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-064-z Pembrolizumab

Stand: Juli 2024

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Pembrolizumab **[zur neoadjuvanten und adjuvanten Behandlung des triple-negativen Mammakarzinoms]** **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“. Nicht berücksichtigt wurden Arzneimittel mit expliziter Zulassung für das HER2-positive sowie das HR-positive Mammakarzinom.
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:** – Olaparib: Beschluss vom 16. Februar 2023 – Pembrolizumab: Beschluss vom 15. Dezember 2022 **Richtlinie zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Absatz 2 SGB V; Anlage 3**; Inkrafttreten: 7. Oktober 2020 – Anforderungen an die Ausgestaltung von strukturierten Behandlungsprogrammen für Patientinnen mit Brustkrebs **Richtlinie zu Untersuchungs- und Behandlungsmethoden im Krankenhaus** (Richtlinie Methoden Krankenhausbehandlung); in Kraft getreten am 20. März 2019 – Protonentherapie beim Mammakarzinom **Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie** – Wirkstoffe, die in zulassungsüberschreitenden Anwendungen (Off-Label-Use) nicht verordnungsfähig sind: – Gemcitabin in der Monotherapie beim Mammakarzinom der Frau
Die Vergleichstherapie soll nach dem allgemein anerkannten	Siehe systematische Literaturrecherche

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

Pembrolizumab
[zur neoadjuvanten und adjuvanten Behandlung des triple-negativen Mammakarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab L01XC18 Keytruda	zugelassenes Anwendungsgebiet: Keytruda ist in Kombination mit Chemotherapie zur neoadjuvanten und anschließend nach Operation als Monotherapie zur adjuvanten Behandlung des lokal fortgeschrittenen oder frühen triple-negativen Mammakarzinoms mit hohem Rezidivrisiko bei Erwachsenen angezeigt.
Cyclophosphamid L01AA01 Endoxan	Endoxan ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - Adjuvante Therapie des Mammakarzinoms nach Resektion des Tumors beziehungsweise Mastektomie - […]
Docetaxel L01CD02 generisch	Brustkrebs Docetaxel ist in Kombination mit Doxorubicin und Cyclophosphamid angezeigt für die adjuvante Therapie von Patientinnen mit: - operablem, nodal positivem Brustkrebs, - operablem, nodal negativem Brustkrebs.

	Bei Patientinnen mit operablem, nodal negativem Brustkrebs sollte die adjuvante Therapie auf solche Patientinnen beschränkt werden, die für eine Chemotherapie gemäß den international festgelegten Kriterien zur Primärtherapie von Brustkrebs in frühen Stadien infrage kommen. […]
Doxorubicin L01DB01 z.B. Adrimedac	Doxorubicin ist ein Zytostatikum, das bei folgenden neoplastischen Erkrankungen angezeigt ist: - Mammakarzinom. - […] Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Epirubicin L01DB03 generisch	Epirubicin wird zur Behandlung verschiedener Neoplasien eingesetzt, einschließlich: - Mammakarzinom - […]
Fluorouracil L01BC02 Ribofluor	- Adjuvante Therapie des primären invasiven Mammakarzinoms - […]
Methotrexat L01BA01 z.B. Methotrexat-medac	Mammakarzinome: - in Kombination mit anderen zytostatischen Arzneimitteln zur adjuvanten Therapie nach Resektion des Tumors oder Mastektomie sowie zur palliativen Therapie im fortgeschrittenen Stadium. […]
Paclitaxel L01CD01 generisch	<u>Mammakarzinom</u> Im Rahmen einer adjuvanten Therapie ist Paclitaxel zur Behandlung von Patientinnen mit Lymphknoten-positivem Mammakarzinom nach vorangegangener Therapie mit Anthracyclinen und Cyclophosphamid (AC) angezeigt. Die adjuvante Behandlung mit Paclitaxel kann als Alternative zu einer verlängerten AC-Therapie betrachtet werden. […]
Olaparib L01XK01 Lynparza	Lynparza wird angewendet als: - Monotherapie oder in Kombination mit einer endokrinen Therapie für die adjuvante Behandlung von erwachsenen Patienten mit Keimbahn-BRCA1/2-Mutationen, die ein HER2-negatives Mammakarzinom im Frühstadium mit hohem Rezidivrisiko haben und zuvor mit neoadjuvanter oder adjuvanter Chemotherapie behandelt wurden. […]

Vincristin L01CA02 Vincristinsulfat Teva	Vincristinsulfat-Teva 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: - Soliden Tumoren, einschließlich (metastasierendem) Mammakarzinom. - […]

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-064z (Pembrolizumab)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	17. Juni 2024

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse events
ASCO	American Society of Clinical Oncology
AT	anthracycline and taxane
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BRCA	breast cancer gene
DFS	Disease-free survival
ECRI	ECRI Guidelines Trust
EK	Expertenkonsens
EFS	Event-free survival
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HER-2	Human epidermal growth factor receptor
HR	Hazard Ratio
HRD	homologous recombination deficiency
ICI	immune checkpoint inhibitors
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI (CI)	Konfidenzintervall
LoE	Level of Evidence
NACT	neoadjuvant chemotherapy
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OS	Overall survival
pCR	pathological complete response
PD-1	programmed death 1 cell surface receptor
PgR	Progesteronrezeptor
QoL	Quality of Life
RCT	Randomized controlled trials
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
TNBC	Triple-negative breast cancer
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Neoadjuvante und adjuvante Behandlung des triple-negativen Mammakarzinoms

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

2 Systematische Recherche

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

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 13.03.2024 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 4978 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 14 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Mason SRE et al., 2023 [11].

Platinum-based chemotherapy for early triple-negative breast cancer (Review)

Fragestellung

To evaluate the benefits and harms of platinum-based chemotherapy as adjuvant and neoadjuvant treatment in people with early triplenegative breast cancer.

Methodik

Population:

- participants aged 18 years or older with early TNBC

Intervention/Komparator:

- any chemotherapy regimen that contained platinum chemotherapy compared to regimens without platinum chemotherapy
- either adjuvant (postsurgery) or neoadjuvant (presurgery) delivery of chemotherapy for early TNBC

Endpunkte:

- primary: DFS, OS
- secondary: pCR, completion of regimens, any grade III/IV toxicity, QoL

Recherche/Suchzeitraum:

- up to the 4 April 2022
- standard, extensive Cochrane search methods

Qualitätsbewertung der Studien:

- Cochrane's RoB 1 tool

Ergebnisse

Anzahl eingeschlossener Studien:

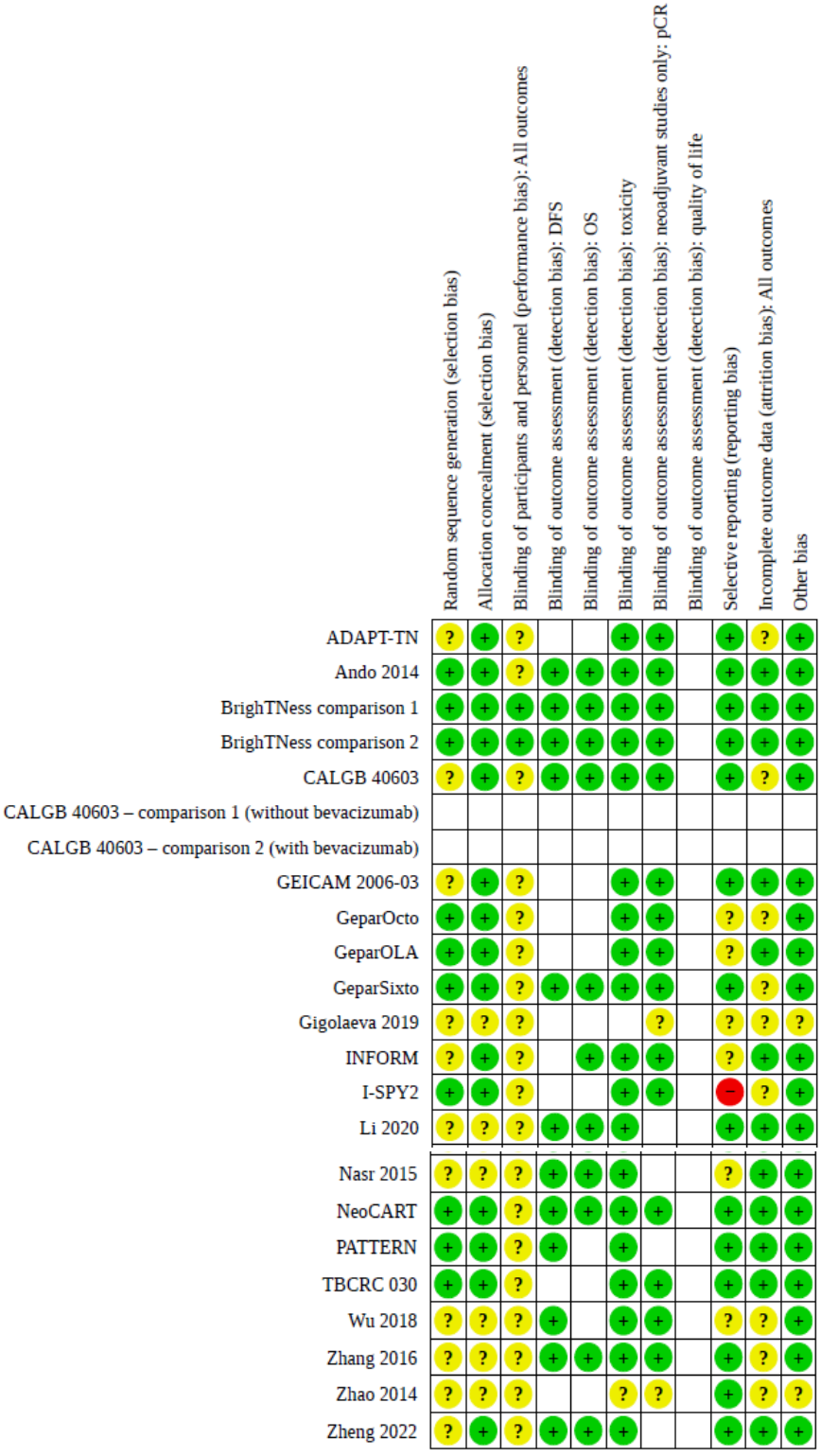
- The 20 included studies, involving 4468 participants, contributed to 21 treatment comparisons

Charakteristika der Population/Studien:

- 15 studies (16 treatment comparisons) involved neoadjuvant chemotherapy with one study combining neoadjuvant and adjuvant therapy, and four studies involved adjuvant chemotherapy
- 17 studies (18 treatment comparisons) used carboplatin, two studies used cisplatin and one study used lobaplatin
- nine studies had an anthracycline-free intervention arm
- six studies stratified results for BRCA mutations, one trial for HRD status, and three by lymph node status

- six studies (seven treatment comparisons) used the same chemotherapy backbone (i.e. platinum agent plus regimen A versus regimen A) and 14 trials used a different backbone (i.e. regimen A versus regimen B)

Qualität der Studien:



Studienergebnisse:

Neoadjuvante Therapie

Summary of findings 1. Platinum-containing chemotherapy compared to chemotherapy without platinum in neoadjuvant therapy for early triple-negative breast cancer

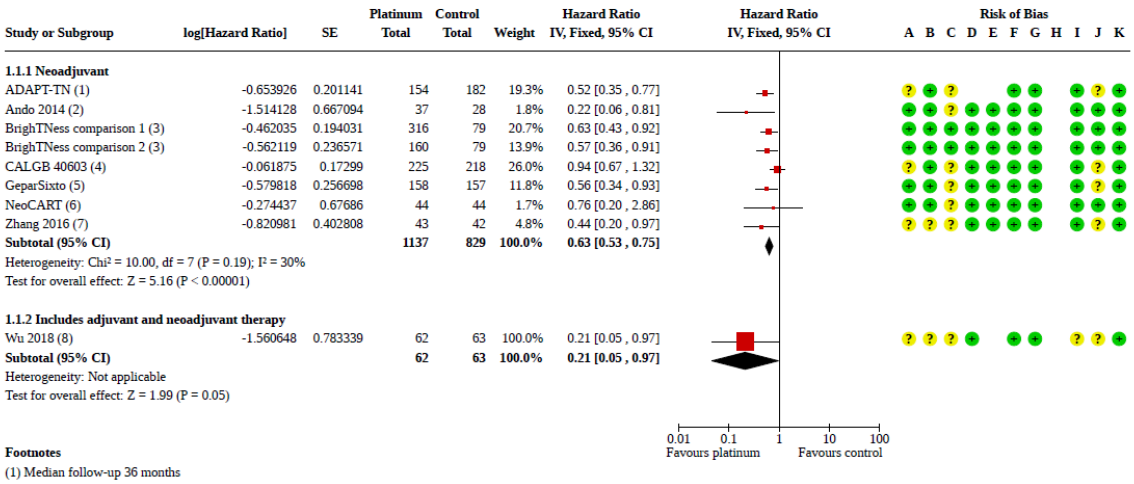
Platinum-containing chemotherapy compared to chemotherapy without platinum in neoadjuvant therapy for early triple-negative breast cancer

Patient or population: neoadjuvant therapy for early triple-negative breast cancer
Setting: outpatient
Intervention: platinum-containing chemotherapy
Comparison: chemotherapy without platinum

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy without platinum	Risk with platinum-containing chemotherapy				
DFS at 2 years assessed with: risk of recurrence follow-up: range 3 years to 7.9 years	**Study population**		**HR 0.63** (0.53 to 0.75)	1966 (8 RCTs)	⊕⊕⊕⊕ **High**	—
	210 per 1000	**138 per 1000** (117 to 162)				
DFS at 5 years follow-up: range 3 years to 7.9 years	**Study population**		**HR 0.63** (0.53 to 0.75)	1966 (8 RCTs)	⊕⊕⊕⊕ **High**	—
	301 per 1000	**202 per 1000** (173 to 235)				
OS at 2 years assessed with: risk of death follow-up: range 1.7 years to 7.9 years	**Study population**		**HR 0.69** (0.55 to 0.86)	1973 (8 RCTs)	⊕⊕⊕⊕ **High**	—
	48 per 1000	**33 per 1000** (27 to 41)				
OS at 5 years follow-up: range 1.7 years to 7.9 years	**Study population**		**HR 0.69** (0.55 to 0.86)	1973 (8 RCTs)	⊕⊕⊕⊕ **High**	—
	190 per 1000	**135 per 1000** (110 to 166)				
Pathological complete response follow-up: range 6 weeks to 9.5 months	305 per 1000	**440 per 1000** (400 to 485)	**RR 1.44** (1.31 to 1.59)	3083 (15 RCTs)	⊕⊕⊕⊕ **High**	—

*__The risk in the intervention group__ (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).

