Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2024-B-016 Datopotamab Deruxtecan

Stand: März 2024

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

Datopotamab Deruxtecan
[zur Behandlung des inoperablen oder metastasierten HR-positiven, HER2-negativen 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“. Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für: - das HER2-positive Mammakarzinom - die endokrin-basierte Therapie
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschluss über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** - Eribulin: Beschluss vom 22. Januar 2015 - Olaparib: Beschluss vom 16. Januar 2020 - Talazoparib: Beschluss vom 20. November 2020 - Sacituzumab Govitecan: Beschluss vom 15. Februar 2024 - Trastuzumab-Deruxtecan: Beschluss vom 20. Juli 2023 **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie – Wirkstoffe, die in zulassungs-überschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind:** - Gemcitabin in der Monotherapie beim Mammakarzinom der Frau **Richtlinie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus (Richtlinie Methoden Krankenhausbehandlung):** - Protonentherapie bei Hirnmetastasen - Protonentherapie beim Mammakarzinom

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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Datopotamab Deruxtecan L01FX35 Datroway	Datroway wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem Hormonrezeptor (HR)-positivem, HER2-negativem Brustkrebs, die bereits eine endokrine Therapie und mindestens eine Chemotherapielinie im fortgeschrittenen Stadium erhalten haben.
Zytostatika	
5-Fluorouracil L01BC02 generisch	Fortgeschrittenes und/oder metastasiertes Mammakarzinom
Capecitabin L01BC06 generisch	• in Kombination mit Docetaxel (siehe Abschnitt 5.1) zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom nach Versagen einer zytotoxischen Chemotherapie. Eine frühere Behandlung sollte ein Anthracyclin enthalten haben. • als Monotherapie zur Behandlung von Patienten mit lokal fortgeschrittenem oder metastasiertem Mammakarzinom, bei denen eine Therapie mit Taxanen und Anthracyclinen versagt hat oder eine weitere Anthracyclinbehandlung nicht angezeigt ist.
Cyclophosphamid L01AA01 Endoxan	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: Endoxan Pulver zur Herstellung einer Injektionslösung: • Palliative Therapie des fortgeschrittenen Mammakarzinoms Endoxan überzogene Tabletten: • Palliative Therapie des metastasierten Mammakarzinoms
Docetaxel L01CD02	*Brustkrebs*

II. Zugelassene Arzneimittel im Anwendungsgebiet	
TAXOTERE	• Die Docetaxel-Monotherapie ist zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die vorausgegangene Chemotherapie sollte ein Anthracyclin oder Alkylanzien enthalten haben. • Docetaxel ist in Kombination mit Capecitabin zur Behandlung von Patientinnen mit lokal fortgeschrittenem oder metastasiertem Brustkrebs nach Versagen einer Chemotherapie angezeigt. Die frühere Behandlung sollte ein Anthracyclin enthalten haben.
Doxorubicin L01DB01 generisch	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: • Mammakarzinom Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Doxorubicin (liposomal) L01DB01 Caelyx	Caelyx ist indiziert: • Als Monotherapie bei Patientinnen mit metastasierendem Mammakarzinom mit erhöhtem kardialen Risiko.
Epirubicin L01DB03 generisch	Epirubicin wird zur Behandlung folgender neoplastischer Erkrankungen eingesetzt: − Mammakarzinom,
Eribulin L01XX41 Halaven	Halaven ist indiziert für die Behandlung von erwachsenen Patienten mit lokal fortgeschrittenem oder metastasiertem Brustkrebs, bei denen nach mindestens einer Chemotherapie zur Behandlung einer fortgeschrittenen Brustkrebserkrankung eine weitere Progression eingetreten ist. Die Vortherapien sollen ein Anthrazyklin und ein Taxan entweder als adjuvante Therapie oder im Rahmen der metastasierten Situation enthalten haben, es sei denn, diese Behandlungen waren ungeeignet für den Patienten.
Ifosfamid L01AA06 Holoxan	Zur Palliativtherapie bei fortgeschrittenen, therapierefraktären bzw. rezidivierenden Mammakarzinomen.
Methotrexat L01BA01	Mammakarzinome:

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	– in Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium
Mitomycin L01DC03 generisch	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: – fortgeschrittenes und/oder metastasierendes Mammakarzinom
Mitoxantron L01DB07 generisch	• ist indiziert zur Behandlung des metastasierten Mammakarzinoms
Paclitaxel L01CD01 generisch	Als Monotherapie ist Paclitaxel indiziert für die Behandlung des metastasierten Mammakarzinoms bei Patientinnen, bei denen eine Standardtherapie mit Anthracyclinen erfolglos war oder für die eine Therapie mit einem Anthracyclin nicht angezeigt ist.
Nab-Paclitaxel L01CD01 Abraxane	Abraxane-Monotherapie ist indiziert für die Behandlung des metastasierten Mammakarzinoms bei erwachsenen Patienten, bei denen die Erstlinientherapie der metastasierten Erkrankung fehlgeschlagen ist und für die eine standardmäßige Anthracyclin-enthaltende Therapie nicht angezeigt ist.
Vinblastin L01CA01 Vinblastinsulfat TEVA	Vinblastin wird manchmal in der Monotherapie, üblicherweise jedoch in Kombination mit anderen Zytostatika und/oder Strahlentherapie zur Behandlung der folgenden malignen Erkrankungen angewendet: – rezidivierendes oder metastasierendes Mammakarzinom (wenn eine Behandlung mit Anthracyclinen nicht erfolgreich war)
Vincristin L01CA02 Vincristin-TEVA	Vincristin wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: – soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom.
Vinorelbin	Behandlung

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01CA04 Navelbine®	– als Monotherapie bei Patientinnen mit metastasierendem Brustkrebs (Stadium 4), bei denen eine Behandlung mit einer anthrazyklin- und taxanhaltigen Chemotherapie versagt hat oder nicht angezeigt ist.
PARP-Inhibitoren	
Olaparib L01XX46 Lynparza	*Mammakarzinom* Lynparza wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom haben. Die Patienten sollten zuvor mit einem Anthrazyklin und einem Taxan im (neo)adjuvanten oder metastasierten Setting behandelt worden sein, es sei denn, die Patienten waren für diese Behandlungen nicht geeignet (siehe Abschnitt 5.1). Patienten mit Hormonrezeptor (HR)-positivem Mammakarzinom sollten außerdem eine Krankheitsprogression während oder nach einer vorherigen endokrinen Therapie aufweisen oder für eine endokrine Therapie nicht geeignet sein.
Talazoparib L01XX60 Talzenna	Talzenna wird als Monotherapie für die Behandlung von erwachsenen Patienten mit BRCA1/2-Mutationen in der Keimbahn angewendet, die ein HER2-negatives, lokal fortgeschrittenes oder metastasiertes Mammakarzinom aufweisen. Die Patienten sollten zuvor mit einem Anthrazyklin und/ oder einem Taxan im (neo)adjuvanten, lokal fortgeschrittenen oder metastasierten Setting behandelt worden sein, es sei denn, sie waren für diese Behandlungen nicht geeignet (siehe Abschnitt 5.1). Patienten mit Hormonrezeptor (HR)-positivem Brustkrebs sollten außerdem bereits eine endokrin-basierte Therapie erhalten haben oder für diese als nicht geeignet eingestuft sein.
Antikörper-Wirkstoff-Konjugat	
Sacituzumab govitecan L01FX17 Trodelvy	Trodelvy ist als Monotherapie zur Behandlung von erwachsenen Patienten mit nicht resezierbarem oder metastasiertem Hormonrezeptor (HR)-positivem, HER2-negativem Mammakarzinom indiziert, die eine Endokrin-basierte Therapie und mindestens zwei zusätzliche systemische Therapien bei fortgeschrittener Erkrankung erhalten haben
Trastuzumab-Deruxtecan L01FD04 Enhertu	Enhertu wird angewendet als Monotherapie zur Behandlung von erwachsenen Patienten mit inoperablem oder metastasiertem HER2-low Brustkrebs, die bereits eine Chemotherapie in der metastasierten Situation erhalten haben oder bei denen während oder innerhalb von 6 Monaten nach Beendigung der adjuvanten Chemotherapie ein Rezidiv aufgetreten ist

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2024-B-016 (Datopotamab deruxtecan)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	29. Februar 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CAP	capecitabine
ECRI	ECRI Guidelines Trust
ERI	eribulin
G-BA	Gemeinsamer Bundesausschuss
GC	Gemcitabine and carboplatin
GEM	gemcitabine
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
HR	Hazard Ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IXA	ixabepilone
KI	Konfidenzintervall
LABC	locally advanced breast cancer
LoE	Level of Evidence
MBC	metastatic breast cancer
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PC	Paclitaxel
PCT	Physician’s choice of chemotherapy
PFS	Progression-free survival
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TNBC	triple-negative breast cancer
TPC	treatment by physician’s choice
TRIP	Turn Research into Practice Database
UTI	utidelone
VIN	vinorelbine
WHO	World Health Organization

1 Indikation

Zur Behandlung erwachsener Patienten mit HR-positivem, HER2-negativem inoperablem oder metastasiertem Brustkrebs, deren Erkrankung unter der endokrinen Therapie fortschreitet und die für diese nicht mehr geeignet sind und die mindestens eine zusätzliche systemische Therapie im inoperablen oder metastasierten Stadium der Erkrankung erhalten haben.

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

2 Systematische Recherche

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

Die Erstrecherche wurde am 17.10.2022 durchgeführt, die folgenden am 05.05.2023 und 30.01.2024. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 4087 Referenzen.

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

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine Cochrane Reviews im Anwendungsgebiet identifiziert.

3.2 Systematische Reviews

National Institute for Health and Care Excellence (NICE), 2023 [7].

Early and locally advanced breast cancer: diagnosis and management.

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

Fragestellung

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

Methodik

Population:

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

Intervention:

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

Komparator:

- Any other hypofractionation radiotherapy schedule

Endpunkte:

- Longest follow up available: Quality of life (using validated measures such as EORTC and BREAST-Q)
- Breast cancer mortality
- All-cause mortality
- Local Recurrence
- Distant recurrence (also referred as distant relapse)
- Normal tissue effects

- Treatment-related adverse events
- Cosmesis (including breast appearance, breast oedema, appearance of scar, breast size, shape, colour, nipple position, shape of areola in comparison with untreated breast)

Recherche/Suchzeitraum:

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

Qualitätsbewertung der Studien:

- GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- N=6

Charakteristika der Population/Studien:

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

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

Qualität der Studien:

- The majority of the evidence ranged from high to very low quality with the main reasons for downgrading being due to imprecision and risk of bias from some of the trials. In some of the evidence, imprecision was rated serious or very serious with the 95% confidence intervals crossing one or two ends of the default minimally important difference (MIDs) thresholds. Some of the studies were downgraded for risk of bias due to lack of information on randomisation, allocation concealment and blinding. All studies were considered fully applicable to the review. There were a wide range of different hypofractionation regimens reported by different studies. This made it difficult for meta-

analysis to be carried out, meaning that most of the evidence for the outcomes were based on the results from single studies.

