systematic review

Trial name/author	Phase	Meno-pausal status	Patients (N)*	Comparisons	Median of ET (N)†	Previous CT	iTT* PFS HR (95% CI)	iTT* OS HR (95% CI)	De novo* PFS HR (95% CI)	Recurrent* PFS HR (95% CI)	Visceral* PFS HR (95% CI)	Bone-only* PFS HR (95% CI)
Endocrine-sensitive patients only												
Ibrahim et al[41]	II	Post-meno	110	AS1402+AI (letrozole) versus AI (letrozole)	0	No	0.95 (0.50 to 1.81)	-	-	-	-	-
SWOG S0226[42]	III	Post-meno	536	Fulvestrant 250 mg+AI (anastrozole) versus AI (anastrozole)	0	No	0.81 (0.67 to 0.98)	-‡	-	-	-	-
Paul et al[43]	II	Post-meno	120	MultiTKI (dasatinib)+AI (letrozole) versus AI (letrozole)	0	≤1 line	No HR	-	-	-	-	-
PALOMA-1[44–46]	II	Post-meno	165	CDK4/6i (palbociclib)+AI (letrozole) versus AI (letrozole)	0	No	0.49 (0.32 to 0.75)	0.90 (0.62 to 1.29)	0.34 (0.19 to 0.60)	0.54 (0.30 to 0.98)	0.55 (0.32 to 0.94)	0.29 (0.09 to 0.95)
PALOMA-2[47–50]	III	Post-meno	666	CDK4/6i (palbociclib)+AI (letrozole) versus AI (letrozole)	0	No	0.58 (0.46 to 0.72)	-	0.61 (0.44 to 0.85)	0.58 (0.41 to 0.82)	0.62 (0.47 to 0.81)	0.41 (0.26 to 0.63)
MONALEESA-2[51–54]	III	Post-meno	668	CDK4/6i (ribociclib)+AI (letrozole) versus AI (letrozole)	0	No	0.56 (0.43 to 0.72)	0.75 (0.52 1.08)	0.45 (0.27 to 0.75)	0.60 (0.45 to 0.81)	0.54 (0.39 to 0.74)	0.69 (0.38 to 1.25)
FALCON[55–57]	III	Post-meno	462	Fulvestrant 500 mg versus AI (anastrozole)	0	Allowed	0.80 (0.64 to 0.999)	0.88 (0.63 to 1.22)	-	-	0.99 (0.74 to 1.33)	-
MINT[58]	II	Post-meno	359	Sapatinib 20 mg+AI (anastrozole) versus AI Sapatinib 40 mg+AI (anastrozole) versus AI (anastrozole)	0	≤1 line	1.37 (0.91 to 2.06) 1.16 (0.77 to 1.75)	-	-	-	-	-
MONARCH 3[59 60]	III	Post-meno	493	CDK4/6i (abemaciclib)+AI (anastrozole or letrozole) versus AI (anastrozole or letrozole)	0	No	0.54 (0.41 to 0.72)	-	0.49 (0.31 to 0.76)	0.58 (0.42 to 0.81)	0.61 (0.42 to 0.87)	0.58 (0.27 to 1.25)
MONALEESA-7[61 62]	III	Pre-meno	672	CDK4/6i (ribociclib)+tamoxifen+goserelin§ versus tamoxifen +goserelin§ CDK4/6i (ribociclib)+AI (anastrozole or letrozole)+goserelin versus AI (anastrozole or letrozole)+goserelin	0	≤1 line	0.59 (0.39 to 0.88) 0.57 (0.44 to 0.74)	0.79 (0.45 to 1.38) 0.70 (0.50 to 0.98)	-	-	-	-
Endocrine-resistant patients only												
TAMRAD[63]	II	Post-meno	111	Everolimus+tamoxifen versus tamoxifen	NR	≤1 line	0.54 (0.36 to 0.81)	0.45 (0.24 to 0.81)	-	-	-	-
BOLERO-2[64–66]	III	Post-meno	724	Everolimus+AI (exemestane) versus AI (exemestane)	NR	≤1 line	0.45 (0.38 to 0.54)	0.89 (0.73 to 1.10)	-	-	0.47 (0.37 to 0.60)	0.33 (0.21 to 0.53)
SoFEA[38]	III	Post-meno	485	Fulvestrant 250 mg+AI (anastrozole) versus fulvestrant 250 mg Fulvestrant 250 mg versus AI (exemestane)	1	≤1 line	0.95 (0.75 to 1.22) 1.06 (0.83 to 1.34)	0.85 (0.64 to 1.14) 1.26 (0.95 to 1.66)	-	-	-	-
CALGB 40302[40]	III	Post-meno	235	Lapatinib+fulvestrant 250 mg versus fulvestrant 250 mg	NR	≤1 line	1.00 (0.78 to 1.30)	-	-	-	-	-
SAKK21/09[41]	II	Post-meno	43	Selumetinib+fulvestrant 500 mg versus fulvestrant 500 mg	1	≤1 line	No HR	-	-	-	-	-
Addison et al[42]	II	Post-meno	116	Bortezomib+fulvestrant 500 mg versus fulvestrant 500 mg	1	≤1 line	0.73 (0.49 to 1.08)	-	-	-	-	-

Continued

Table 1 Continued

Trial name/author	Phase	Meno-pausal status	Patients (N)*	Comparisons	Median of ET (N)†	Previous CT	ITT* PFS HR (95% CI)	ITT* OS HR (95% CI)	De novo* PFS HR (95% CI)	Recurrent* PFS HR (95% CI)	Visceral* PFS HR (95% CI)	Bone-only* PFS HR (95% CI)
PALOMA-3[20 43-45]	III	Both	521	CDK4/6i (palbociclib)+fulvestrant 500 mg versus fulvestrant 500 mg	1	≤1 line	0.46 (0.36 to 0.59)	0.81 (0.64 1.03)	–	–	0.47 (0.34 to 0.63)	0.63 (0.38 to 1.06)
O'Shaughnessy *et al*[46]	II	Post-meno	297	Anti-androgen (abiraterone acetate) versus AI (exemestane)	1	≤1 line	1.1 (0.82 to 1.60)	–	–	–	–	–
				Anti-androgen (abiraterone acetate)+AI (exemestane) versus AI (exemestane)			0.96 (0.70 to 1.32)				0.51 (0.32 to 0.80)	2.09 (1.04 to 4.19)
FERGI[24]	II	Post-meno	168	Pan-PI3Ki (pictilisib)+fulvestrant 500 mg versus fulvestrant 500 mg	1	≤1 line	0.74 (0.52 to 1.06)	–	–	–	0.74 (0.46 to 1.18)	–
BELLE-2[47 48]	III	Post-meno	1147	Pan-PI3Ki (buparlisib)+fulvestrant 500 mg versus fulvestrant 500 mg	1	≤1 line	0.78 (0.67 to 0.89)	0.87 (0.74 to 1.02)	–	–	0.76 (0.63 to 0.90)	0.66 (0.46 to 0.95)
MONARCH 2[33 49]	III	Both	669	CDK4/6i (abemaciclib)+fulvestrant 500 mg versus fulvestrant 500 mg	0	No	0.55 (0.45 to 0.68)	0.76 (0.61 to 0.95)	–	–	0.48 (0.37 to 0.63)	0.54 (0.36 to 0.83)
Musolino *et al*[50]	II	Post-meno	97	MultiTKI (dovitinib)+fulvestrant 500 mg versus fulvestrant 500 mg	NR	No	0.68 (0.41 to 1.14)	0.81 (0.39 to 1.65)	–	–	–	–
Zhao *et al*[51]	II	Post-meno	60	Metformin+AI (letrozole or exemestane) versus AI (letrozole or exemestane)	1	Allowed	1.20 (0.7 to 2.1)	1.10 (0.50 to 2.40)	–	–	–	–
MANTA[18]	II	Post-meno	326	Vistusertib continuous+fulvestrant 500 mg versus fulvestrant 500 mg	1	≤1 line	0.88 (0.63 to 1.24)	–	–	–	–	–
				Vistusertib intermittent+fulvestrant 500 mg versus fulvestrant 500 mg			0.79(0.55 to 1.12)					
				Everolimus+fulvestrant 500 mg versus fulvestrant 500 mg			0.63 (0.42 to 0.92)					
				Everolimus+fulvestrant 500 mg versus vistusertib continuous+fulvestrant 500 mg			0.63 (0.45 to 0.90)					
				Vistusertib continuous+fulvestrant 500 mg versus vistusertib intermittent+fulvestrant 500 mg			1.11 (0.81 to 1.52)					
PrE0102[52]	II	Post-meno	130	Everolimus+fulvestrant 500 mg versus fulvestrant 500 mg	NR	≤1 line	0.61 (0.40 to 0.92)	1.31 (0.72 to 2.38)	–	–	–	–
BELLE-3[53]	III	Post-meno	432	Pan-PI3Ki (buparlisib)+fulvestrant 500 mg versus fulvestrant 500 mg	2	Allowed	0.67 (0.53 to 0.84)	–	–	–	0.56 (0.43 to 0.74)	–
KCSG BR10–04/ FLAG[54]	II	Both	138	Fulvestrant 500 mg+goserelin versus goserelin	0	Allowed	0.61 (0.37 to 0.998)	0.60 (0.28 to 1.32)	0.73 (0.26 to 2.01)	–	0.67 (0.34 to 1.34)	–
				AI (anastrozole)+goserelin versus goserelin			0.98 (0.62 to 1.55)	0.52 (0.23 to 1.19)	0.69 (0.24 to 1.96)		1.04 (0.54 to 1.97)	
ACE[55]	III	Post-meno	365	Tucidinostat+AI (exemestane) versus AI (exemestane)	NR	≤1 line	0.75 (0.58 to 0.98)	–	–	–	0.69 (0.50 to 0.96)	–
FAKTION**[57]				Capivasertib+fulvestrant 500 mg versus fulvestrant 500 mg			0.58 (0.39 to 0.84)	0.59 (0.34 to 1.05)				

Both endocrine-sensitive and endocrine-resistant patients

Continued

Table 1 Continued

Trial name/author	Phase	Meno-pausal status	Patients (N)*	Comparisons	Median of ET (N)†	Previous CT	ITT* PFS HR (95% CI)	ITT* OS HR (95% CI)	De novo* PFS HR (95% CI)	Recurrent* PFS HR (95% CI)	Visceral* PFS HR (95% CI)	Bone-only* PFS HR (95% CI)
EGF30008[57]	III	Post-meno	752 ES 200 ER	Lapatinib+AI (letrozole) versus AI (letrozole)	NR	No	ES: 0.94 (0.79 to 1.13) ER: 0.78 (0.57 to 1.07)	–	–	–	–	–
Krop *et al*‡[58]	II	Post-meno	127 ES 120 ER	Anti-androgen (enzalutamide)+AI (exemestane) versus AI (exemestane)	NR	≤1 line	ES: 0.82 (0.54 to 1.26) ER: 1.02 (0.66 to 1.59)	–	–	–	–	–
MONALEESA-3[59 60]	III	Post-meno	367 ES 345 ER	CDK4/6i (ribociclib)+fulvestrant 500 mg versus fulvestrant 500 mg	0	No	ES: 0.58 (0.42 to 0.80)	ES: 0.70 (0.48 to 1.02)	–	–	–	–
					1	No	ER: 0.57 (0.43 to 0.74)	ER: 0.73 (0.53 to 1.004)				

*Only for hormone receptor-positive/HER2-negative patients, without other molecular selection.
†Median number of ET lines for advanced breast cancer.
‡Result was not provided separately for hormone-receptor positive/HER2-negative patients, therefore it was not included in the analysis.
§Arm/trial not included in the network meta-analysis.
¶Results published only in meeting abstracts (without a full publication) at the time of literature search.
AI, aromatase inhibitor; CDK, cyclin-dependent kinase; CDK4/6i, CDK4/6 inhibitor; CT, chemotherapy; ER, endocrine-resistant; ES, endocrine-sensitive; ET, endocrine therapy; ITT, intention-to-treat population; multiTKI, multi-tyrosine kinase inhibitor; NR, not reported; OS, overall survival; pan-PI3K, pan-PI3K inhibitor; PFS, progression-free survival; post-meno, post-menopausal patients only; pre-meno, pre-menopausal patients only.

Lee CH et al., 2020 [13].

Merkmale der eingeschlossenen Studien / Patienten

Table S4. Basic Characteristics of Included Randomized Trials

Study/ Year	Study Design	Treatment Design	Median Age/PFS	Population Analysis	HR+ (%)/ menopausal	Visceral metastases(%)	Inclusion Criteria
Rose 2003	OP, RCT, phase 2	Letrozole 2.5mg	64/5.7m	713	52.1/100	52.1	progressed after anti-oestrogen therapy
		Anastrozole 1mg	63/5.7m				
Buzdar 1997	RCT, phase 2	Anastrozole 1 mg	NA/NA	258	NA/100	NA	Progressed after tamoxifen therapy.
		Anastrozole 10 mg	NA/NA				
		Megestrol acetate 160mg	NA/NA				
Buzdar 2001	DB, RCT phase 2	Letrozole 0.5mg	66.5/NA	602	NA/100	NA	previously treated with anti-estrogen therapy
		Letrozole 2.5mg	66.5/NA				
		Megestrol acetate 160mg	65.9/NA				
Dombernowsky 1998	DB, RCT phase 2	Letrozole 0.5mg	64.6/NA	362	NA/100	NA	previously treated with anti-estrogen therapy
		Letrozole 2.5mg	63.6/NA				
		Megestrol acetate 160mg	64/NA				
Gershanovich AR/BC3 1996	OP, RCT, phase 2	Letrozole 0.5mg	NA/NA	377	NA/100	NA	previously treated with anti-estrogen therapy
		Letrozole 2.5mg	NA/NA				
		aminoglutethimide 250 mg twice	NA/NA				
Kaufmann 2000	DB, RCT phase 2	Exemestane 25mg	65/NA	769	NA/100	NA	progressed after tamoxifen therapy.
		Megestrol acetate 160mg	65/NA				
Howell 2002	OP, RCT, phase 2	Fulvestrant 250 mg	67/5.5m	451	NA/100	NA	progressed after anti-oestrogen therapy
		Anastrozole 1mg	66/5.1m				
Osborne 2002	DB, PB, RCT phase 2	Fulvestrant 250 mg	63/5.4m	400	21.1/100	21.1	progressed after anti-oestrogen therapy
		Anastrozole 1mg	62/3.4m				
Xu (NCT00327769) 2010	DB, PB, RCT phase 3	Fulvestrant 250 mg	53/3.6m	234	NA/100	NA	progressed after anti-oestrogen therapy
		Anastrozole 1mg	54/5.3m				
Chia EFECT 2008	DB, PB, RCT phase 3	Fulvestrant 500/250 mg	63/3.7m	693	56.9/100	56.9	progressed after NSAI therapy
		Exemestane 25mg	63/3.7m				

Di Leo_a CONFIRM 2010	DB, PB, RCT phase 3	Fulvestrant 500 mg	61/6.5m	736	63.9/100	63.9	progressed after anti-oestrogen therapy
		Fulvestrant 250 mg	61/5.5m				
Johnston SoFEA (NCT00253422) 2013	DB, PB, RCT phase 3	Fulvestrant 250mg + anastrozole 1mg	63/4.4m	723	58.9/100	58.9	progressed after NSAI therapy
		Fulvestrant 250mg + Placebo	63/4.8m				
		Exemestane 25mg	68/3.4m				
Dirix 2008	OP, RCT, phase 2	Exemestane 25mg + celecoxib 800mg	56/5.85m	111	76.5/NA	76.5	progressed after tamoxifen therapy.
		Exemestane 25mg	56/4.0m				
Yardley BOLERO-2 (NCT00863655) 2013	DB, PB, RCT phase 3	Exemestane 25mg + Everolimus 10mg	62/7.8m	724	16.1/100	16.1	progressed after NSAI therapy
		Exemestane 25mg + Placebo	61/3.2m				
Yardley_b E2112 (NCT02115282) 2013	DB, PB, RCT phase 2	Exemestane 25mg + Entinostat 5mg	63/4.3m	130	60.1/100	60.1	progressed after NSAI therapy
		Exemestane 25mg + Placebo	62/2.3m				
Cristofanilli PALOMA-3 (NCT01942135) 2016	DB, PB, RCT phase 3	Fulvestrant 500mg + Palbociclib 125mg	57/9.5m	521	59.7/79.3	59.7	progressed after anti-oestrogen therapy
		Fulvestrant 500mg + Placebo	56/4.6m				
Zhang (NCT01300351) 2016	DB, RCT phase 2	Fulvestrant 250 mg	55/8.0m	221	NA/100	NA	progressed after anti-oestrogen therapy
		Fulvestrant 500 mg	55/4.0m				
Pritchard FINDER2 (NCT00313170) 2010	DB, RCT phase 2	Fulvestrant 250 mg	63/3.1m	144	77.7/100	77.7	progressed after anti-oestrogen therapy
		Fulvestrant 500 mg -> Fulvestrant 250 mg	69/6.1m				
		Fulvestrant 500 mg	67/6.0m				
Ohno FINDER1	DB, RCT phase 2	Fulvestrant 250 mg	61/6.0m	143	56.6/100	56.6	progressed after anti-oestrogen therapy

(NCT00305448) 2010		Fulvestrant 500 mg -> Fulvestrant 250 mg	62/7.5m				
		Fulvestrant 500 mg	61/6.0m				
Jonat 1996	OP, RCT, phase 3	Anastrozole 1mg	65/4.7m	378	NA/100	NA	progressed after tamoxifen therapy.
		Anastrozole 10mg	66/5.6m				
		Megestrol acetate 160mg	64/4.3m				
Campos 2009	OP, RCT, phase 2	Anastrozole 1mg	61/4.2m	128	NA/100	NA	progressed after anti-oestrogen therapy
		Exemestane 25mg	64/3.7m				
Di Leo_b BELLE-3 (NCT01633060) 2018	DB, PB, RCT phase 3	Fulvestrant 500 mg + Buparlisib 100mg	60/3.9m	432	72.9/100	72.9	progressed after aromatase inhibitors and mTOR inhibitor combination therapy
		Fulvestrant 500 mg + Placebo	62/1.8m				
Baselga_b BELLE-2 (NCT01610284) 2017	DB,PB,RCT, phase 3	Fulvestrant 500 mg + Buparlisib 100mg	62/6.9m	1147	59.1/100	59.1	progressed after AI therapy
		Fulvestrant 500 mg + Placebo	61/5.0m				
Musolino (NCT01528345) 2017	DB,PB ,RCT, phase 2	Fulvestrant 500 mg + Dovitinib 500mg	63/5.5m	97	67.1/100	67.1	progressed after anti-oestrogen therapy
		Fulvestrant 500 mg + Placebo	63/5.5m				
Krop FERGI (NCT01437566) 2016	DB, PB, RCT phase 2	Fulvestrant 500 mg + Pictilisib 340mg	60/6.6m	168	55.3/100	55.3	progressed after AI therapy
		Fulvestrant 500 mg + Placebo	63/5.1m				
Slamon MONALEESA-3 (NCT02246621) 2018	DB, PB, RCT phase 3	Fulvestrant 500 mg + Ribociclib 600mg	63/14.6m	345	60.5/100	60.5	progressed after anti-oestrogen therapy
		Fulvestrant 500 mg + Placebo	63/9.1m				
Sledge MONARCH-2 (NCT02107703) 2017	DB, PB, RCT phase 3	Fulvestrant 500 mg + Abemaciclib 300mg	59/16.4m	669	55.8/82.3	55.8	progressed after anti-oestrogen therapy
		Fulvestrant 500 mg + Placebo	62/9.3m				
O'Shaughnessy (NCT01381874) 2015	OP, RCT, phase 2	Exemestane 25mg	63/3.7m	297	46.1/100	46.1	progressed after NSAI therapy
		abiraterone acetate plus prednisone	62/3.7m				

		abiraterone acetate plus prednisone plus exemestane	64/4.5m				
Zaman (NCT01160718) 2015	DB,PB, RCT phase 2	Fulvestrant 500 mg + Selumetinib 75mg	66/5.6m	46	57.1/100	57.1	progressed after AI therapy
		Fulvestrant 500 mg + Placebo	69/3.7m				
Krop[$] (NCT02007512) 2017	DB, PB, RCT	Exemestane 25mg + Placebo	NA/3.9m	120	NA/NA	NA	progressed after anti-oestrogen therapy
		Exemestane 50mg + Enzalutamide 160mg	NA/3.6m				
Baselga[$] SANDPIPER (NCT02340221) 2017	DB, PB, RCT, 2ce, C2 previous)	Fulvestrant 500 mg + Taselisib 4mg	NA/7.4m	516	NA/100	NA	progressed after AI therapy
		Fulvestrant 500 mg + Placebo	NA/5.4m				
Tryfonidis (NCT00066378) 2015	DB,PB, RCT phase 2	Anastrozole 1mg + Gefitinib 500mg	64/NA	71	NA/100	NA	previously treated with anti-estrogen therapy
		Anastrozole 1mg	63/NA				

HR: hormone receptor; OP: Open label DB: double blind, MC: Multiple center, RCT: randomized controlled trial, NA: not available, AI : aromatase inhibitor
[$]: data from conference abstract

Rugo HS et al., 2016 [21].

ASCO-Guidelines: Definitions for Types + Strengths of recommendation, Strengths of evidence

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

Definitions for Types of recommendations

Type of Recommendation	Definition
Evidence based	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
Formal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (ie, "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (ie, "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.

Definitions for Strengths of evidence

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

Definitions for Strengths of recommendation

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

ASCO-Guidelines: Endocrine therapy for women with hormone receptor–positive metastatic breast cancer.

Ergebnisse der syst. Literaturauswertung: Systematic reviews:

Table 1. Main Findings From Systematic Review (all included meta-analyses)

Study	Evidence Base	Main Findings
Endocrine *v* chemotherapy		
Wilcken[8]	Six trials including 692 patients with MBC (for OS comparison)	No significant difference in OS was detected (hazard ratio, 0.94; 95% CI, 0.79 to 1.12; $P = .5$), with nonsignificant heterogeneity detected
	Compared single-agent endocrine treatment with single-agent chemotherapy	Significant benefit in response rates (eight trials involving 817 women) for chemotherapy over endocrine therapy was detected (RR, 1.25; 95% CI, 1.01 to 1.54; **$P = .04$**)
		Authors conclude that standard first-line treatment for patients with MBC should be endocrine therapy rather than chemotherapy, except in presence of rapidly progressing disease
Single-agent *v* single-agent hormone therapies		
Chi[30]	23 trials including 7,242 patients (patients with advanced breast cancer were subset of total population)	Toremifene was associated with more vaginal bleeding (OR, 0.45; 95% CI, 0.26 to 0.80; **$P < .05$**) and greater decrease in serum triglyceride levels (SMD, −1.15; 95% CI, −1.90 to −0.39; **$P < .05$**) than tamoxifen
	Compared toremifene and tamoxifen	Evidence suggests toremifene could be an alternative to tamoxifen for patients with advanced breast cancer
Cope[31]	11 RCTs including 5,808 postmenopausal women with advanced breast cancer after endocrine therapy failure	Fulvestrant 500 mg was superior to fulvestrant 250 mg, megestrolacetate, and anastrozole for PFS (**$P < .05$**)
	Compared fulvestrant 500 mg, fulvestrant 250 mg, fulvestrant 250 mg loading dose, anastrozole 1 mg, megestrol acetate, letrozole 2.5 mg, letrozole 0.5 mg, and exemestane	
Xu[32]	Six RCTs including 2,560 postmenopausal patients with HR-positive advanced breast cancer	AIs were superior to tamoxifen alone for response (ORR; OR, 1.56; 95% CI, 1.17 to 2.07; **$P < .05$**) and CBR (OR, 1.70; 95% CI, 1.24 to 2.33; **$P < .05$**)
	Compared AIs *v* tamoxifen	
Single-agent *v* combination endocrine therapies		
Tan[33]	Two RCTs including patients with HR-positive advanced breast cancer (total patients, NR)	None of the comparisons for PFS, OS, or response showed statistically significant difference
	Compared fulvestrant + AI *v* AI alone (both studied anastrozole in combination with fulvestrant)	
Valachis[34]	Four RCTs including 2,125 patients with HR-positive advanced breast cancer	No difference detected between fulvestrant + AIs and tamoxifen for OS, TTP, CBR, or ORR
	Compared fulvestrant + AIs *v* tamoxifen	Hormonal agents other than fulvestrant were associated with great likelihood of joint disorders (**$P < .05$**)
Endocrine therapy ± mTOR inhibitors		
Bachelot[35]	Six RCTs (total patients, NR)	Everolimus + exemestane was superior to fulvestrant 250 mg and fulvestrant 500 mg for PFS and TTP (hazard ratio, 0.47; 95% CI, 0.38 to 0.58; **$P < .05$** and hazard ratio, 0.59; 95% CI, 0.45 to 0.77; **$P < .05$**, respectively)
	All patients had HR-positive, HER2-negative advanced breast cancer	Analysis suggests that everolimus + exemestane is superior to fulvestrant 250 mg and 500 mg for PFS and TTP in patients with HR-positive, HER2-negative breast cancer with disease progression after endocrine therapy; however, there are no RCTs currently available providing direct comparison
	Included studies identified by systematic literature review (sources: Cochrane Library, National Horizon Scanning Centre, and NICE Web sites)	
	Comparisons were: everolimus + exemestane or everolimus + tamoxifen *v* fulvestrant	

Abbreviations: AI, aromatase inhibitor; CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mTOR, mammalian target of rapamycin; NICE, National Institute for Health and Care Excellence; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, response rate; TTP, time to progression.

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

2020-B-324

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 16.11.2020

Indikation gemäß Beratungsantrag

Zur Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei "der Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie"**?**

Endokrine Therapie in Kombination mit einem CDK -4/6-Inhibitor.

Wie sieht die Versorgungspraxis in Deutschland aus?

Die endokrine Therapie ist abhängig von der evtl. erfolgten endokrinen Vortherapie – dem Abstand zu einer evtl. Vortherapie, dem Menopausenstatus, der Begleiterkrankungen. Wichtig ist die Begrifflichkeit der primären resp. der sekundären Resistenz.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie" **die regelhaft berücksichtigt werden?**

Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ob und welche endokrine Vortherapie erfolgt ist und ob sie bereits beendet ist (und wenn beendet wie lange bereits beendet).

- Wenn unter einer Therapie mit einem Aromatasehemmer eine Metastasierung auftritt, wird ein Wechsel auf eine Therapie mit Fulvestrant (mit CDK 4/6) durchgeführt.
- Wenn die Metastasierung unter Tamoxifen aufgetreten ist, wird die weitere Therapie mit einem Aromatasehemmer als Kombinationspartner gewählt.
- Ist die Aromatasetherapie bereits seit zwei Jahren beendet, so wird erneut mit einem Aromatasehemmer therapiert.

Bitte begründen Sie Ihre Ausführungen.

Zu den CDK-4/6-Inhibitoren sind die Paloma-Studien bez. Palbociclib, die Monaleesa-Studien zu Ribociclib und die Monarch-Studien zum Abemaciclib heranzuziehen (hier sind jeweils unterschiedliche Studien zu den unterschiedlichen hormonellen Therapien gelaufen).

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Der pU plant folgende spezielle Patientenpopulationen zu untersuchen:

- postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben
- postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie

Ergibt sich bei Berücksichtigung dieser Patientencharakteristika bzw. der beschriebenen Behandlungssituation eine andere Vergleichstherapie?

Bitte begründen Sie Ihre Ausführungen.

In der aktuellen Zulassungs-Situation ergibt sich für eine Untergruppe dieser Patienten (Patientinnen mit einer BRCA1/2-Mutation) die Behandlungsoption mit einem PARPp-Inhibitor. Ein Vergleich der Wirksamkeit von einem PARP-Inhibitor vs. CDK 4/6 plus endokrin in dieser besonderen Gruppe liegt bisher nicht vor. In der Behandlungsrealität wird aktuell eher erst mit CDK 4/6 behandelt und dann (bei Progress) mit einem PARP-Inhibitor.

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

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Kontaktdaten

Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) der Deutschen Krebsgesellschaft (DKG)

Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG)

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)

Deutsche Gesellschaft für Senologie (DGS)

Indikation gemäß Beratungsantrag

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Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei

“der Behandlung von Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie“

Zusammenfassung

Behandlungsstandard ist die endokrin-basierte Therapie, d. h. die Kombination einer endokrinen Therapie mit einem CDK4/6-Inhibitor. Welche endokrine Therapie eingesetzt wird, hängt vor allem von der Vortherapie in der (neo-)adjuvanten Situation ab und vom Eintritt des Rezidivs ab. Tritt ein Rezidiv innerhalb der ersten zwei Jahre unter einer adjuvanten endokrinen Therapie oder unter einer adjuvanten endokrinen Therapie, aber erst nach den ersten 2 Jahren oder innerhalb von 12 Monaten nach abgeschlossener adjuvanter endokriner Therapie auf, spricht man von primärer bzw. sekundärer endokriner Resistenz.

Derzeit existiert kein prädiktiver Faktor, mit dem sich eine Subgruppe definieren ließe, die nicht oder besonders von der Behandlung mit einem CDK4/6-Inhibitor profitiert. Auch existieren bisher keine direkt vergleichenden Daten zur Überlegenheit eines spezifischen CDK4/6-Inhibitors in Bezug auf die Gesamtüberlebenszeit.

Eine Chemotherapie sollte nur bei drohendem Organversagen und Notwendigkeit einer schnellen Remission eingesetzt werden.

Ein weiterer prädiktiver Faktor ist der BRCA-Mutationsstatus.

Zusammenfassung

Der therapeutische Standard hat sich seit unserer letzten Stellungnahme zu diesem Thema (Verfahren 2020-B-214 vom 25. August 2020) nicht geändert.

Kontaktdaten

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Stand des Wissens

Das Hormonrezeptor-(HR)-positive, humanen Wachstumsfaktor-Rezeptor-2-(HER2)-negative, lokal fortgeschrittene oder metastasierte Mammakarzinoms ist eine nicht heilbare Erkrankung. Dennoch konnte in den letzten Jahren insbesondere durch den Einsatz von CDK4/6-Inhibitoren die Prognose, d.h. die mittlere Überlebenszeit, bei gleichzeitig möglichst lang andauerndem Erhalt einer hohen Lebensqualität verbessert werden [1-13]. Verlängerung des Überlebens und Erhalt bzw. Verbesserung der Lebensqualität (z.B. durch Reduktion von Symptomen) sind zugleich die beiden wichtigsten Therapieziele in dieser inkurablen Behandlungssituation [14, 15]. Hieraus ergibt sich auch, dass Therapien mit spürbaren Nebenwirkungen nach Möglichkeit vermieden werden sollten. Nebenwirkungen, die durch die Patientin nicht wahrgenommen werden (z.B. Laborveränderungen) spielen, sofern die oben genannten Therapieziele erreicht werden, eine untergeordnete Rolle. Entsprechend sollte eine Chemotherapie solange wie möglich vermieden werden.

Postmenopausale Patientinnen

Postmenopausale Patientinnen bilden die größte Gruppe. Die endokrin-basierte Therapie stellt die erste Therapieoption dar [14-17]. Hierfür kommen folgende Substanzkombinationen in Frage:

- CDK4/6-Inhibitor (Abemaciclib, Palbociclib oder Ribociclib) + nicht-steroidaler Aromataseinhibitor
- CDK4/6-Inhibitor (Abemaciclib, Palbociclib oder Ribociclib) + Fulvestrant
- Aromataseinhibitor Monotherapie
- Fulvestrant Monotherapie
- Tamoxifen Monotherapie

Aus oben genannten Gründen sollte nach Möglichkeit ein CDK4/6-Inhibtor eingesetzt werden, wobei keinerlei Evidenz für die Überlegenheit eines der drei CDK4/6-Inhibitoren existiert. Die Wahl des endokrinen Partners orientiert sich an Vortherapien und Komorbiditäten [14, 15].

Prämenopausale Patientinnen

Prämenopausale Patientinnen stellen aufgrund des jungen Alters eine besondere Herausforderung dar. Prämenopausale Patientinnen werden unter GnRH-Analoga-Therapie oder nach Ovarektomie analog zu postmenopausalen Patientinnen behandelt; auch hier ist der Einsatz des CDK4/6-Inhibitors Therapie der Wahl [14, 15, 18]. Tamoxifen kann zudem ohne den gleichzeitigen Einsatz eines GnRH-Analogons eingesetzt werden, wobei der Kombination mit GnRH der Vorzug zu geben ist.

Dementsprechend ist der Therapiestandard bei prämenopausalen Frauen:

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- CDK4/6-Inhibitor (Abemaciclib, Palbociclib oder Ribociclib) + nicht-steroidaler Aromataseinhibitor + GnRH-Analogon
- CDK4/6-Inhibitor (Abemaciclib, Palbociclib oder Ribociclib) + Fulvestrant + GnRH-Analogon
- Tamoxifen + GnRH-Analogon
- Aromataseinhibitor + GnRH-Analogon (bei Kontraindikationen gegen Tamoxifen)

<u>BRCA1/2 mutiertes Mammakarzinom</u>

Eine weitere Therapie-Optionen für post- und prämenopausale Patientinnen sowie Patienten mit HR-positivem, HER2-negativem, lokal fortgeschrittenem oder metastasiertem Mammakarzinom ist bei Vorliegen einer pathogenen Keimbahnmutation in den Genen BRCA1 oder BRCA2 der Einsatz von PARP-Inhibitoren als Monotherapie (Olaparib oder Talazoparib), sofern in der (neo)adjuvanten Therapiesituation bereits eine Anthrazyklin- oder Taxan-haltige Chemotherapie erfolgt ist oder deren Einsatz nicht möglich ist [19, 20].

<u>Chemotherapie (Zytostatika)</u>

Eine Chemotherapie sollte nur eingesetzt werden, wenn bei drohendem Organausfall eine schnelle Remission vonnöten ist; hierbei wird aufgrund des günstigeren therapeutischen Index einer Monochemotherapie der Vorzug gegeben [14-17]. Die Wahl der Behandlung orientiert sich an Vortherapie, Alter und Komorbiditäten [14, 15].

Wie sieht die Versorgungspraxis in Deutschland aus?

Die Versorgungspraxis entspricht den Leitlinien. Die CDK4/6 Inhibitoren haben sich in der Versorgung schnell durchgesetzt.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von

„Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs als initiale endokrine Therapie oder bei Frauen mit vorangegangener endokriner Therapie“

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die regelhaft berücksichtigt werden?

Ja, siehe obige Ausführungen

Der pU plant folgende spezielle Patientenpopulationen zu untersuchen:

- postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs, die noch keine initiale endokrine Therapie erhalten haben
- postmenopausale Frauen mit Hormonrezeptor (HR)-positivem, humanem epidermalen Wachstumsfaktor-Rezeptor-2 (HER2)-negativem lokal fortgeschrittenem oder metastasiertem Brustkrebs mit vorangegangener endokriner Therapie

Ergibt sich bei Berücksichtigung dieser Patientencharakteristika bzw. der beschriebenen Behandlungssituation eine andere Vergleichstherapie?

Nein

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