- DFS
  - Platinum based chemotherapy improved DFS compared to non-platinumcontaining chemotherapy (HR 0.63, 95% CI 0.53 to 0.75; P < 0.001, I^2= 30%; 7 studies, 8 treatment comparisons; high-certainty evidence). (n=1966 people, ca. 500 DFS events)

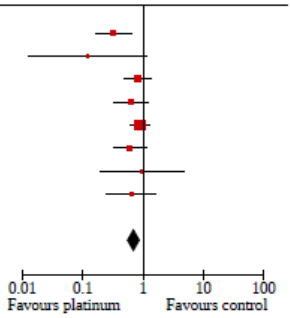


Footnotes
(1) Median follow-up 36 months
(2) Median follow-up 6.6 years
(3) Median follow-up 4.5 years
(4) Median follow-up 7.9 years
(5) Median follow-up 47.3 months
(6) Median follow-up 37 months
(7) Median follow-up 55 months. Includes relapse events only
(8) Median follow-up not reported

- OS
  - Platinum chemotherapy reduced mortality (HR 0.69, 95% CI 0.55 to 0.86; P = 0.001, I^2 = 29%; 7 studies, 8 treatment comparisons; high-certainty evidence) (n=1973 participants, 307 deaths)

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
ADAPT-TN (1)	-1.139434	0.349056	154	182	10.8%	0.32 [0.16 , 0.63]
Ando 2014 (2)	-2.120264	1.164396	37	38	1.0%	0.12 [0.01 , 1.18]
BrighTNess comparison 1 (3)	-0.198451	0.269406	316	79	18.1%	0.82 [0.48 , 1.39]
BrighTNess comparison 2 (3)	-0.462035	0.331456	160	79	12.0%	0.63 [0.33 , 1.21]
CALGB 40603 (4)	-0.116534	0.186911	225	218	37.6%	0.89 [0.62 , 1.28]
GeparSixto (5)	-0.510826	0.319588	158	154	12.9%	0.60 [0.32 , 1.12]
NeoCART (6)	-0.040822	0.821693	44	44	1.9%	0.96 [0.19 , 4.81]
Zhang 2016 (7)	-0.446287	0.479853	43	42	5.7%	0.64 [0.25 , 1.64]
Total (95% CI)			**1137**	**836**	**100.0%**	**0.69 [0.55 , 0.86]**

Heterogeneity: Chi² = 9.82, df = 7 (P = 0.20); I² = 29%
Test for overall effect: Z = 3.23 (P = 0.001)
Test for subgroup differences: Not applicable



Footnotes
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(5) Median follow-up 47.3 months
(6) Median follow-up 37 months
(7) Median follow-up 55 months

- pCR
  - Platinum chemotherapy was associated with a large improvement in the rate of pCR (RR 1.44, 95% CI 1.31 to 1.59, P = 0.009, I^2 = 52%; 15 studies, 16 treatment comparisons, 3083 participants; high certainty evidence)

Adjuvante Therapie

Summary of findings 2. Platinum-containing chemotherapy compared to chemotherapy without platinum in adjuvant therapy for early triple-negative breast cancer

Platinum-containing chemotherapy compared to chemotherapy without platinum in adjuvant therapy for early triple-negative breast cancer

Patient or population: adjuvant therapy for early triple-negative breast cancer
Setting: outpatient
Intervention: platinum-containing chemotherapy
Comparison: chemotherapy without platinum

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy without platinum	Risk with platinum-containing chemotherapy				
DFS at 2 years assessed with: risk of recurrence follow-up: range 4.3 years to 8 years	**Study population**		**HR 0.69** (0.54 to 0.88)	1256 (4 RCTs)	⊕⊕⊕⊕ **High**	—
	148 per 1000	**105 per 1000** (83 to 131)				
DFS at 5 years follow-up: range 4.3 years to 8 years	**Study population**		**HR 0.69** (0.54 to 0.88)	1256 (4 RCTs)	⊕⊕⊕⊕ **High**	—
	169 per 1000	**120 per 1000** (95 to 150)				
OS at 2 years assessed with: risk of death follow-up: range 4.3 years to 8 years	**Study population**		**HR 0.70** (0.50 to 0.96)	1256 (4 RCTs)	⊕⊕⊕⊕ **High**	—
	53 per 1000	**37 per 1000** (27 to 50)				

OS at 5 years follow-up: range 4.3 years to 8 years	**Study population**		**HR 0.70** (0.50 to 0.96)	1256 (4 RCTs)	⊖⊖⊖⊖ **High**	–
	81 per 1000	**57 per 1000** (41 to 78)				

*__The risk in the intervention group__ (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; **DFS:** disease-free survival; **HR:** hazard ratio; **OS:** overall survival; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Anmerkung/Fazit der Autoren

- Platinum-based chemotherapy using carboplatin in the adjuvant or neoadjuvant setting improved long-term outcomes of DFS and OS in early TNBC, regardless of the examined subgroups. This was at the cost of more frequent chemotherapy delays and dose reductions, and greater haematological toxicity.
- Though there are certainly increased haematological toxicities associated with platinum chemotherapy, permanent toxicity such as grade III/IV neuropathy and treatment-related death were not different between groups.
- These findings support the use of platinum-based chemotherapy for people with early TNBC. The optimal dose and regimen are not defined by this analysis, but there is a suggestion that similar relative benefits result from the addition of carboplatin to either anthracycline-free regimens or those containing anthracycline agents.

Kommentare zum Review

- Notably, the BrighTNess study has more than one intervention that was split into two treatment comparisons (BrighTNess comparison 1; BrighTNess comparison 2), which is why the number of studies and treatment comparisons included in an analysis may differ.
- Es liegt ein weiteres SR zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Feng et al. 2022 [3] (neoadjuvante Behandlung)

3.2 Systematische Reviews

Elmakaty I et al., 2023 [2].

Comparative efficacy and safety of PD-1/PD-L1 inhibitors in triple negative breast cancer: a systematic review and network meta-analysis of randomized controlled trials

Fragestellung

- to compare the efficacy and safety of inhibitors of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) in treating TNBC.

Methodik

<u>Population:</u>

- patients with confirmed TNBC

Intervention/ Komparator:

- FDA-approved PD-1/PD-L1 inhibitors vs.
  - a different ICI,
  - multiple agents' chemotherapy regimen,
  - single agent chemotherapy regimen or
  - placebo

Endpunkte:

- OS, PFS, pCR, AEs

Recherche/Suchzeitraum:

- All databases were searched from the inception date until the 2nd of November 2022

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool (RoB 2.0)

Ergebnisse

Anzahl eingeschlossener Studien:

- 12 RCTs. (n= 5324 patients)

Charakteristika der Population:

- All 12 trials included were two-arm trials that reported results from 5324 patients with median ages ranging from 48 to 59.1 years. There were seven phase III trials and five phase II trials.
- Six studies looked at the effect of PD-1/PD-L1 inhibitors on unresectable, invasive, or metastatic (advanced) TNBC [33, 35-37, 40, 43], **four looked at non-metastatic/early-stage TNBC [39, 41, 42, 44],** and two looked at treated metastatic TNBC for maintenance therapy [34, 38].

Table 1 Characteristics of included trials

Trial	NCT	First author	Year	Phase	No. of TNBC patients	Median age	Cancer stage	ICI used	Treatment arm	Control arm	Dose of ICI used	Duration of ICI used	Median follow-up time	PD-L1 expression positivity
SAFIR02-BREAST [38]	NCT02299999	Bachelot	2021	II	82	56 years	Metastatic treated TNBC for maintenance	Durvalumab	Durvalumab	Continuation of induction Chemotherapy	10 mg/kg q2wk	7 cycles	19.7 months	52%
KEYNOTE-355 [35]	NCT02819518	Cortes	2020	III	847	53.5 years	Untreated locally recurrent inoperable or metastatic TNBC	Pembrolizumab	Pembrolizumab + Investigator's choice chemotherapy	Placebo + Investigator's choice chemotherapy	200 mg q3wk	Up to 35 administrations or disease progression	26 months	75%
Garrido-Castro [43]	NCT03414684	Garrido-Castro	2022	II	78	59.1 years	Metastatic TNBC	Nivolumab	Nivolumab + Carboplatin	Carboplatin	360 mg IV q3wk	Not mentioned	23.5 months	39%
NeoTRIPaPDL1 [36]	NCT02620280	Gianni	2022	III	280	50 years	Invasive TNBC	Atezolizumab	Atezolizumab + Carboplatin + Nab-paclitaxel	Carboplatin + Nab-paclitaxel	1200 mg IV q3wk	8 cycles	On-going	56%
GeparNuevo [37]	NCT02685059	Loibl	2022	II	174	49.5 years	Primary, non-metastatic invasive TNBC	Durvalumab	Durvalumab + Nab-paclitaxel then epirubicin/cyclophosphamide	Placebo + Nab-paclitaxel then epirubicin/cyclophosphamide	First dose 0.75 g then 1.5 g q4wk	6 cycles	43.7 months	87%
IMpassion131 [33]	NCT03125902	Miles	2021	III	651	54 years	Unresectable locally or metastatic TNBC	Atezolizumab	Atezolizumab + Paclitaxel	Placebo + Paclitaxel	840 mg day 1,15 q4wk	6 cycles	14.5 months	45%
IMpassion031 [39]	NCT03197935	Mittendorf	2020	III	333	51 years	Early-stage TNBC	Atezolizumab	Atezolizumab + Nab-paclitaxel/ Doxorubicin/ Cyclophosphamide	Placebo + Nab-paclitaxel + Doxorubicin/ Cyclophosphamide	840 mg IV q2wk	6 cycles	20 months	46%
IMpassion130 [40]	NCT02425891	Schmid	2022	III	902	55 years	Advanced TNBC	Atezolizumab	Atezolizumab + Nab-paclitaxel	Placebo + Nab-paclitaxel	840 mg day 1,15 q4wk	6 cycles	12.9 months	41%

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Table 1 (continued)

Trial	NCT	First author	Year	Phase	No. of TNBC patients	Median age	Cancer stage	ICI used	Treatment arm	Control arm	Dose of ICI used	Duration of ICI used	Median follow-up time	PD-L1 expression positivity
Nci 10,013 [44]	NCT02883062	Ademuyiwa	2021	II	67	52 years	Stage II-III TNBC	Atezolizumab	Carboplatin + Paclitaxel	Atezolizumab + Carboplatin + Paclitaxel	1200 mg q3wk	4 cycles	6 months	Not done yet
KEYNOTE-522 [41]	NCT03036488	Schmid	2020	III	1174	48–49 years	Primary, non-metastatic TNBC (Stage II and III)	Pembrolizumab	Pembrolizumab + Paclitaxel/Carboplatin + Doxorubicin OR Epirubicin/Cyclophosphamide	Placebo + Paclitaxel/Carboplatin + Doxorubicin OR Epirubicin/Cyclophosphamide	200 mg IV q3wk	Neoadjuvant up to 8 cycles	15.5 months	84%
KEYNOTE-119 [34]	NCT02555657	Winer	2021	III	622	52 years	Metastatic treated TNBC	Pembrolizumab	Pembrolizumab	Investigator's choice mono-chemotherapy	200 mg IV q3wk	Up to 35 administrations	31.5 months	65%
I-SPY2 Trial [42]	NCT01042379	Nanda	2020	II	114	50 years	Stage II-III TNBC	Pembrolizumab	Pembrolizumab + Paclitaxel + Doxorubicin/Cyclophosphamide	Paclitaxel + Doxorubicin/Cyclophosphamide	200 mg IV q3wk	4 cycles	3 yrs	Not done yet

NCT National Clinical Trial; *TNBC* Triple Negative Breast Cancer; *ICI* Immune Checkpoint Inhibitor; *PD-L1*, Programmed Cell Death Ligand 1; q2wk. once every 2 weeks; q3wk. once every 3 weeks; q4wk. once every 4 weeks

Gemeinsamer Bundesausschuss

Qualität der Studien:

B Unique ID	Study ID	D1	D2	D3	D4	D5	Overall
Garrido-Castro	NCT03414684	!	+	+	!	+	!
NeoTRIPaPDL1	NCT002620280	+	+	+	!	+	!
GeparNuevo	NCT02685059	+	+	+	+	+	+
Nci 10013	NCT02883062	!	+	+	!	+	!
KEYNOTE-355	NCT02819518	+	+	+	+	+	+
SAFIR02-BREAST	NCT02299999	+	+	+	!	+	!
KEYNOTE-522	NCT03036488	+	+	+	+	+	+
KEYNOTE-119	NCT02555657	+	+	+	!	-	-
I-SPY2 Trial	NCT01042379	+	+	+	!	+	!
IMpassion031	NCT03197935	!	+	+	+	+	!
IMpassion130	NCT02425891	+	+	+	+	+	+
IMpassion131	NCT03125902	+	+	+	+	+	+

D1	Randomisation process	+	Low risk
D2	Deviations from the intended intervention	!	Some concerns
D3	Missing outcome data	-	High risk
D4	Measurement of the outcome		
D5	Selection of the reported result		

Studienergebnisse:

- pCR: The number of patients who achieved a complete response was reported in six trials [36, **39, 41, 42, 44 (Anm. FBMed: non-metastatic/early-stage TNBC)**]: three on Atezolizumab [36, 39, 44], two on Pembrolizumab [41, 42], and one on Durvalumab [37], all in the neoadjuvant setting to chemotherapy. Pembrolizumab in combination with chemotherapy significantly increased the odds of achieving pCR compared to chemotherapy alone (OR 2.79, 95% CI 1.07 to 7.24, SUCRA = 82.1%, 2 studies, 709 patients), whereas Atezolizumab showed an insignificant increase in pCR (OR 1.94, 95% CI 0.86 to 4.37, SUCRA = 62.3, 3 studies, 674 patients) (complete SUCRA values in Additional file 1: Table S5). In the GeparNuevo trial, the calculated OR of achieving pCR with Durvalumab and chemotherapy was 1.45 (95% CI 0.80 to 2.63) [37]

Hinweis FBMed: Auf die Extraktion der Ergebnisse zu den übrigen Endpunkten wurde verzichtet, da diese in der Studie gepoolt dargestellt werden (Ergebnisse zu metastasiertem TNBC, frühem TNBC sowie Erhaltungstherapie, siehe Studiencharakteristika).