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

Studienergebnisse:

Benefits and harms

- The entire body of evidence could not differentiate between the effectiveness of all the included hypofractionation regimens compared to each other for the outcomes of mortality, local recurrence, or distant recurrence (defined as the location of a subsequent cancer in relation to the first episode that led to treatment). This indicates

that regimens that require fewer fractions over fewer weeks may have a similar level of effectiveness, or are non-inferior, to those that require a higher number of fractions over a greater number of weeks. While some of the point estimates of effect favoured one treatment over another, most of the results had wide confidence intervals which crossed the line of no effect. Based on this, the committee could not differentiate between the effects of different hypofractionation regimens. For further information please see the summary of the effectiveness evidence tables.

- The committee discussed how shorter regimens with fewer fractions may have benefits for people who are having radiotherapy, especially those in the groups identified in the equalities and health inequalities assessment (EHIA). Many of the issues that people face when they are having radiotherapy are associated with the time and costs relating to travel to multiple appointments. The time needed to attend multiple appointments can be a particular issue for people who need to arrange appointments around work or carer responsibilities, or for those who live far from their nearest treatment centre. As such, the committee highlighted that a shorter treatment duration time may make treatment more accessible for many people. However, the committee acknowledged that there are some people for whom potential adverse effects may make the shorter treatment duration less acceptable. For example, they discussed how, in their experience, some groups of people (for example, people with high BMI or fibromyalgia), may experience a greater number of adverse events such as skin reactions, breast oedema or pain. In these instances, treatment with a longer regimen may be more appropriate.
- In addition to the benefits for people who are having radiotherapy, the committee highlighted how using fewer fractions has benefits for the centres that are providing radiotherapy. A hypofractionation regimen with fewer fractions over a shorter period of time means that centres can treat people more quickly compared to when radiotherapy takes place over a longer period of time, thereby reducing waiting lists.
- The evidence could not differentiate between the number of adverse events when comparing radiotherapy with 26 Gy in 5 fractions and radiotherapy with 40 Gy in 15 fractions (please see Table 8). The committee noted that there were fewer clinician assessed adverse events, and higher quality of life measurements related to swollen breasts and harder or firmer breasts, for the 15 fraction regimen. However, the difference between the two regimens was not clinically meaningful for these outcomes and the committee did not think that this indicated any potential serious harms. In the committee's experience, these effects should also reduce over time as they are due to acute toxicity effects. The committee also discussed how, in their experience, many people who are given radiotherapy will favour higher doses per fraction in a shorter duration, than lower doses over a longer duration because they consider that the benefits of reduced number of appointments outweigh the risks of increased adverse events. For this reason, the committee made a recommendation in favour of offering a regimen over one week with fewer fractions (26 Gy in 5 fractions) for most people.
- The committee discussed how the clinical evidence for the 26 Gy in 5 fractions was for people who were offered whole breast radiotherapy. They noted that there was no evidence on the use of the 26 Gy in 5 fractions for people who are offered partial breast radiotherapy. However, people who are offered partial breast radiotherapy are considered at lower risk of disease recurrence than those offered whole breast radiotherapy. The committee therefore decided they could extrapolate the evidence from people in the higher risk group to those who have partial breast radiotherapy without any major concerns about differences in regimen effectiveness or safety. The committee also highlighted that current practice is already changing towards offering people who have partial breast radiotherapy the 26 Gy in 5 fractions regimen and that the decision between offering partial or whole breast radiotherapy can change based

on clinical judgement and assessment during the radiotherapy planning process. As such, based on their clinical experience and judgement, the committee included people who have had partial breast radiotherapy in the recommendations, as they agreed that excluding it may disadvantage a large group of people and contradict current practice.

- As discussed above in the quality of the evidence section, there was limited evidence on the use of the 26 Gy over 5 fractions regimen for people with conditions that increase sensitivity to radiotherapy or people who have received implant-based reconstruction. As such, the committee made a recommendation to consider the 40 Gy in 15 fractions regimen in these groups of people as there was no evidence which evaluated the benefits and harms of the lower fraction regimen for these people. The use of the 40 in 15 regimen for these groups is in line with current practice. They also recommended that the 15 fraction regimen should be considered for other people who have factors that may make 15 fractions more acceptable. The committee discussed examples of people who may prefer the 15 fraction regimen, such as those with a high BMI, increased breast separation (a measurement of breast size changes un breast cancer) or fibromyalgia who may experience greater acute adverse events, including breast oedema and pain with the 5 fraction regimen. This may also include people whose radiotherapy plans are outside the dosimetry used within the FAST-Forward trial. The committee thought that decisions on treatments for these groups should be based on discussions of the potential benefits and harms between a patient and a clinician, and included links to the NICE guidelines on patient experience and on shared decision making. This should ensure that information is provided in a way that is most useful for the patient, and that their individual circumstances are considered when choosing the most appropriate regimen.
- As noted above under the quality of the evidence, people who were receiving regional lymph node radiotherapy were not represented in the evidence. The committee therefore thought it was important that this group continued to receive the 40 Gy in 15 fraction regimen until further evidence is available on the effectiveness of the 26 in 5 regimen. They also made a recommendation to highlight the need for research on this issue.
- In addition to the number of fractions, the committee also discussed the dose per fraction. The committee noted that RCTs with long term follow up had already established the dose per fraction over a specified time period (for example, the FAST-Forward trial, Brunt et al. 2020 comparing doses over 5 weeks). They also noted that the FAST-Forward study did include a comparison between 26 Gy and 27 Gy per fraction, both over 5 fractions. The committee noted that the incidence of adverse events was lower in the 26 Gy group, with no clear difference in effectiveness. For example, there was a lower incidence of normal tissue effects, adverse events, swollen breasts and skin problems in the breast for people randomised to receive 26 Gy in 5 fractions compared to 27 Gy in 5 fractions. They agreed that this supported the use of this regimen in current practice.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Outcomes	No of Participants (studies) Follow up	Relative effect (95% CI)	Absolute effects		Interpretation of effect (quality)
			Risk with 26Gy/5 fractions	Risk difference with 40Gy/15 fractions (95% CI)	
All-cause mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.03 (0.78 to 1.36)	66 per 1000	2 more per 1000 (from 14 fewer to 24 more)	Could not differentiate (low quality evidence)
Breast cancer related mortality [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 0.89 (0.61 to 1.31)	39 per 1000	4 fewer per 1000 (from 15 fewer to 12 more)	Could not differentiate (low quality evidence)
Local relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.48 (0.86 to 2.57)	15 per 1000	7 more per 1000 (from 2 fewer to 24 more)	Could not differentiate (moderate quality evidence)
Loco-regional relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 1.49 (0.94 to 2.37)	21 per 1000	10 more per 1000 (from 1 fewer to 29 more)	Could not differentiate (moderate quality evidence)
Distant relapse [MID +/- 0.8 to 1.25]	2729 (1 study[1]) 5 years	RR 0.78 (0.56 to 1.09)	56 per 1000	12 fewer per 1000 (from 24 fewer to 5 more)	Could not differentiate (moderate quality evidence)
Acute skin toxicity - 1 point [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	RR 1.39 (0.86 to 2.22)	455 per 1000	177 more per 1000 (from 64 fewer to 555 more)	Could not differentiate (moderate quality evidence)
Acute skin toxicity - 2 points [MID +/- 0.8 to 1.25] CTCAE	60 (1 study[3]) 18 months	RR 6.11 (0.76 to 49.21)	30 per 1000	155 more per 1000 (from 7 fewer to 1000 more)	Could not differentiate (very low quality evidence)
Late skin toxicity [MID +/- 0.8 to 1.25] RESS-RTOG/EORTC	60 (1 study[3]) 18 months	RR 0.55 (0.22 to 1.34)	333 per 1000	150 fewer per 1000 (from 260 fewer to 113 more)	Could not differentiate (very low quality evidence)
Subcutaneous tissue toxicity - 1 point [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	RR 0.94 (0.39 to 2.25)	259 per 1000	16 fewer per 1000 (from 158 fewer to 324 more)	Could not differentiate (very low quality evidence)
Subcutaneous tissue toxicity - 2 points [MID +/- 0.8 to 1.25] RESS-EORTC	60 (1 study[3]) 18 months	RR 0.07 (0 to 1.3)	185 per 1000	172 fewer per 1000 (from 185 fewer to 56 more)	Could not differentiate (very low quality evidence)
Cosmetic results - 1 point [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	RR 1.29 (0.83 to 1.99)	519 per 1000	150 more per 1000 (from 88 fewer to 513 more)	Could not differentiate (low quality evidence)
Cosmetic results - 2 points [MID +/- 0.8 to 1.25]	60 (1 study[3]) 18 months	RR 0.69 (0.37 to 1.29)	481 per 1000	149 fewer per 1000 (from 303 fewer to 140 more)	Could not differentiate (very low quality evidence)
Adverse events (clinician assessed) [MID +/- 0.8 to 1.25]	12448 (1 study[1]) 5 years	RR 0.87 (0.79 to 0.96)	122 per 1000	16 fewer per 1000 (from 5 fewer to 26 fewer)	Favours 40 Gy in 15 fractions but is less than the defined MID (moderate quality evidence)
EORTC QLQ-BR23 - Arm or shoulder pain [MID +/- 0.8 to 1.25]	5136 (1 study[1]) 5 years	RR 0.9 (0.8 to 1.02)	175 per 1000	18 fewer per 1000 (from 35 fewer to 4 more)	No meaningful difference (high quality evidence)
EORTC QLQ-BR23 - Swollen arm or hand [MID +/- 0.8 to 1.25]	5128 (1 study[1]) 5 years	RR 0.83 (0.64 to 1.08)	48 per 1000	8 fewer per 1000 (from 17 fewer to 4 more)	Could not differentiate (moderate quality evidence)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Anmerkung/Fazit der Autoren

Recommendations supported by this evidence review

This evidence review supports recommendations 1.10.13 to 1.10.16

Yan F et al., 2021 [12].

PARP inhibitor treatment of advanced breast cancer beyond the BRCA-mutated type: a meta-analysis.