Anmerkung/Fazit der Autoren

Only trials evaluating early-stage TNBC showed a significant improvement in pCR, implying that PD-1/ PD-L1 inhibitors may be most effective when started early in the disease course.

Lin Y-Y et al., 2022 [10].

Neoadjuvant therapy in triple-negative breast cancer: A systematic review and network meta-analysis

Fragestellung

To better inform clinical practice, we performed a systematic review and network meta-analysis of randomized controlled trials (RCTs) to estimate the comparative efficacy and acceptability of existing neoadjuvant regimens in early TNBC.

Methodik

Population:

- Patients with histologically confirmed, clinical stage I-III, primary TNBC

Intervention/ Komparator:

- neoadjuvant chemotherapy with or without targeted therapies or immunotherapies

Endpunkte:

- primary: pCR
- secondary: all-cause treatment discontinuation, DFS, EFS, OS

Recherche/Suchzeitraum:

- A literature search in PubMed, Embase, Web of Science, and Cochrane Central Register of Clinical trials as well as online archives of American Society of Clinical Oncology, European Society of Medical Oncology, and San Antonio Breast Cancer Symposium was conducted from inception to April 28, 2021. A repeated literature search was conducted from inception to February 12, 2022, to identify any updated publications. Citation lists of relevant literature were also reviewed for eligible studies.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 41 RCTs. A total of 7109 TNBC patients were included.

Charakteristika der Population:

Table 1
Study characteristics.

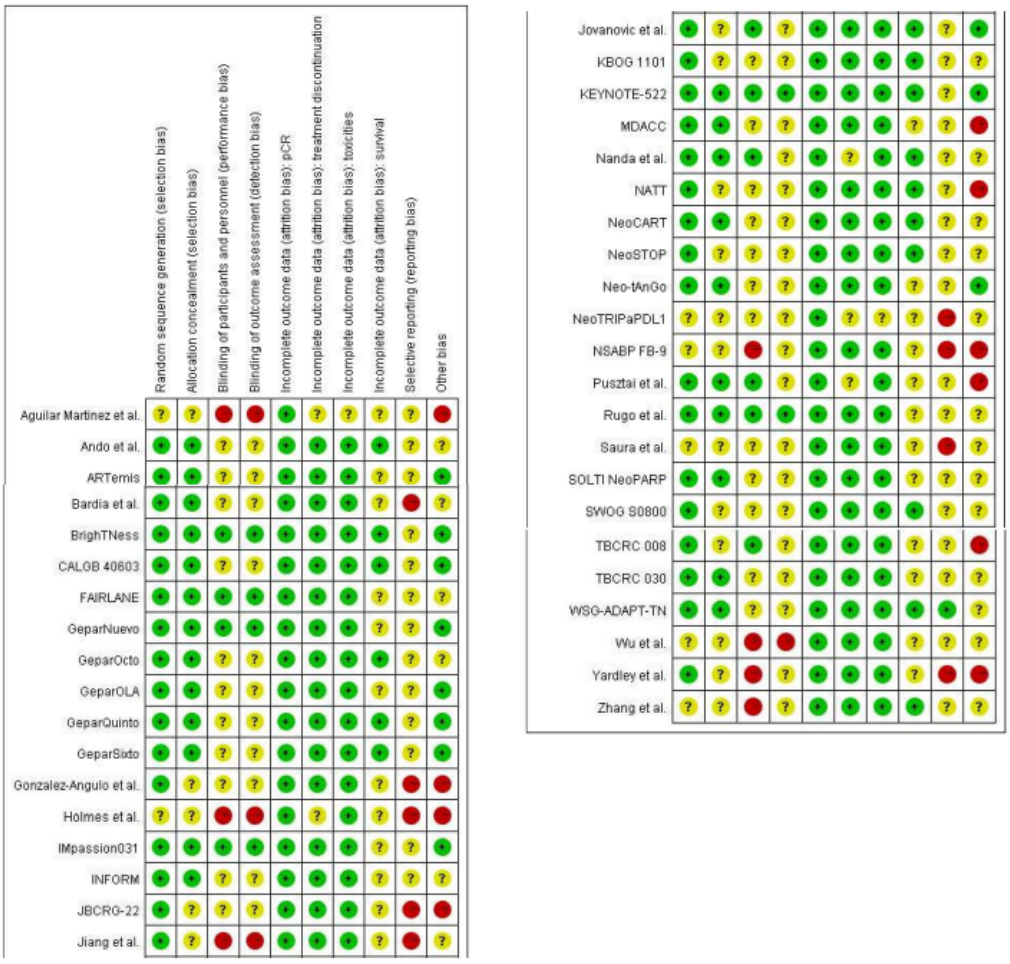
Study	Year	Phase	Design	Treatment arm	No. of TNBC pts	No. of ITT pts	Median age, y (range)	Clinical stage	Primary endpoint
Ando et al.	2014	II	Multicenter, open-label, randomized (1:1)	Carboplatin + paclitaxel→ FEC	37	91	47 (30–69)	II-III	ypT0/is pN0
				Paclitaxel→ FEC	38	88	47 (30–70)		
GeparOcto	2019	III	Multicenter, open-label, randomized (1:1)	Paclitaxel + doxorubicin→ carboplatin	203	475	48 (21–76)	I-III	ypT0/is pN0
				Epirubicin→ paclitaxel→ cyclophosphamide	200	470	48 (23–76)		
Zhang et al.	2016	II	Multicenter, open-label, randomized (1:1)	Carboplatin + paclitaxel	44	44	48 (24–73)	II-III	ypT0/is pN0
				Epirubicin + paclitaxel	43	43	46 (24–65)		
NeoCART	2020	II	Multicenter, open-label, randomized (1:1)	Carboplatin + docetaxel	44	44	50 (38–59)	II-III	ypT0/is pN0
				EC→ docetaxel	44	44	49 (40–56)		
NeoSTOP	2021	II	Multicenter, open-label, randomized (1:1)	Carboplatin + docetaxel	52	52	54 (29–70)	I-III	ypT0/is pN0
				Carboplatin + paclitaxel→ AC	48	48	51 (32–69)		
Aguilar Martinez et al.	2015	II	Single-center, randomized (1:1)	Cisplatin + paclitaxel→ cisplatin + doxorubicin	30	30	NR	NR	ypT0/is pN0
				Paclitaxel→ FAC	31	31			
TBCRC 030	2020	II	Multicenter, open-label, randomized (1:1)	Cisplatin	72	72	53 (28–82)	I-III	ypT0/is pN0
				Paclitaxel	67	67			
INFORM	2020	II	Multicenter, open-label, randomized (1:1)	Cisplatin	44	60	40 (31–49)*	I-III	ypT0/is pN0
				AC	38	58	44 (34–54)*		
Neo-tAnGo	2014	III	Multicenter, open-label, randomized (1:1:1:1)	EC→ Paclitaxel	73	404	NR	II-III	ypT0/is pN0
				Paclitaxel→ EC					
				EC→ Paclitaxel + gemcitabine	84	408			
				Paclitaxel + gemcitabine→ EC					
WSG-ADAPT-TN	2018	II	Multicenter, open-label, randomized (1:1)	Carboplatin + nab-paclitaxel	146	146	NR	I-III	ypT0/is pN0
				Gemcitabine + nab-paclitaxel	178	178			
TBCRC 008	2015	II	Multicenter, double-blind, randomized (1:1)	Vorinostat + carboplatin + nab-paclitaxel	12	30	48 (31–68)	II-III	ypT0/is pN0
				Carboplatin + nab-paclitaxel	12	31	48 (24–72)		
JBCRG-22	2021	II	Multicenter, randomized (1:1:1:1)	Carboplatin + eribulin→ FEC or AC	22	22	47.5 (26–63)*	I-III	ypT0/is pN0
				Carboplatin + paclitaxel→ FEC or AC	23	23	44 (28–64)*		
				Eribulin + capecitabine→ FEC or AC	27	27	60 (37–70)*		
				Eribulin + cyclophosphamide→ FEC or AC	27	27	59 (35–70)*		
Jiang et al.	2021	II	Single-center, open-label, randomized (1:1)	Vinorelbine + epirubicin	19	45	48 (26–66)	II-III	ypT0/is pN0
				Paclitaxel + epirubicin	17	46	50 (30–68)		
MDACC	2011	III	Multicenter, open-label, randomized (1:1)	Capecitabine + docetaxel→ FEC	30	300	49 (42–57)	II-III	Relapse-free survival
				Paclitaxel→ FEC	28	301	47 (40–55)		
Wu et al.	2018	II	Single-center, open-label, randomized (1:1)	Lobaplatin→ docetaxel + epirubicin	62	62	47 (33–70)	I-III	ypT0/is pN0
				Docetaxel + epirubicin	63	63			
KBOG 1101	2019	II	Multicenter, open-label, randomized (1:1)	FEC→ docetaxel + AC or EC	33	53	54.1 (12.4)**	II-III	ypT0 pN0
				Docetaxel + cyclophosphamide	33	50	53.6 (10.4)**		
NATT	2013	III	Multicenter, open-label, randomized (1:1)	Docetaxel + AC or EC	26	51	47.2 (26–62)*	II-III	ypT0/is pN0
				Docetaxel + cyclophosphamide	23	45	48 (25–69)*		
NSABP FB-9	2015	II	Multicenter, open-label, randomized (1:2)	Paclitaxel→ AC	8	19	48 (34–67)	II-III	ypT0/is pN0
				Eribulin→ AC	9	30	50 (28–70)		
Yardley et al.	2018	II	Multicenter, open-label, randomized (2:1)	Eribulin + cyclophosphamide	19	54	53 (23–77)	II-III	ypT0/is pN0
				Docetaxel + cyclophosphamide	6	22	51 (38–73)		
Saura et al.	2013	II	Multicenter, open-label, randomized (1:1)	AC→ ixabepilone	73	148	48 (25–79)	II-III	ypT0/is pN0
				AC→ paclitaxel	71	147	46 (26–74)		
SWOG S0800	2016	II	Multicenter, open-label, randomized (2:1:1)	Bevacizumab + nab-paclitaxel→ AC	32	98	51.7 (22–71)	II-III	ypT0/is pN0
				Nab-paclitaxel→ AC, or AC→ nab-paclitaxel	35	113	51.3 (31–75)		
ARTemis	2015	III	Multicenter, open-label, randomized (1:1)	Bevacizumab + docetaxel→ FEC	119	388	NR	II-III	ypT0/is pN0
				Docetaxel→ FEC	122	393			
GeparQuinto	2012	III	Multicenter, open-label, randomized (1:1)	Bevacizumab + EC→ docetaxel	323	956	49 (21–75)	I-III	ypT0 pN0
				EC→ docetaxel	340	969	48 (24–78)		

GeparSixto	2014	II	Multicenter, open-label, randomized (1:1)	Bevacizumab + carboplatin + paclitaxel + doxorubicin	158	295	48 (21–75)	II-III	ypT0 pN0
				Bevacizumab + paclitaxel + doxorubicin	157	293	47 (21–78)		
CALGB 40603	2015	II	Multicenter, open-label, randomized (2:2)	Carboplatin + paclitaxel→ AC	111	113	NR	II-III	ypT0/is
				Bevacizumab + paclitaxel→ AC	105	110			
				Bevacizumab + carboplatin + paclitaxel→ AC	110	112			
				Paclitaxel→ AC	107	108			
BrighTNess	2018	III	Multicenter, double-blind, randomized (2:1:1)	Veliparib + carboplatin + paclitaxel→ AC	316	316	50 (41–59)	II-III	ypT0/is pN0
				Carboplatin + paclitaxel→ AC	160	160			
				Paclitaxel→ AC	158	158			
GeparOLA	2020	II	Multicenter, open-label, randomized (2:1)	Olaparib + paclitaxel→ EC	50	69	48 (25–71)	I-III	ypT0/is pN0
				Carboplatin + paclitaxel→ EC	27	37	45 (26–67)		
Rugo et al.	2016	II	Multicenter, open-label, randomized (2:1)	Veliparib + carboplatin + paclitaxel→ AC	72	72	48.5 (27–70)	II-III	ypT0/is pN0
				Paclitaxel→ AC	44	44	47.5 (24–71)		
SOLTI NeoPARP	2015	II	Multicenter, open-label, randomized (1:1:1)	Iniparib 11.2 mg/kg + paclitaxel	46	46	49 (27–78)	II-III	ypT0/is
				Iniparib 5.6 mg/kg + paclitaxel	48	48	49 (30–75)		
				Paclitaxel	47	47	50 (29–73)		
KEYNOTE-522	2020	III	Multicenter, double-blind, randomized (2:1)	Pembrolizumab + carboplatin + paclitaxel→ pembrolizumab + AC or EC	401	784	49 (22–80)	II-III	ypT0/is pN0
				Carboplatin + paclitaxel→ AC or EC	201	390	48 (24–79)		
Nanda et al.	2020	II	Multicenter, open-label, adaptively randomized	Pembrolizumab + paclitaxel→ AC	29	69	50 (27–71)	II-III	ypT0/is pN0
				Paclitaxel→ AC	85	181	47 (24–77)		
Pusztai et al.	2020	II	Multicenter, open-label, adaptively randomized	Durvalumab + olaparib + paclitaxel→ AC	21	73	46 (28–71)	II-III	ypT0/is pN0
				Paclitaxel→ AC	142	299	48 (24–80)		
NeoTRIPaPDL1	2020	III	Multicenter, open-label, randomized (1:1)	Atezolizumab + carboplatin + nab-paclitaxel	138	138	50 (24–79)	II-III	5-year event free survival
				Carboplatin + nab-paclitaxel	142	142			
IMpassion031	2020	III	Multicenter, double-blind, randomized (1:1)	Atezolizumab + nab-paclitaxel→ atezolizumab + AC	165	165	51 (22–76)	II-III	ypT0/is pN0
				Nab-paclitaxel→ AC	168	168	51 (26–78)		
GeparNuevo	2019	II	Multicenter, double-blind, randomized (1:1)	Durvalumab + nab-paclitaxel→ durvalumab + EC	88	88	49.5 (25–74)	I-III	ypT0 pN0
				Nab-paclitaxel→ EC	86	86	49.5 (23–76)		
FAIRLANE	2019	II	Multicenter, double-blind, randomized (1:1)	Ipatasertib + paclitaxel	76	76	51 (29–78)	I-III	ypT0/is pN0
				Paclitaxel	75	75	54 (31–78)		
Jo Chien et al.	2020	II	Multicenter, open-label, adaptively randomized	MK-2206 + paclitaxel→ AC	32	94	53 (25–73)	II-III	ypT0/is pN0
				Paclitaxel→ AC	24	57	46 (28–71)		
Gonzalez-Angulo et al.	2014	II	Single-center, open-label, randomized (1:1)	Everolimus + paclitaxel→ FEC	23	23	46 (32–75)	II-III	mTOR pathway inhibition
				Paclitaxel→ FEC	27	27	52 (30–65)		
Jovanovic et al.	2017	II	Multicenter, double-blind, randomized (2:1)	Everolimus + cisplatin + paclitaxel	96	96	52 (43–57.25)	II-III	ypT0/is pN0
				Cisplatin + paclitaxel	49	49	52 (43–58)		
Holmes et al.	2015	II	Multicenter, open-label, randomized (2:1)	MM-121 + paclitaxel→ AC	56	56	NR	II-III	ypT0 pN0
				Paclitaxel→ AC	29	29			
Bardia et al.	2018	II	Multicenter, open-label, randomized (1:1)	LCL-161 + paclitaxel	105	105	NR	II-III	>7.5% increase in ypT0 rate
				Paclitaxel	102	102			

→ = followed by. EC = epirubicin plus cyclophosphamide. FEC = 5-fluorouracil plus epirubicin plus cyclophosphamide. AC = doxorubicin plus cyclophosphamide. FAC = 5-fluorouracil plus doxorubicin plus cyclophosphamide. NR = not reported. * Mean age (range). ** Mean age (standard deviation).

- Of the 41 RCTs, 17 exclusively enrolled TNBC patients; 37 were multicenter trials; 10 were phase III trials.

Qualität der Studien:



eFigure 2 (b). Risk of bias summary

Studienergebnisse:

- **Primary outcome: pCR**
  - Network meta-analysis of pCR included all 27 neoadjuvant regimens (Fig. 1). A random-effects, consistency model was applied as it provided a better fit to the data. All treatments were compared with anthracycline- and taxane-based ChT, and 8 treatments were associated with significantly higher pCR rates (Fig. 2), including PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT (OR 3.95; 95% CrI 1.81–9.44), bevacizumab plus platinum plus anthracycline- and taxane-based ChT (3.35; 1.89–6.13), and PARP inhibitor plus platinum plus anthracyclineand taxane-based ChT (2.39; 1.40–4.37).
  - The Bayesian ranking results were consistent with the pooled analysis, with PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT yielding the highest probability of being the most efficacious neoadjuvant treatment for TNBC (SUCRA = 0.90)

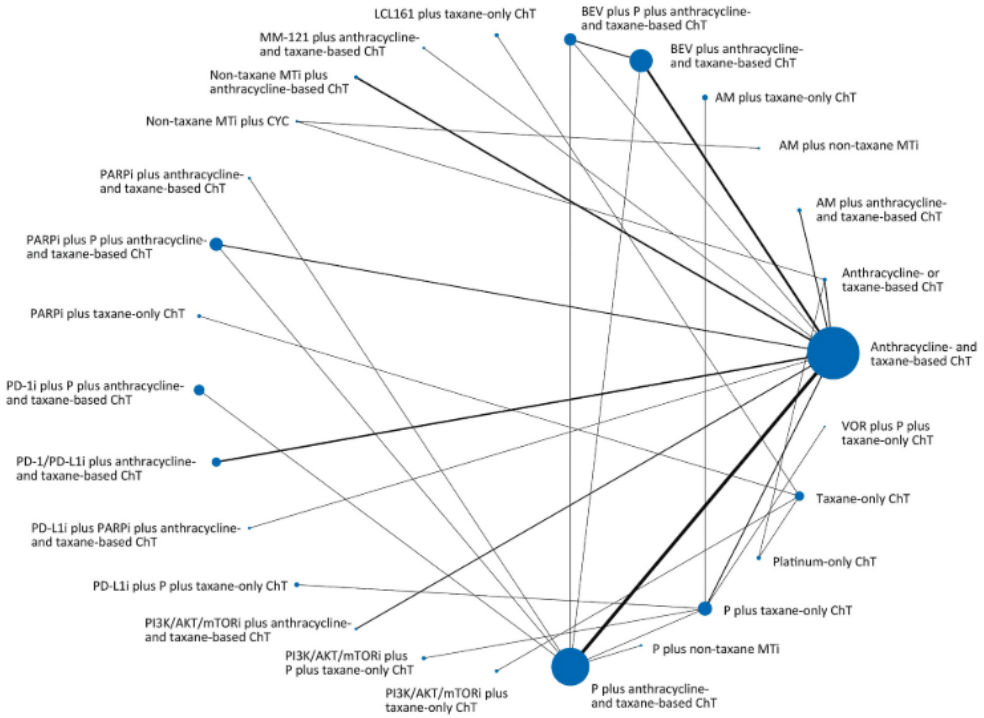


Fig. 1. Network meta-analysis of the proportion of patients achieving pathologic complete response (a 2-column fitting image). AM = antimetabolite. MTi = microtubule inhibitor. T = taxane. BEV = bevacizumab. P = platinum. A = anthracycline. CYC = cyclophosphamide. PARPi = PARP inhibitor. PD-1i = PD-1 inhibitor. PD-L1i = PD-L1 inhibitor. PD-1/PD-L1i = PD-1/PD-L1 inhibitor. PI3K/AKT/mTORi = PI3K/AKT/mTOR inhibitor. VOR = vorinostat.

Treatment	No. of Trials	No. of Patients	Odd Ratio (95% CrI)
PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT	1	401	3.95 (1.81-9.44)
Bevacizumab plus platinum plus anthracycline- and taxane-based ChT	2	268	3.35 (1.89-6.13)
PD-L1 inhibitor plus platinum plus taxane-only ChT	1	138	3.03 (1.10-8.75)
PD-1/PD-L1 inhibitor plus anthracycline- and taxane-based ChT	3	282	2.74 (1.65-4.77)
Platinum plus taxane-only ChT	7	489	2.73 (1.45-5.30)
PD-L1 inhibitor plus PARP inhibitor plus anthracycline- and taxane-based ChT	1	21	2.55 (0.72-9.18)
PARP inhibitor plus platinum plus anthracycline- and taxane-based ChT	2	388	2.39 (1.40-4.37)
Platinum plus anthracycline- and taxane-based ChT	10	902	2.26 (1.62-3.32)
PARP inhibitor plus anthracycline- and taxane-based ChT	1	50	1.94 (0.57-6.71)
Bevacizumab plus anthracycline- and taxane-based ChT	5	736	1.87 (1.27-2.88)
PI3K/AKT/mTOR inhibitor plus anthracycline- and taxane-based ChT	2	55	1.85 (0.70-5.06)
PI3K/AKT/mTOR inhibitor plus platinum plus taxane-only ChT	1	96	1.62 (0.52-5.23)
Antimetabolite plus taxane-only ChT	1	178	1.40 (0.50-3.99)
Vorinostat plus platinum plus taxane-only ChT	1	12	1.36 (0.20-9.09)
Antimetabolite plus anthracycline- and taxane-based ChT	2	114	1.03 (0.49-2.20)
Platinum plus non-taxane microtubule inhibitor	1	22	0.97 (0.23-4.06)
Non-taxane microtubule inhibitor plus anthracycline-based ChT	3	101	0.82 (0.39-1.76)
MM-121 plus anthracycline- and taxane-based ChT	1	56	0.74 (0.24-2.30)
Antimetabolite plus non-taxane microtubule inhibitor	1	27	0.68 (0.03-35.53)
Non-taxane microtubule inhibitor plus cyclophosphamide	2	46	0.65 (0.04-26.98)
Anthracycline- or taxane-based ChT	4	100	0.39 (0.12-1.15)
Platinum-only ChT	2	116	0.28 (0.05-1.39)
PI3K/AKT/mTOR inhibitor plus taxane-only ChT	1	76	0.27 (0.03-2.73)
LCL161 plus taxane-only ChT	1	105	0.23 (0.02-2.24)
Taxane-only ChT	4	291	0.20 (0.03-1.52)
PARP inhibitor plus taxane-only ChT	1	94	0.20 (0.02-1.92)

Fig. 2. Forest plot for the estimates of pathologic complete response improvement of different treatments using anthracycline- and taxane-based chemotherapy as a reference treatment (a 2-column fitting image). Green box indicates significantly in favor of the compared treatment. Grey box indicates non-significant result. CrI = credible interval. ChT = chemotherapy. . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

- **Secondary:**
  - Premature treatment discontinuation: Compared with anthracycline- and taxane-based ChT, PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT significantly increased the incidence of all-cause premature treatment discontinuation (OR 3.25; 95% CrI 1.26–8.29). (8 direct comparisons; comparative analysis involved 24 regimens from 33 RCTs (n=9489, TNBC and non-TNBC combined)
  - DFS/EFS: Compared with anthracycline- and taxane-based ChT, PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT (HR 0.42; 95% CrI 0.19–0.81), and platinum plus anthracycline- and taxane-based ChT (0.67; 0.44–0.92) were associated with significantly improved DFS/EFS. (18 RCTs, n=5247 patients, 10 neoadjuvant treatments)
  - OS: Compared with anthracycline- and taxane-based ChT, PD-1 inhibitor plus platinum plus anthracycline- and taxane-based ChT was not associated with improved OS (0.55; 0.24–1.15; 0.82) (15 RCTs, n=4863 patients, 10 treatment strategies)

Anmerkung/Fazit der Autoren

This systematic review and network meta-analysis identified PD-1 inhibitor combined with platinum and anthracycline- and taxane-based ChT as the superior neoadjuvant regimen in TNBC, with consistent improvement in pCR and DFS/EFS.

He Q et al., 2021 [5].

Platinum-Based Chemotherapy and Immunotherapy in Early Triple-Negative Breast Cancer: A Meta-Analysis and Indirect Treatment Comparison

Fragestellung

However, there has not been enough study to directly compare platinum drugs with ICIs. In lieu of head-to-head randomized control trials, we summarized recent and relevant trials and performed an indirect comparison between the two treatments of TNBC.

Methodik

Population:

- Patients with early tnbc

Intervention:

- Carboplatin-based chemotherapy *or* ICIs with AT-based NACT

Komparator:

- AT-based NACT

Endpunkte:

- pCR

Recherche/Suchzeitraum:

- A literature review was conducted in PubMed, Embase, and the Cochrane library (last updated in February 2021).

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs (n=1647 patients of whom 845 received standard AT-based NACT and 802 received ICIs plus chemotherapy or platinumbased chemotherapy)

Charakteristika der Population:

- four trials compared platinum-based with AT-based NACT, while three compared ICIs plus chemotherapy with chemotherapy alone
- two of the studies included other subtypes of breast cancer

TABLE 1 | Characteristics of eligible studies.

Study	Year	Phase	Population	Platinum/ICI group	pCR	AT group	pCR
BrignTNess (13)	2018	3	stage II–III TNBC	PCb-AC	57.50%	P-AC	31.01%
CALGB (14)	2014	2	stage II–III TNBC	PCb-ddAC	48.65%	P-ddAC	29.25%
GEICAM/2006-03 (15)	2012	2	TNBC	EC-DCb	29.79%	EC-D	34.78%
GeparOcto (16)	2019	3	T1c-T4a-d TNBC and HER2+ BC	PMCb	51.72%	ddEPC	48.50%
GeparNuevo (17)	2019	2	T2-T4a-d TNBC	Durva(nab-P-ddEC)	53.40%	nab-P-ddEC	44.20%
I-SPY2 (18)	2020	2	high-risk stage II–III BC	PembroP-AC	67.80%	P-AC	21.35%
IMpassion031 (19)	2020	3	stage II–III TNBC	Atezo(nab-P-AC)	57.60%	nab-P-AC	41.10%

pCR, pathological complete response; A, doxorubicin; C, cyclophosphamide; Cb, carboplatin; D, docetaxel; E, epirubin; M, non-pegylated liposomal doxorubicin; P, paclitaxel; nab-P, nab-paclitaxel; dd, dose-dense; Durva, durvalumab; Pembro,pembrolizumab; Atezo, atezolizumab.

Qualität der Studien:

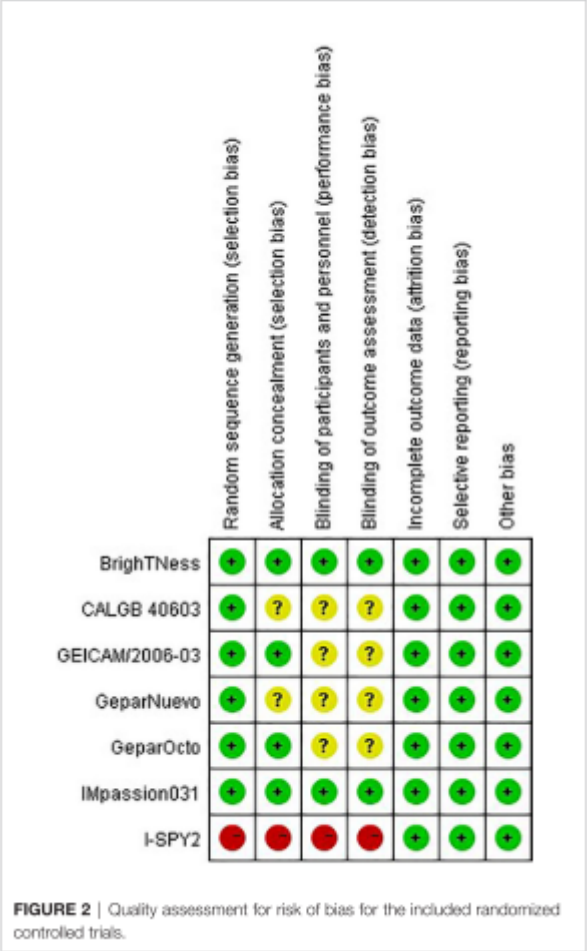


FIGURE 2 | Quality assessment for risk of bias for the included randomized controlled trials.