Fragestellung

We conducted this meta-analysis to compare the efficacy and safety of PARP inhibitors with or without chemotherapy versus chemotherapy alone for advanced breast cancer

Methodik

Population:

- Patients with advanced breast cancer

Intervention:

- PARP inhibitor, either as monotherapy or in combination with chemotherapy

Komparator:

- chemotherapy

Endpunkte:

- overall response (complete response and partial response), PFS, OS and toxicities

Recherche/Suchzeitraum:

- The PubMed, Embase and Web of Science databases were comprehensively searched for eligible studies from database inception to 13 November 2020

Qualitätsbewertung der Studien:

- The methodological quality of each study was estimated using a 12-item scale addressing the following: adequate randomization, allocation concealment, patient blinded, care provider blinded, outcome assessor blinded, acceptable drop-out rate, intention-to-treat analysis, avoidance of selective reporting, similarity of baseline, similar or avoided cofactor, patient compliance and similarity of timing

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs

Charakteristika der Population:

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

Study	Year	Interval time	Trial phase	Patient characteristics	Previous lines of cytotoxic chemotherapy	Regimen	Patients (n)
Diéras	2020	2014.07–2018.01	III	Metastatic or locally advanced, unresectable breast cancer; HER2-negative; germline *BRCA1/2* mutation; ECOG PS score 0–2	≤2	Veliparib + PC	337
						Placebo + PC	172
Litton	2018	2013.10–2017.04	III	Locally advanced or metastatic breast cancer; HER2-negative; germline *BRCA1/2* mutation; ECOG PS score 0–2	≤3	Talazoparib	287
						PCT	144
Han	2018	2012.01–2015.04	II	Locally recurrent or metastatic breast cancer; germline *BRCA1/2* mutation; ECOG PS score 0–2	≤2	Veliparib + PC	97
						Placebo + PC	99
Robson	2017	2014.08–2015.11	III	Metastatic breast cancer; HER2-negative; germline *BRCA1/2* mutation; ECOG PS score 0–1	≤2	Olaparib	205
						PCT	97
O'Shaughnessy	2014	2009.07–2010.03	III	Metastatic or locally recurrent; triple negative; ECOG PS score 0–1	≤2	Iniparib + GC	261
						GC	258
O'Shaughnessy	2011	2007.10–2009.03	II	Metastatic; triple negative; ECOG PS score 0–1	≤2	Iniparib + GC	61
						GC	62

Qualität der Studien:

Table 2. Methodological quality of the included studies based on the 12-item scoring system.

Author	Randomized adequately†	Allocation concealed	Patient blinded	Care provider blinded	Outcome assessor blinded	Acceptable drop-out rate‡	ITT analysis§	Avoided selective reporting	Similar baseline	Similar or avoided cofactor	Patient compliance¶	Similar timing	Quality#
Diéras V	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Litton JK	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Han HS	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
Robson M	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
O'Shaughnessy J (2014)	Yes	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High
O'Shaughnessy J (2011)	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

†Only if the method of sequence made was explicitly introduced could get a 'yes'; sequences generated by 'dates of admission' or 'patients number' received a 'no'.
‡Drop-out rate <20% could get a 'yes', otherwise 'no'.
§Only a 'yes' if all randomized participants were analyzed in the group they were allocated to.
¶If >75% patients wore respective devices for at least 3 weeks, 'yes'; otherwise 'no'.
#>7 'yes' items means 'high'; 5–7 means 'moderate'; ≤4 means 'low'.
ITT: Intention to treat.

Studienergebnisse:

- ORR of PARP inhibitor contained regimens versus chemotherapy alone
  - All included studies reported the difference in ORR between the experimental and control groups. There was significant heterogeneity (I2 = 82%; p < 0.0001), and the random effects model was used for statistical analysis. The pooled analysis showed

that the experimental group had a significantly higher ORR than the control group (OR: 2.14; 95% CI: 1.27–3.61; p = 0.004)

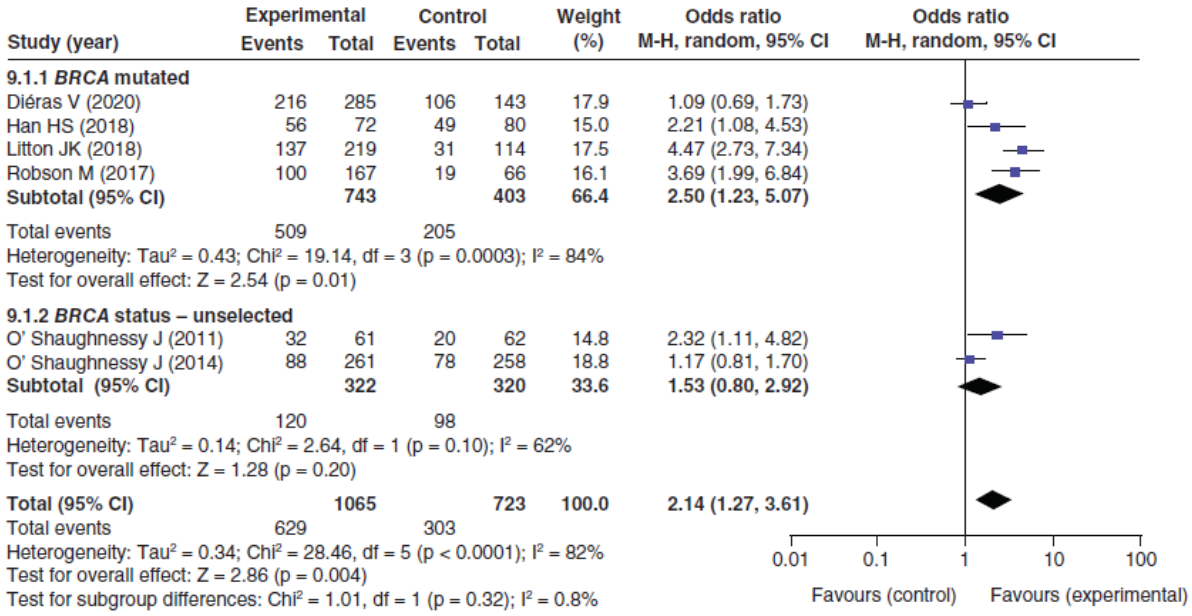

Figure 2. Forest plot of objective response rate comparison between the two groups.

- PFS of PARP inhibitor-containing regimens versus chemotherapy alone
  - All six studies reported the information of HR for PFS. Heterogeneity among the studies was not statistically significant (I2 = 28%; p = 0.23), and the fixed effects model was used for statistical analysis. PFS was significantly longer for patients in the experimental group than in the control group (HR: 0.68; 95% CI: 0.61–0.76; p<0.00001)

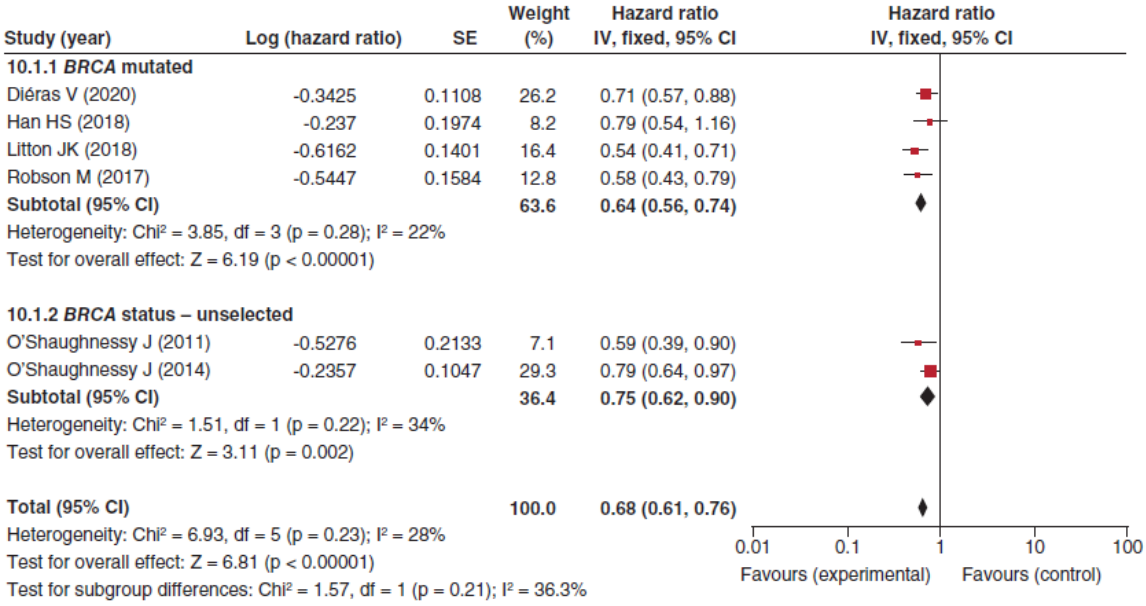

Figure 3. Forest plot of progression-free survival comparison between the two groups.

- OS of PARP inhibitor-containing regimens versus chemotherapy alone
  - All six studies reported the information of HR for OS. Heterogeneity among the studies was not statistically significant (I2 = 0%; p = 0.003), and the fixed effects model

was used for statistical analysis. OS was significantly longer for patients in the experimental group than in the control group (HR: 0.83; 95% CI: 0.74–0.94; p<0.00001)

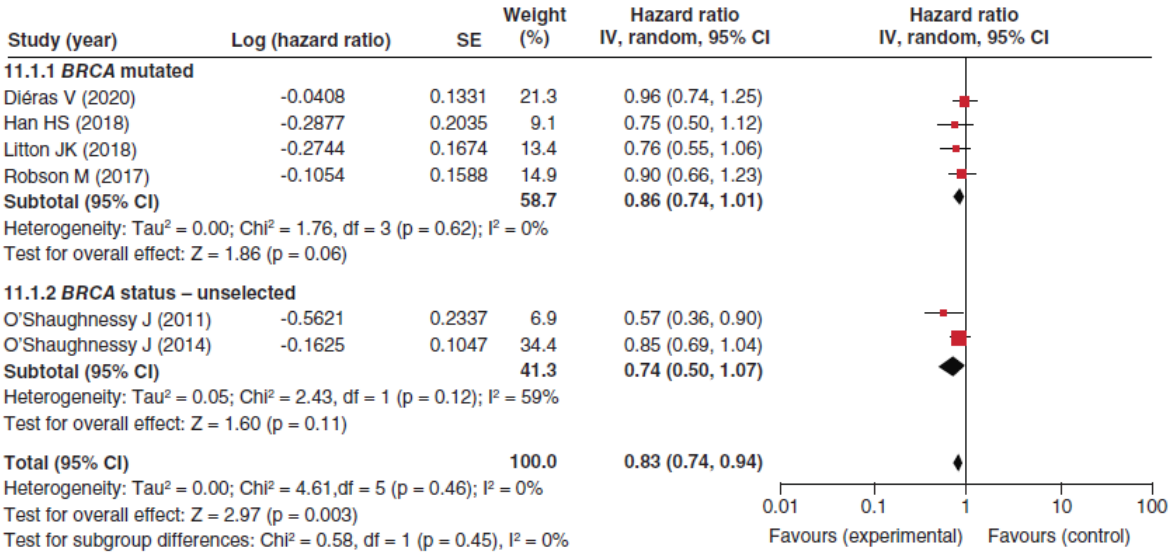

Figure 4. Forest plot of overall survival comparison between the two groups.

Table 3. The incidence of grade ≥3 hematologic events: comparison between the two groups.

Adverse events	Events in experimental group (n)/total patients	Events in control group (n)/total patients	Heterogeneity I² (%)	Effects model	Odds ratio (95% CI)	p-value
Anemia	364/1232	157/787	88	Random	1.95 (0.92–4.11)	0.08
Neutropenia	598/1232	430/787	80	Random	0.78 (0.48–1.25)	0.30
Thrombocytopenia	300/1027	149/696	53	Fixed	1.67 (1.32–2.11)	<0.0001
Leukopenia	187/1232	121/787	23	Random	0.97 (0.71–1.33)	0.86

Table 4. The incidence of grade ≥3 nonhematologic events: comparison between the two groups.

Adverse events	Events in experimental group/total patients	Events in control group/total patients	Heterogeneity I² (%)	Effects model	Odds ratio (95% CI)	p-value
Fatigue	65/1232	42/787	49	Fixed	1.15 (0.76–1.73)	0.50
Nausea	28/1232	21/787	0	Fixed	0.84 (0.47–1.50)	0.56
Headache	20/1175	10/728	0	Fixed	1.29 (0.61–2.73)	0.50
Vomiting	29/1232	11/787	0	Fixed	1.62 (0.81–3.24)	0.17
Diarrhea	30/1232	22/787	51	Random	0.85 (0.32–2.24)	0.74
Decreased appetite	6/715	2/393	0	Fixed	1.49 (0.31–7.04)	0.62
Back pain	16/715	6/393	0	Fixed	1.46 (0.55–3.84)	0.45
Dyspnea	29/1027	19/696	0	Fixed	1.20 (0.66–2.15)	0.50
Palmar-plantar erythrodysesthesia syndrome	16/827	13/388	52	Random	0.37 (0.07–1.77)	0.21

Anmerkung/Fazit der Autoren

The results of our meta-analysis show that PARP inhibitors, either combined with chemotherapy or as a single agent, are effective for advanced breast cancer with BRCA mutations. Advanced TNBC with BRCA status unselected can also benefit from regimens containing PARP inhibitors. Attention should be focused on the grade ≥3 hematologic events of anemia and thrombocytopenia during treatment with regimens containing PARP inhibitors.

Kommentare zum Review

Zugelassen sind nur Olaparib und Talazoparib, die in den Studien von Litton und Robson untersucht wurden. Die Einzelstudien von Litton und Robson zeigten statistisch signifikante positive Effekte zugunsten der von Olaparib bzw. Talazoparib im Hinblick auf PFS und ORR, jedoch nur für BRCA positive Patientinnen (für BRCA negative Patientinnen liegen keine Ergebnisse vor). Für OS zeigte sich kein statistisch signifikanter Unterschied in den Einzelstudien.

Es liegen weitere SRs mit vergleichbarer Fragestellung mit vergleichbaren Schlussfolgerungen vor:

- Liu X et al., 2021 [3]. Efficacy and Safety of PARP Inhibitors in Advanced or Metastatic Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis.
- Shao F et al., 2021 [8]. PARP inhibitors in breast and ovarian cancer with BRCA mutations: a meta-analysis of survival.
- Sun X et al., 2021 [9]. Efficacy and safety of PARP inhibitors in patients with BRCA-mutated advanced breast cancer: A meta-analysis and systematic review.
- Sun X et al., 2023 [10]. Efficacy and safety of PARP inhibitors in patients with BRCA-mutated advanced breast cancer: an updated systematic review and meta-analysis of randomized controlled trials
- Chen Z et al., 2021 [2]. Deep exploration of PARP inhibitors in breast cancer: monotherapy and combination therapy.
- Wang J et al., 2020 [11]. Comparative efficacy, safety, and acceptability of single-agent poly (ADP-ribose) polymerase (PARP) inhibitors in BRCA-mutated HER2-negative metastatic or advanced breast cancer: a network meta-analysis.
  - In dieser Studie wurden nur Olaparib und Talazoparib untersucht und auch in Form einer Netzwerkmetaanalyse (NMA) verglichen. Es ist unklar, ob die Studien tatsächlich die Anforderungen der Ähnlichkeitsannahme für eine NMA erfüllen, da nicht genügend Informationen zu den Patientencharakteristika vorliegen und die Kontrollmedikation in den beiden Studien offenbar nicht gleich war. In der NMA zeigte sich kein Unterschied zwischen Olaparib und Talazoparib in Bezug auf Wirksamkeit und Sicherheit.

Zhao Q et al., 2021 [13].

Network meta-analysis of eribulin versus other chemotherapies used as second- or later-line treatment in locally advanced or metastatic breast cancer

Fragestellung

A systematic literature review (SLR) was conducted to identify and synthesize available randomized controlled trial (RCT) evidence on the efficacy and safety of ChTs used in patients who have received one or more previous systemic therapies in the LABC/MBC setting. Bayesian network meta-analysis (NMA) was then used to compare the relative efficacy and safety of ERI as a 2 L+ treatment for LABC/MBC versus other ChTs in the overall population and in subgroups of triple negative breast cancer (TNBC) and HR-positive/HER2-negative populations.

Methodik

<u>Population:</u>

- Patients with LABC or MBC who had received at least one prior therapy

- LABC or MBC defined as stage IV, any T, and N, M1a
- Target populations were HER2-negative or TNBC, but HER2-positive populations were also included

Intervention:

- Eribulin mesylate (Halaven®) (ERI)

Komparator:

- BSC, placebo, or all therapies listed as monotherapy or in combination with other treatments
- Carboplatin (Paraplatin®)
- Cisplatin (Platinol®; Platinol®-AQ)
- Cyclophosphamide (Cytoxan®; Neosar®)
- Doxorubicin (Adriamycin®; Rubex®)
- Doxorubicin liposomal (Doxil®)
- Epirubicin (Ellence®)
- Capecitabine (Xeloda®) (CAP
- Fluorouracil (Adrucil®)
- Gemcitabine (Gemzar®) (GEM)
- Methotrexate (amethopterin)
- Docetaxel (Taxotere®)
- Ixabepilone (Ixempra®) (IXA)
- Paclitaxel (Taxol®; Onxal™)
- Protein-bound paclitaxel (Abraxane®)
- Vinorelbine (Navelbine®) (VIN)
- TPC: use of TPC involved administration of any single-agent chemotherapy, hormonal, or biological treatment approved for the treatment of cancer administered according to local practice, radiotherapy, or as symptomatic treatment alone.

Endpunkte:

- Efficacy: OS, PFS, response (including ORR, CR, PR, SD,PD)
- Safety: AEs, SAEs, discontinuation, and death

Recherche/Suchzeitraum:

- peer-reviewed RCTs published from 1 January 2007 to 22 March 2019 in Embase, MEDLINE (via PubMed), and the Cochrane Library

Qualitätsbewertung der Studien:

- The quality of RCTs was assessed using the Centre for Reviews and Dissemination tool according to the National Institute for Health and Care Excellence (NICE) Guide to the Methods of Technology Appraisal

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 4494 patients were included in the seven trials. All patients had LABC or MBC and had received prior treatment with anthracyclines and taxanes.

Charakteristika der Population:

- Two trials enrolled metastatic patients only [19, 25] and the remainder enrolled a mix of metastatic and locally advanced patients.
- The frequency of treatments evaluated as monotherapy or combination therapy in the seven RCTs included in the NMA were CAP (five studies), ERI (three studies), IXA (three studies), GEM (one study), UTI (one study), VIN (one study), and TPC (one study).

Table 2 Overview of Study Characteristics of Trials Included in the NMA

Trial	Brief Patient Description	RCT Design	Treatments	N Randomized	Objectives
Study 301 *NCT00337103* Kaufman 2015 [12] Twelves 2016 [13] Cortes 2015 [14] Pivot 2018 [15]	Women with MBC who had received prior anthracycline- and taxane-based therapy	Phase III Open-label	1) ERI 2) CAP	1102	To compare ERI with CAP in patients with LABC or MBC.
EMBRACE *NCT00388726* Cortes 2011 [16] Twelves 2015 [17] Cardoso 2011 [18]	Women with heavily pre-treated (third line to fifth line) locally recurrent or MBC	Phase III Open-label	1) ERI 2) TPC: 25% VIN, 19% GEM, 18% CAP, 15% taxanes, 10% anthracyclines, 10% other chemo, 4% hormonal therapy	1102	To compare OS of women with heavily pre-treated MBC receiving ERI or real-life treatment choices.
Pallis, 2012 [19] *NCT00431106*	Women with MBC, pre-treated and/or resistant to anthracyclines and taxanes	Phase III Blinding NR	1) CAP 2) VIN + GEM	172	To demonstrate superiority of combination treatment in terms of PFS.
Vahdat, 2013 [20] *NCT00879086*	Women with locally recurrent or MBC who had received prior taxane therapy, at least one prior cytotoxic chemotherapy for advanced disease, and progressed during last anti-cancer treatment	Phase II Open-label	1) ERI 2) IXA	104	To assess the incidence of neuropathy.
CA163–046 *NCT00080301* Thomas, 2007 [21] Hortobagyi, 2010 [22] Rugo 2018 [23]	Women with LABC or MBC, pre-treated with or resistant to anthracyclines and taxanes	Phase III Open-label	1) IXA + CAP 2) CAP	752	To describe the results of OS from the CA163–046 phase III study.
CA163–048 *NCT00082433* Sparano 2010 [24] Rugo 2018 [23]	Women previously treated with an anthracycline- and taxane-containing regimen	Phase III Open-label	1) IXA + CAP 2) CAP	1221	To assess whether the combination improved survival compared with CAP monotherapy.
Zhang 2017 [25] *NCT02253459*	Female patients with MBC refractory to anthracycline and taxane	Phase III Open-label	1) UTI + CAP 2) CAP	405	To compare the efficacy and safety of UTI + CAP vs. CAP alone in patients with MBC.