Studienergebnisse:

- Altogether, four trials comparing platinum-based and AT-based NACT did not show a statistically significant improvement in pCR rate (P = 0.16); 265 out of 521 patients (50.86%) reached pCR in the experimental group, and 204 out of 511 patients (39.92%) reached pCR in the control group (OR, 1.48; 95%CI, 0.86–2.56). Trials have considerable heterogeneity (I2 = 77%) and evaluation with random-effects model was done (Figure 4).
- A summary OR obtained with random effect models indicates that compared with AT-based NACT, the addition of ICIs significantly improved the pCR rates (P = 0.02) with 161 out of281 (57.30%) reaching PCR in the experimental group and 124 out of 346 patients (35.84%) reaching pCR in the control group (OR, 2.64; 95%CI, 1.24–5.61). Trials have considerable heterogeneity (I2 = 76%)

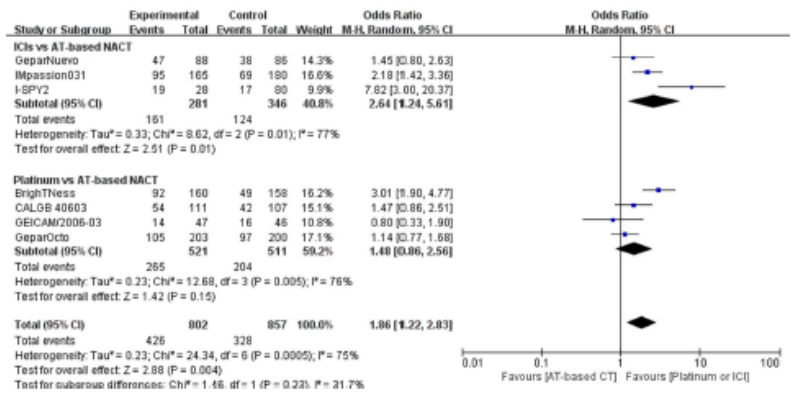


FIGURE 4 | Forest plot showing pooled OR of pCR in patients receiving ICIs *vs* AT-based NACT and platinum-based *vs* AT-based NACT in early TNBC patients.

- In the indirect comparison anchored in AT-based NACT (Table 2), ICIs plus chemotherapy demonstrated significant improvement in PCR rate versus platinum-based chemotherapy (p = 0.00445, OR, 1.78; 95%CI, 0.70–4.53)
  - Sensitivity analysis: Notably, when omitting ISPY2 study in ICIs versus AT-based NACT comparison, heterogeneity was significantly decreased (I^2 = 77 to I^2 = 16, Figure 6). Similarly, in platinum versus AT-based NACT comparison, heterogeneity was eliminated when excluding BrighTNess study (I^2 = 76 to I^2 = 0, Figure 6). When simultaneously excluding the two studies and evaluating with fixed-effect model, the result from the indirect comparison demonstrated that ICIs plus chemotherapy improved the pCR rate than platinum-based chemotherapy (OR, 1.61; 95%CI, 1.02–2.54) with statistical significance (P = 0.02), which was consistent with the primary comparison.

TABLE 2 | Results of indirect comparison.

	OR	95%CI	P
pCR	1.78	0.70–4.53	0.00445
pCR*	1.61	1.02–2.54	0.02199
discontinuation related to AE	0.46	0.26–0.82	0.00015
grade 3-4 neutropenia	0.2	0.03–1.56	<0.00001
grade 3-4 anemia	0.04	0.01–0.22	<0.00001
grade 3-4 thrombocytopenia	0.05	0.00–0.72	<0.00001

**Results excluding I-SPY2 and BrighTNess study.*

Anmerkung/Fazit der Autoren

ICIs plus chemotherapy showed increased pCR rate and decreased adverse effects compared with platinum-based chemotherapy in early TNBC. However, subgroup analysis and survival data to explore the proper patients for each treatment remains scarce. Therefore, further studies with powered direct comparisons of these two treating regimens are required.

Huo X et al., 2021 [6].

The role of capecitabine-based neoadjuvant and adjuvant chemotherapy in early-stage triple-negative breast cancer: a systematic review and meta-analysis

Fragestellung

To further clarify the role of capecitabine in TNBC, in the present study, we conducted a meta-analysis to investigate the effect of capecitabine as neoadjuvant and adjuvant chemotherapy on survival in TNBC patients.

Methodik

Population:

- TNBC patients

Intervention/ Komparator:

- neoadjuvant or adjuvant chemotherapy including capecitabine in the experimental arm and chemotherapy without capecitabine in the control arm

Endpunkte:

- disease-free survival (DFS) and overall survival (OS) and grade 3–5 drug-related adverse events (AEs)

Recherche/Suchzeitraum:

- Randomized controlled trials (RCTs) were identified using a computerized search of the databases PubMed and Embase (up to December 2019).

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs. A total of 3842 TNBC patients were included in this meta-analysis.
- There were seven and one studies that used capecitabine as adjuvant and neoadjuvant chemotherapy, respectively, and one study that used capecitabine as both neoadjuvant and adjuvant chemotherapy. From the available data of TNBC, there were 1757 cases of adjuvant chemotherapy with capecitabine and 1713 cases of adjuvant chemotherapy without capecitabine, along with 448 cases of neoadjuvant chemotherapy with capecitabine and 428 cases of neoadjuvant chemotherapy without capecitabine.

Charakteristika der Population:

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

Study	Author	Update year	Trial Phase	Capecitabine arm	Control arm	*N* (Capecitabine/ Control)	TNBC, *N* (X/ Control)	Median follow-up (month)	Design	Setting
FinXX Trial	Joensuu	2017	III	DX + CEX	D + CEF	751/744	93/109	123.6	Addition	Adjuvant
GEICAM/ 2003–10	Martín	2015	III	ED-X	EC-D	715/669	95/71	79.2	Replace	Adjuvant
GAIN	V. Mo	2017	III	EC-PX	EPC	1511/1512	213/208	74	Replace	Adjuvant
US ncology 01062	O'Shaughnessy	2015	III	AC-DX	AC-D	1307/1304	396/384	60	Addition	Adjuvant
CREATE-X	Masuda	2017	III	X	None	443/444	139/147	43.2	Addition	Adjuvant
CIBOMA 2004/01	Lluch	2019	III	ED-X	EC-D	448/428	448/428	87.6	Addition	Neo/ Adjuvant
Gepar TRIO	Minckwitz	2013	III	DAC-NX	DAC-DAC	301/321	NA	62	Replace	Neoadjuvant
CBCSG-010	Li	2019	III	DX-XEC	D-FEC	297/288	297/288	67	Addition	Adjuvant
CALGB49907	Muss	2019	III	X	CMF/ AC	307/326	76/78	136.8	Replace	Adjuvant

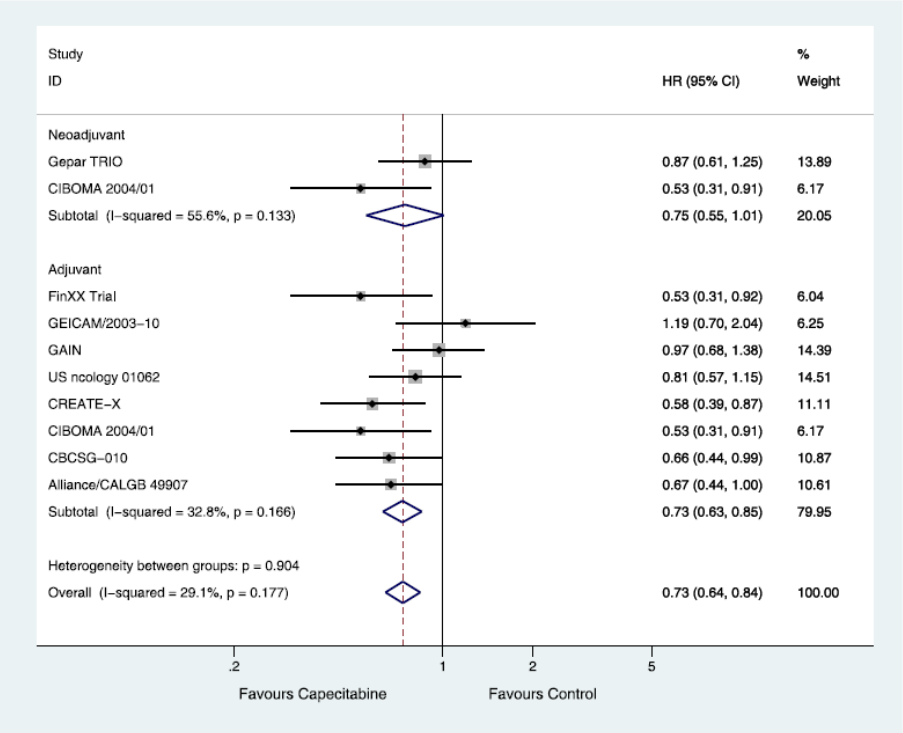
X capecitabine, *C* cyclophosphamide, *M* methotrexate, *F* 5-fluorouracil, *A* doxorubicin, *E* epirubicin, *D* docetaxel, *BEV* bevacizumab, *P* paclitaxel, *N* nab-paclitaxe, *NA* not available, *N* number

Qualität der Studien:

Study	Year	Randomization	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias
FinXX Trial	2017	Low	High	Low	Low	Low	Low
GEICAM/2003-10	2015	Low	High	Low	Low	Low	Low
GAIN	2017	Low	High	Low	Low	Low	Low
US ncology 01062	2015	Low	High	Low	Low	Unknown	Low
CREATE-X	2017	Low	Low	Low	Low	Low	Low
CIBOMA 2004/01	2019	Low	Low	Low	Unknown	Unknown	Low
Gepar TRIO	2013	Low	High	High	Low	Unknown	Low
CBCSG-010	2019	Low	Low	Unknown	Unknown	Low	Low
CALGB 49907	2019	Low	High	Low	Unknown	Low	Low

Studienergebnisse:

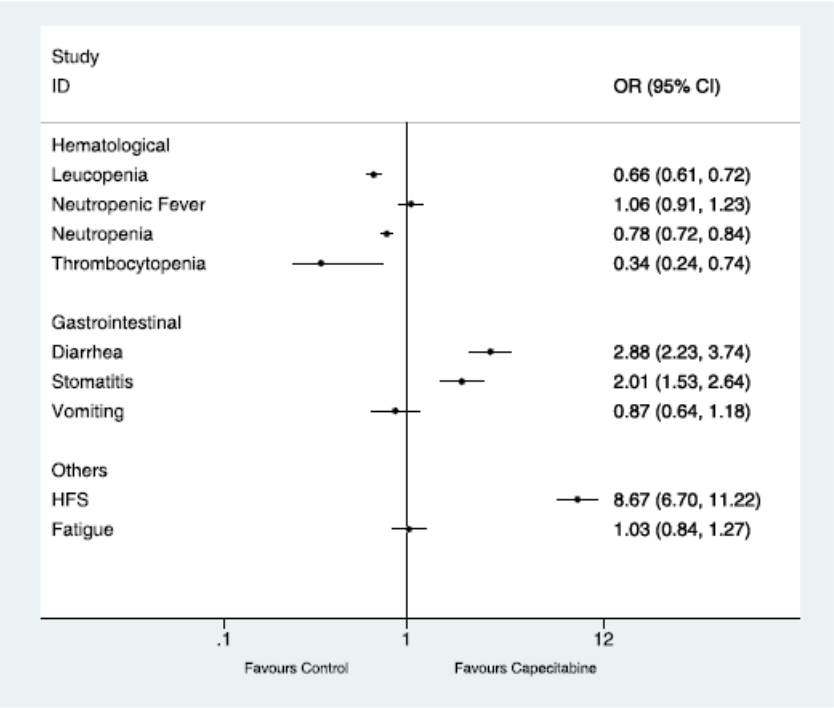
- DFS was significantly improved upon using capecitabine adjuvant chemotherapy (HR = 0.73; 95% CI, 0.63–0.85; P < 0.001) with low heterogeneity (P = 0.166, I2 = 32.8%), […] (Fig. 4).



- **Fig. 4** Effects of using capecitabine as neoadjuvant or adjuvant chemotherapy on subgroup analysis of disease-free survival (DFS)

Hinweis FBMed: Für die Endpunkte OS und AE liegen nur gepoolte Ergebnisse (adjuvant + neoadjuvant) vor.

- The combined capecitabine regimens in neoadjuvant and adjuvant chemotherapy […] significantly improved OS (HR = 0.63; 95% CI, 0.53–0.77; P < 0.001) with low heterogeneity (P = 0.702, I2 = 0).
- There were four grade 3–5 hematological AEs, three grade 3–5 gastrointestinal AEs, and two grade 3–5 other AEs. Figure 6 shows an overview of the safety profile for grade 3–5 AEs in the capecitabine and capecitabine-free chemotherapy groups.



- **Fig. 6** An overview of the safety profile for grade 3–5 adverse events (AEs) in capecitabine and capecitabine-free chemotherapy groups

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis showed that neoadjuvant and adjuvant chemotherapy combined with capecitabine significantly improved both DFS and OS in earlystage TNBC patients. DFS was significantly improved in the groups with the addition of capecitabine, adjuvant chemotherapy, and lymph node positivity, but not in those with the replacement of capecitabine, neoadjuvant chemotherapy, or lymph node negativity. Capecitabine regimens were related to higher risks of grade 3–5 AEs, namely, diarrhea, stomatitis, and HFS, but negatively correlated with the risks of leucopenia, neutropenia, and thrombocytopenia.

Kommentare zum Review

- Nicht alle Therapien, die in diesem systematischen Review verglichen wurden, sind in dieser Indikation zugelassen. Sie wurden hier jedoch ergänzend dargestellt.
- Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:
  - Zhang Z et al., 2021 [13]
  - Zhou W et al., 2021 [14]
  - Li Y et al., 2020 [9]

3.3 Leitlinien

Korde LA et al., 2021 [7].

American Society of Clinical Oncology (ASCO)

Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline

sowie

Korde LA et al., 2022 [8].

American Society of Clinical Oncology (ASCO)

Use of Immune Checkpoint Inhibitor Pembrolizumab in the Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer: ASCO Guideline Rapid Recommendation Update

Zielsetzung/Fragestellung

The purpose of this guideline is to develop recommendations concerning the optimal use of systemic neoadjuvant therapy, including chemotherapy, endocrine therapy, and targeted therapy for patients with invasive breast cancer.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- systematic review–based guideline (up to August 31, 2020)
- Literature searches of selected databases, including The Cochrane Library and Medline (via PubMed) are performed.

LoE/GoR

- GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is

confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Sonstige methodische Hinweise

- Das ASCO Guidelines Methodology Manual ist hier zu finden: https://www.asco.org/practice-patients/guidelines/guideline-methodology

Recommendations

Clinical question 1: Which patients with breast cancer are appropriate candidates for neoadjuvant systemic therapy?

Recommendation 1.3: Neoadjuvant systemic therapy should be offered to patients with high-risk HER2-positive or TNBC in whom the finding of residual disease would guide recommendations related to adjuvant therapy (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Literature review and analysis. Use of neoadjuvant systemic therapy in patients with high-risk HER2-positive or TNBC.

The systematic review identified two studies that support the use of neoadjuvant systemic therapy in patients with high-risk HER2-positive or TNBC in whom the finding of residual disease would prompt a change in adjuvant therapy. The Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) open-label, phase III trial [10] evaluated the safety and efficacy of adjuvant chemotherapy in patients with HER2-negative primary breast cancer who had residual invasive disease after they had received neoadjuvant chemotherapy that contained taxane, anthracycline, or both. CREATE-X randomly assigned 910 patients to receive standard postoperative adjuvant treatment either with capecitabine or without. Analyses revealed that adjuvant capecitabine prolonged both DFS and OS. In safety analyses, the most frequent adverse event observed in the capecitabine group was hand-foot syndrome; this occurred in 325 of 443 patients (73.4%). In the subset of patients with triple-negative disease—about 30% of patients studied—the DFS rate was 69.8% among patients who received capecitabine versus 56.1% in the control group (hazard ratio [HR], 0.58; 95% CI, 0.39 to 0.87); the OS rate was 78.8% versus 70.3% (HR, 0.52; 95% CI, 0.30 to 0.90). In the subset of patients with HR-positive breast cancer, there were numerical improvements in DFS and OS that did not meet statistical significance. The DFS rate was 76.4% in the capecitabine group and 73.4% in the control group (HR for recurrence, second, cancer, or death, 0.81; 95% CI, 0.55 to 1.17), and OS rates were 93.4% and 90%, respectively (HR for death, 0.73; 95% CI, 0.38 to 1.40).

The KATHERINE open-label, phase III clinical trial compared adjuvant trastuzumab emtansine (T-DM1) with trastuzumab in patients with stage I to III, HER2-positive breast cancer who had residual invasive disease in the breast or axilla after completing neoadjuvant chemotherapy plus HER2-targeted therapy.[9] Patients were randomly assigned to receive either postoperative T-DM1 (n 5 743) at a dose of 3.6 mg per kilogram of body weight, or trastuzumab (n 5 743) at a dose of 6 mg per kilogram intravenously every 3 weeks for 14 cycles (42 weeks). A majority of patients (80%) received trastuzumab as their sole HER2-targeted therapy in the neoadjuvant setting; approximately 18% received dual neoadjuvant HER2targeted therapy with trastuzumab and pertuzumab. Invasive disease or death occurred in 91 (12.2%) of patients who received adjuvant T-DM1 and in

165 (22.2%) patients who received trastuzumab. The estimated invasive DFS at 3 years was significantly higher in the T-DM1 group than in the trastuzumab group (88.3% v 77%; HR, 0.50; 95% CI, 0.39 to 0.64; P , .001). Similarly, the risk of distant recurrence was lower in patients who received T-DM1 than in patients who received trastuzumab (HR, 0.60; 95% CI, 0.45 to 0.79). Grade 3 or higher adverse events occurred in 190 (25.7%) patients who received T-DM1 and in 111 (15.4%) of patients who received trastuzumab, including thrombocytopenia (5.7% v 0.3%) and peripheral sensory neuropathy (1.4% v0%). Serious adverse events occurred in 94 patients (12.7%) in the T-DM1 group and in 58 patients (8.1%) in the trastuzumab group. Adverse events leading to discontinuation of T-DM1 included thrombocytopenia, elevated liver function test abnormalities, and peripheral sensory neuropathy. Patients who were unable to complete T-DM1 received trastuzumab to complete a year of HER2-targeted therapy.

Clinical interpretation.

The CREATE-X and KATHERINE trials establish that, in patients with TNBC or HER2-positive disease, the presence or absence of residual disease after neoadjuvant therapy alters treatment recommendations in the adjuvant setting. Thus, neoadjuvant therapy is the treatment of choice in all but small, node-negative, TNBC, or HER2-positive tumors.

Clinical question 3: What neoadjuvant systemic therapy regimens are recommended for patients with TNBC?

Recommendation 3.1: Patients with TNBC who have clinically node-positive and/or at least T1c disease should be offered an anthracycline- and taxane-containing regimen in the neoadjuvant setting (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.2. Patients with cT1a or cT1bN0 TNBC should not routinely be offered neoadjuvant therapy outside of a clinical trial (Type: evidence-based; benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 3.3. Carboplatin may be offered as part of a neoadjuvant regimen in patients with TNBC to increase likelihood of pCR. The decision to offer carboplatin should take into account the balance of potential benefits and harms (Type: evidence-based; benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Recommendation 3.4. There is insufficient evidence to recommend routinely adding the immune checkpoint inhibitors to neoadjuvant chemotherapy in patients with earlystage TNBC (Type: informal consensus; Evidence quality: intermediate; Strength of recommendation: moderate).

Literature review and analysis. Neoadjuvant chemotherapy in patients with TNBC.

There is no direct evidence from phase III randomized clinical trials regarding the optimal neoadjuvant chemotherapy regimen in patients with TNBC. However, there is broad consensus based on key randomized clinical trials [6] and an individual patient data meta-analysis [89] that chemotherapy regimens appropriate for adjuvant treatment by stage are also appropriate for neoadjuvant treatment. On this basis, the Expert Panel recommends that patients with clinically node-positive and/or at least T1c TNBC be offered an anthracycline- and taxanebased neoadjuvant regimen.

There is less agreement concerning the addition of carboplatin to the standard anthracycline-based neoadjuvant chemotherapy regimen in patients with TNBC. In high-risk patients, the addition of platinum to the standard neoadjuvant chemotherapy regimen of paclitaxel and AC (doxorubicin and cyclophosphamide) or EC (epirubicin and cyclophosphamide) has been shown consistently to improve pCR rates,[11-13,56,57,59] by up to 20%. The meta-analysis by Poggio et al [56] of nine RCTs (2,109 patients) that evaluated the safety and efficacy of platinum-based versus platinum-free neoadjuvant chemotherapy in patients with TNBC found, for instance, that platinum-based neoadjuvant chemotherapy increased pCR rates significantly from 37.0% to 52.1% (odds ratio [OR], 1.96; 95% CI, 1.46 to 2.62, P , .001). Not surprisingly, there was a significantly greater risk of grade 3 and 4 hematological adverse events observed with platinum-based neoadjuvant chemotherapy. Petrelli et al [59] found a similar increased pCR rate in a meta-analysis of RCTs that investigated platinumbased neoadjuvant chemotherapy in TNBC. Neoadjuvant chemotherapy that contained carboplatin or cisplatin significantly increased the pCR rate compared with non– platinum-containing neoadjuvant chemotherapy (relative risk [RR], 1.45; 95% CI, 1.25 to 1.68; P , .0001).

However, the effect of adding platinums on long-term outcomes such as DFS and OS is much less certain.91 None of the relevant trials has been adequately powered to evaluate survival outcomes. In CALGB 40603 (Alliance),12 carboplatin significantly improved pCR breast or axilla (54% v41%, P5 .0029) in patients with stage II-III TNBC when added to weekly paclitaxel for 12 weeks followed by AC once every 2 weeks for four cycles. In patients who received carboplatin, grade $ 3 thrombocytopenia and neutropenia occurred more commonly; these patients were also more likely to require dose modification, skipped doses, or early treatment discontinuation because of toxicity. Patients who achieved a pCR had improved event-free survival and OS comparedwith patients who did not achieve a pCR at a median 3-year follow-up.[92] There was no improvement in survival outcome, however, with the addition of carboplatin to the standard neoadjuvant chemotherapy regimen.

The GeparSixto randomized phase II clinical trial included patients with stage II or III HER2-positive (n5 273) or TNBC (n 5 315). Patients received 18 weeks of neoadjuvant weekly paclitaxel, weekly nonpegylated liposomal doxorubicin, and bevacizumab every 21 days, and were randomly assigned to either concurrent weekly carboplatin or no additional treatment. Those who received carboplatin had an improvement in pCR (pCR 53.2% with carboplatin v36.9% without carboplatin, P5 .005).[13] Treatment discontinuation was more frequent in patients who received carboplatin than in those who did not receive carboplatin (48% v 39%).

Loibl et al [11] reported the results of a phase III, double-blind, placebo-controlled trial (BrighTNess) that evaluated the addition of the poly (ADP-ribose) polymerase (PARP) inhibitor, veliparib, and carboplatin or carboplatin alone compared with standard neoadjuvant taxane-based chemotherapy followed by AC in patients with stage II-III TNBC. The study randomly assigned 316 patients to paclitaxel plus carboplatin plus veliparib; 160 patients to paclitaxel plus carboplatin; and 158 patients to paclitaxel alone. The pCR rates were 58% in patients who received paclitaxel and carboplatin; 53% in patients who received paclitaxel, carboplatin, and veliparib; and 31% in patients who received paclitaxel alone. The difference between the latter two groups was statistically significant (P , .0001). Not surprisingly, grade 3 or 4 toxicities (eg, anemia, neutropenia, and thrombocytopenia) occurred more frequently among patients who received carboplatin. Event-free survival and OS were secondary end points in this trial and have not been reported yet.

Literature review and analysis. Use of immune checkpoint inhibitors in the treatment of early-stage TNBC.

There has been increasing interest in studying the efficacy and safety of immunotherapy in many solid tumors, breast cancer among them.93

Pembrolizumab and atezolizumab have

both been studied in the metastatic setting, and atezolizumab is FDA-approved for first-line treatment of PD-L1– positive TNBC and several phase II trials have suggested increased pCR rates.[94]

The systematic literature review conducted for this guideline identified two phase III randomized clinical trials that addressed the role of immune checkpoint inhibitors in the treatment of nonmetastatic TNBC.[14,51]

The KEYNOTE-522 randomized, double-blind, phase III trial evaluated the combination of carboplatin or paclitaxel with or without pembrolizumab followed by AC with or without pembrolizumab in patients with stage II or stage III TNBC.[14]

At the second interim analysis with a median duration of follow-up of 15.5 months, the data showed that adding pembrolizumab to carboplatin or paclitaxel significantly improved pCR rates. The percentage of patients with a pCR in the pembrolizumab plus neoadjuvant chemotherapy group was 64.8% (260 of 401 patients) versus 51.2% in the placebo plus neoadjuvant chemotherapy group (103 of 201 patients; estimated treatment difference, 13.6 percentage points; 95% CI, 5.4 to 21.8; P , .001). The investigators also reported the preliminary event-free survival rate in the two arms with 104 of the 327 expected events needed for the final analysis. The estimated percentage of patients at 18 months who were alive without disease progression that precluded definitive surgery, without local or distant recurrence and without a second primary tumor, was 91.3% (95% CI, 88.8 to 93.3) for patients in the pembrolizumab-chemotherapy group and was 85.3% (95% CI, 80.3 to 89.1) for patients in the placebo-chemotherapy group. Treatment-related adverse events that were grade 3 or higher occurred in 76.8% and 72.2% of the patients in the pembrolizumabchemotherapy group and the placebo-chemotherapy group, respectively. The most commonly occurring grade 3 or greater adverse events in both treatment groups were anemia, neutropenia, febrile neutropenia, and decreased neutrophil count. Hypothyroidism, hyperthyroidism, and adrenal insufficiency were more commonly noted in patients who received pembrolizumab.

The IMpassion031 randomized, double-blind, phase III neoadjuvant treatment trial evaluated atezolizumab versus placebo combined with nab-paclitaxel followed by AC in patients with early-stage TNBC.[51] Analyses revealed that adding atezolizumab to nab-paclitaxel followed by AC improved the pCR rate significantly irrespective of patients' PD-L1 status: pCR was observed in 95 of 165 patients in the atezolizumab plus chemotherapy group (58%; 95% CI, 50 to 65) versus in 69 of 168 patients in the placebo plus chemotherapy group (41%; 34 to 49; rate difference 17%, 95% CI, 6 to 27; one-sided P5 .0044). The trial was not powered for long-term survival outcomes (event-free survival and OS). Serious, treatment-related adverse events occurred in 37 (23%) patients in atezolizumab plus chemotherapy group and in 26 (16%) patients in chemotherapy plus placebo group. Commonly reported ($ 20% incidence) adverse events were similar between the two treatment groups and mostly driven by chemotherapy effects.

Clinical interpretation.

The choice of neoadjuvant regimen should be appropriate to the stage and subtype of disease. Outside of a clinical trial, regimens for neoadjuvant treatment of TNBC mirror the adjuvant regimens, and generally involve polychemotherapy with both an anthracycline and a taxane. The addition of platinum agents during the taxane component augments the pCR rate so may be considered for high clinical risk, for example, node-positive disease; however, it is not known whether the addition of platinum improves invasive DFS or OS. In

lower-risk patients or those with cardiac risk factors in whom the risks associated with an anthracycline may be more worrisome, a taxane-based regimen such as docetaxel plus cyclophosphamide or carboplatin given for six cycles may be substituted.[95] Immune checkpoint inhibitors added to chemotherapy in TNBC may augment pCR, although long-term outcomes and toxicity in patients receiving these drugs in the neoadjuvant setting are still undergoing evaluation.