Abbreviations: *CAP* CApecitabinek, *ERI* Eribulin, *GEM* Gemcitibine, *HER2* Human epidermal growth factor receptor 2, *IXA* Ixabepilone, *LABC* Locally advanced breast cancer, *MBC* Metastatic breast cancer, *NR* Not reported, *OS* Overall survival, *PFS* Progression-free survival, *RCT* Randomized controlled trial, *TPC* Treatment by physician's choice, *UTI* Utidelone, *VIN* Vinorelbine

Qualität der Studien:

- Most RCTs were assessed as having a low risk of bias

Supplementary Figure S1. Risk of Bias Assessment Results (Centre for Reviews and Dissemination Tool)

Trial	Was randomisation carried out appropriately?	Was the concealment of treatment allocation adequate?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate?	Were appropriate methods used to account for missing data?	Overall Bias
Study 301/NCT00337103	+	?	+	−	+	+	+	?	+
EMBRACE/NCT00388726	+	−	+	+	+	+	+	?	+
Pallis 2012/NCT00431106	+	?	+	?	+	+	+	?	+
Vahdat 2013/NCT00879086	+	−	+	?	+	+	+	?	+
CA163-046/NCT00080301	?	−	+	+	+	+	+	?	+
CA163-048/NCT00082433	?	−	−	−	+	+	+	?	?
Zhang 2017/NCT02253459	+	?	+	−	+	+	+	?	+

+ Low risk
? Some concerns
− High risk

NOTE: Overall risk of bias assessment scores were graded as 'low risk' if seven or more of the domains were scored as 'low' or 'some concerns', as 'some concerns' if five or six of the domains were scored as 'low' or 'some concerns', and as 'high risk' if four or less of the domains were scored as 'low' or 'some concerns'.

<u>Studienergebnisse:</u>

- Direct head-to-head efficacy and safety comparisons versus ERI were available for CAP and TPC, and other comparators were compared indirectly.
- Studies reporting treatment with VIN monotherapy, docetaxel (DOC) monotherapy, GEM+DOC, and CAP+DOC were identified by the SLR, but did not connect to the networks.
- Overall survival:
  - ERI-treated patients had statistically longer OS compared with those treated with TPC (HR: 0.81; 95% CrI: 0.66–0.99) or GEM+VIN (HR: 0.62; 95% CrI: 0.42–0.90)

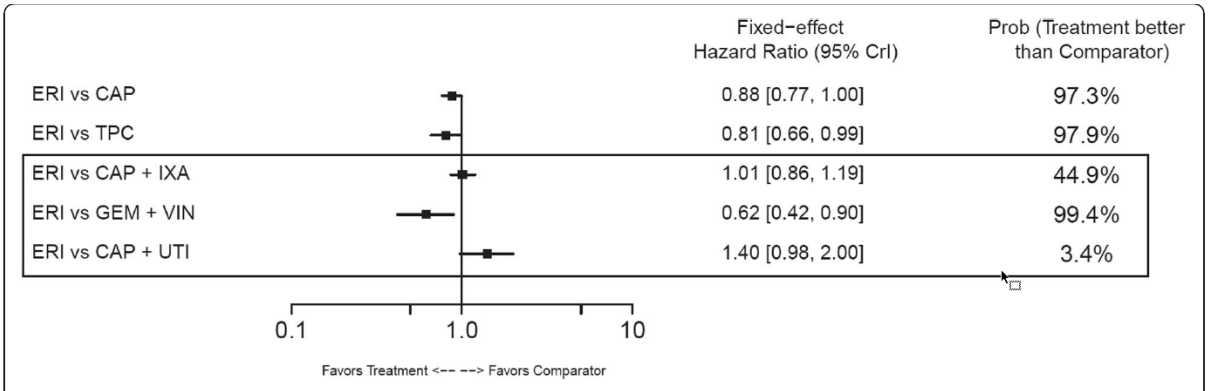

Fig. 10 Forest Plot of Overall Survival Treatment Comparison. Estimates derived only from indirect comparisons shown in black box. Included references: Study 301 (Kaufman 2015; Twelves 2016), EMBRACE (Twelves 2015; Cardoso 2011; Cortes 2011), CA163–046 (Hortobagyi 2010; Rugo 2018), Sparano 2010, Pallis 2012, Zhang 2017. Abbreviations: CAP = capecitabine; CrI = credible interval; ERI = eribulin; GEM = gemcitabine; IXA = ixabepilone; TPC = treatment by physician's choice; UTI = utidelone; VIN = vinorelbine

  - In the TNBC subgroup, ERI had statistically longer OS compared with CAP (HR: 0.70; 95% CrI: 0.54–0.90)

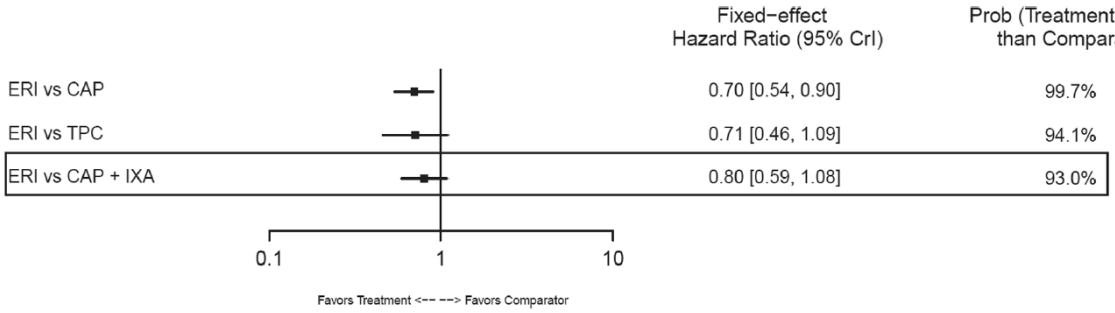

Fig. 11 Forest Plot of Overall Survival Treatment Comparison: TNBC Subgroup Analysis. Estimates derived only from indirect comparisons shown in black box. Included references: Study 301 (Twelves 2016), EMBRACE (Cortes 2011), CA163–046 (Hortobagyi 2010; Rugo 2018), Sparano 2010. Abbreviations: CAP = capecitabine; CrI = credible interval; ERI = eribulin; IXA = ixabepilone; TNBC = triple negative breast cancer; TPC = treatment by physician's choice.

- In the HR-positive/HER2-negative subgroup, ERI treated patients also had statistically longer OS than those treated with CAP (HR: 0.84; 95% CrI: 0.71– 0.98)

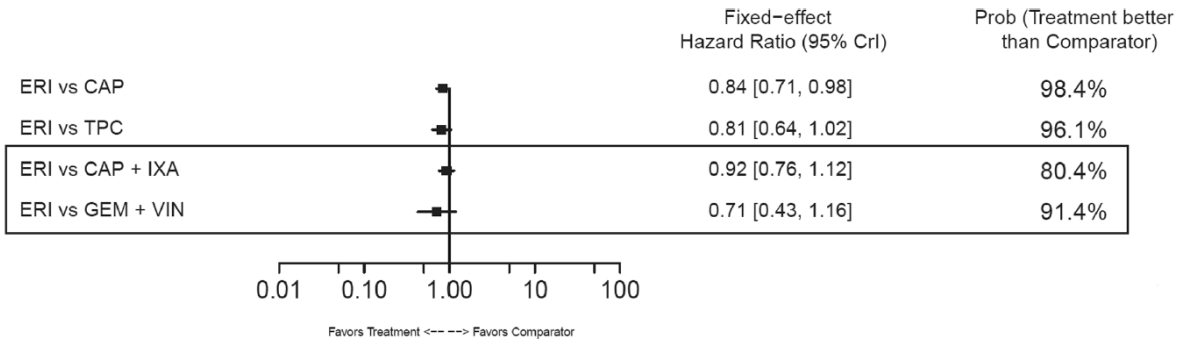

Fig. 12 Forest Plot of Overall Survival Treatment Comparison: HER2– Subgroup Analysis. Estimates derived only from indirect comparisons shown in black box. Included references: Study 301 (Twelves 2016), EMBRACE (Cortes 2011), CA163–046 (Hortobagyi 2010; Rugo 2018), Sparano 2010, Pallis 2012. Abbreviations: CAP = capecitabine; CrI = credible interval; ERI = eribulin; GEM = gemcitabine; HER2 = human epidermal growth factor receptor 2; IXA = ixabepilone; TPC = treatment by physician's choice; VIN = vinorelbine

- Progression-free survival
  - ERI was associated with a significantly longer PFS compared with TPC (HR: 0.76; 95% CrI: 0.64–0.90) and a significantly shorter PFS versus CAP+IXA (HR: 1.40; 95% CrI: 1.17–1.67) and CAP+UTI (HR:1.61; 95% CrI: 1.23–2.12).
  - No statistical differences for ERI versus comparators were observed in the TNBC subgroup, whose network had only two comparisons. In the
  - HR-positive/HER2-negative subgroup, which comprised three treatment comparisons, patients treated with CAP+IXA had statistically longer PFS than those treated with ERI (HR: 1.29; 95% CrI:1.05–1.58).
- Safety

  In safety outcome analyses, there was a trend toward ERI reducing treatment discontinuation due to AEs across all comparators, with statistical advantages compared with CAP+IXA (HR: 0.25; 95% CrI: 0.13-0.47), CAP+UTI (HR: 0.33; 95% CrI: 0.11–0.87), and IXA (HR: 0.27; 95% CrI: 0.09–0.75). No statistical differences between the other comparisons were observed. No statistical differences were found between ERI and any comparator for SAEs.

Anmerkung/Fazit der Autoren

This NMA of available RCTs suggests that ERI may provide a favorable OS benefit in overall LABC/MBC populations and TNBC subgroups compared to standard treatments. Specifically, the NMA suggests that ERI provides a statistically significant OS benefit compared with TPC and GEM+VIN in 2 L+ treatment of patients with LABC/MBC and

compared with CAP in TNBC and HR positive/ HER2-negative subgroups. ERI shows significantly lower rates of discontinuation due to AEs than CAP+IXA, CAP+UTI, and IXA. These NMA findings further support the clinical value of treatment with ERI in LABC/MBC.

Kommentare zum Review

- Einige der Vergleichssubstanzen sind im AWG nicht verordnungsfähig (siehe Markierung)
- Unklar, welche Therapien unter TPC subsumiert wurden.

3.3 Leitlinien

Moy B et al., 2023 [6].

ASCO (American Society of Clinical Oncology)

Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO guideline update

Zielsetzung/Fragestellung

ASCO Rapid Recommendations Updates highlight revisions to select ASCO guideline recommendations as a response to the emergence of new and practice-changing data.

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:

- In 2021, ASCO published a guideline on chemotherapy and targeted therapy for patients with human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer that is either endocrinepretreated or hormone receptor–negative.
- That guideline was updated in August 2022 to incorporate the results of the DESTINY-Breast04 trial.
- The results of the TROPiCS-023 trial, published on October 10, 2022, provided another signal to update.
- A targeted electronic literature search was conducted to identify any additional phase III randomized controlled trials of treatment options in this patient population. No additional randomized controlled trials were identified. The original guideline Expert Panel was reconvened to review new evidence from TROPiCS-023 and approve the revised recommendation.

LoE/ GoR

- AMSTAR-2, GRADE

Sonstige methodische Hinweise

- The rapid updates are supported by an evidence review and follow the guideline development processes outlined in the ASCO Guideline Methodology Manual.

RECOMMENDATION

UPDATED RECOMMENDATION

- Patients with hormone receptor–positive HER2negative metastatic breast cancer who are refractory to endocrine therapy and have received at least two prior lines of chemotherapy for metastatic disease may be offered sacituzumab govitecan (SG). (Type: Evidence-based, benefits outweigh harms; Evidence quality: Moderate; Strength of recommendation: Strong.)

Referenzen aus Leitlinien

EVIDENCE REVIEW TROPiCS-023 was an international, randomized, phase III trial that compared sacituzumab govitecan (SG) (n = 272) against four other chemotherapy options (single-agent eribulin, vinorelbine, capecitabine, or gemcitabine), which comprised treatment of physician's choice (TPC) (n = 271) in 543 patients with endocrine-resistant hormone receptor–positive and HER2-negative locally recurrent inoperable or metastatic breast cancer who had received 2-4 prior chemotherapy regimens for metastatic disease. The primary end point for TROPiCS-02 was progressionfree survival (PFS) as assessed by blinded independent central review.

Burstein HJ et al., 2021 und Moy MD et al., 2021, 2022 [1,4,5]

ASCO (American Society of Clinical Oncology)

- Burstein HJ et al., 2021: Endocrine treatment and targeted therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer: ASCO Guideline Update
- Moy MD et al., 2022: Chemotherapy and Targeted Therapy for Patients With Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer That is Either Endocrine-Pretreated or Hormone Receptor–Negative: ASCO Guideline Update

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

Zielsetzung/Fragestellung

- Burstein HJ et al., 2021: "This focused update of the 2016 guideline provides a new recommendation for the use of alpelisib in the treatment of patients with HR-positive MBC; addresses the role of biomarkers in treatment selection for this patient population; and amends prior recommendations concerning the use of CDK4/6 inhibitors in the treatment of these patients. The remaining recommendations from the 2016 guideline are unchanged because there were no new potentially practice changing data to support substantive revisions (Table 1). The evidence supporting these unchanged recommendations is reviewed in the previous guideline publication."
- Moy MD et al., 2022: "[…] (2) What are the indications for chemotherapy versus endocrine therapy in endocrine-pretreated ER positive metastatic breast cancer? (3) Is there an optimal sequence of nonendocrine agents for patients with hormone receptor–positive but HER2-negative metastatic breast cancer who are no longer benefiting from

endocrine therapy (with or without BRCA1 or BRCA2 germline mutations)? […] Note that although this guideline provides recommendations for chemotherapy and targeted therapy for patients with HER2-negative MBC that is either endocrine-pretreated or HR-negative, a companion guideline [Burstein HJ et al., 2021] provides endocrine therapy (ET) and targeted therapy recommendations, including cyclin-dependent kinase (CDK) 4/6 and PI3 kinase inhibition, for HR-positive MBC patients."

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Burstein HJ et al., 2021:
  - RCT und Meta-Analysen: January 1, 2016 to December 31, 2020 in PubMed
  - Lebensqualität: January 1, 2016 to Feb 18, 2021 in PubMed
- Moy MD et al., 2022:
  - RCT und Meta-Analysen: January 1, 2014-February 29, 2020; updated with a targeted search in April 2021

LoE

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

GoR

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

Sonstige methodische Hinweise

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

Empfehlungen aus Burstein HJ et al., 2021 [1]

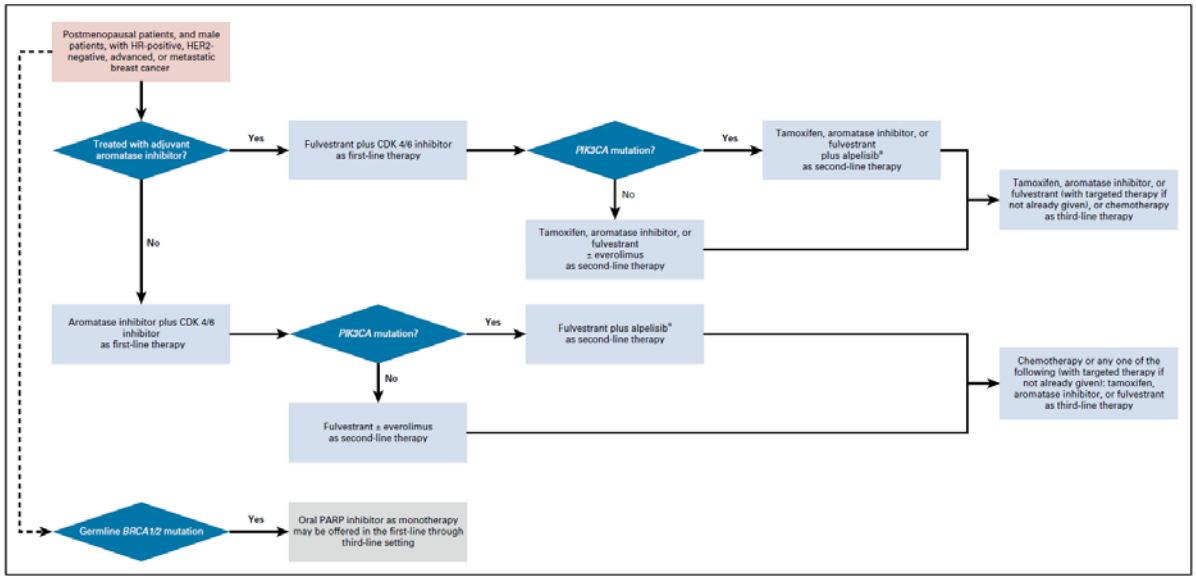

FIG 1. Algorithm for endocrine treatment and targeted therapy for HR-positive, HER2-negative MBC. [a]Patients receiving alpelisib should have laboratory and symptom monitoring weekly for the first 4 weeks of therapy to avoid serious toxicity. CDK, cyclin-dependent kinase; HER2, human epidermal growth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

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

New Recommendations from 2021 Focused Guideline Update

Recommendation	Evidence Rating
Alpelisib in combination with ET should be offered to postmenopausal patients in combination with fulvestrant, and to male patients, with HR-positive, HER2-negative, *PIK3CA*-mutated, ABC, or MBC following prior ET including an AI, with or without a CDK4/6 inhibitor. Careful screening for and management of common toxicities are required	Type: evidence-based, benefits outweigh harms Evidence quality: high Strength of recommendation: moderate
To guide the decision to use alpelisib in combination with fulvestrant in postmenopausal patients, and in male patients, with HR-positive MBC, clinicians should use next-generation sequencing in tumor tissue or cell-free DNA in plasma to detect *PIK3CA* mutations. If no mutation is found in cell-free DNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional patients with *PIK3CA* mutations	Type: evidence-based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
There are insufficient data at present to recommend routine testing for *ESR1* mutations to guide therapy for HR-positive, HER2-negative MBC. Existing data suggest reduced efficacy of AIs compared with the selective estrogen receptor degrader fulvestrant in patients who have tumor or ctDNA with *ESR1* mutations	Type: informal consensus Evidence quality: insufficient Strength of recommendation: moderate
Patients with metastatic HR-positive but HER2-negative breast cancer with germline *BRCA1* or *2* mutations who are no longer benefiting from ET may be offered an oral PARP inhibitor in the first- through third-line setting rather than chemotherapy *Qualifying statements: Small single-arm studies show that oral PARP inhibitor therapy demonstrates high response rates in MBC encoding DNA repair defects, such as germline PALB2 mutation carriers and somatic BRCA mutations. It should be noted that the randomized PARP inhibitor trials made no direct comparison with taxanes, anthracyclines, or platinums; comparative efficacy against these compounds is unknown*	Type: evidence-based, benefits outweigh harms Evidence quality: intermediate Strength of recommendation: strong
A nonsteroidal AI and a CDK4/6 inhibitor should be offered to postmenopausal patients and to premenopausal patients combined with chemical ovarian function suppression, and to male patients (with a gonadotropin-releasing hormone analog) with treatment-naïve HR-positive MBC	Type: evidence-based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Fulvestrant and a CDK4/6 inhibitor should be offered to patients with progressive disease during treatment with AIs (or who develop a recurrence within 1 year of adjuvant AI therapy) with or without one line of prior chemotherapy for metastatic disease, or as first-line therapy. Treatment should be limited to those without prior exposure to CDK4/6 inhibitors	Type: evidence-based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong

Recommendations Unchanged From 2016 Guideline

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

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

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

Update: Burstein HJ et al., 2021 [1].

Clinical Question 1: Should alpelisib be given to postmenopausal women, and to male patients, with HRpositive, HER2-negative, PIK3CA-mutated, ABC, or MBC?

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

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

Patients who received alpelisib-fulvestrant had significantly prolonged progression-free survival (PFS), the primary study end point (11.0 months v 5.7 months, P , .001). This benefit was not observed in the group of patients without PIK3CA-mutated breast cancer who received alpelisib-fulvestrant. In safety analyses, the most frequent AEs observed in the overall population were hyperglycemia and rash. Grade 3 hyperglycemia occurred in 36.6% of patients in the alpelisib-fulvestrant group and in 0.7% of patients in the placebo-fulvestrant group; rash occurred in 9.9% of patients in the alpelisib-fulvestrant group and 0.3% of patients in the placebo-fulvestrant group. Grade 3 diarrhea occurred in 6.7% of patients who received alpelisib-fulvestrant versus 0.3% of patients who received placebo-fulvestrant.

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

[…]

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

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

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

inhibitor before initiation of PIK3CA- or mammalian target of rapamycin (mTOR)-targeted therapy.

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

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

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

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

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

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

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

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

There are limited data for the use of everolimus after CDK4/ 6 inhibitors. Following CDK4/6 inhibitor therapy, the duration of treatment with everolimus paired with ongoing ET is diminished compared with that seen among patients without prior CDK4/6 inhibitor

treatment, with clinical evidence for 4 to 5 months' treatment duration.54 Thus, everolimus may be an option in second or subsequent lines of endocrine-based therapy, although the clinical benefits in contemporary practice in patients treated with CDK4/6 inhibitors are not well defined.

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

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

Recommendation 2.3
Patients with metastatic HR-positive but HER2-negative breast cancer with germline BRCA1 or 2 mutations who are no longer benefiting from ET may be offered an oral PARP inhibitor in the first-line through to third-line setting rather than chemotherapy (type: evidence-based; benefits outweigh harms; evidence quality: intermediate; strength of recommendation: strong).

Literature review and analysis

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

patients who received olaparib was 36.6%; it was 50.5% in the group that received standard chemotherapy. HRQoL measures were also superior with olaparib than with chemotherapy: treatment with olaparib lead to improvements in the functioning, symptoms, and HRQoL. One exception was the nausea or vomiting symptom score, which was worse among patients who received olaparib.49

[…]

Clinical interpretation

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

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Clinical Question 3: What is the role of CDK4/6 inhibitors in the treatment of patients with HR-positive MBC?

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

Literature review and analysis.

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

[…]

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

awaited, but crossover to CDK4/6 inhibitors from placebo following disease progression may affect these results.

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

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

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

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Recommendation 3.2

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

Literature review and analysis. […]

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

[…]

Clinical interpretation. The survival benefits seen with the addition of CDK4/6 inhibitors to fulvestrant in the chemotherapy naive second-line setting are impressive, and along with tolerability and maintained or improved quality of life, have further solidified the role of these targeted agents in the treatment of metastatic HR-positive breast cancer. For the majority of patients, treatment with CDK4/6 inhibitors in the first-line setting is preferable, but combinations with fulvestrant may be optimal for those intolerant to AIs; for those who have developed recurrent disease within 1 year of last adjuvant AI therapy; or for those for whom single-agent ET is the preferred first-line treatment. We learned inadvertently from these trials that prior chemotherapy affects PFS and OS in response to subsequent ET. In PALOMA-3, approximately one third of patients had received prior chemotherapy, compared with none in MONARCH-2 and MONALEESA-3. Interestingly, the PFS to

fulvestrant alone was shorter in PALOMA-3 compared with the other two trials, although the impact of adding the CDK4/6 inhibitor was similar by hazard ratios across all three trials. A subset analysis also suggests that the survival impact in PALOMA-3 was limited to those patients who had not received prior chemotherapy. These data serve to further emphasize the importance of sequential ET before use of chemotherapy for the treatment of HR-positive MBC, except in situations with primary endocrine resistance or immediately life-threatening visceral disease.

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

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

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Update: Moy MD et al., 2022 [4]

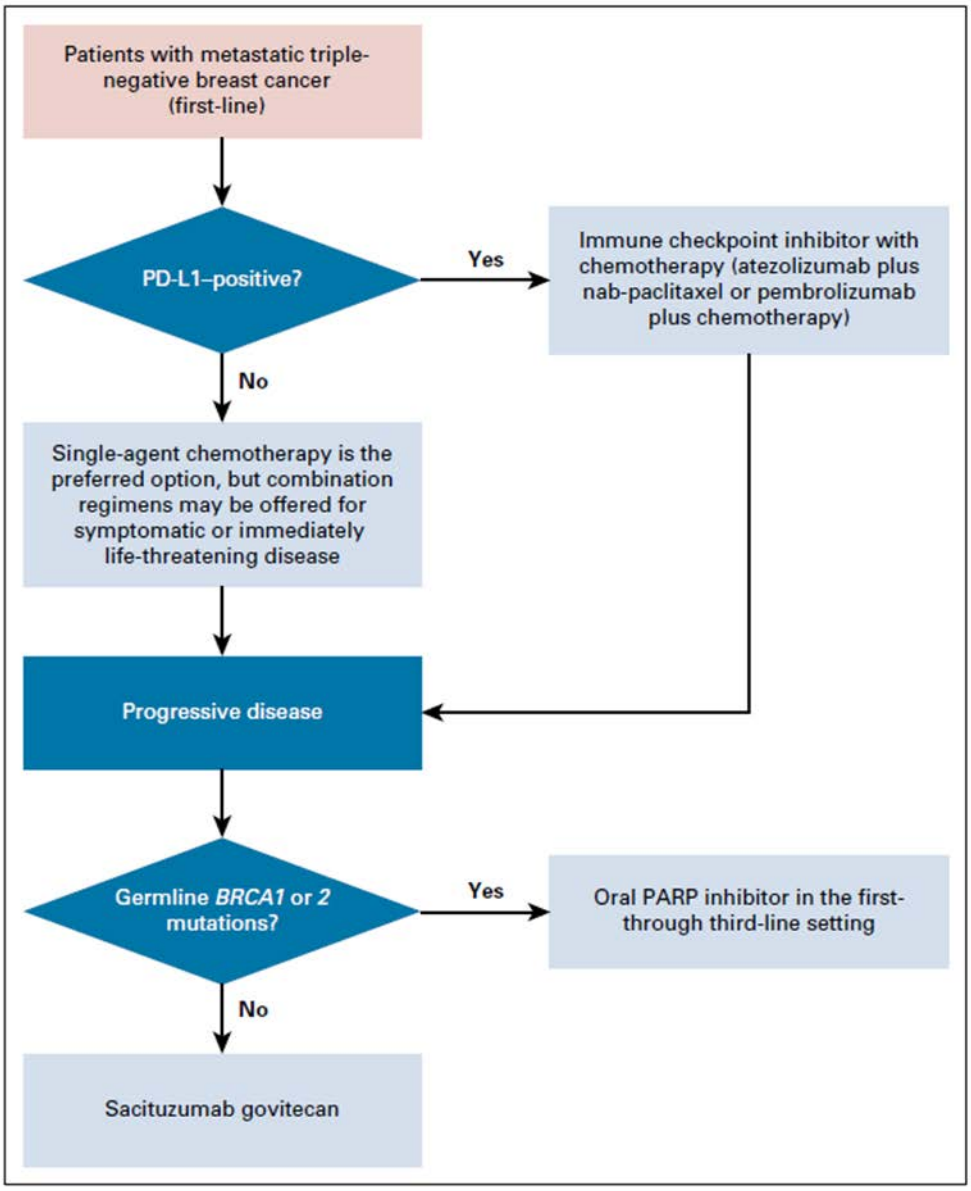

FIG 1. Treatment algorithm for first-line treatment for patients with metastatic triple-negative breast cancer. PARP, poly (ADP-ribose) polymerase.

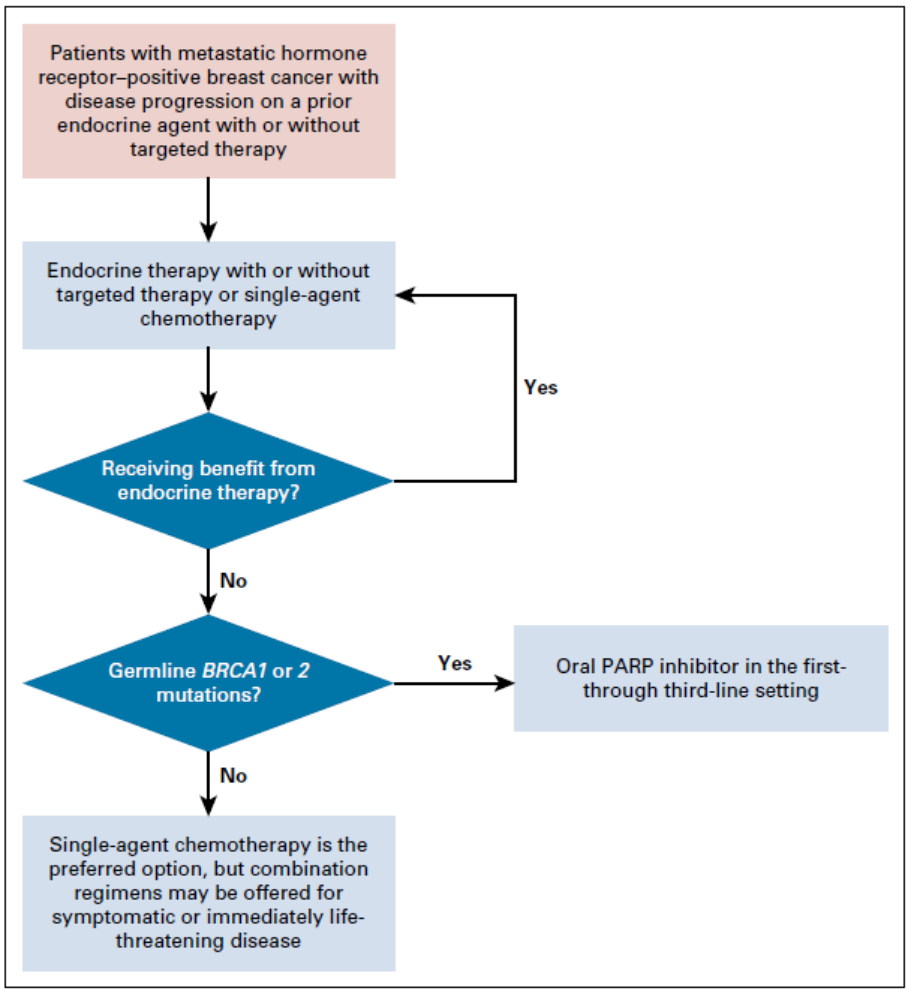

FIG 2. Treatment algorithm for chemotherapy and targeted therapy for patients with HER2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor–negative. HER2, human epidermal growth factor receptor 2; PARP, poly (ADP-ribose) polymerase; PD-L1, programmed cell death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

Recommendations

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

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

Literature update and analysis: The systematic review identified three clinical trials and a meta-analysis addressing optimal therapy for women with metastatic HR-positive breast cancer with progressive disease on a nonsteroidal AI. […]

Clinical interpretation: The treatment choice between ET with targeted agents such as CDK 4/6 inhibitors, everolimus, and alpelesib and single-agent chemotherapy should be based on individualized assessments of risks and benefits, prior treatment response, tumor burden, pace of disease, and patient preferences. Individual considerations should include the robustness of the patient's prior response to ET, QoL, side effects, comorbid conditions,

and out-of-pocket treatment costs. Notably, the results of the systematic review should be interpreted with caution since there were significant limitations, including stage migration and unmeasured variables that might have led to patients enrolling in a chemotherapy rather than an ET clinical trial.

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

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

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

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

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

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

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

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

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

regarding goals of care. The conversation about integration of supportive care and eventual consideration of hospice care should start early in the management of MBC.

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 01 of 12, January 2024) am 29.01.2024

#	Suchfrage
1	[mh ^"Breast Neoplasms"]
2	(breast*):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR malignan*):ti,ab,kw
4	((local* NEXT advanced) OR metastat* OR metastas* OR recurren* OR relaps* OR progression*):ti,ab,kw
5	(#1 OR (#2 AND #3)) AND #4
6	#5 with Cochrane Library publication date from Jan 2019 to present, in Cochrane Reviews

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#	Suchfrage
1	breast neoplasms/TH[majr]
2	breast[tiab]
3	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR malignan*[tiab]
	ohne lesion* - da das nur für Frühformen gilt nicht für metast.
4	advance*[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR relaps*[tiab] OR progression*[tiab] OR progressive*[tiab] OR neoplasm metastasis/TH OR neoplasm recurrence, local/TH
5	treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR chemotherapy[tiab] OR chemotherapies[tiab] OR immunotherapy[tiab] OR immunotherapies[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab] OR Combined Modality Therapy/TH
6	#2 AND #3 AND #4 AND #5
7	#1 AND #4
8	#6 OR #7
9	(#8) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR

#	Suchfrage
	studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR technical report[ptyp] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
10	((#9) AND ("2019/01/01"[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] OR preprint[pt])

Leitlinien in Medline (PubMed) am 29.01.2024

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

Iterative Handsuche nach grauer Literatur, abgeschlossen am 30.01.2024

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

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4. **Moy B, Rumble RB, Carey LA.** Chemotherapy and targeted therapy for human epidermal growth factor receptor 2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor-negative: ASCO guideline rapid recommendation update. J Clin Oncol 2022;40(26):3088-3090.
5. **Moy B, Rumble RB, Come SE, Davidson NE, Di Leo A, Gralow JR, et al.** Chemotherapy and targeted therapy for patients with human epidermal growth factor receptor 2-negative metastatic breast cancer that is either endocrine-pretreated or hormone receptor-negative: ASCO guideline update. J Clin Oncol 2021;39(35):3938-3958.
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7. **National Institute for Health and Care Excellence (NICE).** Evidence review for the effectiveness of different external beam hypofractionation radiotherapy regimens in people with early-stage or locally advanced invasive breast cancer: early and locally advanced breast cancer: diagnosis and management: evidence review M [online]. London (GBR): NICE; 2023. [Zugriff: 20.02.2024]. URL: https://www.nice.org.uk/guidance/ng101/evidence/m-effectiveness-of-different-external-beam-hypofractionation-radiotherapy-regimens-in-people-with-earlystage-or-locally-advanced-invasive-breast-cancer-pdf-13071102158.
8. **Shao F, Duan Y, Zhao Y, Li Y, Liu J, Zhang C, et al.** PARP inhibitors in breast and ovarian cancer with BRCA mutations: a meta-analysis of survival. Aging (Albany NY) 2021;13(6):8975-8988.
9. **Sun X, Wang X, Zhang J, Zhao Z, Feng X, Liu L, et al.** Efficacy and safety of PARP inhibitors in patients with BRCA-mutated advanced breast cancer: A meta-analysis and systematic review. Breast 2021;60:26-34.
10. **Sun X, Xu S, Li Y, Lv X, Wei M, He M.** Efficacy and safety of PARP inhibitors in the treatment of BRCA-mutated breast cancer: an updated systematic review and meta-analysis of randomized controlled trials. Expert Rev Clin Pharmacol 2023;16(3):245-256.
11. **Wang J, Zhang Y, Yuan L, Ren L, Zhang Y, Qi X.** Comparative efficacy, safety, and acceptability of single-agent poly (ADP-ribose) polymerase (PARP) inhibitors in BRCA-mutated HER2-negative metastatic or advanced breast cancer: a network meta-analysis. Aging (Albany NY) 2020;13(1):450-459.

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

Verfahrens-Nr.: 2024-B-016

Verfasser	
Institution	Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) der Deutschen Krebsgesellschaft (DKG) Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) Deutsche Gesellschaft für Senologie (DGS)
Sachverständige	
Datum	19. März 2024

Indikation
Zur Behandlung erwachsener Patienten mit inoperablem oder metastasiertem HR-positivem und HER2-negativem (IHC 0, IHC 1+ oder ICH 2+/ISH-) Brustkrebs, deren Erkrankung unter der endokrinen Therapie fortschreitet und die für diese nicht mehr geeignet sind und die mindestens eine zusätzliche systemische Therapie im inoperablen oder metastasierten Stadium der Erkrankung erhalten haben.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?
Zusammenfassung Der Standard in der Behandlung von Patientinnen und Patienten (Pat.) mit inoperablem oder metastasiertem, HR-positivem, HER2-negativem (IHC 0, IHC 1+ oder ICH 2+/ISH-) Mammakarzinom, deren Erkrankung unter der endokrinen Therapie fortschreitet und die für diese nicht mehr geeignet sind und die mindestens eine zusätzliche systemische Therapie im inoperablen oder metastasierten Stadium der Erkrankung erhalten haben, ist eine Therapie nach ärztlicher Maßgabe unter besonderer Berücksichtigung der - Biologie der Erkrankung - Krankheitsaktivität / Symptomatik - Vortherapie - Komorbidität. Optionen sind - Endokrine Therapie: Aromatasehemmer, Fulvestrant, Exemestan/Everolimus - ESR1mut: Elacestrant - PIK3CAmut: Fulvestrant/Alpelisib

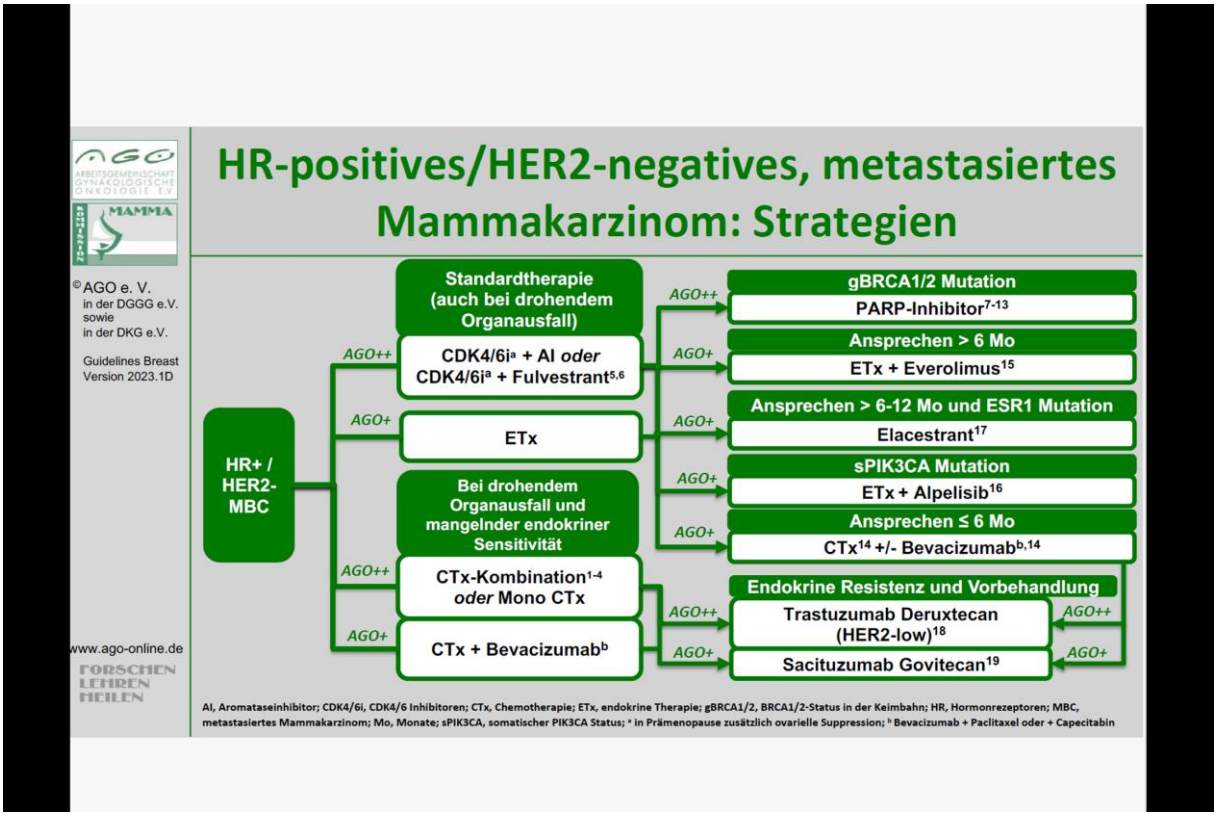
- gBRCAmut: Olaparib oder Talazoparib
- Gabe eines Antikörper-Wirkstoff-Konjugats wie Sacituzumab Govitecan (nach zwei Vortherapien) oder Trastuzumab Deruxtecan (bei HER2 low-Status nach einer Vortherapie oder Rezidiv innerhalb von 6 Monaten nach Abschluss einer adj. Chemotherapie)
- Chemotherapie: Capecitabin, Vinorelbin, Eribulin, (liposomale) Anthrazykline, ggf. auch Retherapie mit Taxanen. Capecitabin und Taxane können ggf. um Bevacizumab erweitert werden.

<u>Fragestellu</u>

Der therapeutische Standard hat sich seit unserer letzten Expertise zu dieser Indikation nicht grundlegend geändert. Das bereits erwähnte Elacestrant ist jetzt zugelassen und steht auch für das Patientenkollektiv dieser Anfrage zur Verfüfung.

<u>Stand des Wissens</u>

Ein Algorithmus zu den Therapiestrategien beim HR+/HER2-, metastasierten Mammakarzinom ist in der Abbildung dargestellt [1].



Bei 30-40% der Pat. entsteht unter Therapie mit Aromatase-Inhibitoren eine erworbene endokrine Resistenz. Verantwortlich sind häufig Mutationen im ESR1-Gen [2]. Ein Wechsel der endokrinen Therapie kann diese Resistenz umgehen. Konzepte mit neuen, oralen SERD (Selective Estrogen Receptor Degrader) werden gezielt bei Pat. mit erworbener endokriner Resistenz und Nachweis von

ESR1-Mutationen getestet. Im September 2023 wurde Elacestrant für die EU zugelassen. Basis der Zulassung war die randomisierte Phase-III-Studie EMERALD zum Vergleich von Elacestrant vs endokriner Therapie (Standard of Care, SOC) [3]. Hier führte Elacestrant bei Pat. mit aktivierender ESR1-Mutation gegenüber endokriner Therapie (Fulvestrant, AI) zur signifikanten Verlängerung des progressionsfreien Überlebens. Elacestrant führte nicht zur Steigerung der Ansprechrate, zur Verlängerung der Gesamtüberlebenszeit oder zur Verbesserung von Parametern der Lebensqualität. Die Rate schwerer unerwünschter Ereignisse wurde durch Elacestrant gering gesteigert.
Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
Ja, diese sind oben dargestellt.

Referenzliste:

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