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95. Yu KD, Ye FG, He M, et al: Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer: A phase 3 randomized clinical trial. JAMA Oncol 6:1390-1396, 2020

2022 Updated Recommendation

For patients with T1cN1-2 or T2-4N0 (stage II or III), earlystage TNBC, the Panel recommends use of pembrolizumab (200 mg once every 3 weeks or 400 mg once every 6 weeks) in combination with neoadjuvant chemotherapy, followed by adjuvant pembrolizumab after surgery. Adjuvant pembrolizumab may be given either concurrent with or after completion of radiation therapy.

Given that irAEs associated with pembrolizumab therapy can be severe and permanent, careful screening for and management of common toxicities are required. The ASCO guideline for management of irAEs in patients treated with immune checkpoint inhibitor therapy offers detailed practice recommendations and should be consulted by clinicians who prescribe pembrolizumab for patients with early-stage TNBC, https://ascopubs.org/doi/full/10.1200/ JCO.21.01440 (Type: Evidence based, benefits outweigh harms; Evidence quality: Intermediate; Strength of recommendation: Moderate).

Qualifying Statements

Results from KEYNOTE-522 are based on continued pembrolizumab in the adjuvant setting. There is uncertainty concerning the optimal adjuvant treatment given independent benefits of capecitabine in TNBC and olaparib in patients with germline BRCA mutations without pembrolizumab. There are no data to support the use of pembrolizumab in combination with either capecitabine or olaparib.

Evidence Review

With a median follow-up of 39.1 months, the updated analysis showed a statistically significant improvement in EFS among patients who received pembrolizumab plus neoadjuvant chemotherapy, followed by adjuvant pembrolizumab after surgery, compared with patients who received control therapy (3-year EFS 84.5% v 76.8%; hazard ratio 0.63, 95% CI, 0.48 to 0.82; P < .001). At 36 months, the estimated overall survival (OS) in the pembrolizumab-chemotherapy group was 89.7% (95% CI, 87.3 to 91.7); the estimated OS in the placebo-chemotherapy group was 86.9% (95% CI, 83.0 to 89.9). Eighty patients (10.2%) in the pembrolizumab-chemotherapy group died, and 55 patients (14.1%) in the placebo-chemotherapy group died (hazard ratio for death, 0.72; 95% CI, 0.51 to 1.02). Of note, OS data—presented solely for descriptive purposes—were immature for this planned interim analysis and follow-up is ongoing.2 Across the neoadjuvant and adjuvant phases of the trial, treatment-related adverse events (TRAEs) that were grade 3 or higher occurred in 77.1% and 73.3% of the patients in the pembrolizumab-chemotherapy group and in the placebo-chemotherapy group, respectively. Most adverse events occurred in the neoadjuvant treatment phase versus the adjuvant phase. The most commonly occurring grade 3 or higher TRAEs in the pembrolizumab-chemotherapy and placebo-chemotherapy groups were neutropenia (34.5% v 33.4%), neutrophil count decrease (18.6% v 23.1%), and anemia (18.0% v 14.9%). Four deaths in the pembrolizumab-chemotherapy group and one death in the placebo-chemotherapy group were attributed to TRAEs. TRAEs that led to discontinuation of the trial regimen occurred in 27.7% of patients in the pembrolizumab-chemotherapy group and 14.1% of patients in the placebo-chemotherapy group. Grade 3 or higher immune-mediated adverse events (irAEs) occurred in 12.9% of patients in the pembrolizumab chemotherapy group and 1.0% of patients in the placebo-chemotherapy group. There was a higher incidence of any-grade endocrine disorders—hypo- or hyperthyroidism, adrenal insufficiency, thyroiditis, and hypophysitis—seen in the pembrolizumab-chemotherapy group (26.8%) than in the placebo-chemotherapy group (9.1%).

Denduluri N et al., 2021 [1].

American Society of Clinical Oncology (ASCO)

Selection of optimal adjuvant chemotherapy and targeted therapy for early breast cancer: ASCO Guideline Update.

sowie

Giordano S et al., 2022 [4].

American Society of Clinical Oncology (ASCO)

Abemaciclib with Endocrine Therapy in the Treatment of High-Risk Early Breast Cancer: ASCO Optimal Adjuvant Chemotherapy and Targeted Therapy Guideline Rapid Recommendation Update

Zielsetzung/Fragestellung

The aim of this work is to update key recommendations of the ASCO guideline adaptation of the Cancer Care Ontario guideline on the selection of optimal adjuvant chemotherapy regimens for early breast cancer and adjuvant targeted therapy for breast cancer.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft teilweise zu (Für die in Vorgängerversionen der Leitlinie publizierten Empfehlungen konnten keine Empfehlungsstärken, Evidenzgrade oder Evidenz identifiziert werden. Sie sind jedoch in den ursprünglichen Versionen der Leitlinie publiziert.);
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- systematic review–based guideline
- Literature searches of selected databases, including The Cochrane Library and Medline (via PubMed) are performed.

LoE/GoR

- GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Strength of recommendations: The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is

confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Sonstige methodische Hinweise

- Das ASCO Guidelines Methodology Manual ist hier zu finden: https://www.asco.org/practice-patients/guidelines/guideline-methodology

Recommendations

TABLE 1. Complete List of Recommendations From 2018 ASCO Guideline Adaptation and From the ASCO 2020 Focused Guideline Update

Recommendation	Evidence Rating
New Recommendations From 2020 Focused Guideline Update	
Patients with HER2-positive breast cancer with pathologic invasive residual disease at surgery after standard preoperative chemotherapy and HER2-targeted therapy should be offered 14 cycles of adjuvant T-DM1, unless there is disease recurrence or unmanageable toxicity.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Clinicians may offer any of the available and approved formulations of trastuzumab, including trastuzumab, trastuzumab and hyaluronidase-oysk, and available biosimilars.	Type: evidence based, benefits outweigh harms Evidence quality: high Strength of recommendation: strong
Recommendations Unchanged From 2018 Guideline Adaptation[a]	
In patients who can tolerate it, use of a regimen containing anthracycline-taxane is considered the optimal strategy for adjuvant chemotherapy, particularly for patients deemed to be at high risk.	
For patients with high-risk disease who will not receive a taxane, an optimal-dose anthracycline three-drug regimen (cumulative dose of doxorubicin ≥ 240 mg/m^2 or epirubicin ≥ 600 mg/m^2, but no higher than 720 mg/m^2) that contains cyclophosphamide is recommended. The cumulative dose of doxorubicin in two-drug regimens should not exceed 240 mg/m^2.	
The addition of gemcitabine or capecitabine to an anthracycline-taxane regimen is not recommended for adjuvant chemotherapy.	
In patients age 65 years or older, capecitabine is not recommended as an adjuvant chemotherapy option in lieu of standard regimens, such as doxorubicin-cyclophosphamide or cyclophosphamide-methotrexate-fluorouracil (with oral cyclophosphamide).	
For patients in whom anthracycline-taxane is contraindicated, cyclophosphamide-methotrexate-fluorouracil (with oral cyclophosphamide) is an acceptable chemotherapy alternative to doxorubicin-cyclophosphamide. Of note, the ASCO Panel recommends classic cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide days 1 to 14 with IV methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (eg, TAILORx; Trial Assigning Individualized Options for Treatment) on the basis of convenience and tolerability, despite the absence of efficacy data from randomized controlled trials.	
These adjuvant chemotherapy regimens can be used for patients with early breast cancer:	
Fluorouracil-epirubicin-cyclophosphamide × 3 → docetaxel × 3 (superior to fluorouracil-epirubicin-cyclophosphamide × 6)	
Doxorubicin-cyclophosphamide × 4 → docetaxel × 4 (superior to doxorubicin-cyclophosphamide × 4)	
Docetaxel-doxorubicin-cyclophosphamide × 6 (superior to fluorouracil-doxorubicin-cyclophosphamide × 6)	
Doxorubicin-cyclophosphamide × 4 → paclitaxel administered once per week	
Dose-dense doxorubicin-cyclophosphamide → paclitaxel administered once every 2 weeks	
Dose-dense epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2 every 2 weeks four cycles → paclitaxel 175 mg/m^2 every 2 weeks for four cycles	
Docetaxel-cyclophosphamide × 4 is recommended as an alternative to doxorubicin-cyclophosphamide × 4 and offers improved disease-free survival and overall survival. Classic cyclophosphamide-methotrexate-fluorouracil with oral cyclophosphamide for six cycles is another option. As mentioned before, the ASCO Panel recommends classic cyclophosphamide-methotrexate-fluorouracil (oral cyclophosphamide days 1 to 14 with IV methotrexate-fluorouracil days 1 and 8, repeated once every 28 days for six cycles) as the default adjuvant cyclophosphamide-methotrexate-fluorouracil regimen. However, the Panel also recognizes that an all-IV cyclophosphamide-methotrexate-fluorouracil regimen once every 21 days is often used in clinical practice and was accepted by some clinical trials (eg, TAILORx) on the basis of its convenience and tolerability, despite the absence of efficacy data from randomized controlled trials.	
Only patients with HER2-positive breast cancer (overexpressed on the basis of immunohistochemistry [3+] or amplified on the basis of in situ hybridization [ratio > 2.0 or average HER2 copy number ≥ 6.0]) should be offered adjuvant trastuzumab.	
Trastuzumab plus chemotherapy is recommended for all patients with HER2-positive, node-positive breast cancer and for patients with HER2-positive, node-negative breast cancer (> 1 cm)	
Trastuzumab therapy can be considered in small, node-negative tumors (≤ 1 cm).	
Trastuzumab can be administered with any acceptable adjuvant chemotherapy regimen.	

The administration of trastuzumab concurrently with the anthracycline component of a chemotherapy regimen is not recommended because of the potential for increased cardiotoxicity.
Trastuzumab should be preferentially administered concurrently (not sequentially) with a nonanthracycline chemotherapy regimen.
Less cardiotoxicity is seen with docetaxel-carboplatin-trastuzumab than with doxorubicin-cyclophosphamide → docetaxel-trastuzumab, and docetaxel-carboplatin-trastuzumab is recommended for patients at higher risk for cardiotoxicity.
No phase III evidence exists for the addition of trastuzumab to some chemotherapy regimens, such as docetaxel-cyclophosphamide. However, those regimens might be in use and are reasonable options, particularly for mitigating cardiotoxicity in certain patients.
Patients should be offered 1 year total of adjuvant trastuzumab, with regular assessments of cardiac function during that period.
Patients with early-stage, HER2-negative breast cancer with pathologic invasive residual disease at surgery after standard anthracycline and taxane-based preoperative therapy may be offered up to six to eight cycles of adjuvant capecitabine.
Qualifying Statements. If clinicians decide to use capecitabine, then the Expert Panel preferentially supports the use of adjuvant capecitabine in the hormone receptor–negative, HER2-negative patient subgroup. The capecitabine dose used in the CREATE-X study (1,250 mg/m^2 twice daily) is associated with higher toxicity in patients age ≥ 65 years.
Clinicians may add 1 year of adjuvant pertuzumab to trastuzumab-based combination chemotherapy in patients with early-stage, HER2-positive breast cancer.
Qualifying Statements. The Expert Panel preferentially supports pertuzumab in the node-positive, HER2-positive population, in view of the clinically insignificant absolute benefit observed among node-negative patients. After a median follow up of 3.8 years, pertuzumab was found to offer a modest disease-free survival benefit; the first planned interim analysis did not show an overall survival benefit. There are no data to guide the duration of pertuzumab in patients who received neoadjuvant pertuzumab and achieved a pathologic complete response.
Clinicians may use extended adjuvant therapy with neratinib in patients with early-stage, HER2-positive breast cancer.
Neratinib causes substantial diarrhea, and diarrhea prophylaxis must be used.
Qualifying Statements. The Expert Panel preferentially favors the use of neratinib in hormone receptor–positive and node-positive patients. At 5.2-year follow up, no overall survival benefit has been observed. Patients who began neratinib within 1 year of trastuzumab completion seemed to derive the greatest benefit. There are no data on the added benefit of neratinib in patients who also received pertuzumab in the neoadjuvant or adjuvant setting.

Abbreviations: HER2, human epidermal growth factor receptor 1; IV, intravenous; T-DM1, trastuzumab emtansine.
[a]Evidence and analysis for recommendations unchanged from 2018 are described in Eisen et al,[5] and later by Denduluri et al,[1,3] in ASCO's adaptation of the Cancer Care Ontario guideline in 2016 and in the 2018 focused update of that adaptation.

2021 Updated Recommendations

- On the basis of a secondary predefined analysis conducted by the FDA (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208716s006s007s008lbl.pdf), 2 years of abemaciclib (150 mg twice daily) plus ET (endocrine therapy) may be offered to patients with hormone receptor– positive, HER2-negative, node-positive early breast cancer with a high risk of recurrence and a Ki-67 score of ≥ 20% as determined by an FDA-approved test (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).
- The Panel also recommends, on the basis of analyses reported by Harbeck et al, that abemaciclib for 2 years plus ET for ≥ 5 years may be offered to the broader ITT population of patients with resected, hormone receptor– positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence, defined as having ≥ 4 positive ALNs or as having 1-3 positive ALNs and one or more of the following features: histologic grade 3 disease, tumor size ≥ 5 cm, or Ki-67 index ≥ 20% (Type: evidence-based, benefits outweigh harms; Evidence quality: moderate; Strength of recommendation: strong).

Qualifying Statements

- Although exploratory analyses suggested similar HRs in favor of abemaciclib regardless of Ki-67 status, there were relatively few Ki-67 low tumors in monarchE. When discussing treatment options with patients, the potential benefits (improved IDFS) should be weighed against the potential harms (treatment toxicity and financial cost).

National Institute for Health and Care Excellence (NICE), 2018 (Update: Januar 2024) [12].

Early and locally advanced breast cancer: diagnosis and treatment

Zielsetzung/Fragestellung

This guideline covers diagnosing and managing early and locally advanced breast cancer. It aims to help healthcare professionals offer the right treatments to people, taking into account the person's individual preferences.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. […] All searches were conducted in MEDLINE, Embase and The Cochrane Library, with some additional database searching in AMED, PsycINFO and CINAHL for certain topic areas.

LoE

Tabelle 5: Levels of overall quality of outcome evidence in GRADE

Overall quality of outcome evidence in GRADE	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	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	Any estimate of effect is very uncertain.

GoR

- NICE reflects the strength of the recommendation in the wording. NICE uses 'offer' (or words such as 'measure', 'advise', or 'refer') to reflect a strong recommendation usually where there is clear evidence of benefit. […] uses 'consider' to reflect a recommendation for which the evidence of benefit is less certain.

Sonstige methodische Hinweise

- This guideline updates and replaces NICE guideline CG80 (February 2009), and NICE technology appraisal guidance 107, 108, 109 and 112 (published 2006).

Recommendations

Adjuvant therapy planning

1.6.6 Consider adjuvant therapy after surgery for people with invasive breast cancer, and ensure that recommendations are recorded at the multidisciplinary team meeting. [2009]

1.6.7 Base recommendations about adjuvant therapy on multidisciplinary team assessment of the prognostic and predictive factors, and the possible risks and benefits of the treatment. Make decisions with the person after discussing these factors. [2009, amended 2018]

Adjuvant chemotherapy for invasive breast cancer

1.8.1 For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline. Please refer to the summaries of product characteristics for individual taxanes and anthracyclines because there are differences in their licensed indications. [2018]

1.8.2 Discuss with people the benefits and risks of adding a taxane to anthracycline-containing regimens […] and:

- the benefits of reduced cardiac toxicity and reduced nausea
- the risks of additional side effects, including neuropathy, neutropenia and hypersensitivity
- the different side effects and dosing frequencies of different docetaxel and paclitaxel regimens, and the additional clinic visits that may be needed
- that absolute benefit is proportional to absolute risk of recurrence.

Please refer to the summaries of product characteristics for individual taxanes and anthracyclines because there are differences in their licensed indications. [2018]

1.8.3 Weekly and fortnightly paclitaxel should be available locally because these regimens are tolerated better than 3-weekly docetaxel, particularly in people with comorbidities. [2018]

Background

There was good evidence of improved survival when taxanes are added to anthracycline-based chemotherapy in people with node-positive and node-negative breast cancer. In both groups, the benefits and risks of treatment should be discussed because of the potential side effects associated with taxanes. Three-weekly docetaxel was identified as a regimen with potentially more toxicity than weekly or fortnightly paclitaxel.

Adjuvant bisphosphonate therapy

1.9.1 Offer bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer. [2018]

1.9.2 Consider bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy for postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence. Risk can be estimated using a range of standardised tools and clinical expertise. [2018]

Background

There was good evidence that treatment with sodium clodronate and zoledronic acid improved disease-free and overall survival in postmenopausal women with node-positive invasive breast cancer.

There was little evidence of benefit for other bisphosphonates. The committee recommended considering zoledronic acid or sodium clodronate treatment for other high-risk populations (such as postmenopausal women with node-negative invasive breast cancer and a high risk of recurrence), based on the evidence that sodium clodronate has overall survival benefits in mixed populations.

Although there is evidence that intravenous (IV) bisphosphonates have a higher risk of osteonecrosis of the jaw, oral bisphosphonates have a higher risk of gastrointestinal problems.

There is also a risk of atypical femoral fractures and osteonecrosis of the external auditory canal with bisphosphonates. Because each drug and regimen has different risks, the potential benefits and risks should be discussed with women to help them make an informed choice.

There was little evidence on survival, particularly for premenopausal women on ovarian suppression, those with node-positive or node-negative disease, and those with positive or negative oestrogen or progestogen statuses. There was not enough evidence to make a recommendation relating to the use of adjuvant bisphosphonates in premenopausal women. The committee agreed that further research is needed to determine the long-term survival benefits and the groups of people most likely to benefit from adjuvant bisphosphonates. So they made a research recommendation on groups of people who would benefit from the use of adjuvant bisphosphonates.

The committee did not look at the evidence relating to the use of bisphosphonates for bone health or for the use of baseline dual-energy X-ray absorptiometry (DEXA) scanning, so did not make any new recommendations.

Radiotherapy

1.10.1 Use a radiotherapy technique that minimises the dose to the lung and heart. [2018]

1.10.2 Use a deep inspiratory breath-hold radiotherapy technique for people with left-sided breast cancer to reduce the dose to the heart. [2018]

Background

There was good evidence that radiotherapy to the internal mammary nodes reduced locoregional recurrence and improved survival. However, the committee took into account the potential for lung and heart toxicity, so recommended using a radiotherapy technique that minimises this risk.

There was evidence that deep inspiratory breath-hold radiotherapy techniques reduce the mean radiotherapy heart dose for adults with left-sided invasive breast cancer receiving whole-breast radiotherapy. The committee did not identify any harms. There was also evidence that deep inspiration breath-hold radiotherapy techniques did not reduce the target coverage of whole-breast radiotherapy.

There was no evidence about the use of deep inspiration breath-hold radiotherapy techniques for people with right-sided breast cancer, so the committee did not make separate recommendations for this subgroup.

Radiotherapy after breast-conserving surgery

1.10.3 Offer whole-breast radiotherapy to women with invasive breast cancer who have had breast-conserving surgery with clear margins. [2018]

1.10.4 Consider partial breast radiotherapy (as an alternative to whole-breast radiotherapy) for women who have had breast-conserving surgery for invasive cancer (excluding lobular type) with clear margins and who:

- have a low absolute risk of local recurrence (defined as women aged 50 and over with tumours that are 3 cm or less, N0, ER-positive, HER2-negative and grade 1 to 2) and
- have been advised to have adjuvant endocrine therapy for a minimum of 5 years. [2018]

1.10.5 When considering partial breast radiotherapy (see recommendation 1.10.4), discuss the benefits and risks, and explain that:

- local recurrence with partial breast radiotherapy at 5 years is equivalent to that with whole-breast radiotherapy
- the risk of local recurrence beyond 5 years is not yet known
- there is a potential reduction in late adverse effects. [2018]

1.10.6 When delivering partial breast radiotherapy, use external beam radiotherapy. [2018]

1.10.7 Consider omitting radiotherapy for women who:

- have had breast-conserving surgery for invasive breast cancer with clear margins and
- have a very low absolute risk of local recurrence (defined as women aged 65 and over with tumours that are T1N0, ER-positive, HER2-negative and grade 1 to 2) and
- are willing to take adjuvant endocrine therapy for a minimum of 5 years. [2018]

1.10.8 When considering omitting radiotherapy for the population in recommendation 1.10.7, discuss the benefits and risks […] and explain that:

- without radiotherapy, local recurrence occurs in about 50 women per 1,000 at 5 years, and with radiotherapy, occurs in about 10 women per 1,000 at 5 years
- overall survival at 10 years is the same with or without radiotherapy
- there is no increase in serious late effects if radiotherapy is given (for example, congestive cardiac failure, myocardial infarction or secondary cancer. [2018]

Background

There is evidence that whole-breast radiotherapy after breast-conserving surgery reduces the risk of recurrence and increases overall survival. It also decreases rates of depression and anxiety.

However, because the risk of breast cancer recurring at 5 years is very low and there are harms associated with radiotherapy, the benefits of radiotherapy for women with a very low risk of recurrence are less certain. For these women, the committee agreed that healthcare professionals should fully discuss the benefits and risks with women before a decision is made.

Good evidence showed that partial breast radiotherapy led to similar results to whole-breast radiotherapy after breast-conserving surgery in women with a low risk of local recurrence. In addition, it may have fewer treatment-related adverse effects. There was evidence for multicatheter interstitial brachytherapy but this was not recommended because it is not currently available in England.

Radiotherapy after mastectomy

1.10.10 Offer adjuvant postmastectomy radiotherapy to people with node-positive (macrometastases) invasive breast cancer or involved resection margins. [2018]

1.10.11 Consider adjuvant postmastectomy radiotherapy for people with node-negative T3 or T4 invasive breast cancer. [2018]

1.10.12 Do not offer radiotherapy following mastectomy to people with invasive breast cancer who are at low risk of local recurrence (for example, most people who have lymph node-negative breast cancer). Risk can be estimated using a range of standardised tools and clinical expertise. [2018]

Background

The committee agreed that adjuvant postmastectomy radiotherapy should be offered to people who have macroscopically node-positive invasive breast cancer or have involved resection margins. This is because the evidence showed a beneficial effect on survival and local recurrence. Although the evidence was limited and the committee acknowledged that radiotherapy is associated with lung and cardiac morbidity, they concluded that for this group of women, the benefits of radiotherapy outweigh the harms.

There was evidence of a beneficial effect of postmastectomy radiotherapy on local recurrence and overall survival for people with node-negative invasive breast cancer. However, the committee agreed that there was a risk of over-treatment if all people with node-negative invasive breast cancer received postmastectomy radiotherapy. Therefore, the committee recommended that adjuvant postmastectomy radiotherapy should be considered for people with node-negative T3 or T4 invasive breast cancer. There was no

evidence for this specific subgroup but they would be considered at increased risk of recurrence and mortality relative to smaller, node-negative invasive breast cancers because of the size of the tumour.

The committee agreed that radiotherapy after mastectomy should not be offered to women with early invasive breast cancer who are at low risk of local recurrence (for example, most women who are lymph node-negative) because the evidence showed limited benefit in survival and local recurrence.

Dose fractionation

1.10.13 Use external beam radiotherapy giving 40 Gy in 15 fractions as standard practice for women with invasive breast cancer after breast-conserving surgery or mastectomy. [2009]

Breast boost following breast-conserving surgery

1.10.14 Offer an external beam boost to the tumour bed for women with invasive breast cancer and a high risk of local recurrence, following whole-breast radiotherapy. Risk can be estimated using a range of standardised tools and clinical expertise. [2009, amended 2018]

1.10.15 Inform women of the risk of side effects associated with an external beam boost to the tumour bed following whole-breast radiotherapy. [2009, amended 2018]

Radiotherapy to nodal areas

1.10.16 Do not offer adjuvant radiotherapy to regional lymph nodes to people with invasive breast cancer who have been shown to have histologically lymph node-negative breast cancer. [2009, amended 2018]

1.10.17 Do not offer adjuvant radiotherapy to the axilla after axillary clearance for invasive breast cancer. [2009, amended 2018]

1.10.18 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 4 or more involved axillary lymph nodes. [2009]

1.10.19 Offer adjuvant radiotherapy to the supraclavicular fossa to people with invasive breast cancer and 1 to 3 positive lymph nodes if they have other poor prognostic factors (for example, T3 and/or histological grade 3 tumours) and good performance status. [2009]

1.10.20 Consider including the internal mammary chain within the nodal radiotherapy target for people with node-positive (macrometastases) invasive breast cancer. [2018]

Background

There was good evidence that radiotherapy to the internal mammary nodes reduced locoregional recurrence and improved survival. However, the committee took into account the potential for lung and heart toxicity, and agreed the importance of using a radiotherapy technique that minimises this risk.

Neoadjuvant chemotherapy regimens

1.11.4 For people with ER/PR/HER2-negative (triple-negative) invasive breast cancer, consider a neoadjuvant chemotherapy regimen that contains both a platinum and an anthracycline. [2018]

1.11.5 Discuss the benefits and risks of adding a platinum to an anthracyclinecontaining neoadjuvant chemotherapy regimen (see table 6), and in particular the risk of increased toxicity. [2018]

Table 6 Benefits and risks of adding a platinum to anthracycline-containing neoadjuvant chemotherapy for triple-negative invasive breast cancer

Category	Effect of adding a platinum to anthracycline-containing (with or without taxane) neoadjuvant chemotherapy
Effect on breast conservation rate	Adding a platinum improves response rates compared with anthracycline-based (with or without taxane) chemotherapy. This may mean that some women who would otherwise need a mastectomy can be offered breast-conserving surgery
Effect on pathological complete response rate (no residual cancer found at surgery)	Adding a platinum improves the chances of all signs of cancer disappearing in both the breast and lymph nodes in the axilla, compared with anthracycline-based (with or without taxane) neoadjuvant chemotherapy
Effect on survival	No increase in overall survival with platinum-based chemotherapy
Side effects: Platinum-based therapy is only suitable for fit patients with no significant comorbidities	Adding a platinum may mean that side effects are more severe. Anaemia, thrombocytopenia, neutropenia and febrile neutropenia are seen more frequently with platinum-based chemotherapy On average, if 1,000 women with triple-negative breast cancer receive platinum-containing neoadjuvant chemotherapy, about 70 additional women would experience severe or life-threatening side effects compared with non-platinum neoadjuvant chemotherapy Bone marrow suppression and renal problems are likely in older people

Background

There was evidence that platinum-containing neoadjuvant chemotherapy regimens can improve pathological complete response rate and breast conservation rate in people with triple-negative invasive breast cancer. However, the committee took into account that platinum-containing regimens can cause anaemia, thrombocytopenia, neutropenia and febrile neutropenia, as well as bone marrow problems and renal problems in older people. The committee agreed that healthcare professionals should have a full discussion with people about the benefits and risks of these regimens.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2024) am 13.03.2024

#	Suchfrage
1	[mh ^"Breast Neoplasms"]
2	(breast OR mamma*):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesion* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Mar 2019 to present

Systematic Reviews in PubMed am 13.03.2024

verwendete Suchfilter ohne Änderung:

Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 14.02.2023.

#	Suchfrage
1	breast neoplasms/therapy[majr]
2	(breast[ti]) OR mamma*[ti]
3	(#2) AND (tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesion*[tiab] OR malignan*[tiab])
4	(#3) AND (treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
5	#1 OR #4
6	(#5) AND (systematic review[ptyp] OR meta-analysis[ptyp] OR network meta-analysis[mh] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR ((evidence-based medicine[mh] OR evidence synthes*[tiab]) AND review[pt]) OR ((("evidence based" [tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) 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

#	Suchfrage
	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])
7	((#6) AND ("2019/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Leitlinien in PubMed am 13.03.2024

verwendete Suchfilter ohne Änderung:

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

#	Suchfrage
1	breast neoplasms[majr]
2	(breast[ti]) OR mamma*[ti]
3	(#2) AND (((((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesion*[ti]) OR malignan*[ti]
4	#1 OR #3
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] *OR recommendation*[ti])*
6	(((#5) AND ("2019/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt] OR preprint[pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 13.03.2024

- 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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Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO