National Institute for Health and Care Excellence

Advanced breast cancer: diagnosis and treatment

[A] Evidence review for platinum-containing chemotherapy regimens

NICE guideline CG81

Evidence review underpinning recommendations 1.2.1, 1.6.1, 1.7.6, 1.7.14, 1.7.23 and a recommendation for research in the NICE guideline

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FINAL

NICE National Institute for Health and Care Excellence

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1 Platinum-containing chemotherapy regimens

1.1 Review question

What is the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced:

- triple negative breast cancer
- breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants?

1.1.1 Introduction

There are currently no recommendations on the use of platinum-containing chemotherapy regimens for people with advanced breast cancer which is triple negative or who have germline BRCA1 or BRCA2 pathogenic variants in the advanced breast cancer guideline (CG81). Triple negative breast cancer is a type of breast cancer in which cells do not over express receptors for oestrogen and progesterone or human epidermal growth factor. BRCA genes encode proteins that suppress tumour growth, meaning that the risk of developing breast cancer is increased in people with mutations to these genes. Some, but not all, people with triple negative breast cancer (TNBC) will have germline BRCA1 or BRCA2 pathogenic variants, and some people with germline BRCA1 or BRCA2 pathogenic variants will have other subtypes of breast cancer.

New evidence has been identified by the NICE surveillance review (2023) on platinum-containing chemotherapy regimens for people with advanced breast cancer. This evidence may support the development of advice in this area.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	**Inclusion:**
	• Adults (18 and over) with invasive adenocarcinoma of the breast with distant metastases (M1) who have:
	  ○ Triple negative breast cancer
	  ○ Breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants
	
	Exclusion:
	• Adults (18 and over) with metastases to the breast from other primary tumours
	• Adults (18 and over) with non-epithelial breast tumours (for example, angiosarcoma, lymphoma)
	• Adults (18 and over) with benign breast conditions (for example, fibroadenoma, benign phyllodes tumours)

Intervention	Any chemotherapy regimen containing a platinum agent. Platinums of interest:

	• Carboplatin (all doses and regimens) • Cisplatin (all doses and regimens). All of these comparisons will be included: 1. Regimen A + platinum agent vs regimen A 2. Regimen A + platinum agent vs regimen B 3. Single agent platinum vs regimen C
Comparator	Any chemotherapy regimen without a platinum agent. • We will exclude any chemotherapies which are not used in UK clinical practice

Outcomes	**Primary outcomes (critical outcomes)**
	• Progression-free survival
	• Overall survival
	• Objective tumour response rates
	Secondary outcomes (important outcomes)
	• Cancer-specific survival (or breast cancer mortality if cancer-specific survival is not reported)
	• Adverse events
	  ○ Anaemia
	  ○ Fatigue
	  ○ Hair loss (alopecia)
	  ○ Leukopenia
	  ○ Nausea/vomiting
	  ○ Nephrotoxicity
	  ○ Neuropathy (also reported as peripheral neuropathy)
	  ○ Neutropenia
	  ○ Neutropenic sepsis (reported as febrile neutropenia)
	  ○ Ototoxicity (including tinnitus and hearing loss, with all types analysed together)
	  ○ Thrombocytopenia
	  ○ Treatment-related death
	• Adherence to / completion of treatment
	• Quality of life

Study type	• Systematic reviews of randomised controlled trials (RCTs) • RCTs

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The following methods were specific for this evidence review:

1. The Cochrane systematic review by Egger et al. (2020) was included as the protocol was sufficiently similar to the protocol for this review. Four of the included studies in the systematic review had chemotherapies which are not used in UK clinical practice (see Table 1 for excluded chemotherapies) and data from these studies was not used for the current review. The remaining 6 included studies reported on platinum-containing regimens in people with advanced triple negative breast cancer and met our inclusion criteria for that particular population in our review protocol (see Table 2 for the included studies in our review). Outcomes for these studies were extracted directly from the Cochrane review. Characteristics of the studies were taken from the studies themselves, and they were also assessed for any additional relevant outcomes not included in the Cochrane review. A systematic search was carried out to identify potentially relevant studies not included in the Cochrane systematic review by Egger et al. (2020).

2. The committee had a discussion about the type of chemotherapies included in the platinum-containing regimens reported by Egger et al. (2020). They agreed to exclude studies with chemotherapies which are not used in UK clinical practice. Lobaplatin and oxaliplatin are not licensed in the UK and were not included in the analysis for this review.

3. The committee agreed to only include adverse events where severity grade was specified using the Common Terminology Criteria for Adverse Events (CTCAE). Adverse events at severity levels 1 and 2 were not reported for any adverse event outcome except hair loss, fatigue and ototoxicity. Grades 3 and 4 severity were reported (combined) for all outcomes.

4. In the Egger et al. (2020) Cochrane review, there were 3 type of studies included (3 different comparison types) and the committee agreed to include them all:

    1. studies where the treatments were identical apart from the platinum

    2. studies where one study arm contained a platinum and the other did not and the treatments in each arm were not identical otherwise

    3. studies with single treatment in each arm.

5. The risk of bias was assessed using Cochrane's risk of bias (RoB) 1 tool by the Egger et al. (2020) Cochrane review. We took their assessment for the studies included by Egger et al. (2020). We used Cochrane's RoB 2 tool to assess the new included study (Liu et al. 2024) as this is the preferred checklist listed in Developing NICE guidelines: the manual. Egger et al. (2020) specified that “lack of blinding can affect risk of bias in different ways for different outcomes” and that they assessed blinding of outcome assessment by dividing outcomes into 2 classes: 1) overall survival and 2) all other outcomes. They justified this division saying that assessment of overall survival was unlikely to be affected by non-blinding. They also divided the ‘incomplete outcome data’ risk of bias domain into 2 outcome classes: 1) time-to event outcomes and 2) dichotomous outcomes. Based on these divisions, our approach to reach an overall judgement about the risk of bias for outcomes from each primary study was as follows:

    a. Low risk of bias: outcome was judged to be at low risk of bias for all domains or to have some concerns about lack of blinding of participants and personnel (only for overall survival). Additionally, for the ‘incomplete outcome data’ risk of bias domain: time-to-event analysis was intention-to-treat (ITT) or if the highest percentage of randomised participants excluded from effect estimation was less than 10% for dichotomous outcomes.

b. Some concerns or moderate risk of bias: outcome was judged to be at unclear risk of bias for random sequence generation, allocation concealment or blinding of outcome assessment (apart from overall survival; see above) or selective reporting. Additionally, for the 'incomplete outcome data' risk of bias domain: time-to-event analysis was modified intention-to-treat (mITT) or if the highest percentage of randomised participants excluded from effect estimation was between 10% and 15% for dichotomous outcomes.

c. High risk of bias: outcome was judged to be at high risk of bias for at least one domain or to have multiple domains at unclear risk of bias. Outcomes from open-label trials were judged to be at high risk of bias (apart from overall survival). Additionally, for the 'incomplete outcome data' risk of bias domain: time-to-event analysis was per-protocol or if the highest percentage of randomised participants excluded from effect estimation was more than 15% for dichotomous outcomes.

6. We assessed applicability of the includes studies in Egger et al. (2020) based on our review protocol.

7. Where subgroup analyses were carried out the null hypothesis that there were no subgroup differences was rejected if the p value for the test for subgroup differences was <0.05.

8. In the protocol for all time-to-event and dichotomous outcomes, any statistically significant difference was deemed to be clinically important, and we used the line of no effect as one of the downgrades for imprecision. Our certainty in the outcome was therefore downgraded once for imprecision in GRADE if either end of the 95% confidence interval crossed the line of no effect. Certainty in the outcome was also downgraded if the number of participants contributing to the outcome did not meet a certain threshold. The threshold was decided using the power calculation of a reference study. The reference study used was one of our included studies (Tutt et al. 2018); a large UK based study, with a power calculation of 370 participants. Outcomes with a smaller sample size than 370 were therefore downgraded for imprecision.

9. For adverse events, when meta-analyses included 2 or more studies but some of these studies reported zero events in both arms and only 1 study reported events in either arm, the evidence for that adverse event was not downgraded for inconsistency. In meta-analyses with some studies reporting zero events (in one or both arms), the absolute risk was calculated using data from all studies in the analysis, including zero event studies.

10. Yardley et al. 2011 reported a 3-arm study. We followed the same approach as Egger et al. (2020) when we extracted additional data from Yardley et al. 2011 (additional adverse events: neutropenia, febrile neutropenia, thrombocytopenia, fatigue and neuropathy). This approach was to half the number of participants in the control group (chemotherapy regimen without platinum) to allow for both comparisons with the 2 chemotherapy regimens containing platinum to be included in the same meta-analysis. Therefore, Yardley et al. 2011 was regarded as a single study with 2 comparisons.

11. Time-to-event outcomes were analysed using the same methods as in the Cochrane systematic review by Egger et al. (2020). They stated that for time-to-event outcomes they extracted the hazard ratio (HR) and associated variance directly from the trial publication(s) if reported and that 'these were used to calculate observed (O) minus expected (E) numbers of events and logrank variance (V) for each treatment-comparison using the methods described by Tierney 2007 or Parmar 1998'. Tierney and

colleagues published an update on their 2007 publication (Tierney et al. 2025) including a calculator to estimate O minus E number of events and logrank V which we used with the new included study in this review (Liu et al. 2024).

12. We used the same definition as in the Cochrane systematic review by Egger et al. (2020) for overall survival (time elapsed between randomisation to date of death from any cause) and progression-free survival (time elapsed between randomisation and event, with event defined as disease progression or death from any cause). This means that the actual data reported as overall survival was the number of participants who died from any cause. Progression-free survival was reported as the number of participants who had either disease progression or those who died from any cause.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 08/04/2025. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR); Embase (Ovid); Epistemonikos; Medline ALL (Ovid). Limits were applied to remove animal studies; editorials; letters; news items; commentaries; conference abstracts; conference posters; case reports; and non-English language publications.

Standard NICE filters were used to limit to randomised controlled trials.

The searches for the cost effectiveness evidence were run on 10/04/2025. The following databases were searched: Embase (Ovid); International Health Technology Assessment Database (INAHTA) and Medline ALL (Ovid). Limits were applied to remove animal papers, non-English language papers, conference abstracts, editorials and letters. The validated NICE Cost Utility Filter was used on MEDLINE ALL and Embase.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2015 PRESS Guideline Statement. Further details and full search strategies for each database are provided in appendix B.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 480 references (see appendix B for the literature search strategy). Evidence from the list of references of included studies (5 references) was also reviewed.

In total 485 references were screened at title and abstract level against the review protocol, with 454 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full texts of 7 systematic reviews and 24 articles were ordered for closer inspection. One systematic review and 7 trials (published in 8 articles) met the criteria specified in the review protocol (appendix A). For a summary of the included studies see Table 2 and Table 4.

Study characteristics were extracted from the primary studies apart from the follow-up time for Yardley et al. (2018) which was not reported in the primary study and was taken from the Cochrane systematic review (Egger et al. 2020).

Although comparison types were presented separately in Table 2, Table 3 and Table 4, they were analysed together unless there were subgroup differences.

Included studies reported data on most of the outcomes listed in the review protocol (appendix A) apart from cancer-specific survival and quality of life.

There were no eligible studies reporting on regimen A plus platinum agent compared to regimen A.

There were no studies reporting data on people with advanced breast cancer with germline BRCA1 or BRCA2 pathogenic variants of receptor sub-types other than TNBC.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.13 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Cochrane systematic review (for full details of included primary studies, see Egger et al. 2020)

Author (year)	Primary studies from Egger et al. 2020 included in the NICE review	Population covered by systematic review	Intervention	Comparator	Outcomes	Risk of bias / applicability of systematic review
Egger (2020)	• Fan 2012 • Mustafa 2019 • Stemmler 2011 • Tutt 2018 • Yardley 2018 • Zhang 2018	**Inclusion criteria** **Type of studies** Properly randomised controlled clinical trials (i.e. where the trial report asserts that the trial was randomised and there was no evidence to suggest otherwise) were eligible for inclusion. Because individual trials may compare one or more platinum-based regimens to one or more non-platinum-based regimens, there were more 'treatment-comparisons' (i.e. platinum regimen versus non-platinum regimen comparisons) than studies in the review **Type of participants** Participants are women with metastatic triple negative breast cancer (mTNBC), whether newly diagnosed or recurrent, who may have been purposely selected for mTNBC, or inadvertently selected as a subgroup. Treatment-comparisons that included groups of women with loco-regionally recurrent disease or women with non-TNBC were only	• Any chemotherapy regimen containing a platinum agent	• Any chemotherapy regimen without a platinum agent	• Overall survival • Progression-free survival / time to progression • Time to treatment failure • Objective tumour response rate • Toxicity rates • Quality of life	• Low • Partially applicable

		eligible for inclusion if it was possible to distinguish between these groups (i.e. where data were reported separately) or if the proportion of women in each group represented at least 80% of the total group. There were no age restrictions. **Exclusion criteria** None reported				

See appendix D for full evidence tables.

Summary of studies included in the effectiveness evidence – Primary studies

Study characteristics were extracted from the primary studies apart from the follow-up time for Yardley et al. (2018) which was not reported in the primary study and was taken from the Cochrane systematic review (Egger et al. 2020).

Although we are presenting comparison types separately in Table 3 and Table 4, we analysed them together unless there were subgroup differences.

Table 3 Summary of studies included in the effectiveness evidence – Regimen A plus platinum agent compared to regimen B

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
Fan (2013)	Location: China Total sample size: 53 Follow-up time: median 24 months [IQR: NR]	Women: 100% mTNBC: 100% Median age: • platinum (48 years, range: 32 to 67) • non-platinum (49 years, range: 27 to 71) **Key inclusion criteria** • age 18 years or more • histologically confirmed ER-, PR-, and HER2- primary breast cancer • at least one measurable lesion according to RECIST 1.0 • no prior treatment of advanced disease • anthracyclines should have been given in the neoadjuvant or adjuvant setting • ECOG score 1 or more • adequate organ function • previous paclitaxel was allowed **Key exclusion criteria** • original primary tumour or subsequent relapse was known	• Docetaxel 75 mg/m2 plus cisplatin 75 mg/m2 IV infusion day 1 every 3 weeks for up to six cycles, until disease progression, unacceptable toxicity or patient consent withdrawal	• Docetaxel 75 mg/m2 IV infusion day 1 plus capecitabine 1000 mg/m2 bid, 2 weeks on, 1 week off every 3 weeks for up to six cycles, until disease progression, unacceptable toxicity or patient consent withdrawal	• Progression-free survival • Overall survival • Objective tumour response rate • Adverse events • Adherence to / completion of treatment	• Overall survival: high RoB, directly applicable • Other time-to-event outcomes: high RoB, directly applicable • Dichotomous outcomes: high RoB, directly applicable

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		to be positive for any of ER, PR or HER2 or if they had been treated for advanced disease • previous treatment with a platinum or docetaxel was not allowed				
Liu (2024)	Location: China Total sample size: 187 Follow-up time: not reported	Women: 100% mTNBC: 100% Median age: 53 years (range: 29 to 75) **Key inclusion criteria:** • age 18 to 75 years • without previous systemic therapy for advanced breast cancer • diagnosis with negative ER, PR, and HER2 phenotype • ECOG PS grade 0 to 2 • measurable disease by CT or MRI according to RECIST version 1.1 • at least 6 months from the last adjuvant chemotherapy to recurrence or metastasis • and expected survival 12 weeks or more **Key exclusion criteria:** • none reported	• Gemcitabine (1,000mg/m2) on days 1 and 8 plus carboplatin area under curve 2 on days 1 and 8 every 21 days. After 6–8 cycles, patients continued to receive gemcitabine as maintenance therapy until progression	• Gemcitabine (1,000mg/m2) on days 1 and 8 plus oral capecitabine (1000mg/m2 twice a day) on days 1–14 every 21days. After 6–8 cycles, patients continued to receive gemcitabine as maintenance therapy until progression	• Progression-free survival • Overall survival • Objective tumour response rate • Adverse events • Adherence to / completion of treatment	• Overall survival: moderate RoB, directly applicable • Other time-to-event outcomes: high RoB, directly applicable • Dichotomous outcomes: high RoB, directly applicable

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
Mustafa (2019)	Location: Egypt Total sample size: 110 Follow-up time: median 12 months	Women: 100% mTNBC: 100% Mean age: 46 years **Key inclusion criteria:** • metastatic triple-negative breast cancer • no previous use of chemotherapy for metastatic disease • at least one extracranial lesion which could be measured by MRI or CT in accordance with the response evaluation criteria in solid tumours • ECOG PS 0 to 2 **Key exclusion criteria:** • without triple-negative breast cancer • the potential of giving birth to a child with no willingness to use the adequate contraception • symptomatic or unstable CNS metastases • life expectancy not to be more than three months	• Cisplatin Plus Gemcitabine (cisplatin 75 mg/m2 on day 1; gemcitabine 1000 mg/m2 on days 1 and 8). Both drugs administered intravenously every 3 weeks for eight cycles at maximum or until the development of disease progress or the intolerable toxic effect	• Paclitaxel Plus Gemcitabine (paclitaxel 175 mg/m2 on day1; gemcitabine 1000 mg/m2 on days 1 and 8). Both drugs administered intravenously every 3 weeks for eight cycles at maximum or until the development of disease progress or the intolerable toxic effect	• Objective tumour response rate	• Dichotomous outcomes: high RoB, directly applicable

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
Stemmler (2011)	Location: Germany Total sample size: 141 Follow-up time: median 11.1 months (95% CI 7.6 to 14.6 months)	Women: 100% mTNBC: not reported Median age: • platinum (60 years; range: 36 to 74) • gemcitabine and vinorelbine (58 years; range: 38 to 77) • gemcitabine and capecitabine (60 years; range: 34 to 78) **Key inclusion criteria:** • age 18 to 70 years • one previous anthracycline-based regimen (in the adjuvant or in the metastatic setting) • no limit on number of previous chemotherapy regimens (except gemcitabine-, vinorelbine-, cisplatin- or capecitabine-containing regimens), or on the number of previous hormonal therapies • immunotherapy or local radiotherapy was allowed • at least one bi-dimensionally measurable lesion outside a previous radiation port • Karnofsky performance status 70% or more	• Gemcitabine 1000 mg/m2+ cisplatin 30 mg/m2. Treatment for a maximum of six (3 week) cycles	• Non-platinum-containing regimen A: Gemcitabine 1000 mg/m2 + vinorelbine 25 mg/m2. Treatment for a maximum of six (3 week) cycles • Non-platinum-containing regimen B: Gemcitabine 1000 mg/m2 + capecitabine 1.300 mg/m2. Treatment for a maximum of six (3 week) cycles	• Objective tumour response rate	• Dichotomous outcomes: high RoB, partially applicable

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• minimal life expectancy of 12 weeks • adequate haematological, renal, cardiac and hepatic function **Key exclusion criteria:** • pregnant, lactating or refused effective contraception • having only bone metastasis • known brain metastases or a secondary malignancy • history of another primary malignant disease other than in situ carcinoma of the uterine cervix or adequately treated basal cell skin cancer • active infection or any other concomitant severe clinical condition making implementation of the protocol including pre-hydration difficult • other cyto-toxic, immune or hormonal agents or radiation therapy • history of DPD-deficiency				

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
Yardley (2018)	Location: multicentre (Australia, Austria, Brazil, Canada, France, Germany, Greece, Italy, Portugal, Spain, UK, US) Total sample size: 191 Follow-up time: estimated minimum follow-up (1 month, based on first event on PFS curve); estimated maximum follow-up (35 months based on last censoring tick on OS curve)	Women: 100% mTNBC: 100% Median age: • platinum regimen A (55 years; range: 27 to 82) • platinum regimen B (59 years; range: 30 to 79) • non-platinum (53 years; range: 27 to 80) **Key inclusion criteria:** • women 18 years and older with mTNBC • no prior cytotoxic chemotherapy for metastatic breast cancer • measurable disease per RECIST v1.1 • ECOG PS 0 to 1 • prior adjuvant or neoadjuvant anthracycline therapy (unless not indicated by physician) **Key exclusion criteria:** • none reported	• Platinum-containing regimen A: Nab-paclitaxel 125 mg/m2 plus carboplatin area under the curve 2. All agents were given on days 1 and 8 every 3 weeks • Platinum-containing regimen B: Gemcitabine 1000 mg/m2 plus carboplatin area under the curve 2. All agents were given on days 1 and 8 every 3 weeks	• Nab-paclitaxel 125 mg/m2 plus gemcitabine 1000 mg/m2. All agents were given on days 1 and 8 every 3 weeks	• Progression-free survival • Overall survival • Objective tumour response rate • Adverse events • Adherence to / completion of treatment	• Overall survival: moderate RoB, directly applicable • Other time-to-event outcomes: high RoB, directly applicable • Dichotomous outcomes: high RoB, directly applicable

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
Zhang (2018) Hu (2015)	Location: China Total sample size: 236 Follow-up time: median follow-up was 54.7 months (IQR 47.5 to 60.7 months)	Women: 100% mTNBC: 100% Median age: 47 years (IQR: 42 to 56) **Key inclusion criteria:** • age 18 to 70 years • metastatic triple-negative breast cancer with no previous chemotherapy for metastatic disease • at least one extracranial measurable lesion by MRI or CT according to RECIST, version 1.1 • ECOG PS 0 to 1 • previous use of taxanes in the adjuvant or neoadjuvant setting was acceptable if relapse occurred at least 6 months after completion of the primary locoregional and neoadjuvant or adjuvant therapies **Key exclusion criteria:** • non-triple-negative breast cancer • child-bearing potential but unwillingness to use adequate contraception • symptomatic or unstable CNS metastases	• Cisplatin plus gemcitabine (cisplatin 75 mg/m2 on day 1; gemcitabine 1250 mg/m2 on days 1 and 8) intravenously every 3 weeks for a maximum of eight cycles, or until disease progression or intolerable toxic effects developed	• Paclitaxel plus gemcitabine (paclitaxel 175 mg/m2 on day 1; gemcitabine 1250 mg/m2 on days 1 and 8) intravenously every 3 weeks for a maximum of eight cycles, or until disease progression or intolerable toxic effects developed	• Progression-free survival • Overall survival • Objective tumour response rate • Adverse events • Adherence to / completion of treatment	• Overall survival: moderate RoB, directly applicable • Other time-to-event outcomes: high RoB, directly applicable • Dichotomous outcomes: high RoB, directly applicable

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• life expectancy of less than 3 months • participation in other trials within 4 weeks before enrolment • reduced haematological, hepatic, or renal functions • congestive heart failure • any concurrent medical disorder that could potentially increase the risk of toxic effects • other invasive malignant diseases within the past 5 years except excised basal cell skin carcinoma and cervical carcinoma in situ				

AUC: area under the curve; BRCA1 or 2: breast cancer gene 1 or 2; CI: confidence interval; CNS: central nervous system; CT: computed tomography scan; DPD: dihydropyrimidine dehydrogenase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER-: oestrogen receptor negative; HER2-; human epidermal growth factor receptor 2 negative; IQR: interquartile range; IV: intravenous; MRI: magnetic resonance imaging; mTNBC: metastatic triple negative breast cancer; NR: not reported; OS: overall survival; PFS: progression-free survival; PR-: progesterone receptor negative; RECIST: Response Evaluation Criteria in Solid Tumours; RoB: risk of bias.

Table 4 Summary of studies included in the effectiveness evidence – Single agent platinum compared to regimen C

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
Tutt (2018)	Location: UK Total sample size: 376 Follow-up time: not reported	Women: 100% mTNBC: platinum (n=174, 92.6%); non-platinum (n=180, 95.7%) Median age:	• Carboplatin (AUC 6 every 3 weeks for six cycles)	• Docetaxel (100 mg/m2 every 3 weeks for six cycles)	• Progression-free survival • Overall survival • Objective tumour	• Overall survival: high RoB, directly applicable • Other time-to-event outcomes:

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• platinum (55.7 years; IQR: 47.6 to 62.9) • non-platinum (54.9 years; IQR: 47.9 to 63.5) **Key inclusion criteria:** • fit to receive either study drug • have measurable confirmed advanced breast cancer unsuitable for local therapy with histologically confirmed ER, PR, and HER2 negative primary invasive breast cancer or confirmed germline BRCA1 or BRCA2 pathogenic variant carrier with any ER, PR and HER2 status • ECOG PS 0 to 2 • adequate renal function **Key exclusion criteria:** • original primary tumour or subsequent relapse known to be positive for any of ER, PR, or HER2 receptors unless patient is a known germline BRCA1 or BRCA2 pathogenic variant carrier • unfit for chemotherapy or with neuropathy >grade 1 (sensory or motor)			response rate • Adverse events • Adherence to / completion of treatment	high RoB, directly applicable • Dichotomous outcomes: high RoB, directly applicable

Author (year)	Location/Total sample size/Follow-up time	Mean or median age/Key inclusion and exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• previous chemotherapy for metastatic disease other than an anthracycline • previous taxane in adjuvant chemotherapy within 12 months of trial entry • previous treatment with a platinum chemotherapy drug • life expectancy of less than 3 months • bone limited disease • pregnant, lactating or potentially childbearing women not using adequate contraception				

AUC: area under the curve; BRCA1 or 2: breast cancer gene 1 or 2; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER-: oestrogen receptor negative; HER2-; human epidermal growth factor receptor 2 negative; IQR: interquartile range; mTNBC: metastatic triple negative breast cancer; OS: overall survival; PFS: progression-free survival; PR-: progesterone receptor negative; RoB: risk of bias.

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Interpreting the effectiveness evidence

Interpretation of hazard ratios (HR): A hazard ratio of less than 1 indicates that the intervention group experienced a lower hazard of the event than the control group. A hazard ratio of more than 1 indicates that the intervention group experienced a higher hazard of the event than the control group. For all outcomes expressed as HRs, the event is negative and so a HR less than 1 is favourable for the intervention (for overall survival, the

event is death from any cause; for progression-free survival the event is progression or death from any cause; for cancer-specific survival the event is death from cancer).

In the absence of published minimally important differences (MIDs) clinical decision thresholds were agreed with the committee and used to interpret the evidence. The line of no effect (in this case represented by 1.0) was used as a clinical decision threshold for dichotomous outcomes. No data was identified for quality of life (the only outcomes with a published MID).

The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables:

For outcomes without a published MID or where the clinical decision threshold is set as the line of no effect, results are divided into 2 groups as follows:

- The evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- It was not possible for the evidence to differentiate between comparators if the 95% CI crosses the line of no effect (shortened to 'could not differentiate').

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Overall survival

Table 5 Overall survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with non-platinum regimens	Risk with Platinum				
Overall survival: main analysis (relative effect less than 1 favours platinum-containing chemotherapy regimen)	626 per 1,000	583 per 1,000 (531 to 640)	HR 0.89 (0.77 to 1.04)	1043 (5 RCTs)	Low	Could not differentiate

CI: confidence interval; HR: hazard ratio.

*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).

**See full GRADE tables in appendix F for reasons for downgrading the evidence.

Progression-free survival

Table 6 Progression-free survival

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with non-platinum regimens	Risk with Platinum				
Progression-free survival: main analysis (relative effect less than 1 favours platinum-containing chemotherapy regimen)	928 per 1,000	875 per 1,000 (794 to 935)	HR 0.79 (0.60 to 1.04)	1043 (5 RCTs)	Very low	Could not differentiate
Progression-free survival: subgroup analysis by type of regimen comparison - Regimen A + platinum agent vs regimen B	899 per 1,000	809 per 1,000 (704 to 892)	HR 0.72 (0.53 to 0.97)	667 (4 RCTs)	Very low	Effect favours platinum-containing chemotherapy regimen
Progression-free survival: subgroup analysis by type of regimen comparison - Single agent platinum vs regimen C	973 per 1,000	981 per 1,000 (960 to 993)	HR 1.10 (0.89 to 1.35)	376 (1 RCT)	Very low	Could not differentiate
Progression-free survival: subgroup analysis by BRCA 1/2 gene status - germline BRCA1 or BRCA2 pathogenic variants	962 per 1,000	833 per 1,000 (636 to 960)	HR 0.55 (0.31 to 0.99)	57 (2 RCTs)	Very low	Effect favours platinum-containing chemotherapy regimen
Progression-free survival: subgroup analysis by germline BRCA 1/2 gene status – germline BRCA1 or BRCA2 gene wild-type	965 per 1,000	975 per 1,000 (936 to 993)	HR 1.10 (0.82 to 1.48)	391 (2 RCTs)	Very low	Could not differentiate

CI: confidence interval; HR: hazard ratio.

*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).

**See full GRADE tables in appendix F for reasons for downgrading the evidence.

Objective tumour response rate

Table 7 Objective tumour response rate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with non-platinum regimens	Risk with Platinum				
Objective tumour response rate: main analysis (relative effect greater than 1 favours platinum-containing chemotherapy regimen)	394 per 1,000	519 per 1,000 (417 to 649)	RR 1.32 (1.06 to 1.65)	1170 (7 RCTs)	Very low	Effect favours platinum-containing chemotherapy regimen
Objective tumour response rate: subgroup analysis by type of regimen comparison - Regimen A + platinum agent vs regimen B	420 per 1,000	593 per 1,000 (475 to 736)	RR 1.41 (1.13 to 1.75)	794 (6 RCTs)	Very low	Effect favours platinum-containing chemotherapy regimen
Objective tumour response rate: subgroup analysis by type of regimen comparison - Single agent platinum vs regimen C	340 per 1,000	313 per 1,000 (235 to 419)	RR 0.92 (0.69 to 1.23)	376 (1 RCT)	Very low	Could not differentiate
Objective tumour response rate: subgroup analysis by BRCA 1/2 gene status - germline BRCA1 or BRCA2 pathogenic variants	346 per 1,000	727 per 1,000 (412 to 1,000)	RR 2.10 (1.19 to 3.72)	57 (2 RCTs)	Very low	Effect favours platinum-containing chemotherapy regimen
Objective tumour response rate: subgroup analysis by germline BRCA 1/2 gene status – germline BRCA1 or BRCA2 gene wild-type	385 per 1,000	366 per 1,000 (235 to 566)	RR 0.95 (0.61 to 1.47)	451 (2 RCTs)	Very low	Could not differentiate

CI: confidence interval; RR: risk ratio.

*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).

**See full GRADE tables in appendix F for reasons for downgrading the evidence.

Treatment-related death

Table 8 Treatment-related death

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)*	Interpretation of effect
	Risk with non-platinum regimens	Risk with Platinum				
Treatment-related death (relative effect less than 1 favours platinum-containing chemotherapy regimen)	4 per 1,000	4 per 1,000 (1 to 19)	RR 1.06 (0.24 to 4.61)	1030 (5 RCTs)	Very low	Could not differentiate

CI: confidence interval; RR: risk ratio.

*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).

**See full GRADE tables in appendix F for reasons for downgrading the evidence.

Adverse events

Table 9 Adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with non-platinum regimens	Risk with Platinum				
Anaemia (relative effect less than 1 favours platinum-containing chemotherapy regimen)	38 per 1,000	114 per 1,000 (54 to 242)	RR 3.04 (1.43 to 6.45)	1030 (5 RCTs)	Very low	Effect favours non-platinum chemotherapy regimen
Leukopenia (relative effect less than 1 favours platinum-containing chemotherapy regimen)	184 per 1,000	222 per 1,000 (180 to 277)	RR 1.21 (0.98 to 1.51)	1030 (5 RCTs)	Very low	Could not differentiate
Neutropenia (relative effect less than 1 favours platinum-containing chemotherapy regimen)	251 per 1,000	388 per 1,000 (253 to 596)	RR 1.55 (1.01 to 2.38)	1030 (5 RCTs)	Very low	Effect favours non-platinum chemotherapy regimen
Neutropenic sepsis (relative effect less than 1 favours platinum-containing chemotherapy regimen)	17 per 1,000	34 per 1,000 (16 to 76)	RR 2.06 (0.93 to 4.55)	1030 (5 RCTs)	Very low	Could not differentiate
Thrombocytopenia (relative effect less than 1 favours platinum-containing chemotherapy regimen)	46 per 1,000	185 per 1,000 (69 to 492)	RR 4.02 (1.51 to 10.71)	1030 (54 RCTs)	Very low	Effect favours non-platinum chemotherapy regimen
Fatigue - Grade 1 and 2 (relative effect less than 1 favours platinum-containing chemotherapy regimen)	551 per 1,000	628 per 1,000 (502 to 788)	RR 1.14 (0.91 to 1.43)	842 (4 RCTs)	Very low	Could not differentiate
Fatigue - Grade 3 and 4 (relative effect less than 1 favours platinum-containing chemotherapy regimen)	111 per 1,000	52 per 1,000 (19 to 139)	RR 0.47 (0.17 to 1.25)	790 (3 RCTs)	Very low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with non-platinum regimens	Risk with Platinum				
Hair loss - Grade 1 and 2 (relative effect less than 1 favours platinum-containing chemotherapy regimen)	38 per 1,000	75 per 1,000 (8 to 745)	RR 1.96 (0.20 to 19.53)	789 (3 RCTs)	Very low	Could not differentiate
Nausea/vomiting (relative effect less than 1 favours platinum-containing chemotherapy regimen)	12 per 1,000	65 per 1,000 (27 to 153)	RR 5.44 (2.30 to 12.86)	842 (4 RCTs)	Low	Effect favours non-platinum chemotherapy regimen
Neuropathy (relative effect less than 1 favours platinum-containing chemotherapy regimen)	42 per 1,000	8 per 1,000 (3 to 23)	RR 0.20 (0.08 to 0.54)	1030 (5 RCTs)	Low	Effect favours platinum-containing chemotherapy regimen
Ototoxicity - Grade 1 and 2 (relative effect less than 1 favours platinum-containing chemotherapy regimen)	10 per 1,000	37 per 1,000 (10 to 130)	RR 3.65 (1.03 to 12.96)	602 (2 RCTs)	Low	Effect favours non-platinum chemotherapy regimen
Ototoxicity - Grade 3 and 4 (relative effect less than 1 favours platinum-containing chemotherapy regimen)	0 per 1,000***	0 per 1,000 (0 to 0)	RR 2.98 (0.31 to 28.52)	602 (2 RCTs)	Very low	Could not differentiate

CI: confidence interval; RR: risk ratio.

*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).

**See full GRADE tables in appendix F for reasons for downgrading the evidence.

*** Absolute effects could not be estimated because there were 0 events in one of the arms.

Adherence to / completion of treatment

Table 10 Adherence to / completion of treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of the evidence
	Risk with non-platinum regimens	Risk with Platinum				
Treatment discontinuation due to adverse event (relative effect less than 1 favours platinum-containing chemotherapy regimen)	111 per 1,000	97 per 1,000 (45 to 208)	RR 0.88 (0.41 to 1.88)	1030 (5 RCTs)	Very low	Could not differentiate

CI: confidence interval; RR: risk ratio.

*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).

**See full GRADE tables in appendix F for reasons for downgrading the evidence.

See appendix F for full GRADE.

Advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants

There were no studies reporting data on people with advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants other than triple negative. There was data reported as subgroup analysis of BRCA gene status within the advanced triple negative breast cancer population (see Table 6 and Table 7 above).

1.1.7 Economic evidence

1.1.7.1 Included studies

No economic studies were identified which were applicable to this review question. (see economic study selection flow chart in appendix G).

1.1.7.2 Excluded studies

No economic studies were reviewed at full text and excluded from this review.

1.1.8 Summary of included economic evidence

No economic studies were identified which were applicable to this review question.

1.1.9 Economic model

No original economic modelling was completed for this review question.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

Chemotherapy for advanced breast cancer aims to control or slow the growth of the cancer and also to relieve some symptoms. As a result, the committee agreed that the critical outcomes for this review were survival outcomes (overall survival and progression-free survival) and objective tumour response rate (proportion of participants who experienced a complete or partial tumour response). In addition, objective tumour response can be used by clinicians to make decisions about changes to management or treatment.

The committee acknowledged the importance of other outcomes including cancer-specific survival and quality of life in decision making. Cancer-specific survival and quality of life were not expected to be widely reported and therefore they were considered important but not critical to decision making. Quality of life can be severely affected by chemotherapy.

The committee noted that many people expect to experience adverse events while on chemotherapy. However, they agreed that the risk of adverse events (especially severe ones) and types of adverse events that people with advanced triple negative breast cancer (TNBC) may experience with platinum-based chemotherapy is likely to influence their decision about whether to accept a particular treatment and whether to continue taking it. Therefore, they agreed that adverse events and treatment discontinuation due to adverse events were also important outcomes for decision making. These outcomes were especially important given the lack of evidence about effects of treatment on quality of life.

1.1.10.2 The certainty of the evidence

Advanced triple negative breast cancer

Overall, the outcomes ranged from low to very low certainty with the main reasons for downgrading being due to risk of bias, inconsistency and imprecision of the evidence. Most

of the outcomes were judged to be at high risk of bias due to poor reporting about random sequence generation and treatment allocation concealment, being open-label trials, having incomplete outcome data, and lack of a registered protocol. Some of the outcomes were downgraded once for imprecision as the 95% confidence interval crossed the line of no effect (in this case represented by the value of 1.0). Certainty in the outcome was also downgraded if the number of participants contributing to the outcome did not meet a certain threshold. The threshold was decided using the power calculation of a reference study. The reference study used was one of our included studies (Tutt et al. 2018); a large UK based study, with a power calculation of 370 participants. Outcomes with a smaller sample size than 370 were therefore downgraded for imprecision.

Most of the evidence for adverse events had wide confidence intervals which may be because sample size and number of events were small. These wide confidence intervals indicate that there was substantial uncertainty around the evidence for adverse events (for example, the magnitude of the effect) and this was reflected in the very low certainty of evidence. The committee therefore was unable to use this evidence to support their decision making regarding adverse events.

The majority of the outcome data related to the critical outcomes: overall survival (OS), progression-free survival (PFS), and objective treatment response rate (OTRR). Treatment discontinuation due to adverse events was the second most reported outcome. There was less evidence for individual adverse events. There was no evidence at all on cancer-specific survival and quality of life.

The committee had specified that a number of subgroup analyses be carried out to help them with drafting recommendations. There were 2 types of studies included in this evidence review which were also included in the Cochrane systematic review by Egger et al. (2020). These were:

- studies with one arm containing a platinum and the other without a platinum and where the rest of treatments in each arm were not identical
- studies with single treatments in both arms, with one arm having a platinum and the other arm a different chemotherapy agent.

The committee agreed to include both types of studies but specified that a subgroup analysis be carried out to look at whether the effects of these 2 types of trials were consistent with each other. The subgroup analyses were carried out for the critical outcomes of OS, PFS, and OTRR. There were no detectable subgroup differences for OS on any of the subgroup analyses (p value of the test for subgroup differences was ≥0.05) (Figure 2, Figure 3 and Figure 4). (See benefits and harms for more about subgroup analyses with statistically significant differences.)

No subgroup differences were detectable for PFS and OTRR between the groups based on the type of platinum agent (cisplatin compared to carboplatin, Figure 7 and Figure 11).

Subgroup analyses by line of therapy (first line versus second or third line) were not necessary for OS and PFS because studies reporting on these outcomes included only participants with first-line therapy (more than 80% of participants) and no participants or less than 20% of participants with second or third-line therapy. Two additional studies reported data on OTRR without detectable subgroup differences between the groups based on the line of therapy (first-line therapy compared to second or third-line therapy, Figure 12).

Subgroup analyses by BRCA gene status in people with advanced TNBC was limited because this was only reported by 2 studies (Tutt et al. 2018 and Zhang et al. 2018). The

data for this subgroup analysis was reported by a single study (Tutt et al. 2018) for OS, but there were no detectable subgroup differences (Figure 4). (See benefits and harms for more about subgroup analyses with statistically significant differences.)

The committee highlighted that some participants in the trials included in this review may have 'crossed over' to receive the regimen that they were not supposed to have according to what they were allocated at the beginning of the trial. This means that some participants may have received both a platinum-containing chemotherapy regimen and a chemotherapy regimen without a platinum. Some of the reasons for this 'cross over' could be due to toxicity or disease progression with the allocated regimen. Two trials reported this 'cross over'. Tutt et al. (2018) included 'response to cross over treatment' as a secondary endpoint which showed similar results as the primary endpoint (OTRR with intention-to-treat analysis). Zhang et al. (2018) included in their discussion that there was 'cross over' between the 2 groups after progression because participants were treated with a range of other drugs after progression, but the authors did not report any analyses to explore the effect of 'crossing over' on outcomes. The effect of 'crossing over' might be expected to dilute any difference in effect between the two arms, for overall survival, but would not be likely to affect response rates or progression as these would be specific to the treatment of interest. Reporting did not allow the committee to assess the full extent of any dilution.

Advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants

The only studies reporting data on people with germline BRCA1 or BRCA2 pathogenic variants included people with advanced TNBC. As no evidence for other receptor subtypes was identified, and evidence on people with advanced TNBC and germline BRCA1 or BRCA2 pathogenic variants was covered in the section above, it is not repeated here. The committee agreed that this was an important topic for further research and made a recommendation for research for this population (see appendix K).

1.1.10.3 Benefits and harms

Advanced triple negative breast cancer

The committee were aware that the included studies in this review defined TNBC in different ways. Some studies reported that TNBC referred to histological confirmation of the 3 receptors being negative: oestrogen, progesterone and HER2. Other studies only mentioned TNBC without a specific definition. The committee highlighted that technically a person would be diagnosed with TNBC when all 3 of the receptors were negative but that realistically this is not always done. Particularly progesterone receptor testing may not be done but people should not be excluded from recommendations about TNBC if they test negative to both oestrogen and HER2 receptors and their progesterone receptor status is unknown.

The committee discussed the evidence for platinum-containing chemotherapy regimens for people with advanced TNBC and noted that there were no statistically significant differences between regimens containing platinum agents compared to regimens without platinum agents for OS and PFS (main analyses) and that the evidence was uncertain or very uncertain. Based on this evidence and on their clinical experience, the committee agreed that both types of regimens (with or without platinum agents) are expected to be effective in people with advanced TNBC, with neither likely to be inferior to the other.

The committee also noted that there was a statistically significant improvement in OTRR with regimens containing platinum agents compared to regimens without platinum agents (risk

ratio 1.32, 95% CI 1.06 to 1.65) but that the evidence was of very low certainty, due to very serious risk of bias and very serious inconsistency. This indicates variation between the studies which may be partly due to the non-platinum agents of the regimens differing. The evidence of improved response rate was therefore not robust enough to recommend regimens containing platinum agents over regimens without platinum agents.

Subgroup analyses were carried out where there was data. Subgroup differences were detected for some of the analyses (see certainty of the evidence for more about subgroup analyses without statistically significant differences).

For PFS (Figure 6) and OTRR (Figure 10) there was a statistically significant difference between subgroups for the analysis based on the type of regimen comparison. There was an improvement in both outcomes with platinum containing regimens (regimen A + platinum agent) compared to regimen B, but the evidence could not differentiate between the results for the groups of studies comparing single agent platinum vs regimen C. There were no studies comparing regimen A + platinum agent vs regimen A. The committee did not make separate recommendations based on the type of chemotherapy regimen because the evidence was of very low certainty.

There was also a statistically significant difference between subgroups for the analysis based on BRCA gene status. There was an improvement in both outcomes (PFS - Figure 8 and OTRR - Figure 13) with platinum containing regimens over non-platinum containing regimens in the BRCA 1/2 gene pathogenic variants subgroup in people with advanced TNBC. For both analyses, the evidence could not differentiate between arms in the germline BRCA1 or BRCA2 gene wild-type. The committee did not make separate recommendations for people with advanced TNBC and germline BRCA1 or BRCA2 pathogenic variants because the evidence was of very low certainty.

The committee discussed the evidence for adverse events and noted that there was low to very low certainty evidence about the effect of regimens containing platinum agents compared to regimens without platinum agents. This meant that the committee could not draw conclusions from this evidence, but noted that in their experience there may be increased risk of some adverse events such as anaemia, neutropenia, or thrombocytopenia. They agreed that there should be a consideration of the potential increased risk of these adverse events when discussing the balance between the benefits and risks of using these regimens. The committee noted that all treatments have different side effect profiles (with this review focussing primarily on the side effects most associated with regimens containing platinum elements).

Advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants

There were no studies reporting data on people with advanced breast cancer of other receptor sub-types (apart from TNBC) with germline BRCA1 or BRCA2 pathogenic variants.

Drafting recommendations

Platinum based chemotherapy for people with advanced TNBC

In 2025 the NICE guideline on advanced breast cancer was reordered to reflect the sequence of treatment by receptor subtype. This change reflects current practice, is consistent with the structure of the related NICE guideline on early and locally advanced breast cancer (NG101) and facilitates incorporation of relevant NICE technology appraisal guidance. In 2009, when the original guideline was developed, no specific recommendations

were made for people with advanced triple negative breast cancer. Instead, there were 4 separate recommendations on chemotherapy that applied to all people with advanced breast cancer. These recommendations were revisited by the current committee as part of this review work and stood down where they were judged to no longer be relevant to current practice or merged into the new chemotherapy recommendations where they still contained relevant information.

The committee noted that the 2009 recommendation about offering systemic sequential therapy to the majority of people with advanced breast cancer who have decided to be treated with chemotherapy was no longer relevant because of changes in practice due to the large number of new systemic anti-cancer therapies (SACTs) that have been developed targeting breast cancer cells expressing specific receptor subtypes. They agreed to amend this recommendation for people with triple negative breast cancer so that systemic sequential chemotherapy is offered specifically where it is indicated.

The committee agreed that the decision about which chemotherapy to use is a complex one that takes many factors into account (see below for more about this point) and needs to be tailored to the individual. The committee agreed that it was not possible from the evidence presented to differentiate between regimens containing platinum agents compared to regimens without platinum agents for OS and PFS and the evidence for OTRR was weak. They decided, based on the evidence about platinums and their experience, to supplement the recommendation for sequential chemotherapies discussed above with a recommendation listing the systemic sequential chemotherapy options that could be considered. The non-exhaustive list includes anthracyclines, capecitabine, carboplatin, taxanes and vinorelbine. The list of options was taken from the 2009 recommendation, but with the addition of carboplatin based on this review. The committee noted that although the evidence in this review included carboplatin and cisplatin, carboplatin is the only platinum used in UK practice currently. As no subgroup differences were observed between carboplatin and cisplatin, the committee agreed that the evidence supported naming carboplatin specifically. The last part of this recommendation consists of a cross reference to technology appraisals (TAs) for eribulin and gemcitabine with paclitaxel.

The committee noted the limited evidence on the greater effectiveness of platinum-containing chemotherapy regimens compared to non-platinum containing regimens for people with advanced TNBC and with germline BRCA1 or BRCA2 pathogenic variants. They did not think that this evidence was robust or certain enough to support making separate recommendations for this subgroup of people. They noted that there are 2 NICE technology appraisals (which do not cover platinum-containing chemotherapy regimens) with recommendations for people with advanced breast cancer and with germline BRCA1 or BRCA2 pathogenic variants (TA1040 on olaparib and TA952 on talazoparib). These technology appraisals were incorporated into the guideline.

Factors to consider when choosing systemic anti-cancer therapy (SACT) for all people with advanced breast cancer

The committee discussed the factors that would affect the choice of chemotherapy for people with TNBC. They agreed that the decision is nuanced and affected by a range of factors about the person, the characteristics of their cancer (including tumour characteristics as well as their genetic characteristics such as their BRCA1/2 gene status) and their treatment history. These factors are overarching and not relevant only to decisions about chemotherapy, or only for people with advanced TNBC. Therefore, the committee decided to make a recommendation that applies to all types of SACT and all people with advanced breast cancer.

The committee agreed that there should be a balance between clinical outcomes and patient reported outcomes when making decisions about chemotherapy regimens. However, there was no evidence available on quality of life and the committee had to use their own expertise and experience to try to fill this gap. The committee included lay members who were able to bring their experiences, and those of people in the patient networks they are involved in, to the discussions.

The committee agreed that it is important to discuss the person's preferences and ask about their personal circumstances when health professionals explain the benefits and risks of having a chemotherapy regimen containing a platinum or other SACT regimens. They were aware that, in addition to clinical factors (including the potential benefits in terms of OS, PFS, OTRR, and the risk of adverse events), there are a range of factors that will influence a person's choice of whether to have SACT and their preferred SACT regimen. This could include the number of cycles of chemotherapy and spacing of the cycles. For example, people who have childcare and other caring responsibilities, or those who will have to take unpaid time off from work, may prefer certain regimens or decline this treatment.

The committee highlighted that clinicians would look at what comorbidities the person had, the characteristics of the cancer (for example their PD-L1 [programmed death-ligand 1] status or whether they have germline BRCA1 or BRCA2 pathogenic variants) and what SACT the person had had before when deciding what regimen to offer. They would also look at the clinical benefits of each treatment, alongside what side effects the person had experienced with any previous SACT and how well the treatments were tolerated, as well as how the individual felt about the potential side effects that may be caused by the different options available, to inform the current choice of treatment. The committee also highlighted that NHS funding agreements (including those covered by TAs for individual SACT drugs) and commissioning policies (including those covered by the NHS England Cancer Drugs Fund list) would affect what SACT options are available to individuals.

The committee, and in particularly the patient representatives, noted that in their experience many people undergoing chemotherapy and other SACT are aware of and prepared to accept some adverse events in order to access the oncological benefits of effective treatments. They also highlighted that it is important to have a balance between oncological effectiveness and the risk of severe side effects requiring hospitalisation and that the risk of these may vary between individuals. The committee noted that some of the side effects can be mitigated (for example, giving platinum agents weekly instead of every three weeks to reduce neutropenia). They therefore agreed that it is important to take into account the expected side effects of the possible SACT regimens and how they are delivered (for example, oral or intravenous) and scheduled when deciding between SACT regimens.

In conclusion, the committee drafted a recommendation that covered the points discussed above to help with decision making about the choice of SACTs, including chemotherapy regimens. They also agreed that a discussion should take place with the person who has advanced breast cancer about the benefits and risks of any relevant SACT options but because this is covered by recommendations about communicating risks, benefits and consequences discussing treatment options in the NICE guideline on shared decision making they did not need to make a separate recommendation here.

The committee also agreed that it is important that people with advanced breast cancer have opportunities to be involved in research to help improve the evidence base about which treatments are most effective and might benefit people with advanced breast cancer. All available opportunities that may be suitable for the person should be looked at, and the committee noted that this should happen throughout the treatment pathway (including early on) and not only after standard treatment lines are exhausted. The opportunities should not

be limited to their centre, but taking part in research in other centres may involve travelling further. There may also be non-clinical studies, for example looking at their views and experiences of treatment. The committee therefore recommended that research opportunities should be discussed with the person, including the benefits and risks of entering clinical trials and other studies and that people with advanced breast cancer should be supported to participate in research if they wish to do so.

The availability of relevant clinical trials can also affect the choice of treatments available to the individual. The committee noted that information about these can be accessed via websites such as Be Part of Research and ISRCTN: The UK's clinical study registry, and that clinicians may also be aware of ongoing trials that could be suitable for the individual with advanced breast cancer based on their characteristics mentioned above. They included this information in the recommendation about factors to take into account when making decisions about the choice of SACT discussed above.

1.1.10.4 Cost effectiveness and resource use

No previous economic evidence was identified which was relevant to this review question.

These recommendations are unlikely to lead to a significant change in practice. Treatment in this area is already highly nuanced and based on patient preference and previous treatment. The recommendations largely highlight what treatments are available. There is also not a large cost differential between platinum and non-platinum treatments.

The evidence suggested that adverse events might be more common with platinum-containing regimens which may lead to increased treatment costs. However, the committee expect the number of people changing from non-platinum-containing regimens to platinum containing regimens to be small.

Any resource impact from these recommendations is expected to be small and outweighed by the benefits of more personalised treatment.

1.1.10.5 Other factors the committee took into account

In the 2009 version of this guideline, the chemotherapy recommendations applied to patients with advanced breast cancer without mention of receptor subtype because this was not used to determine treatment at that time. In updating the guideline, the current committee have inserted sections for SACT recommendations for people with triple-negative; HER2-positive; and Hormone-receptor-positive, HER2-negative advanced breast cancer. They repeated the 2009 recommendation for sequential chemotherapy in each section but adapted it to mention the specific receptor subtype.

The committee agreed that the rationale behind the new recommendation on the types of chemotherapy regimens for people with TNBC also applied to people with HER2-positive or Hormone-receptor-positive HER2-negative breast cancer. They therefore included the same recommendation in both of these sections of the guidelines, but without the inclusion of carboplatin as the evidence for the effectiveness of platinum-based regimens was not considered in relation to advanced breast cancer of these receptor subtypes.

The committee noted that the equality and health inequalities assessment that accompanies this update highlighted a large number of issues that could act as barriers to people with advanced TNBC with or without germline BRCA1 or BRCA2 pathogenic variants and may constrain their decisions about whether to have chemotherapy and the type of chemotherapy regimen (platinum based or non-platinum based). However, they noted that many of these

issues were societal and not within the committee's ability to address. For example, problems associated with being able to afford to take time off work and having access to affordable transport to take them to appointments or limited availability of healthcare facilities and long waiting times. However, there are local initiatives in some places that provide free transport and extended or weekend clinic hours that may help those who require this type of support.

The committee discussed issues related to communication of information in a way that is accessible for people with a range of needs (including those with low health literacy, people who have severe learning disabilities, people who are neurodiverse). They noted that some groups, such as people with learning disabilities and autism, may need reasonable adjustments to be made to overcome barriers to access and enable them to make informed decisions. The committee noted that making reasonable adjustments is a legal requirement as stated in the Equality Act 2010. They also noted that there is a newly released Reasonable Adjustment Digital Flag (RADF) and Information Standard. This mandates the identification of people who need reasonable adjustments and the recording, sharing and maintenance of this information with relevant health care providers.

The committee also agreed that factors such as having physical or learning disabilities, comorbidities, or being older should not prevent someone from being offered a chemotherapy regimen that includes a platinum or any SACT. However, they acknowledged that these people may need additional support to overcome any barriers they face when deciding what is the right option for them and to help them access treatment.

The committee agreed that it was not necessary for them to make recommendations to address the issues discussed above around communication and shared decision making because they are already covered by other NICE guidelines. They noted that the following sections are particularly relevant:

- enabling patients to actively participate in their care (covering communication and information), knowing the patient as an individual in the NICE guideline on patient experience in adult NHS services
- putting shared decision making into practice and communicating risks, benefits and consequences in the NICE guideline on shared decision making.

The committee noted that cross references to these guidelines are already present at the top of each guideline and so did not need to include additional cross references to them.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.1, 1.6.1, 1.7.6, 1.7.14, 1.7.23 and the research recommendation on germline BRCA1 or BRCA2 pathogenic variants.

1.1.12 References – included studies

1.1.12.1 Effectiveness

Egger, Sam J, Chan, Matthew Ming Ki, Luo, Qingwei et al. (2020) Platinum-containing regimens for triple-negative metastatic breast cancer. The Cochrane database of systematic reviews 10: cd013750

Fan, Y, Xu, B H, Yuan, P et al. (2013) Docetaxel-cisplatin might be superior to docetaxel-capecitabine in the first-line treatment of metastatic triple-negative breast cancer. Annals of oncology : official journal of the European Society for Medical Oncology 24(5): 1219-25

Hu, Xi-Chun, Zhang, Jian, Xu, Bing-He et al. (2015) Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial. The Lancet. Oncology 16(4): 436-46

Liu, X., Zhao, W., Jia, Y. et al. (2024) A non-inferiority, phase III trial of gemcitabine plus capecitabine versus gemcitabine plus carboplatin as first-line therapy and tumor-infiltrating lymphocytes as a prognostic biomarker in patients with advanced triple-negative breast cancer. Therapeutic Advances in Medical Oncology 16

Mustafa, Sharehan Hassan Soliman, Zamzam, Maha Lotfy, Abdel Mohsen, Soheir El-sayed et al. (2019) Cisplatin Plus Gemcitabine Versus Paclitaxel Plus Gemcitabine as First-Line Therapy for Metastatic Triple Negative Breast Cancer. EJHM 74(8): 1878-1883

Stemmler HJ, diGioia D, Freier W et al. (2011) Randomised phase II trial of gemcitabine plus vinorelbine vs gemcitabine plus cisplatin vs gemcitabine plus capecitabine in patients with pretreated metastatic breast cancer. British journal of cancer 104(7): 1071-1078

Tutt, Andrew, Tovey, Holly, Cheang, Maggie Chon U et al. (2018) Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. Nature medicine 24(5): 628-637

Yardley, D A, Coleman, R, Conte, P et al. (2018) nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial. Annals of oncology : official journal of the European Society for Medical Oncology 29(8): 1763-1770

Zhang, J, Lin, Y, Sun, X J et al. (2018) Biomarker assessment of the CBCSG006 trial: a randomized phase III trial of cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine as first-line therapy for patients with metastatic triple-negative breast cancer. Annals of oncology: official journal of the European Society for Medical Oncology 29(8): 1741-1747

1.1.13.2 Economic

No economic studies were identified which were applicable to this review question.

1.1.13 References – other

Tierney, J.F., Burdett, S. & Fisher, D.J. Practical methods for incorporating summary time-to-event data into meta-analysis: updated guidance. Syst Rev 14, 84 (2025). https://doi.org/10.1186/s13643-025-02752-z

Appendices

Appendix A – Review protocols

Review protocol for platinum-containing chemotherapy regimens in people with advanced breast cancer that is triple negative and/or who have germline BRCA1 or BRCA2 pathogenic variants

ID	Field	Content
1.	Review title	1.1 What is the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced: • triple negative breast cancer • breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants?
2.	Review question	1.1 What is the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced: • triple negative breast cancer • breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants?
3.	Objective	To assess the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced: • triple negative breast cancer • breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistimonikos • MEDLINE ALL For the economics review the following databases will be searched: • Embase • MEDLINE ALL • INAHTA Searches will be restricted by: • English language • Human studies

		• Abstracts, conference presentations, and theses will be excluded. • Systematic reviews and RCTs The following standard NICE filters will be used to limit results by study type: cost effectiveness studies /systematic reviews / randomised controlled trials The information services team at NICE will quality assure the principal search strategy. Any revisions or additional steps will be agreed by the review team before being implemented. The full search strategies for all databases will be published in the final review.
5.	Condition or domain being studied	Advanced breast cancer that is triple negative or of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants. Advanced is defined as with distant metastases (M1 using the TNM staging system).

6.	Population	**Inclusion:**
		• Adults (18 and over) with invasive adenocarcinoma of the breast with distant metastases (M1) who have:
		  ○ Triple negative breast cancer
		  ○ Breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants
		Exclusion:
		• Adults (18 and over) who have invasive adenocarcinoma of the breast with distant metastases that is not triple negative and do not have germline BRCA1 or BRCA2 pathogenic variants
		• Adults (18 and over) with newly diagnosed invasive adenocarcinoma of the breast of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0)
		• Adults (18 and over) with metastases to the breast from other primary tumours
		• Adults (18 and over) with non-epithelial breast tumours (for example, angiosarcoma, lymphoma)
		• Adults (18 and over) with benign breast conditions (for example, fibroadenoma, benign phyllodes tumours)

7.	Intervention	Any chemotherapy regimen containing a platinum agent. Platinums of interest: • Carboplatin (all doses and regimens) • Cisplatin (all doses and regimens). All of these comparisons will be included:

		1. Regimen A + platinum agent vs regimen A 2. Regimen A + platinum agent vs regimen B 3. Single agent platinum vs regimen C
8.	Comparator	Any chemotherapy regimen without a platinum agent. • We will exclude any chemotherapies which are not used in UK clinical practice.
9.	Types of study to be included	• Systematic reviews of RCTs • RCTs
10.	Other exclusion criteria	• Abstracts, conference presentations, theses and narrative reviews • Non-human studies • Non-English language studies • Studies where more than 20% of the participants do not meet protocol criteria (have locoregional disease / do not have germline BRCA1 or BRCA2 pathogenic variants (for the BRCA analyses) / do not have TNBC (for the TNBC analysis) and where subgroup data is not available.
11.	Context	There are currently no recommendations on the use of platinum-containing chemotherapy regimens in people with advanced breast cancer that is triple negative and/or who have germline BRCA1 or BRCA2 pathogenic variants of other receptor subtypes. The 2023 NICE surveillance review suggests there may now be some evidence to support the development of advice in this area.
12.	Primary outcomes (critical outcomes)	• Progression-free survival (time to event data) • Overall survival (time to event data) • Objective tumour response rates (OTRR) (dichotomous data) **MIDs:** any statistically significant difference. **Timepoints:** longest reported from each study will be combined.

13.	Secondary outcomes (important outcomes)	• Cancer-specific survival (time to event data) - equivalent to breast cancer mortality
		  ○ Some studies may report cancer-specific survival as breast cancer mortality (dichotomous data). This will be extracted as a proxy outcome where cancer-specific survival data is not reported in the study.
		• Adverse events* (event data)
		  ○ Anaemia
		  ○ Fatigue

		○ Hair loss (alopecia) ○ Leukopenia ○ Nausea/vomiting ○ Nephrotoxicity ○ Neuropathy (also reported as peripheral neuropathy) ○ Neutropenia ○ Neutropenic sepsis (reported as febrile neutropenia) ○ Ototoxicity (including tinnitus and hearing loss, with all types analysed together) ○ Thrombocytopenia ○ Treatment-related death • Adherence to / completion of treatment ○ If not reported, treatment discontinuation due to adverse events will be extracted. • Quality of life (all validated measures including EQ-5D). *Outcomes will only be reported where severity grade is specified using the Common Terminology Criteria for Adverse Events (CTCAE). Outcomes at severity levels 1-2 will not be reported for any adverse event outcome except hair loss, fatigue and ototoxicity. Grade 3-4 severity will be reported (combined) for all outcomes. **MIDs:** • Quality of life MID values from the literature: ○ FACT-G total: 3-7 points ○ FACT-B total: 7-8 points ○ TOI (trial outcome index) of FACT-B: 5-6 points ○ BCS of FACT-B: 2-3 points ○ EORTC QLQ-C30: improvement 11 points and deterioration minus 8 points ○ WHOQOL-100: 1 point Any statistically significant difference will be used for the rest of the important outcomes. **Timepoints:** The longest follow-up periods will be prioritised for all outcomes if multiple time points are reported.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI R5 and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Dual sifting will be performed on at least 10% of records. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary.

		Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates, length of time since the assessment of receptor subtype [e.g. biopsy]), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer. Studies included in an included systematic review will not have a full data extraction form conducted, but study details will be checked and high level details reported in the review.
15.	Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
16.	Strategy for data synthesis	Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as hazard ratios or risk ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 40% and 60% will be considered as serious and very serious heterogeneity, respectively. Where I^2 is 80% or above, consideration will be given to whether the data should be. Heterogeneity will be explored as appropriate using pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.
17.	Analysis of sub-groups	Evidence will be stratified by: • Advanced triple negative breast cancer

<table>
<tr><td></td><td></td><td colspan="3">• Advanced germline BRCA1 or BRCA2 pathogenic variants
Evidence will be subgrouped only for critical outcomes by the following:
• Type of comparison (1, 2 or 3)
• Type of platinum agent (carboplatin, cisplatin)
• First-line therapy: (a) first-line therapy for >80% of participants, (b) second- or third-line therapy for ≥20% of participants
• Within advanced TNBC: with / without BRCA 1/2 gene pathogenic variants
• Within germline BRCA1 or BRCA2 pathogenic variants: receptor subtype (triple negative, HER2+, HR+)
Where evidence is stratified or subgrouped the committee will consider on a case-by-case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.</td></tr>
<tr><td>18.</td><td>Type and method of review</td><td colspan="3">☒ Intervention
☐ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)</td></tr>
<tr><td>19.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>20.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>21.</td><td>Anticipated or actual start date</td><td colspan="3">April 2025</td></tr>
<tr><td>22.</td><td>Anticipated completion date</td><td colspan="3">June 2026</td></tr>
<tr><td rowspan="7">23.</td><td rowspan="7">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td></td><td>X</td></tr>
<tr><td>Piloting of the study selection process</td><td></td><td>X</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td></td><td>X</td></tr>
<tr><td>Data extraction</td><td></td><td>X</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td></td><td>X</td></tr>
<tr><td>Data analysis</td><td></td><td>X</td></tr>
<tr><td>24.</td><td>Named contact</td><td colspan="3">24a. Named contact
NICE</td></tr>
</table>

		24b. Named contact e-mail breastcancerupdate@nice.org.uk **24c. Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
25.	Review team members	• Marie Harrisingh, Technical adviser • Olivia Crane, Senior technical analyst • Yolanda Martinez, Technical analyst • James Hawkins, Health economist adviser • Tzujung Lai, Health economist analyst • Andrea Heath, Information specialist
26.	Funding sources/sponsor	This systematic review is being completed by the Centre for Guidelines which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Advanced breast cancer: diagnosis and treatment.
29.	Other registration details	None
30.	Reference/URL for published protocol	Not applicable
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Advanced breast cancer, triple negative breast cancer, germline BRCA1 or BRCA2 pathogenic variants, platinum chemotherapy.

33.	Details of existing review of same topic by same authors	Not applicable.
34.	Current review status	☐ Ongoing ☐ Completed but not published ☒ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review.

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

This search report is based on the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was adapted from the original CG81 search but changed structurally due to slight changes to the review question.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice (as set out in the Identifying the evidence chapter of the manual) and the eligibility criteria listed in the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations

- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

> Dickersin K, Scherer R & Lefebvre C. (1994) Systematic reviews: identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

No date limits were applied, in adherence to the review protocol for the effectiveness search. A default 15 year date limit was applied for the cost-effectiveness search.

Search filters and classifiers

Effectiveness searches

RCT filters:

- McMaster Therapy – Medline – "best balance of sensitivity and specificity" version
    - Haynes RB e al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. BMJ, 330, 1179-1183.
- McMaster Therapy – Embase "best balance of sensitivity and specificity" version.
    - Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

Cost effectiveness searches

In line with the review protocol, the sensitive version of the validated NICE cost utility filter was used in the MEDLINE and Embase strategies without amendment.

> Hubbard W et al. (2022) Development and validation of paired MEDLINE and Embase search filters for cost-utility studies. *BMC Medical Research Methodology*, 22(1), 310.

Key decisions

Translations of the databases for the effectiveness and cost-effectiveness searches were done as appropriate to the size and interface of the individual databases.

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of	08/04/2025	Wiley	Cochrane Central Register of	127

Controlled Trials (CENTRAL)			Controlled Trials Issue 3 of 12, March 2025	
Cochrane Database of Systematic Reviews (CDSR)	08/04/2025	Wiley	Cochrane Database of Systematic Reviews Issue 4 of 12, April 2025	3
Embase	08/04/2025	Ovid	Embase <1974 to 2025 April 07>	319
Epistemonikos	08/04/2025	https://www.epistemonikos.org/		65 + 82
MEDLINE ALL	08/04/2025	Ovid	Ovid MEDLINE(R) ALL <1946 to April 07, 2025>	129

Search strategy history

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches		
#1	[mh “Breast Neoplasms”]	20565
#2	[mh “Neoplasms, Ductal, Lobular, and Medullary”]	1028
#3	[mh ^“Carcinoma, Lobular”]	219
#4	[mh ^“Carcinoma, Medullary”]	21
#5	[mh ^“Carcinoma, Intraductal, Noninfiltrating”]	309
#6	{OR #1-#5}	20888
#7	[mh Breast]	1146
#8	breast*:ti,ab,kw	68090
#9	#7 or #8	68112
#10	(breast NEXT milk):ti,ab,kw	3394
#11	(breast NEXT tender*):ti,ab,kw	423
#12	#10 or #11	3815
#13	#9 not #12	64297
#14	[mh Neoplasms]	126627
#15	#13 and #14	22457

Searches
#16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 49380
#17 (mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 322
#18 [mh ^"Paget's Disease, Mammary"] 3
#19 (paget* and (breast* or mammary or nipple*)):ti,ab,kw 99
#20 {OR #15-#19} 49748
#21 #6 or #20 50047
#22 [mh "Neoplasm Metastasis"] 7622
#23 ((breast* or mammar* or TNBC or (triple NEAR/3 negativ*) or BRCA*) NEAR/3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)):ti,ab,kw 18509
#24 (breast* or mammar*):ti,ab,kw 68925
#25 ((stage* or grade* or type*) NEAR/2 ("4" or "T4" or iv* or "M1" or mBC)):ti,ab,kw 32297
#26 #24 and #25 2304
#27 #22 or #23 or #26 25682
#28 #21 and #27 19720
#29 [mh ^"Triple Negative Breast Neoplasms"] 568
#30 (triple NEAR/3 negativ*):ti,ab,kw 2490
#31 (TNBC or mTNBC or BLBC):ti,ab,kw 1434
#32 (basal* NEXT (like* or type* or subtype*)):ti,ab,kw 231
#33 {OR #29-#32} 2696
#34 [mh ^"BRCA1 Protein"] 200
#35 [mh ^"BRCA2 Protein"] 165
#36 [mh ^"Genes, BRCA1"] 150
#37 [mh ^"Genes, BRCA2"] 123
#38 (BRCA* NEAR/3 (mutat* or alter* or positive* or gene* or protein* or germ*)):ti,ab,kw 1762
#39 (FANCD1* or gBRCAm*):ti,ab,kw 152
#40 ((D1 or RNF) NEXT protein*):ti,ab,kw 11
#41 (ring finger NEAR/2 (protein* or domain*)):ti,ab,kw 22
#42 {OR #34-#41} 1809
#43 #28 and #33 1648
#44 #28 and #42 425
#45 [mh ^Cisplatin] 6262
#46 [mh ^Carboplatin] 3340
#47 [mh ^"Platinum Compounds"] 136
#48 [mh ^Platinum] 367
#49 (platin* or cisplatin* or platinol* or carboplat* or paraplatin* or platidiam*):ti,ab,kw 30766

Searches
#50 (nsc-119875 or nsc-241240 or cbdca or jm-8 or CDDP or Cis-DDP):ti,ab,kw 1305
#51 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum):ti,ab,kw 77
#52 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum):ti,ab,kw 304
#53 {OR #45-#52} 31108
#54 #43 and #53 478
#55 #44 and #53 185
#56 #54 or #55 in Cochrane Reviews, Cochrane Protocols 3
#57 #54 or #55 in Trials 552
#58 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 563390
#59 "conference":pt 256739
#60 #58 or #59 820129
#61 #57 not #60 127

Database name: Cochrane Database of Systematic Reviews (CDSR)

Searches
#1 [mh “Breast Neoplasms”] 20565
#2 [mh “Neoplasms, Ductal, Lobular, and Medullary”] 1028
#3 [mh ^“Carcinoma, Lobular”] 219
#4 [mh ^“Carcinoma, Medullary”] 21
#5 [mh ^“Carcinoma, Intraductal, Noninfiltrating”] 309
#6 {OR #1-#5} 20888
#7 [mh Breast] 1146
#8 breast*:ti,ab,kw 68090
#9 #7 or #8 68112
#10 (breast NEXT milk):ti,ab,kw 3394
#11 (breast NEXT tender*):ti,ab,kw 423
#12 #10 or #11 3815
#13 #9 not #12 64297
#14 [mh Neoplasms] 126627
#15 #13 and #14 22457
#16 (breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 49380

Searches
#17 (mammar* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab,kw 322
#18 [mh ^"Paget's Disease, Mammary"] 3
#19 (paget* and (breast* or mammary or nipple*)):ti,ab,kw 99
#20 {OR #15-#19} 49748
#21 #6 or #20 50047
#22 [mh "Neoplasm Metastasis"] 7622
#23 ((breast* or mammar* or TNBC or (triple NEAR/3 negativ*) or BRCA*) NEAR/3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)):ti,ab,kw 18509
#24 (breast* or mammar*):ti,ab,kw 68925
#25 ((stage* or grade* or type*) NEAR/2 ("4" or "T4" or iv* or "M1" or mBC)):ti,ab,kw 32297
#26 #24 and #25 2304
#27 #22 or #23 or #26 25682
#28 #21 and #27 19720
#29 [mh ^"Triple Negative Breast Neoplasms"] 568
#30 (triple NEAR/3 negativ*):ti,ab,kw 2490
#31 (TNBC or mTNBC or BLBC):ti,ab,kw 1434
#32 (basal* NEXT (like* or type* or subtype*)):ti,ab,kw 231
#33 {OR #29-#32} 2696
#34 [mh ^"BRCA1 Protein"] 200
#35 [mh ^"BRCA2 Protein"] 165
#36 [mh ^"Genes, BRCA1"] 150
#37 [mh ^"Genes, BRCA2"] 123
#38 (BRCA* NEAR/3 (mutat* or alter* or positive* or gene* or protein* or germ*)):ti,ab,kw 1762
#39 (FANCD1* or gBRCAm*):ti,ab,kw 152
#40 ((D1 or RNF) NEXT protein*):ti,ab,kw 11
#41 (ring finger NEAR/2 (protein* or domain*)):ti,ab,kw 22
#42 {OR #34-#41} 1809
#43 #28 and #33 1648
#44 #28 and #42 425
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#46 [mh ^Carboplatin] 3340
#47 [mh ^"Platinum Compounds"] 136
#48 [mh ^Platinum] 367
#49 (platin* or cisplatin* or platinol* or carboplat* or paraplatin* or platidiam*):ti,ab,kw 30766
#50 (nsc-119875 or nsc-241240 or cbdca or jm-8 or CDDP or Cis-DDP):ti,ab,kw 1305

Searches
#51 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum):ti,ab,kw 77
#52 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum):ti,ab,kw 304
#53 {OR #45-#52} 31108
#54 #43 and #53 478
#55 #44 and #53 185
#56 #54 or #55 in Cochrane Reviews, Cochrane Protocols 3

Database name: Embase

Searches
1 exp breast cancer/ 638983
2 exp breast carcinoma/ 116242
3 exp medullary carcinoma/ 13823
4 ductal breast carcinoma in situ/ 22730
5 exp breast tumor/ 727069
6 exp lobular carcinoma/ 6727
7 or/1-6 739165
8 exp breast/ 131162
9 breast*.ti,ab,kf. 840830
10 8 or 9 874377
11 (breast adj milk).ti,ab,kf. 22479
12 (breast adj tender*).ti,ab,kf. 806
13 11 or 12 23279
14 10 not 13 851098
15 exp neoplasm/ 6247693
16 14 and 15 661513
17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 656370
18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 45198
19 exp Paget nipple disease/ 8066
20 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1980
21 or/16-20 732780
22 7 or 21 866943
23 metastatic breast cancer/ 31433
24 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 207030
25 (breast* or mammar*).ti,ab,kf. 897755

Searches
26 ((stage* or grade* or type*) adj2 ("4" or "T4" or iv* or "M1" or mBC)).ti,ab,kf. 308827
27 25 and 26 16422
28 or/23-24,27 221673
29 22 and 28 218431
30 triple negative breast cancer/ 45213
31 (triple adj3 negativ*).ti,ab,kf. 50683
32 (TNBC or mTNBC or BLBC).ti,ab,kf. 26822
33 (basal* adj (like* or type* or subtype*)).ti,ab,kf. 8208
34 or/30-33 66016
35 BRCA2 protein/ or BRCA1 protein/ 33116
36 (BRCA* adj3 (mutat* or alter* or positive* or gene* or protein* or germ*)).ti,ab,kf. 33313
37 (FANCD1* or gBRCAm*).ti,ab,kf. 585
38 ((D1 or RNF) adj protein*).ti,ab,kf. 2564
39 (ring finger adj2 (protein* or domain*)).ti,ab,kf. 3570
40 or/35-39 55368
41 29 and 34 24172
42 29 and 40 6075
43 cisplatin/ or cisplatin derivative/ 237626
44 carboplatin/ 96309
45 platinum derivative/ or platinum/ 55976
46 (platin* or cisplatin* or platinol* or carboplat* or paraplatin* or platidiam*).ti,ab,kf. 230898
47 (nsc-119875 or nsc-241240 or cbdca or jm-8 or CDDP or Cis-DDP).ti,ab,kf. 13043
48 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab,kf. 3169
49 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab,kf. 5337
50 or/43-49 390136
51 41 and 50 2538
52 42 and 50 1009
53 random:.tw. 2189931
54 placebo:.mp. 554900
55 double-blind:.tw. 260566
56 or/53-55 2478250
57 51 and 56 586
58 52 and 56 204
59 57 or 58 649
60 limit 59 to english language 640
61 nonhuman/ not human/ 5664914

Searches		
62	60 not 61	635
63	limit 62 to (editorial or letter)	2
64	case report/	3098833
65	conference*.db,pt,su.	6228542
66	or/63-65	8910011
67	62 not 66	319

Database name: Epistimonikos – Search 1 - TNBC

Searches
(title:((title:((triple AND negativ*) OR (triple-negativ*) OR (tnbc OR mtnbc OR blbc) OR (basal* AND like) OR (basel-like) OR (basal* AND type) OR (basel-type) OR (basal* AND subtype) OR (basel-subtype)) OR abstract:((triple AND negativ*) OR (triple-negativ*) OR (tnbc OR mtnbc OR blbc) OR (basal* AND like) OR (basel-like) OR (basal* AND type) OR (basel-type) OR (basal* AND subtype) OR (basel-subtype))) AND (title:(platin* OR cisplatin* OR platinol* OR carboplat* OR paraplatin* OR platidiam* OR (nsc-119875 OR "nsc 119875" OR nsc-241240 OR "nsc 241240" OR cbdca OR jm-8 OR "jm 8" OR cddp OR cis-ddp OR "cis ddp") OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR "cis diamminedichloroplatinum" OR cis-dichlorodiammineplatinum OR "cis dichlorodiammineplatinum" OR cis-platinum OR "cis platinum")) OR abstract:(platin* OR cisplatin* OR platinol* OR carboplat* OR paraplatin* OR platidiam* OR (nsc-119875 OR "nsc 119875" OR nsc-241240 OR "nsc 241240" OR cbdca OR jm-8 OR "jm 8" OR cddp OR cis-ddp OR "cis ddp") OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR "cis diamminedichloroplatinum" OR cis-dichlorodiammineplatinum OR "cis dichlorodiammineplatinum" OR cis-platinum OR "cis platinum"))))

Database name: Epistimonikos – Search 2 - BRCA

Searches
(((title:((title:(brca* OR (fancd1* OR gbrcam*) OR (ring AND finger AND protein*) OR (ring-finger-protein*) OR (ring AND finger AND domain*) OR (ring-finger-domain*)) OR abstract:(brca* OR (fancd1* OR gbrcam*) OR (ring AND finger AND protein*) OR (ring-finger-protein*) OR (ring AND finger AND domain*) OR (ring-finger-domain*))) AND (title:(platin* OR cisplatin* OR platinol* OR carboplat* OR paraplatin* OR platidiam* OR (nsc-119875 OR "nsc 119875" OR nsc-241240 OR "nsc 241240" OR cbdca OR jm-8 OR "jm 8" OR cddp OR cis-ddp OR "cis ddp") OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR "cis diamminedichloroplatinum" OR cis-dichlorodiammineplatinum OR "cis dichlorodiammineplatinum" OR cis-platinum OR "cis platinum")) OR abstract:(platin* OR cisplatin* OR platinol* OR carboplat* OR paraplatin* OR platidiam* OR (nsc-119875 OR "nsc 119875" OR nsc-241240 OR "nsc 241240" OR cbdca OR jm-8 OR "jm 8" OR cddp OR cis-ddp OR "cis ddp") OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR "cis diamminedichloroplatinum" OR cis-dichlorodiammineplatinum OR "cis dichlorodiammineplatinum" OR cis-platinum OR "cis platinum"))))

Database name: MEDLINE ALL

Searches
1 exp Breast Neoplasms/ 366836
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 49924
3 Carcinoma, Lobular/ 6264
4 Carcinoma, Medullary/ 3445
5 Carcinoma, Intraductal, Noninfiltrating/ 11041
6 or/1-5 388424
7 exp Breast/ 55671
8 breast*.ti,ab,kf. 609297
9 7 or 8 619328
10 (breast adj milk).ti,ab,kf. 17536
11 (breast adj tender*).ti,ab,kf. 610
12 10 or 11 18143
13 9 not 12 601185
14 exp Neoplasms/ 4095013
15 13 and 14 386421
16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 459534
17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 37877
18 Paget's Disease, Mammary/ 823
19 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1603
20 or/15-19 513748
21 6 or 20 572781
22 exp Neoplasm Metastasis/ 229731
23 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 142144
24 (breast* or mammar*).ti,ab,kf. 661571
25 ((stage* or grade* or type*) adj2 ("4" or "T4" or iv* or "M1" or mBC)).ti,ab,kf. 175713
26 24 and 25 7947
27 or/22-23,26 352933
28 21 and 27 166547
29 Triple Negative Breast Neoplasms/ 13047
30 (triple adj3 negativ*).ti,ab,kf. 28469
31 (TNBC or mTNBC or BLBC).ti,ab,kf. 15193
32 (basal* adj (like* or type* or subtype*)).ti,ab,kf. 4546
33 or/29-32 32614
34 BRCA1 Protein/ or BRCA2 Protein/ 10633

Searches
35 Genes, BRCA1/ or Genes, BRCA2/ 7209
36 (BRCA* adj3 (mutat* or alter* or positive* or gene* or protein* or germ*)).ti,ab,kf. 19672
37 (FANCD1* or gBRCAm*).ti,ab,kf. 234
38 ((D1 or RNF) adj protein*).ti,ab,kf. 2228
39 (ring finger adj2 (protein* or domain*)).ti,ab,kf. 3091
40 or/34-39 29938
41 28 and 33 11872
42 28 and 40 3042
43 Cisplatin/ 61364
44 Carboplatin/ 13631
45 Platinum Compounds/ or Platinum/ 14621
46 (platin* or cisplatin* or platinol* or carboplat* or paraplatin* or platidiam*).ti,ab,kf. 160676
47 (nsc-119875 or nsc-241240 or cbdca or jm-8 or CDDP or Cis-DDP).ti,ab,kf. 10056
48 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab,kf. 2912
49 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab,kf. 4681
50 or/43-49 177792
51 41 and 50 572
52 42 and 50 284
53 exp Randomized Controlled Trial/ 637248
54 randomi?ed.mp. 1177038
55 placebo.mp. 265709
56 or/53-55 1246496
57 51 and 56 119
58 52 and 56 51
59 57 or 58 137
60 limit 59 to english language 134
61 animals/ not humans/ 5291117
62 60 not 61 134
63 limit 62 to (letter or historical article or comment or editorial or news or case reports) 5
64 62 not 63 129
65 64 not overall.pt. 129

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	10/04/2025	Ovid	Embase <1974 to 2025 April 09>	27
International HTA Database	10/04/2025	https://database.inahta.org/		6
MEDLINE ALL	10/04/2025	Ovid	Ovid MEDLINE(R) ALL <1946 to April 09, 2025>	8

Search strategy history

Database name: Embase

Searches		
1	exp breast cancer/	639191
2	exp breast carcinoma/	116260
3	exp medullary carcinoma/	13825
4	ductal breast carcinoma in situ/	22733
5	exp breast tumor/	727286
6	exp lobular carcinoma/	6731
7	or/1-6	739384
8	exp breast/	131189
9	breast*.ti,ab,kf.	841132
10	8 or 9	874685
11	(breast adj milk).ti,ab,kf.	22485
12	(breast adj tender*).ti,ab,kf.	806
13	11 or 12	23285
14	10 not 13	851400
15	exp neoplasm/	6249584
16	14 and 15	661752
17	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf.	656607
18	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf.	45199

Searches	
19	exp Paget nipple disease/ 8066
20	(paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1982
21	or/16-20 733028
22	7 or 21 867194
23	metastatic breast cancer/ 31451
24	((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 207093
25	(breast* or mammar*).ti,ab,kf. 898064
26	((stage* or grade* or type*) adj2 ("4" or "T4" or iv* or "M1" or mBC)).ti,ab,kf. 308919
27	25 and 26 16428
28	or/23-24,27 221738
29	22 and 28 218495
30	triple negative breast cancer/ 45248
31	(triple adj3 negativ*).ti,ab,kf. 50722
32	(TNBC or mTNBC or BLBC).ti,ab,kf. 26843
33	(basal* adj (like* or type* or subtype*)).ti,ab,kf. 8208
34	or/30-33 66055
35	BRCA2 protein/ or BRCA1 protein/ 33116
36	(BRCA* adj3 (mutat* or alter* or positive* or gene* or protein* or germ*)).ti,ab,kf. 33322
37	(FANCD1* or gBRCAm*).ti,ab,kf. 585
38	((D1 or RNF) adj protein*).ti,ab,kf. 2565
39	(ring finger adj2 (protein* or domain*)).ti,ab,kf. 3570
40	or/35-39 55378
41	34 or 40 116424
42	29 and 41 28397
43	cisplatin/ or cisplatin derivative/ 237657
44	carboplatin/ 96325
45	platinum derivative/ or platinum/ 55986
46	(platin* or cisplatin* or platinol* or carboplat* or paraplatin* or platidiam*).ti,ab,kf. 230972
47	(nsc-119875 or nsc-241240 or cbdca or jm-8 or CDDP or Cis-DDP).ti,ab,kf. 13043
48	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab,kf. 3169
49	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab,kf. 5337
50	or/43-49 390210
51	42 and 50 3005
52	cost utility analysis/ 13679

Searches
53 quality adjusted life year/ 39915
54 cost*.ti. 209128
55 (cost* adj2 utilit*).tw. 14044
56 (cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw. 429736
57 (economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw. 74008
58 (qualit* adj2 adjust* adj2 life*).tw. 30338
59 QALY*.tw. 29814
60 (incremental* adj2 cost*).tw. 31694
61 ICER.tw. 14795
62 utilities.tw. 16496
63 markov*.tw. 44146
64 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 79210
65 ((utility or effective*) adj2 analys*).tw. 42012
66 (willing* adj2 pay*).tw. 16774
67 (EQ5D* or EQ-5D*).tw. 29834
68 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 6136
69 (european* adj2 quality adj3 ("5" or five)).tw. 1151
70 or/52-69 701609
71 51 and 70 48
72 limit 71 to english language 48
73 limit 72 to yr="2010 -Current" 48
74 nonhuman/ not human/ 5666782
75 73 not 74 47
76 limit 75 to (editorial or letter) 0
77 case report/ 3099584
78 conference*.db,pt,su. 6229302
79 or/76-78 8911514
80 75 not 79 27

Database name: International HTA Database

Searches
((cisplatin)[mh] OR (carboplatin)[mh] OR (platinum compounds)[mh] OR (platinum)[mh] OR ((platin* or cisplatin* or platinol* or carboplat* or paraplatin* or platidiam* or "nsc-119875" or "nsc-241240" or cbdca or "jm-8" or cddp or "cis-ddp" or biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum or "cis-diamminedichloroplatinum" or "cis-dichlorodiammineplatinum" or "cis-platinum"))) AND (((brca1 protein)[mh] OR (brca2 protein)[mh] OR (genes, brca1)[mh] OR (genes, brca2)[mh] OR (brca* AND (mutat* or alter* or positive* or gene* or protein*

Searches
or germ*)) OR ((fancd1* or gbrcam*)) OR (((d1 or rnf) AND protein*)) OR ((ring finger AND (protein* or domain*)))) OR ((triple negative breast neoplasms)[mh] OR (triple AND negativ*) OR (tnbc or mtnbc or blbc) OR (basal* AND (like* or type* or subtype*))))
Applied date and English language limit

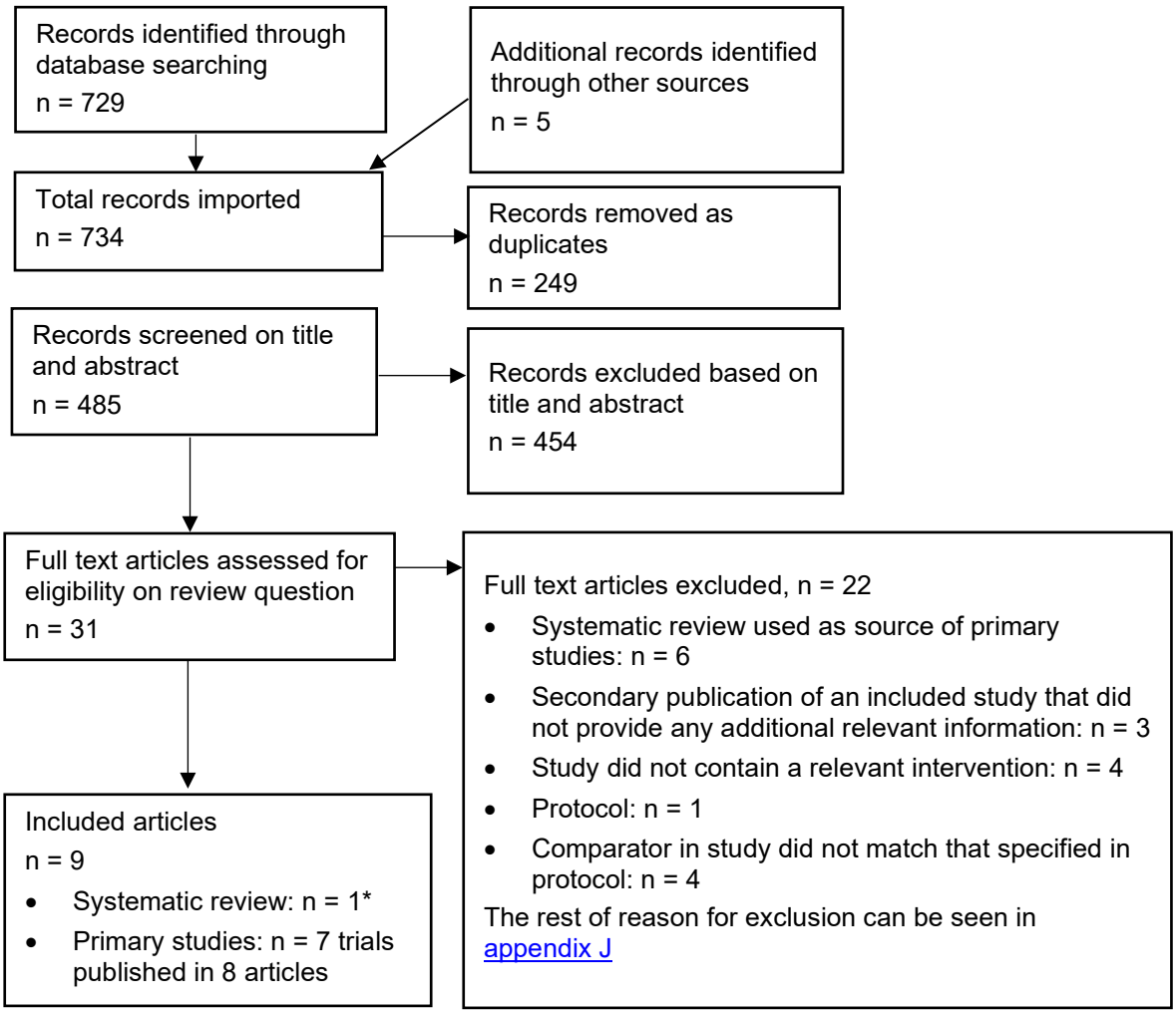
Database name: MEDLINE ALL

Searches
1 exp Breast Neoplasms/ 366751
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 49914
3 Carcinoma, Lobular/ 6263
4 Carcinoma, Medullary/ 3444
5 Carcinoma, Intraductal, Noninfiltrating/ 11035
6 or/1-5 388335
7 exp Breast/ 55669
8 breast*.ti,ab,kf. 609278
9 7 or 8 619310
10 (breast adj milk).ti,ab,kf. 17538
11 (breast adj tender*).ti,ab,kf. 610
12 10 or 11 18145
13 9 not 12 601165
14 exp Neoplasms/ 4094902
15 13 and 14 386344
16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 459482
17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kf. 37877
18 Paget's Disease, Mammary/ 823
19 (paget* and (breast* or mammary or nipple*)).ti,ab,kf. 1603
20 or/15-19 513695
21 6 or 20 572723
22 exp Neoplasm Metastasis/ 229718
23 ((breast* or mammar* or TNBC or (triple adj3 negativ*) or BRCA*) adj3 (metasta* or advanc* or second* or recur* or disseminat* or incur* or malign* or carcino* or invasive or oligometasta*)).ti,ab,kf. 142128
24 (breast* or mammar*).ti,ab,kf. 661549
25 ((stage* or grade* or type*) adj2 ("4" or "T4" or iv* or "M1" or mBC)).ti,ab,kf. 175717

Searches		
26	24 and 25	7939
27	or/22-23,26	352908
28	21 and 27	166520
29	Triple Negative Breast Neoplasms/	13032
30	(triple adj3 negativ*).ti,ab,kf.	28460
31	(TNBC or mTNBC or BLBC).ti,ab,kf.	15197
32	(basal* adj (like* or type* or subtype*)).ti,ab,kf.	4545
33	or/29-32	32605
34	BRCA1 Protein/ or BRCA2 Protein/	10619
35	Genes, BRCA1/ or Genes, BRCA2/	7210
36	(BRCA* adj3 (mutat* or alter* or positive* or gene* or protein* or germ*)).ti,ab,kf.	19662
37	(FANCD1* or gBRCAm*).ti,ab,kf.	234
38	((D1 or RNF) adj protein*).ti,ab,kf.	2228
39	(ring finger adj2 (protein* or domain*)).ti,ab,kf.	3089
40	or/34-39	29923
41	33 or 40	60651
42	28 and 41	14241
43	Cisplatin/	61369
44	Carboplatin/	13628
45	Platinum Compounds/ or Platinum/	14622
46	(platin* or cisplatin* or platinol* or carboplat* or paraplatin* or platidiam*).ti,ab,kf.	160706
47	(nsc-119875 or nsc-241240 or cbdca or jm-8 or CDDP or Cis-DDP).ti,ab,kf.	10053
48	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab,kf.	2912
49	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab,kf.	4681
50	or/43-49	177822
51	42 and 50	721
52	Cost-Benefit Analysis/	97389
53	Quality-Adjusted Life Years/	17670
54	Markov Chains/	16964
55	exp Models, Economic/	16804
56	cost*.ti.	156581
57	(cost* adj2 utilit*).tw.	8635
58	(cost* adj2 (effective* or assess* or evaluat* or analys* or model* or benefit* or threshold* or quality or expens* or saving* or reduc*)).tw.	315850
59	(economic* adj2 (evaluat* or assess* or analys* or model* or outcome* or benefit* or threshold* or expens* or saving* or reduc*)).tw.	53406
60	(qualit* adj2 adjust* adj2 life*).tw.	20048

Searches
61 QALY*.tw. 16305
62 (incremental* adj2 cost*).tw. 19518
63 ICER.tw. 7090
64 utilities.tw. 10408
65 markov*.tw. 35273
66 (dollar* or USD or cents or pound or pounds or GBP or sterling* or pence or euro or euros or yen or JPY).tw. 58908
67 ((utility or effective*) adj2 analys*).tw. 28236
68 (willing* adj2 pay*).tw. 11445
69 (EQ5D* or EQ-5D*).tw. 15860
70 ((euroqol or euro-qol or euroquol or euro-quol or eurocol or euro-col) adj3 ("5" or five)).tw. 4696
71 (european* adj2 quality adj3 ("5" or five)).tw. 854
72 or/52-71 559941
73 51 and 72 8
74 limit 73 to english language 8
75 limit 74 to yr="2010 -Current" 8
76 animals/ not humans/ 5291139
77 75 not 76 8
78 limit 77 to (letter or historical article or comment or editorial or news or case reports) 0
79 77 not 78 8
80 79 not overall.pt. 8

Appendix C – Effectiveness evidence study selection



* This refers to the Cochrane review by Egger et al. (2020) which was the systematic review that met most of the inclusion criteria listed in this review protocol.

Appendix D – Effectiveness evidence

Systematic review

Egger, 2020

Bibliographic Reference	Egger, Sam J; Chan, Matthew Ming Ki; Luo, Qingwei; Wilcken, Nicholas; Platinum-containing regimens for triple-negative metastatic breast cancer.; The Cochrane database of systematic reviews; 2020; vol. 10; cd013750

Study Characteristics

Study design	Systematic review
Study details	Dates searched 27 September 2019 Databases searched The Cochrane Breast Cancer Specialised Register Cochrane Central Register of Controlled Trials (CENTRAL) MEDLINE Embase The WHO International Clinical Trials Registry Platform (ICTRP) ClinicalTrials.gov Sources of funding Cancer Council NSW, Australia
Inclusion criteria	Type of studies Properly randomised controlled clinical trials (i.e. where the trial report asserts that the trial was randomised and there was no evidence to suggest otherwise) were eligible for inclusion. Because individual trials may compare one or more platinum-based regimens to one or more non-platinum-based regimens, there were more 'treatment-comparisons' (i.e. platinum regimen versus non-platinum regimen comparisons) than studies in the review. Type of participants Participants are women with metastatic triple negative breast cancer (mTNBC), whether newly diagnosed or recurrent, who may have been purposely selected for mTNBC, or inadvertently selected as a subgroup. Treatment-comparisons that included groups of women with loco-regionally recurrent disease or women with non-TNBC were only eligible for inclusion if it was possible to distinguish between these groups (i.e. where data were reported separately) or if the proportion of women in each group represented at least 80% of the total group. There were no age restrictions.
Exclusion criteria	None reported
Intervention	Any chemotherapy regimen containing a platinum agent
Comparator	Any chemotherapy regimen without a platinum agent
Outcome(s)	Overall survival (OS)

	Time elapsed between randomisation (or study enrolment or treatment initiation) to date of death from any cause. Progression-free survival/time to progression (PFS/TTP) PFS: time elapsed between randomisation (or study enrolment or treatment initiation) and event, with event defined as disease progression or death from any cause. TTP: time elapsed between randomisation (or study enrolment or treatment initiation) and event, with event defined as disease progression (which sometimes included cause-specific death from the study disease). Time to treatment failure (TTF) Time elapsed between randomisation (or study enrolment or treatment initiation) to treatment discontinuation for any reason, including disease progression, treatment toxicity, participant preference, or death. Objective tumour response rate (OTRR) The proportion of participants who experienced a complete or partial tumour response (versus stable disease or no response). Toxicity rates (multiple condition-specific outcomes) The proportions of participants who experienced a grade 3 or 4 adverse event of nausea and vomiting, nephrotoxicity, anaemia, hair loss and leukopenia, based on WHO criteria or individual protocol-based definitions. We also investigated treatment-related death which, for the purpose of this review, was defined as death due to the toxicity of the drug and not to disease progression or other cause. If an individual trial did not include their definition of a treatment-related death but used the terms "toxic death" or "lethal toxicity," then these deaths were counted as treatment-related deaths. Lastly, in response to a reviewer suggestion, we also examined treatment discontinuation due to adverse events. Quality of life (QoL) measures (multiple outcomes) Generally measured using validated instruments for various QoL domains, but no studies in this review reported QoL results for mTNBC patients.
Number of studies included in the systematic review	10
Studies from the systematic review that are relevant for use in the current review	Fan 2012 Mustafa 2019 Stemmler 2011 Tutt 2018 Yardley 2018 Zhang 2018
Studies from the systematic review that are not relevant for use in the current review	Bhattacharyya 2009 (reason for exclusion: endoxan alone not used in UK routine practice to treat breast cancer) Carey 2012 (reason for exclusion: cetuximab not used in UK routine practice to treat breast cancer) Han 2018 (reason for exclusion: temozolomide not used in UK routine practice to treat breast cancer) Icli 2005 (reason for exclusion: etoposide not used in UK routine practice to treat breast cancer)
Additional comments	For the purposes of the Cochrane review, PFS and TTP were analysed as the same outcome (referred to as PFS/TTP), with preference given to PFS for

	studies reporting both PFS and TTP data. However, all studies included in the NICE review only reported PFS.

Critical Appraisal - ROBIS checklist

Overall risk of bias	Low
Applicability as a source of data	Partially applicable (This Cochrane systematic review included studies that were not relevant to the NICE review (studies with treatments not used in UK routine practice to treat breast cancer).)

Randomised controlled trials

Randomised controlled trials included in Egger et al. 2020

For the 6 RCTs that were included in Egger et al. (2020) see the evidence tables provided in that review for study details and full risk of bias assessments.

Overall risk of bias and applicability for studies included in Egger et al. 2020

Overall risk of bias and applicability for the relevant studies from the Cochrane review was determined by NICE based on information provided in the Cochrane review (see section 1.1.3 Methods and process for more details). The study- level characteristics, risk of bias and applicability are summarised below for these studies.

Fan, 2013

Bibliographic Reference	Fan, Y; Xu, B H; Yuan, P; Ma, F; Wang, J Y; Ding, X Y; Zhang, P; Li, Q; Cai, R G; Docetaxel-cisplatin might be superior to docetaxel-capecitabine in the first-line treatment of metastatic triple-negative breast cancer.; Annals of oncology : official journal of the European Society for Medical Oncology; 2013; vol. 24 (no. 5); 1219-25

Characteristics

Study-level characteristics

Characteristic	Study (N = 53)
% Female No of events	n = 53 ; % = 100
Receptor subtype - Triple negative breast cancer No of events	n = 53 ; % = 100
Timing of receptor subtype test - At recruitment No of events	n = 53 ; % = 100

Arm-level characteristics

Characteristic	Platinum-containing regimen (N = 27)	Non-platinum-containing regimen (N = 26)
Median age (years) (range) Custom value	48 (32 to 67)	49 (27 to 71)

Critical Appraisal - Cochrane Risk of Bias tool

Question	Answer
Risk of bias judgement - overall survival	High (No information about random sequence generation or allocation concealment; no trial registration or published protocol; blinding of outcome assessment was unlikely to influence overall survival assessment)
Risk of bias judgement – other time-to-event outcomes	High (Open-label trial; no information about random sequence generation, allocation concealment or blinding of outcome assessment; no trial registration or published protocol)
Overall Directness - overall survival and other time-to-event outcomes	Directly applicable
Risk of bias judgement - dichotomous outcomes	High (Open-label trial; no information about random sequence generation, allocation concealment or blinding of outcome assessment; no trial registration or published protocol)
Overall Directness - dichotomous outcomes	Directly applicable

Hu, 2015

Bibliographic Reference	Hu, Xi-Chun; Zhang, Jian; Xu, Bing-He; Cai, Li; Ragaz, Joseph; Wang, Zhong-Hua; Wang, Bi-Yun; Teng, Yue-E; Tong, Zhong-Sheng; Pan, Yue-Yin; Yin, Yong-Mei; Wu, Chang-Ping; Jiang, Ze-Fei; Wang, Xiao-Jia; Lou, Gu-Yin; Liu, Dong-Geng; Feng, Ji-Feng; Luo, Jian-Feng; Sun, Kang; Gu, Ya-Jia; Wu, Jiong; Shao, Zhi-Min; Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial.; The Lancet. Oncology; 2015; vol. 16 (no. 4); 436-46

Study details

Secondary publication of another included study- see primary study for details	Zhang, J; Lin, Y; Sun, X J; Wang, B Y; Wang, Z H; Luo, J F; Wang, L P; Zhang, S; Cao, J; Tao, Z H; Wu, J; Shao, Z M; Yang, W T; Hu, X C; Biomarker assessment of the CBCSG006 trial: a randomized phase III trial of cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine as first-line therapy for patients with metastatic triple-negative breast cancer.; Annals of oncology : official journal of

	the European Society for Medical Oncology; 2018; vol. 29 (no. 8); 1741-1747

Mustafa, 2019

Bibliographic Reference	Mustafa, Sharehan Hassan Soliman; Zamzam, Maha Lotfy; Abdel Mohsen, Soheir El-sayed; Hassanen, Ehab Mohammed; Cisplatin Plus Gemcitabine Versus Paclitaxel Plus Gemcitabine as First-Line Therapy for Metastatic Triple Negative Breast Cancer; EJHM; 2019; vol. 74 (no. 8); 1878-1883

Characteristics

Arm-level characteristics

Characteristic	Platinum-containing regimen (N = 55)	Non-platinum-containing regimen (N = 55)
% Female No of events	n = 55 ; % = 100	n = 55 ; % = 100
Age in subgroups - 40 years or more No of events	n = 40 ; % = 72.7	n = 46 ; % = 83.6
Age in subgroups - Less than 40 years No of events	n = 15 ; % = 27.3	n = 9 ; % = 16.4
Timing of receptor subtype test - At recruitment No of events	n = 55 ; % = 100	n = 55 ; % = 100

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Question	Answer
Risk of bias judgement - dichotomous outcomes	High (No information about random sequence generation, allocation concealment or blinding of outcome assessment; no trial registration or published protocol)
Overall Directness - dichotomous outcomes	Directly applicable

Stemmler, 2011

Bibliographic Reference	Stemmler HJ; diGioia D; Freier W; Tessen HW; Gitsch G; Jonat W; Brugger W; Kettner E; Abenhardt W; Tesch H; Hurtz HJ; Rösel S; Brudler O; Heinemann V; Randomised phase II trial of gemcitabine plus vinorelbine vs gemcitabine plus cisplatin vs gemcitabine plus capecitabine in patients with pretreated metastatic breast cancer.; British journal of cancer; 2011; vol. 104 (no. 7)

Characteristics

Arm-level characteristics

Characteristic	Platinum-containing regimen (N = 45)	Non-platinum-containing regimen A (N = 46)	Non-platinum-containing regimen B (N = 50)
% Female No of events	n = 45 ; % = 100	n = 46 ; % = 100	n = 50 ; % = 100
Median age (years) Custom value	60 (range: 36 to 74)	58 (range: 38 to 77)	60 (range: 34 to 78)
Receptor subtype - Hormone receptor positive No of events	n = 26 ; % = 57.8	n = 28 ; % = 60.9	n = 25 ; % = 50
Receptor subtype - Hormone receptor negative No of events	n = 18 ; % = 40	n = 16 ; % = 34.8	n = 18 ; % = 36
Receptor subtype - Hormone receptor unknown No of events	n = 1 ; % = 2.2	n = 2 ; % = 4.4	n = 7 ; % = 14
Receptor subtype - HER2 positive (IHC3+, FISH+) No of events	n = 7 ; % = 15.6	n = 4 ; % = 8.7	n = 5 ; % = 10
Receptor subtype - HER2 negative No of events	n = 30 ; % = 66.7	n = 32 ; % = 69.6	n = 35 ; % = 70
Receptor subtype - HER2 unknown No of events	n = 8 ; % = 17.8	n = 10 ; % = 37	n = 12 ; % = 24
Timing of receptor subtype test - At baseline No of events	n = 45 ; % = 100	n = 46 ; % = 100	n = 50 ; % = 100

Baseline characteristics for all participants including those without triple negative breast cancer.

Critical Appraisal - Cochrane Risk of Bias tool

Question	Answer
Risk of bias judgement - dichotomous outcomes	High (Open-label trial; no information about random sequence generation, allocation concealment or blinding of outcome assessment; 20% of all randomised participants were not assessed/assessable for tumour response)

Question	Answer
Overall Directness - dichotomous outcomes	Partially applicable (All participants had metastatic breast cancer; subgroup data was reported for 26% participants with metastatic triple negative breast cancer)

Tutt, 2018

Bibliographic Reference	Tutt, Andrew; Tovey, Holly; Cheang, Maggie Chon U; Kernaghan, Sarah; Kilburn, Lucy; Gazinska, Patrycja; Owen, Julie; Abraham, Jacinta; Barrett, Sophie; Barrett-Lee, Peter; Brown, Robert; Chan, Stephen; Dowsett, Mitchell; Flanagan, James M; Fox, Lisa; Grigoriadis, Anita; Gutin, Alexander; Harper-Wynne, Catherine; Hatton, Matthew Q; Hoadley, Katherine A; Parikh, Jyoti; Parker, Peter; Perou, Charles M; Roylance, Rebecca; Shah, Vandna; Shaw, Adam; Smith, Ian E; Timms, Kirsten M; Wardley, Andrew M; Wilson, Gregory; Gillett, Cheryl; Lanchbury, Jerry S; Ashworth, Alan; Rahman, Nazneen; Harries, Mark; Ellis, Paul; Pinder, Sarah E; Bliss, Judith M; Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial.; Nature medicine; 2018; vol. 24 (no. 5); 628-637

Characteristics

Arm-level characteristics

Characteristic	Platinum-containing regimen B (N = 188)	Non-platinum-containing regimen (N = 188)
% Female No of events	n = 188 ; % = 100	n = 188 ; % = 100
Median age Median (IQR)	55.7 (47.6 to 62.9)	54.9 (47.9 to 63.5)
Ethnicity - white No of events	n = 159 ; % = 84.6	n = 169 ; % = 89.9
Ethnicity - Asian/Asian British/Other Asian No of events	n = 8 ; % = 4.3	n = 3 ; % = 1.6
Ethnicity - Black/Black British/Other Black No of events	n = 13 ; % = 6.9	n = 10 ; % = 5.3
Ethnicity - Mixed No of events	n = 0 ; % = 0	n = 1 ; % = 0.5
Ethnicity - Not-stated/Missing No of events	n = 8 ; % = 4.3	n = 5 ; % = 2.7
Timing of receptor subtype test - At baseline No of events	n = 188 ; % = 100	n = 188 ; % = 100
BRCA germline mutation - triple negative, without known mutation Those who were tested and no mutation was identified as well as those who were never tested. Information about testing was only	n = 167 ; % = 88.8	n = 171 ; % = 91

Characteristic	Platinum-containing regimen B (N = 188)	Non-platinum-containing regimen (N = 188)
collected if a mutation had been identified prior to trial entry. No of events		
BRCA germline mutation - known BRCA1 No of events	n = 4 ; % = 2.1	n = 1 ; % = 0.5
BRCA germline mutation - known BRCA2 No of events	n = 6 ; % = 3.2	n = 2 ; % = 1.1
BRCA germline mutation - triple negative and known BRCA1/2 No of events	n = 7 ; % = 3.7	n = 9 ; % = 4.8
BRCA germline mutation - not triple negative and no known mutation Those who were tested and no mutation was identified as well as those who were never tested. Information about testing was only collected if a mutation had been identified prior to trial entry. No of events	n = 4 ; % = 2.1	n = 5 ; % = 2.7

Critical appraisal - Critical Appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Question	Answer
Risk of bias judgement - overall survival	High (Blinding of outcome assessment was unlikely to influence overall survival assessment; all randomised participants were included in response rate denominators, but it was not explicitly stated that all participants were assessed/assessable)
Risk of bias judgement – other time-to-event outcomes	High (Open-label trial; time to progression was specified as an outcome on the trial registration but no results for this outcome were reported)
Overall Directness - overall survival and other time-to-event outcomes	Directly applicable
Risk of bias judgement - dichotomous outcomes	High (Open-label trial; primary endpoint was ORR (local assessment of ORR was used for primary analysis however an independent response evaluation committee reviewed reported responses centrally at study completion); time elapsed between randomisation to treatment discontinuation for any reason was specified as an outcome on the trial registration but no results for this outcome were reported; all randomised participants were included in response rate denominators, but it was not explicitly stated that all participants were assessed/assessable)

Question	Answer
Overall Directness - dichotomous outcomes	Directly applicable

Yardley, 2018

Bibliographic Reference	Yardley, D A; Coleman, R; Conte, P; Cortes, J; Brufsky, A; Shtivelband, M; Young, R; Bengala, C; Ali, H; Eakel, J; Schneeweiss, A; de la Cruz-Merino, L; Wilks, S; O'Shaughnessy, J; Gluck, S; Li, H; Miller, J; Barton, D; Harbeck, N; nab-Paclitaxel plus carboplatin or gemcitabine versus gemcitabine plus carboplatin as first-line treatment of patients with triple-negative metastatic breast cancer: results from the tnAcity trial.; Annals of oncology : official journal of the European Society for Medical Oncology; 2018; vol. 29 (no. 8); 1763-1770

Characteristics

Arm-level characteristics

Characteristic	Platinum-containing regimen A (N = 64)	Platinum-containing regimen B (N = 66)	Non-platinum-containing regimen (N = 61)
% Female No of events	n = 64 ; % = 100	n = 66 ; % = 100	n = 61 ; % = 100
Median age (years) Custom value	55 (range: 27 to 82)	59 (range: 30 to 79)	53 (range: 27 to 80)
Ethnicity - white No of events	n = 55 ; % = 86	n = 54 ; % = 82	n = 50 ; % = 82
Ethnicity - Black or African American No of events	n = 6 ; % = 9	n = 8 ; % = 12	n = 9 ; % = 15
Ethnicity - Not collected or reported No of events	n = 3 ; % = 5	n = 4 ; % = 6	n = 2 ; % = 3
Timing of receptor subtype test - At baseline No of events	n = 64 ; % = 100	n = 66 ; % = 100	n = 61 ; % = 100

Critical Appraisal - Cochrane Risk of Bias tool

Question	Answer
Risk of bias judgement - overall survival	Moderate (Blinding of outcome assessment was unlikely to influence overall survival assessment; baseline characteristics were similar across groups except median age was lower in platinum-containing regimen A and non-platinum containing regimen groups compared to platinum-containing regimen B, the platinum-containing regimen A group had a lower proportion of patients who

Question	Answer
	were black or African American or were from Western Europe, and had a disease-free interval of 1 year compared with the non-platinum containing regimen and platinum-containing regimen B groups)
Risk of bias judgement – other time-to-event outcomes	High (Open-label trial; primary endpoint was investigator assessed PFS; baseline characteristics were similar across groups except median age was lower in platinum-containing regimen A and non-platinum containing regimen groups compared to platinum-containing regimen B, the platinum-containing regimen A group had a lower proportion of patients who were black or African American or were from Western Europe, and had a disease-free interval of 1 year compared with the non-platinum containing regimen and platinum-containing regimen B groups)
Overall Directness - overall survival and other time-to-event outcomes	Directly applicable
Risk of bias judgement - dichotomous outcomes	High (Open-label trial; primary endpoint was investigator assessed PFS; baseline characteristics were similar across groups except median age was lower in platinum-containing regimen A and non-platinum containing regimen groups compared to platinum-containing regimen B, the platinum-containing regimen A group had a lower proportion of patients who were black or African American or were from Western Europe, and had a disease-free interval of 1 year compared with the non-platinum containing regimen and platinum-containing regimen B groups)
Overall Directness - dichotomous outcomes	Directly applicable

Zhang, 2018

Bibliographic Reference	Zhang, J; Lin, Y; Sun, X J; Wang, B Y; Wang, Z H; Luo, J F; Wang, L P; Zhang, S; Cao, J; Tao, Z H; Wu, J; Shao, Z M; Yang, W T; Hu, X C; Biomarker assessment of the CBCSG006 trial: a randomized phase III trial of cisplatin plus gemcitabine compared with paclitaxel plus gemcitabine as first-line therapy for patients with metastatic triple-negative breast cancer.; Annals of oncology : official journal of the European Society for Medical Oncology; 2018; vol. 29 (no. 8); 1741-1747

Characteristics

Arm-level characteristics

Characteristic	Platinum-containing regimen (N = 118)	Non-platinum-containing regimen (N = 118)
% Female No of events	n = 118 ; % = 100	n = 118 ; % = 100
Median age (years) Median (IQR)	47 (42 to 57)	48 (43 to 55)

Characteristic	Platinum-containing regimen (N = 118)	Non-platinum-containing regimen (N = 118)
Receptor subtype - both ER and PR less than 1% positivity No of events	n = 118 ; % = 100	n = 116 ; % = 98
Receptor subtype - Others Included ER-negative and PR 1 to 9% positive; ER 1 to 9% positive and PR-negative; and ER 1 to 9% positive and PR 1 to 9% positive No of events	n = 0 ; % = 0	n = 2 ; % = 2
Timing of receptor subtype test - At baseline No of events	n = 118 ; % = 100	n = 118 ; % = 100

Critical Appraisal - Cochrane Risk of Bias tool

Question	Answer
Risk of bias judgement - overall survival	Moderate (Blinding of outcome assessment was unlikely to influence overall survival assessment; modified intention-to-treat analysis was used for time-to-event analysis; baseline characteristics were generally similar across groups except for ECOG PS, number of metastatic organ sites and menopausal status)
Risk of bias judgement – other time-to-event outcomes	High (Open-label trial; extent and/or effectiveness of intended blinding was not clear; assessment of toxicity appeared to be unblinded; modified intention-to-treat analysis was used for time-to-event analysis; baseline characteristics were generally similar across groups except for ECOG PS, number of metastatic organ sites and menopausal status)
Overall Directness - overall survival and other time-to-event outcomes	Directly applicable
Risk of bias judgement - dichotomous outcomes	High (Open-label trial; extent and/or effectiveness of intended blinding was not clear; assessment of toxicity appeared to be unblinded; baseline characteristics were generally similar across groups except for ECOG PS, number of metastatic organ sites and menopausal status)
Overall Directness - dichotomous outcomes	Directly applicable

Randomised controlled trials not included in Egger et al. 2020

Liu, 2024

Bibliographic Reference	Liu, X.; Zhao, W.; Jia, Y.; Shi, Y.; Wang, X.; Li, S.; Zhang, P.; Wang, C.; Hao, C.; Tong, Z.; A non-inferiority, phase III trial of gemcitabine plus capecitabine versus gemcitabine plus carboplatin as first-line therapy and tumor-infiltrating lymphocytes

as a prognostic biomarker in patients with advanced triple-negative breast cancer; Therapeutic Advances in Medical Oncology; 2024; vol. 16

Study details

Trial registration number and/or trial name	NCT02207335
Study type	Randomised controlled trial (RCT)
Study location	China
Study dates	January 2014 to December 2020
Inclusion criteria	Age 18 to 75 years Diagnosed with negative ER, PR, and HER-2 phenotype ER, PR, and HER-2 status was independently confirmed by two independent pathologists based on immunochemical analysis and in situ hybridisation, <10% was used for positively stained cells as the cut-off value for ER/PR negativity in immunohistochemistry (IHC) testing according to the American Society of Clinical Oncology/College of American Pathologists guideline Eastern Cooperative Oncology Group performance status (ECOG PS) of grade 0 to 2 Measurable disease by CT or MRI according to Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) At least 6 months from the last adjuvant chemotherapy to recurrence or metastasis Expected survival 12 weeks or more
Intervention(s)	Gemcitabine (1,000mg/m2) on days 1 and 8 plus carboplatin area under curve 2 on days 1 and 8 every 21 days. After 6–8 cycles, patients continued to receive gemcitabine as maintenance therapy until progression.
Comparator	Gemcitabine (1,000mg/m2) on days 1 and 8 plus oral capecitabine (1000mg/m2 twice a day) on days 1–14 every 21days. After 6–8 cycles, patients continued to receive gemcitabine as maintenance therapy until progression.
Outcome measures	Progression-free survival Defined as the time from randomisation to the first evidence of progression or death. Overall survival Defined as the time from randomisation to death from any cause. Objective tumour response rate Defined as the percentage of patients who achieved complete response (CR) or partial response (PR). Adverse events Recorded at every study visit and graded according to the National Cancer Institute Common Toxicity Criteria version 4.0.
Number of participants	187

Study arms

Platinum-containing regimen (N = 94)

Duration of follow-up	Median PFS was 6.3 months median OS was 21.5 months.
Loss to follow-up	26

Gemcitabine (1,000mg/m2) on days 1 and 8 plus carboplatin area under curve 2 on days 1 and 8 every 21 days. After 6–8 cycles, patients continued to receive gemcitabine as maintenance therapy until progression.

Non-platinum-containing regimen (N = 93)

Duration of follow-up	Median PFS was 6.1 months and median OS was 21.0.
Loss to follow-up	21

Gemcitabine (1,000mg/m2) on days 1 and 8 plus oral capecitabine (1000mg/m2 twice a day) on days 1–14 every 21days. After 6–8 cycles, patients continued to receive gemcitabine as maintenance therapy until progression.

Characteristics

Arm-level characteristics

Characteristic	Platinum-containing regimen (N = 94)	Non-platinum-containing regimen (N = 93)
% Female No of events	n = 94 ; % = 100	n = 93 ; % = 100
Median age (years) Custom value	52 (range: 29 to 75)	53 (range: 30 to 73)
Receptor subtype - TNBC No of events	n = 94 ; % = 100	n = 93 ; % = 100
Timing of receptor subtype test - At recruitment 96 participants (51.3%) had a re-biopsy of recurrent or metastatic lesions but results of the receptor subtypes were not reported No of events	n = 94 ; % = 100	n = 93 ; % = 100

Outcomes

Study timepoints

- 21 month (Overall survival time)
- 6 month (Progression-free survival time)

Overall survival

Outcome	21 month, Platinum-containing regimen vs Non-platinum-containing regimen, N2 = 94, N1 = 93
Overall survival Hazard ratio/95% CI	0.99 (0.71 to 1.39)

Overall survival - Polarity - Lower values are better

Progression-free survival

Outcome	Platinum-containing regimen vs Non-platinum-containing regimen, 21 month, N2 = 94, N1 = 93
Progression-free survival Hazard ratio/95% CI	0.87 (0.65 to 1.17)

Progression-free survival - Polarity - Lower values are better

Objective tumour response rate

Outcome	Platinum-containing regimen, 6 month, N = 94	Non-platinum-containing regimen, 6 month, N = 93
Objective tumour response rate No of events	n = 37 ; % = 39	n = 35 ; % = 38

Objective tumour response rate - Polarity - Higher values are better

Assessment was repeated after every second cycle until disease progression. Each cycle was 21 days. Each person could have had a total of 8 cycles which was approximately 6 months.

Adverse events

Outcome	Platinum-containing regimen, 6 month, N = 94	Non-platinum-containing regimen, 6 month, N = 93
Treatment-related death No of events	n = 0 ; % = 0	n = 0 ; % = 0
Anaemia No of events	n = 11 ; % = 12	n = 4 ; % = 4
Leukopenia No of events	n = 42 ; % = 45	n = 28 ; % = 30
Neutropenia No of events	n = 48 ; % = 51	n = 23 ; % = 25
Neutropenic No of events	n = 11 ; % = 12	n = 2 ; % = 2
Thrombocytopenia No of events	n = 28 ; % = 30	n = 15 ; % = 16
Fatigue - grade 1 and 2 No of events	n = 34 ; % = 36	n = 23 ; % = 25

Outcome	Platinum-containing regimen, 6 month, N = 94	Non-platinum-containing regimen, 6 month, N = 93
Hair loss - grade 1 and 2 No of events	n = 60 ; % = 64	n = 14 ; % = 15
Nausea/vomiting No of events	n = 6 ; % = 6	n = 0 ; % = 0
Neuropathy No of events	n = 0 ; % = 0	n = 4 ; % = 4

Treatment-related death - Polarity - Lower values are better
Anaemia - Polarity - Lower values are better
Leukopenia - Polarity - Lower values are better
Neutropenia - Polarity - Lower values are better
Neutropenic - Polarity - Lower values are better
Thrombocytopenia - Polarity - Lower values are better
Fatigue - grade 1 and 2 - Polarity - Lower values are better
Hair loss - grade 1 and 2 - Polarity - Lower values are better
Nausea/vomiting - Polarity - Lower values are better
Neuropathy - Polarity - Lower values are better
Adverse events were recorded at every study visit.

Adherence to / completion of treatment

Outcome	Platinum-containing regimen, 6 month, N = 94	Non-platinum-containing regimen, 6 month, N = 93
Treatment discontinuation due to adverse event No of events	n = 12 ; % = 13	n = 7 ; % = 8

Treatment discontinuation due to adverse event - Polarity - Lower values are better
Treatment discontinuation due to adverse event. Adverse events were recorded at every study visit.

Critical Appraisal - Cochrane Risk of Bias tool

Question	Answer
Risk of bias judgement - overall survival	Moderate (No information about random sequence generation or allocation concealment; blinding of outcome assessment was unlikely to influence overall survival assessment)
Risk of bias judgement – other time-to-event outcomes	High (Open-label trial; no information about random sequence generation, allocation concealment or blinding of outcome assessment)
Overall Directness - overall survival and other time-to-event outcomes	Directly applicable

Question	Answer
Risk of bias judgement - dichotomous outcomes	High (Open-label trial; no information about random sequence generation, allocation concealment or blinding of outcome assessment)
Overall Directness - dichotomous outcomes	Directly applicable

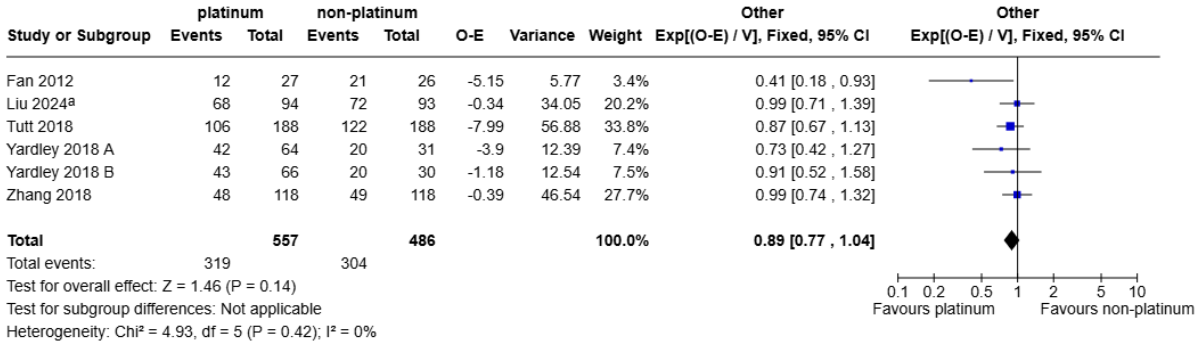
Appendix E – Forest plots

Results from subgroup analyses were assessed using GRADE only when statistically significant subgroup differences were identified (p <0.05).

Advanced triple negative breast cancer

Overall survival

Figure 1 Overall survival: main analysis



Footnotes

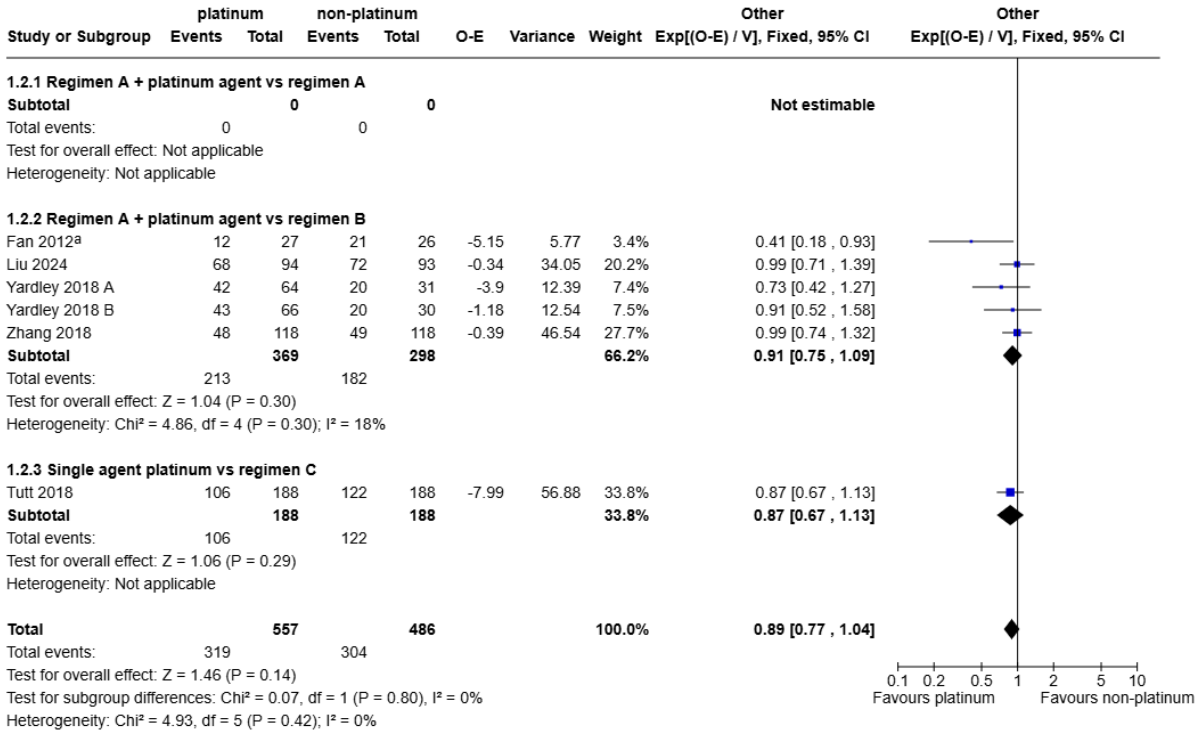
[a]Liu et al. 2024 reported effect estimates with platinum as control arm; HR and 95% CI were inverted to have non-platinum as control arm.

Study	Overall survival time in platinum (median months)	Overall survival time in non-platinum (median months)
Fan 2012*	32.8	21.5
Liu 2024**	21.5	21.0
Tutt 2018*	12.8	12.0
Yardley 2018 A*	16.8	12.1
Yardley 2018 B*	12.6	12.1
Zhang 2018*	22.3	18.6

* Overall survival times taken from the Cochrane systematic review (Egger et al. 2020)

** Overall survival times taken from the primary study (Liu et al. 2024) published after the Cochrane systematic review

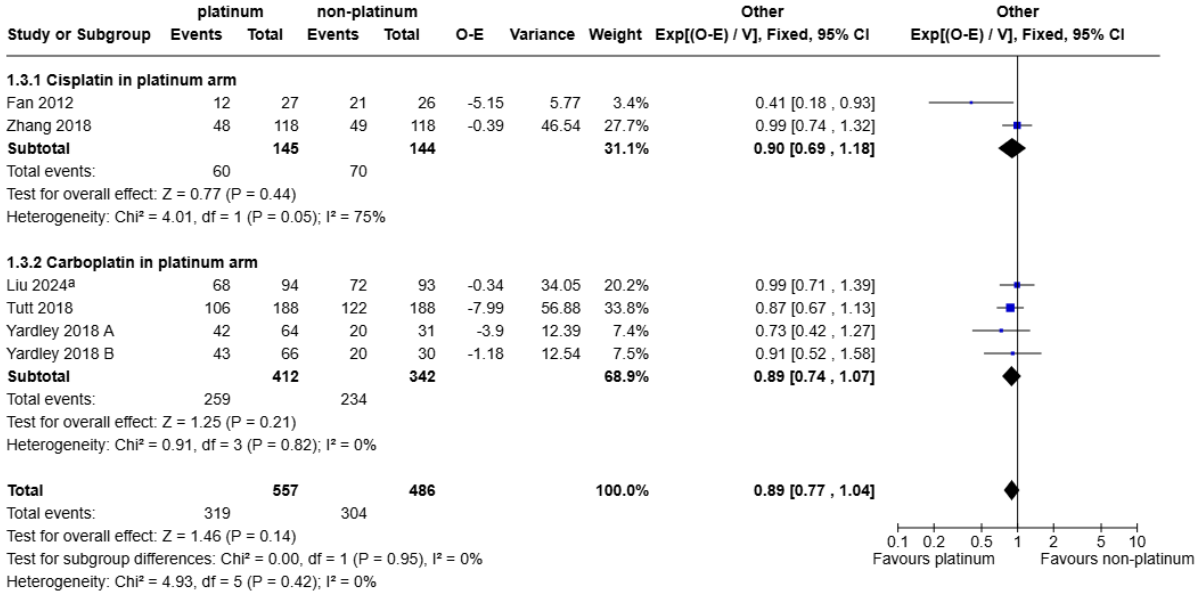
Figure 2 Overall survival: subgroup analysis by type of regimen comparison



Footnotes

[a]Liu et al. 2024 reported effect estimates with platinum as control arm; HR and 95% CI were inverted to have non-platinum as control arm.

Figure 3 Overall survival: subgroup analysis by type of platinum agent in platinum arm



Footnotes

[a]Liu et al. 2024 reported effect estimates with platinum as control arm; HR and 95% CI were inverted to have non-platinum as control arm.

Overall survival: subgroup analysis by line of therapy

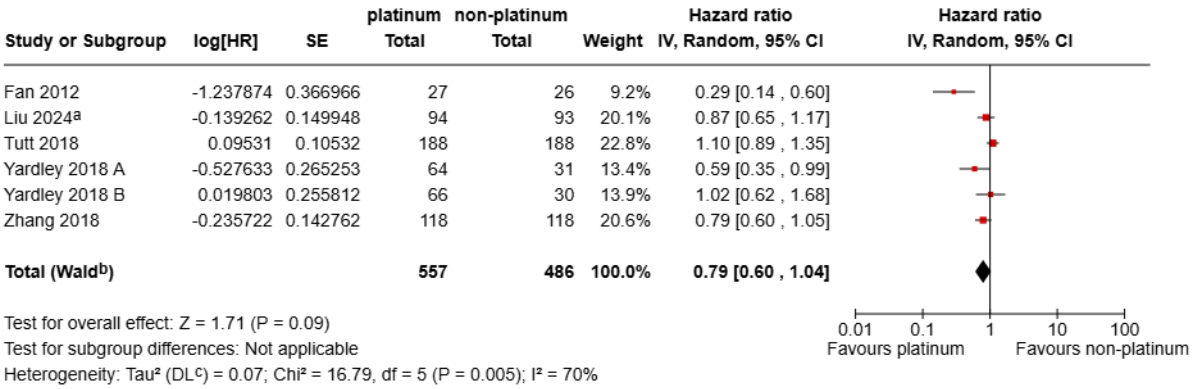
All studies reporting overall survival included participants with first-line therapy (more than 80% of participants) and no participants or less than 20% of participants with second or third-line therapy. Therefore, no subgroup analysis was possible.

Figure 4 Overall survival: subgroup analysis by BRCA 1/2 gene status

Forest plot can be seen in Egger et al. (2020) reported as analysis 6.1.

Progression-free survival

Figure 5 Progression-free survival: main analysis (random effects model: I^2 >40%)



Footnotes

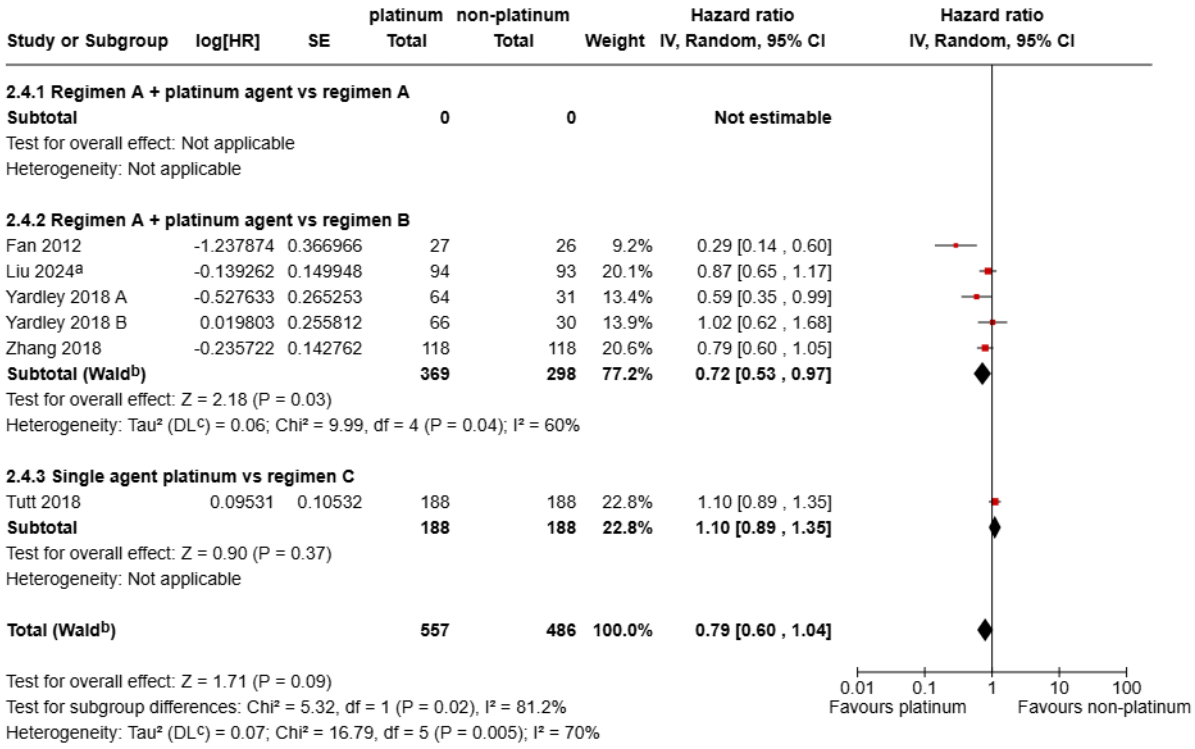
[a]Liu et al. 2024 reported effect estimates with platinum as control arm; HR and 95% CI were inverted to have non-platinum as control arm.
[b]CI calculated by Wald-type method.
[c]Tau² calculated by DerSimonian and Laird method.

Study	Progression-free survival time in platinum (median months)	Progression-free survival time in non-platinum (median months)
Fan 2012*	10.9	4.8
Liu 2024**	6.3	6.1
Tutt 2018*	3.1	4.4
Yardley 2018 A*	8.3	5.5
Yardley 2018 B*	6.0	5.5
Zhang 2018*	7.7	6.5

* Progression-free survival times taken from the Cochrane systematic review (Egger et al. 2020)

** Progression-free survival times taken from the primary study (Liu et al. 2024) published after the Cochrane systematic review

Figure 6 Progression-free survival: subgroup analysis by type of regimen comparison (random effects model: I^2 >40%)



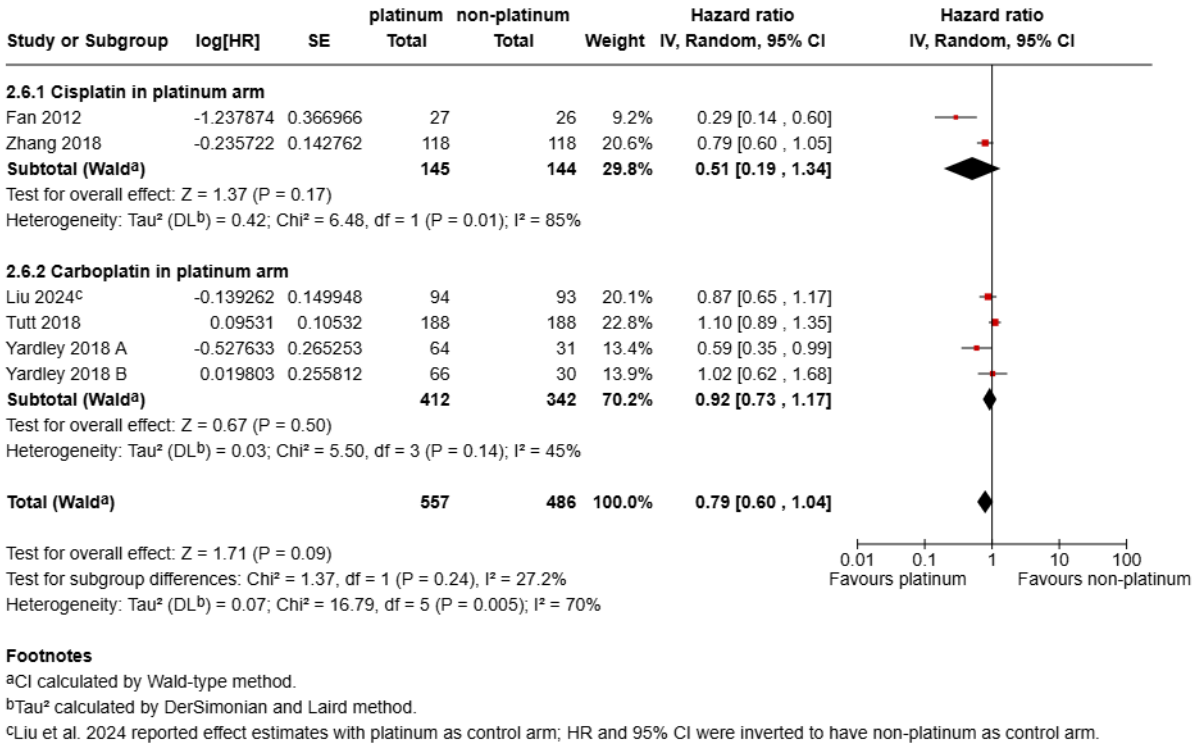
Footnotes

[a]Liu et al. 2024 reported effect estimates with platinum as control arm; HR and 95% CI were inverted to have non-platinum as control arm.

[b]CI calculated by Wald-type method.

[c]Tau² calculated by DerSimonian and Laird method.

Figure 7 Progression-free survival: subgroup analysis by type of platinum agent in platinum arm (random effects model: I^2 >40%)



Footnotes

[a]CI calculated by Wald-type method.

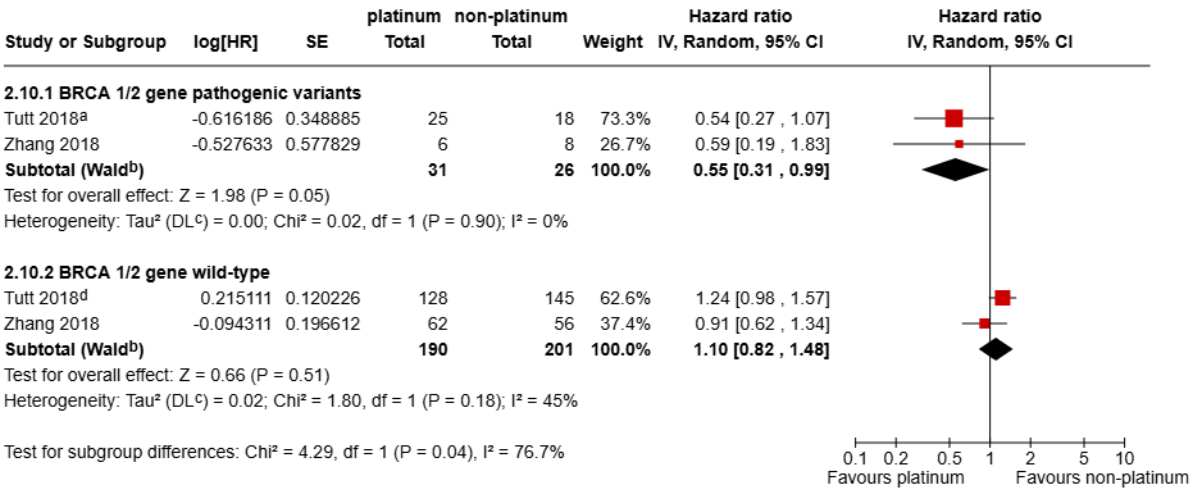
[b]Tau² calculated by DerSimonian and Laird method.

[c]Liu et al. 2024 reported effect estimates with platinum as control arm; HR and 95% CI were inverted to have non-platinum as control arm.

Progression-free survival: subgroup analysis by line of therapy

All studies reporting progression-free survival included participants with first-line therapy (more than 80% of participants) and no participants or less than 20% of participants with second or third-line therapy. Therefore, no subgroup analysis was possible.

Figure 8 Progression-free survival: subgroup analysis by BRCA 1/2 gene status (random effects model: I^2 >40%)



Footnotes

[a]Of the 43 women with BRCA1/2 germline mutations, only 14 (33%) had TNBC (and some of these 14 may have been locally advanced rather than me

[b]CI calculated by Wald-type method.

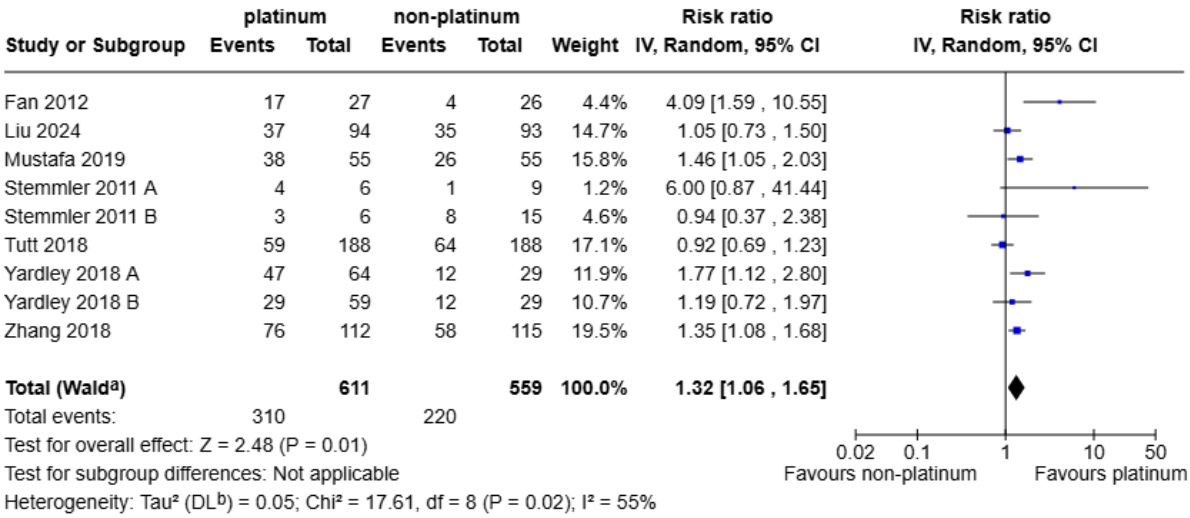
[c]Tau² calculated by DerSimonian and Laird method.

[d]Of the 333 women with BRCA1/2 wild-types, 324 (97%) had TNBC

Note: Heterogeneity for germline BRCA1 or BRCA2 pathogenic variants subgroup should be presented as fixed effects analysis due to no heterogeneity. However, as I^2 is 0%, the fixed and random effects results for this subgroup are identical, and so no extra plot has been added for this result.

Objective tumour response rate

Figure 9 Objective tumour response rate: main analysis (random effects model: I^2 >40%)

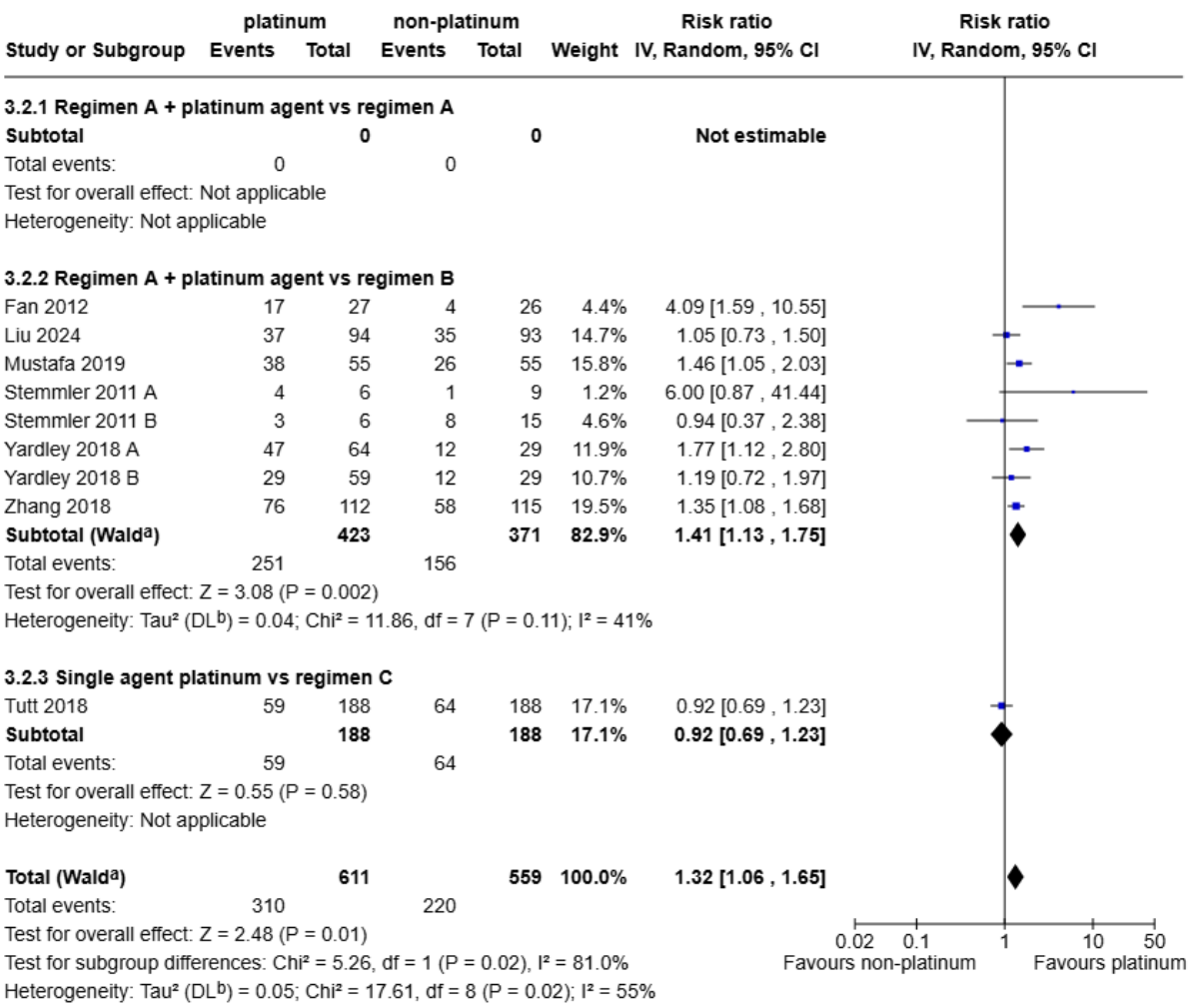


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 10 Objective tumour response rate: subgroup analysis by type of regimen comparison (random effects model: I^2 >40%)

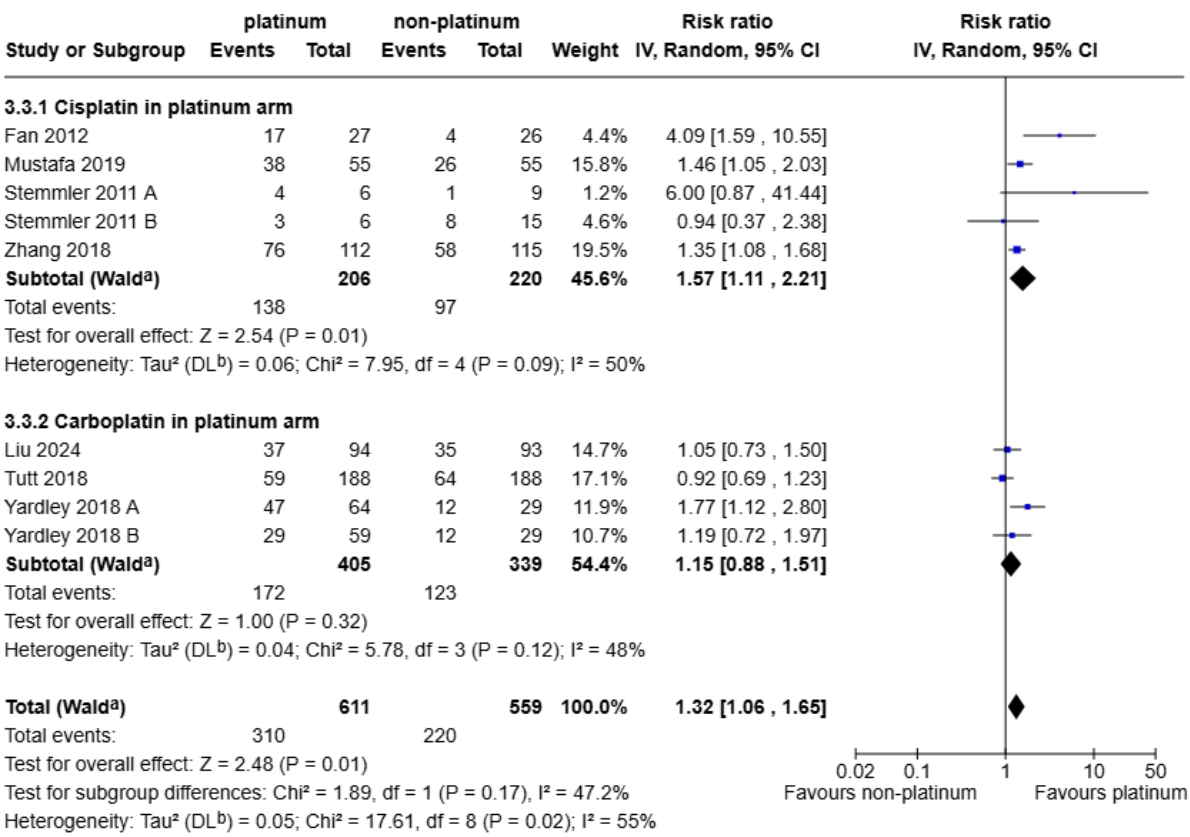


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 11 Objective tumour response rate: subgroup analysis by type of platinum agent in platinum arm (random effects model: I^2 >40%)

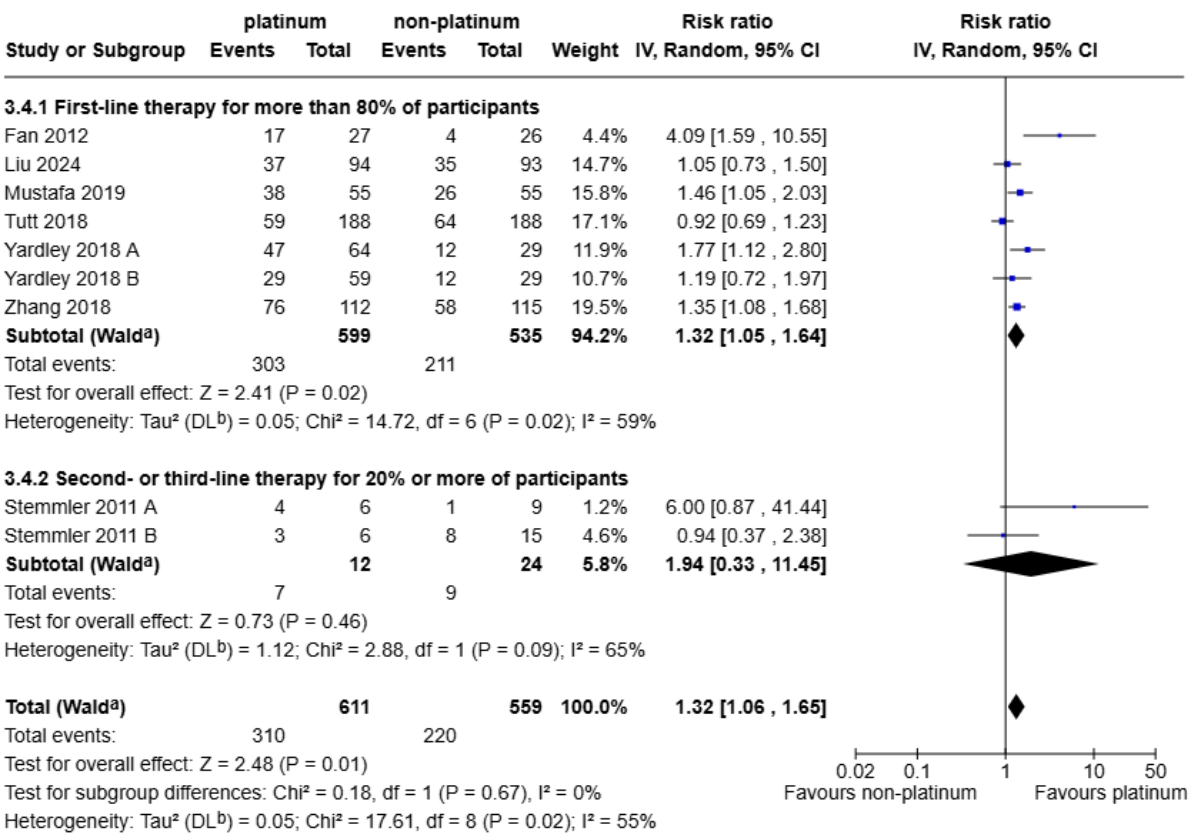


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 12 Objective tumour response rate: subgroup analysis by line of therapy (random effects model: I^2 >40%)

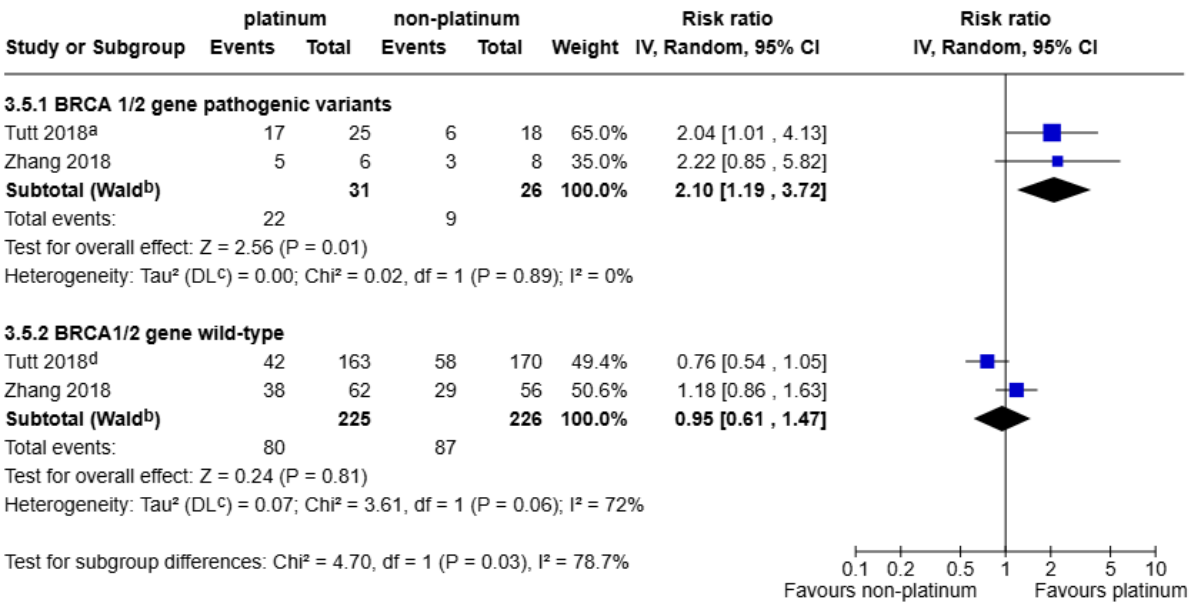


Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 13 Objective tumour response rate: subgroup analysis by BRCA gene status (random effects model: I^2 >40%)



Footnotes

[a]Of the 43 women with BRCA1/2 germline mutations, only 14 (33%) had TNBC (and some of these 14 may have been locally advanced

[b]CI calculated by Wald-type method.

[c]Tau² calculated by DerSimonian and Laird method.

[d]Of the 333 women with BRCA1/2 wild-type, 324 (97%) had TNBC

Note: Heterogeneity for germline BRCA1 or BRCA2 pathogenic variants subgroup should be presented as fixed effects analysis due to no heterogeneity. However, as I^2 is 0%, the fixed and random effects results for this subgroup are identical, and so no extra plot has been added for this result.

Adverse events

Figure 14 Treatment-related death

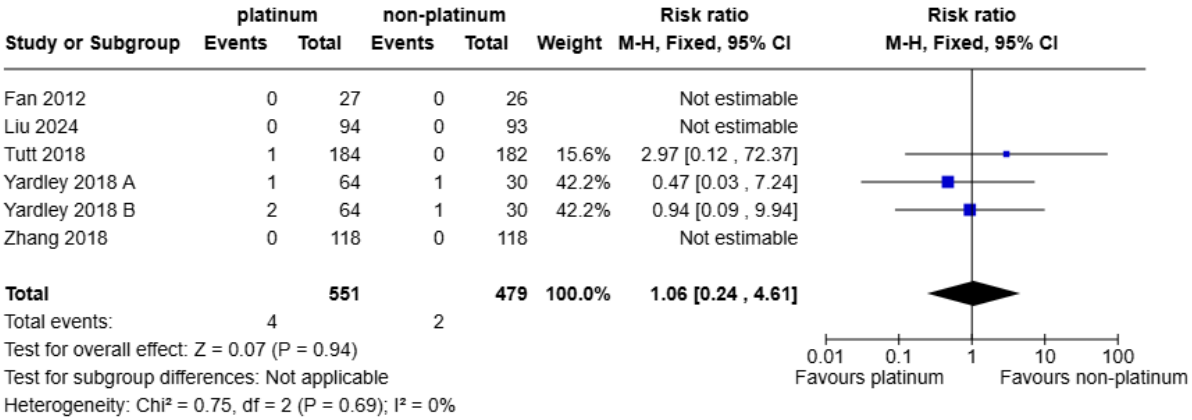
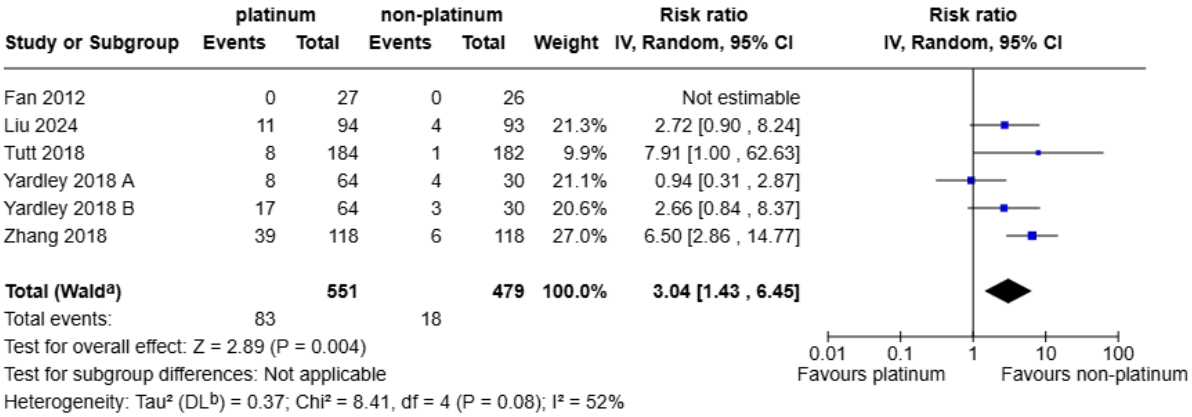


Figure 15 Anaemia (random effects model: I^2 >40%)



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 16 Leukopenia

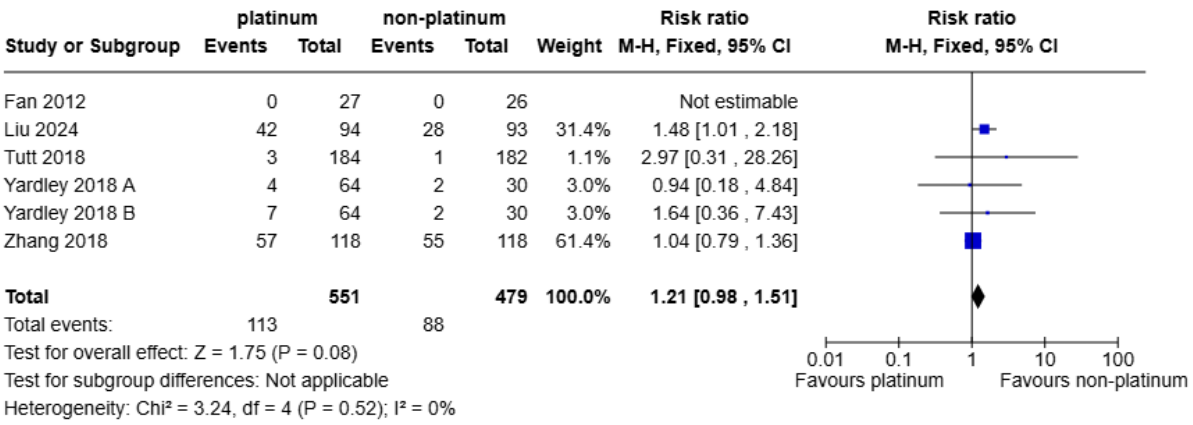
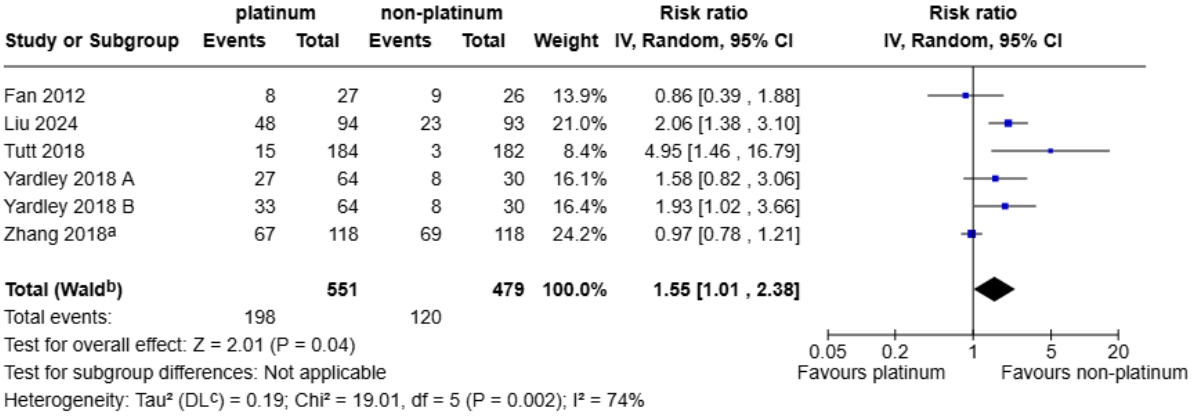


Figure 17 Neutropenia (random effects model: I^2 >40%)



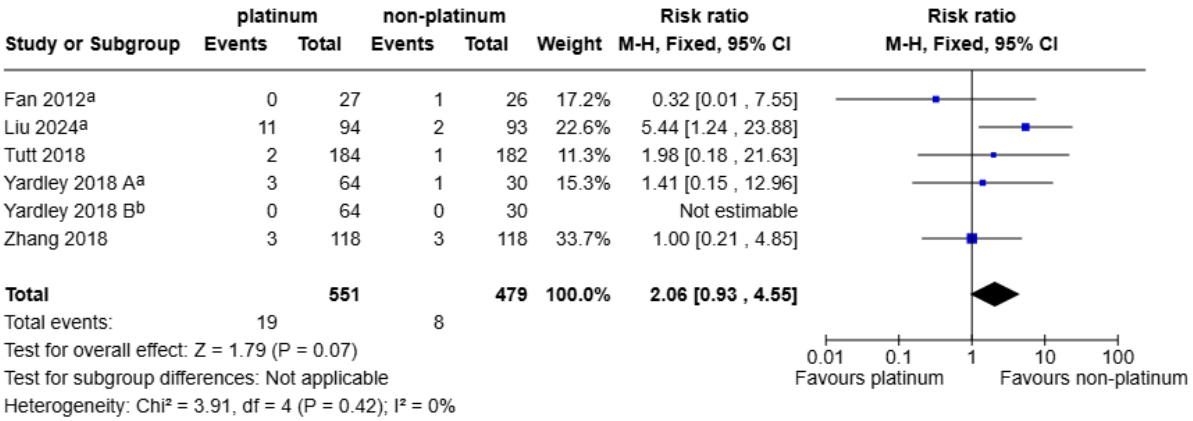
Footnotes

[a]Reported by Hu et al. 2015

[b]CI calculated by Wald-type method.

[c]Tau² calculated by DerSimonian and Laird method.

Figure 18 Neutropenic sepsis

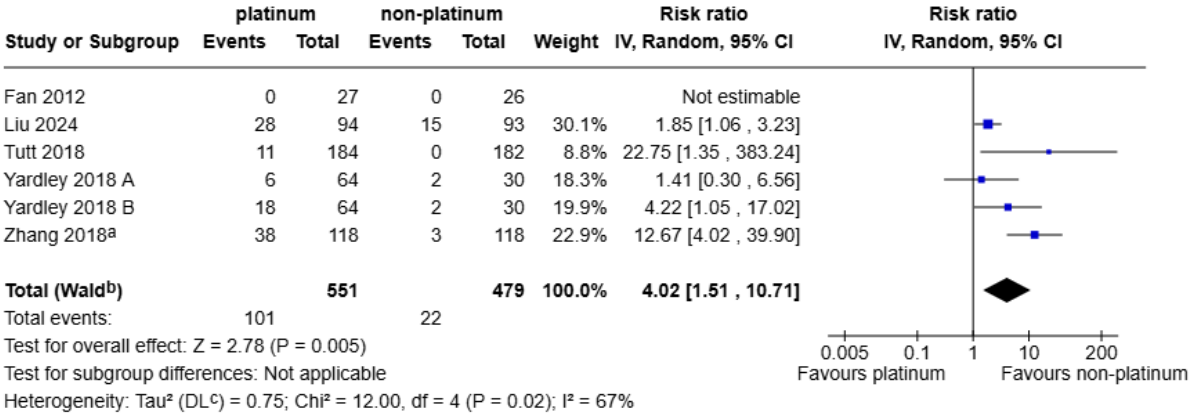


Footnotes

[a]Reported as febrile neutropenia

[b]Reported as febrile neutropenia; non-platinum arm reported 1 event which has already taken to compare to platinum intervention A

Figure 19 Thrombocytopenia (random effects model: I^2 >40%)



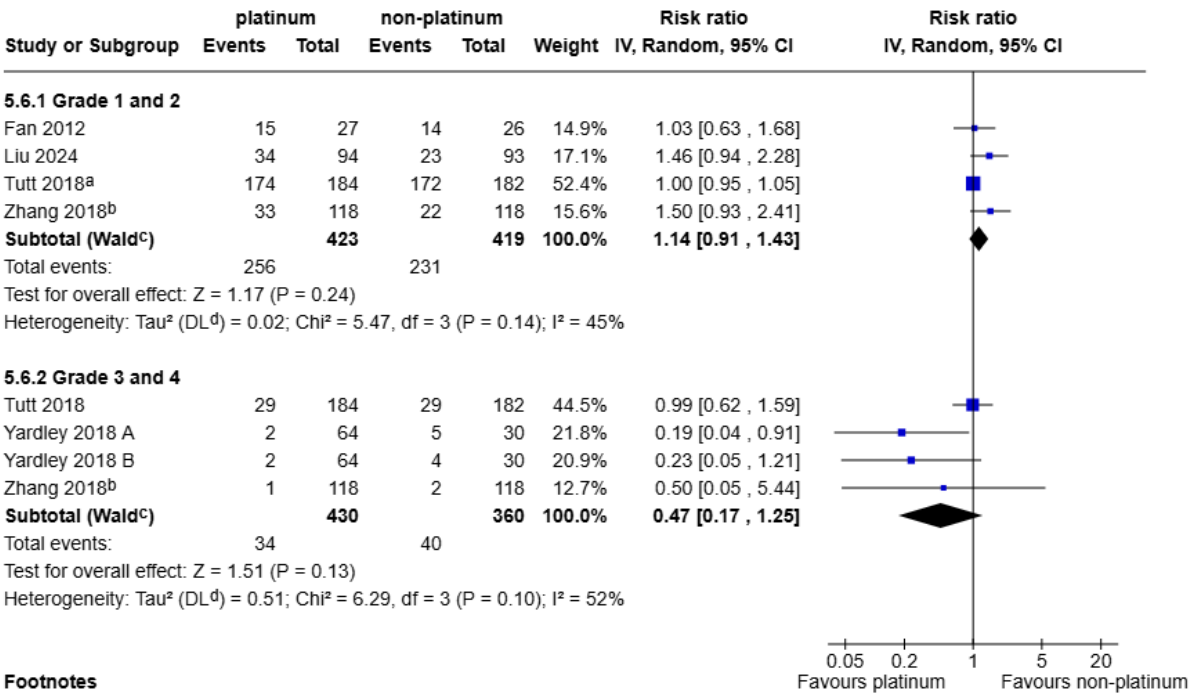
Footnotes

[a]Reported by Hu et al. 2015

[b]CI calculated by Wald-type method.

[c]Tau² calculated by DerSimonian and Laird method.

Figure 20 Fatigue (random effects model: I^2 >40%)



Footnotes

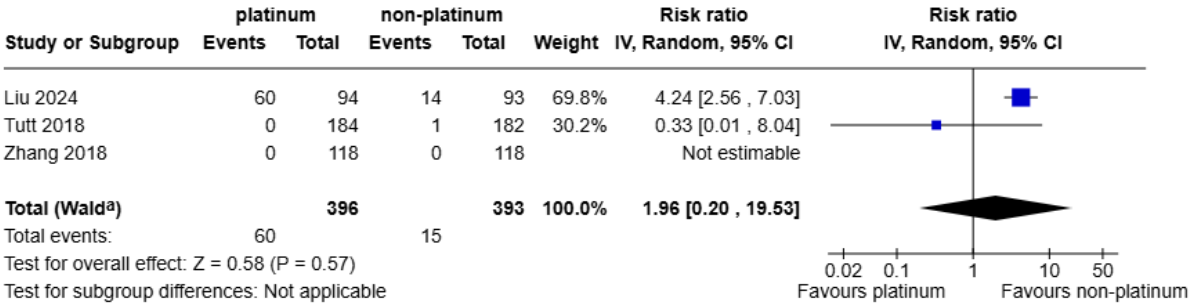
[a]Reported as 'any grade'

[b]Reported by Hu et al. 2015 as fatigue or asthenia

[c]CI calculated by Wald-type method.

[d]Tau² calculated by DerSimonian and Laird method.

Figure 21 Hair loss - Grade 1 and 2 (random effects model: I^2 >40%)



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Figure 22 Nausea/vomiting

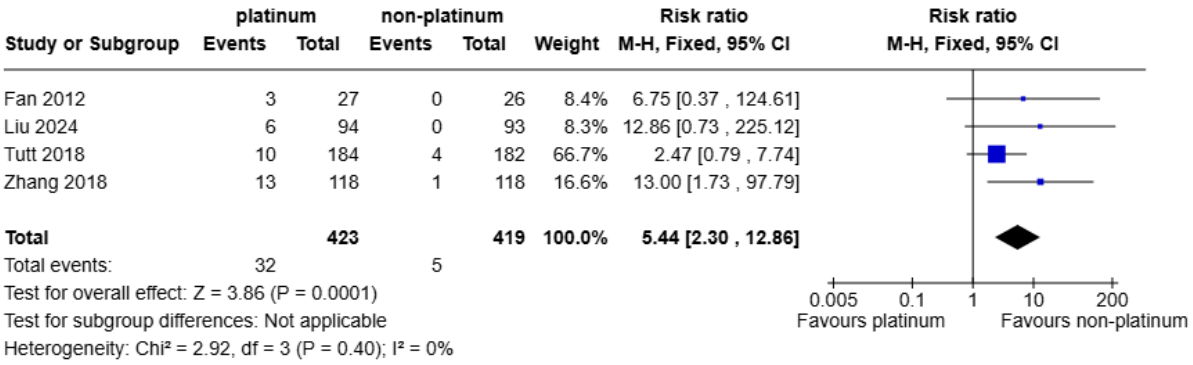
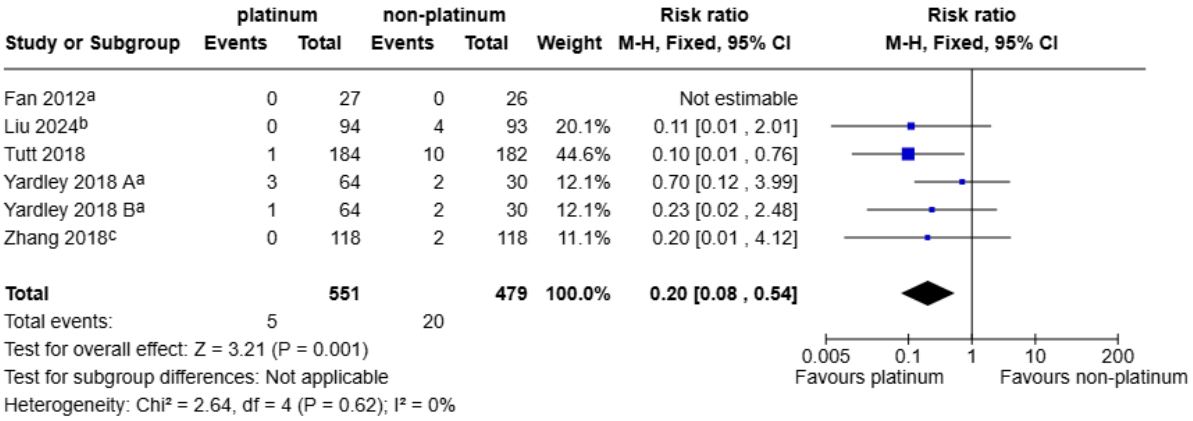


Figure 23 Neuropathy



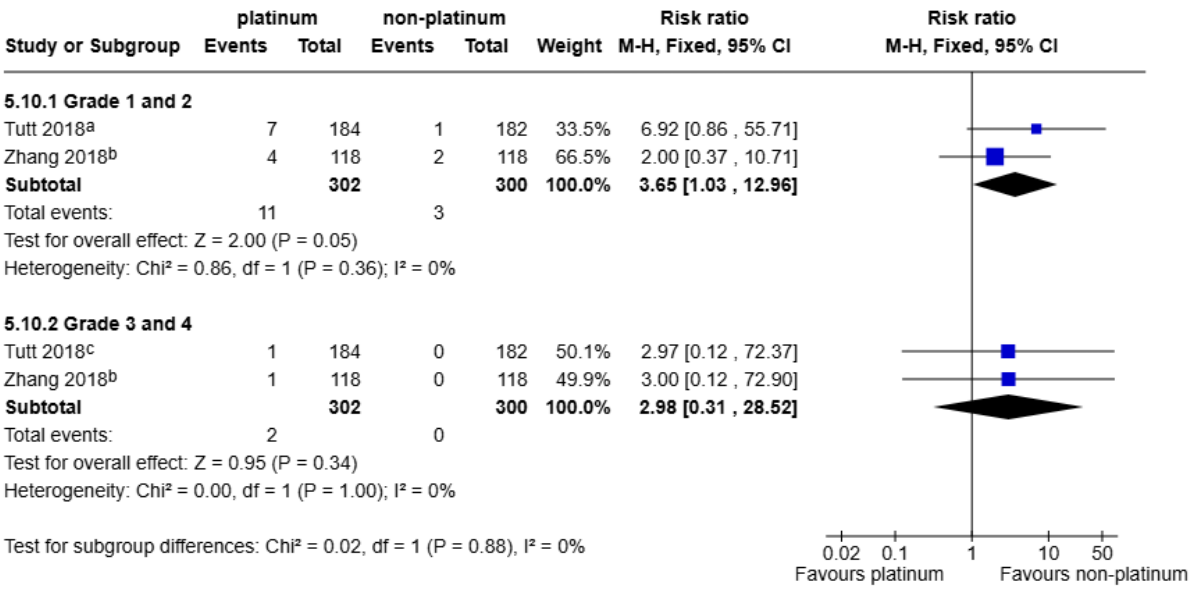
Footnotes

[a]Reported as peripheral neuropathy

[b]Reported as peripheral sensory neuropathy

[c]Reported by Hu et al. 2015 as peripheral neuropathy

Figure 24 Ototoxicity



Footnotes

[a]Reported as 'any grade' of tinnitus

[b]Reported by Hu et al. 2015 as hearing toxicity

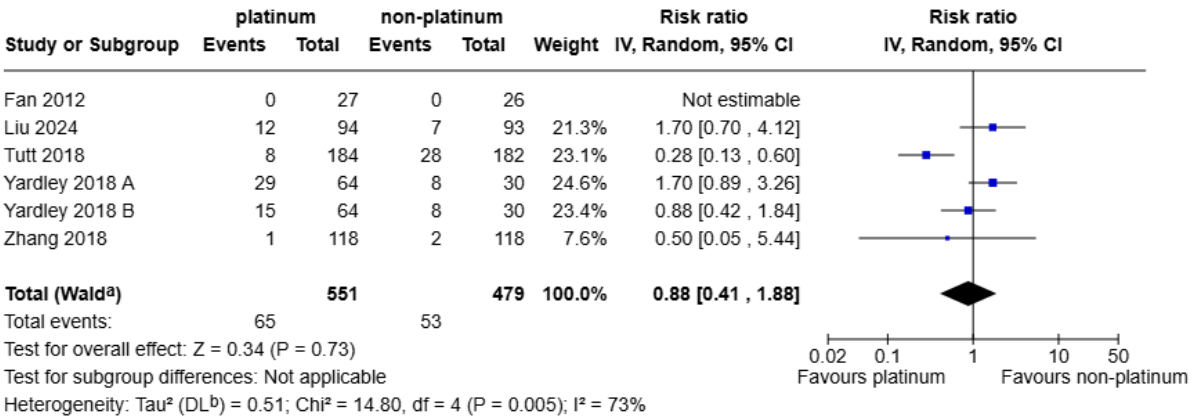
[c]Reported as tinnitus

Figure 25 Nephrotoxicity

No data available.

Adherence to / completion of treatment

Figure 26 Treatment discontinuation due to adverse event (random effects model: I^2 >40%)



Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by DerSimonian and Laird method.

Advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants

There were no studies reporting data on people with advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants. There was data reported as subgroup analysis of BRCA gene status within the advanced triple negative breast cancer population.

Appendix F – GRADE tables

Results from subgroup analyses were assessed using GRADE only when statistically significant subgroup differences were identified ($p < 0.05$).

Advanced triple negative breast cancer

All studies were randomised controlled trials.

Overall survival

Table 11 Overall survival

Certainty assessment					№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Platinum	non-platinum regimens	Relative (95% CI)	Absolute (95% CI)		
Overall survival: main analysis (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
5 (Fan 2012; Liu 2024; Tutt 2018, Yardley 2018A; Yardley 2018 B, Zhang 2018)	serious[a]	not serious	not serious	serious[b]	319/557 (57.3%)	304/486 (62.6%)	HR 0.89 (0.77 to 1.04)	43 fewer per 1,000 (from 95 fewer to 14 more)	Low	CRITICAL

CI: confidence interval; HR: hazard ratio.

Explanations

a. Greater than >50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, outcome was downgraded one level.

b. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level.

Progression-free survival

Table 12 Progression-free survival

Certainty assessment					№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Platinum	non-platinum regimens	Relative (95% CI)	Absolute (95% CI)		
Progression-free survival: main analysis (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
5 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	very serious[d]	not serious	serious[a]	470/557 (84.4%)	451/486 (92.8%)	HR 0.79 (0.60 to 1.04)	53 fewer per 1,000 (from 134 fewer to 7 more)	Very low	CRITICAL
Progression-free survival: subgroup analysis by type of regimen comparison - Regimen A + platinum agent vs regimen B (RE model: I2 >40%)										
4 (Fan 2012; Liu 2024; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	serious[e]	not serious	not serious	290/369 (78.6%)	268/298 (89.9%)	HR 0.72 (0.53 to 0.97)	91 fewer per 1,000 (from 195 fewer to 7 fewer)	Very low	CRITICAL
Progression-free survival: subgroup analysis by type of regimen comparison - Single agent platinum vs regimen C										
1 (Tutt 2018)	very serious[b]	serious[c]	not serious	serious[a]	180/188 (95.7%)	183/188 (97.3%)	HR 1.10 (0.89 to 1.35)	8 more per 1,000 (from 13 fewer to 19 more)	Very low	CRITICAL
Progression-free survival: subgroup analysis by BRCA gene status – germline BRCA1 or BRCA2 pathogenic variants										
2 (Tutt 2018; Zhang 2018)	very serious[b]	not serious	not serious	serious[f]	25/31 (80.6%)	25/26 (96.2%)	HR 0.55 (0.31 to 0.99)	128 fewer per 1,000 (from 326	Very low	CRITICAL

								fewer to 1 fewer)		
Progression-free survival: subgroup analysis by BRCA gene status - germline BRCA1 or BRCA2 gene wild-type (RE model: I2 >40%)										
2 (Tutt 2018; Zhang 2018)	very serious[b]	serious[e]	not serious	serious[a]	183/190 (96.3%)	194/201 (96.5%)	HR 1.10 (0.82 to 1.48)	10 more per 1,000 (from 29 fewer to 28 more)	Very low	CRITICAL

CI: confidence interval; HR: hazard ratio.

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level.

b. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels.

c. Data was only available from one study, outcome was downgraded one level.

d. I2 was >60%, outcome was downgraded two levels.

e. I2 was between 40% and 60%, outcome was downgraded one level.

f. Number of participants was less than 370, outcome was downgraded one level.

Objective tumour response rate

Table 13 Objective tumour response rate

Certainty assessment					№ of patients		Effect		Certainty	Importance
№ of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Platinum**	**non-platinum regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Objective tumour response rate: main analysis (relative effect greater than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
7 (Fan 2012; Liu 2024; Mustafa 2019; Stemmler 2011 A; Stemmler	very serious[b]	very serious[d]	not serious	not serious	310/611 (50.7%)	220/559 (39.4%)	RR 1.32 (1.06 to 1.65)	126 more per 1,000 (from 24	Very low	CRITICAL

2011 B; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)								more to 256 more)		
Objective tumour response rate: subgroup analysis by type of regimen comparison - Regimen A + platinum agent vs regimen B (RE model: I2 >40%)										
6 (Fan 2012; Liu 2024; Mustafa 2019; Stemmler 2011 A; Stemmler 2011 B; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	very serious[d]	not serious	not serious	251/423 (59.3%)	156/371 (42.0%)	RR 1.41 (1.13 to 1.75)	172 more per 1,000 (from 55 more to 315 more)	Very low	CRITICAL
Objective tumour response rate: subgroup analysis by type of regimen comparison - Single agent platinum vs regimen C										
1 (Tutt 2018)	very serious[b]	serious[c]	not serious	serious[a]	59/188 (31.4%)	64/188 (34.0%)	RR 0.92 (0.69 to 1.23)	27 fewer per 1,000 (from 106 fewer to 78 more)	Very low	CRITICAL
Objective tumour response rate: subgroup analysis by BRCA gene status – germline BRCA1 or BRCA2 pathogenic variants										
2 (Tutt 2018; Zhang 2018)	very serious[b]	not serious	not serious	serious[e]	22/31 (71.0%)	9/26 (34.6%)	RR 2.10 (1.19 to 3.72)	381 more per 1,000 (from 66 more to 942 more)	Very low	CRITICAL
Objective tumour response rate: subgroup analysis by BRCA gene status - germline BRCA1 or BRCA2 gene wild-type (RE model: I2 >40%)										
2 (Tutt 2018; Zhang 2018)	very serious[b]	very serious[d]	not serious	serious[a]	80/225 (35.6%)	87/226 (38.5%)	RR 0.95 (0.61 to 1.47)	19 fewer per 1,000 (from 150 fewer to 181 more)	Very low	CRITICAL

CI: confidence interval; RR: risk ratio.

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level.

b. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels.

c. Data was only available from one study, outcome was downgraded one level.

d. I2 was >60%, outcome was downgraded two levels.

e. Number of participants was less than 370, outcome was downgraded one level.

Treatment-related death

Table 14 Treatment-related death

Certainty assessment					№ of patients		Effect		Certainty	Importance
№ of studies	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Platinum**	**non-platinum regimens**	**Relative (95% CI)**	**Absolute (95% CI)**		
Treatment-related death (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
5 (Fan 2012; Liu 2024Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	not serious	not serious	serious[a]	4/551 (0.7%)	2/479 (0.4%)	RR 1.06 (0.24 to 4.61)	0 fewer per 1,000 (from 6 fewer to 30 more)	Very low	IMPORTANT

CI: confidence interval; RR: risk ratio.

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level.

b. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels.

Adverse events

Table 15 Adverse events

Certainty assessment					№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Platinum	non-platinum regimens	Relative (95% CI)	Absolute (95% CI)		
Anaemia (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
5 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	serious[d]	not serious	not serious	83/551 (15.1%)	18/479 (3.8%)	RR 3.04 (1.43 to 6.45)	81 more per 1,000 (from 17 more to 217 more)	Very low	IMPORTANT
Leukopenia (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
4 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	not serious	not serious	serious[a]	113/551 (20.5%)	88/479 (18.4%)	RR 1.21 (0.98 to 1.51)	41 more per 1,000 (from 4 fewer to 99 more)	Very low	IMPORTANT
Neutropenia (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
5 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	very serious[c]	not serious	not serious	198/551 (35.9%)	120/479 (25.1%)	RR 1.55 (1.01 to 2.38)	138 more per 1,000 (from 3 more to 346 more)	Very low	IMPORTANT
Neutropenic sepsis (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
5 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A;	very serious[b]	not serious	not serious	serious[a]	19/551 (3.4%)	8/479 (1.7%)	RR 2.06 (0.93 to 4.55)	19 more per 1,000 (from 1	Very low	IMPORTANT

Yardley 2018 B; Zhang 2018)								fewer to 63 more)		
Thrombocytopenia (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
5 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	very serious[c]	not serious	not serious	101/551 (18.3%)	22/479 (4.6%)	RR 4.02 (1.51 to 10.71)	147 more per 1,000 (from 25 more to 472 more)	Very low	IMPORTANT
Fatigue - Grade 1 and 2 (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
4 (Fan 2012; Liu 2024; Tutt 2018; Zhang 2018)	very serious[b]	serious[d]	not serious	serious[a]	256/423 (60.5%)	231/419 (55.1%)	RR 1.14 (0.91 to 1.43)	77 more per 1,000 (from 50 fewer to 237 more)	Very low	IMPORTANT
Fatigue - Grade 3 and 4 (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
3 (Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	serious[d]	not serious	serious[a]	34/430 (7.9%)	40/360 (11.1%)	RR 0.47 (0.17 to 1.25)	59 fewer per 1,000 (from 92 fewer to 28 more)	Very low	IMPORTANT
Hair loss - Grade 1 and 2 (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
3 (Liu 2024; Tutt 2018; Zhang 2018)	very serious[b]	serious[d]	not serious	serious[a]	60/396 (15.2%)	15/393 (3.8%)	RR 1.96 (0.20 to 19.53)	52 more per 1,000 (from 44 fewer to 1,000 more)	Very low	IMPORTANT
Nausea/vomiting (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
4 (Fan 2012; Liu 2024; Tutt 2018; Zhang 2018)	very serious[b]	not serious	not serious	not serious	32/423 (7.6%)	5/419 (1.2%)	RR 5.44 (2.30 to 12.86)	53 more per 1,000 (from 16	Low	IMPORTANT

								more to 142 more)		
Neuropathy (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
5 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	not serious	not serious	not serious	5/551 (0.9%)	20/479 (4.2%)	RR 0.20 (0.08 to 0.54)	35 fewer per 1,000 (from 41 fewer to 20 fewer)	Low	IMPORTANT
Ototoxicity - Grade 1 and 2 (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
2 (Tutt 2018; Zhang 2018)	very serious[b]	not serious	not serious	not serious	11/302 (3.6%)	3/300 (1.0%)	RR 3.65 (1.03 to 12.96)	27 more per 1,000 (from 0 fewer to 120 more)	Low	IMPORTANT
Ototoxicity - Grade 3 and 4 (relative effect less than 1 favours platinum-containing chemotherapy regimen)										
2 (Tutt 2018; Zhang 2018)	very serious[b]	not serious	not serious	serious[a]	2/302 (0.7%)	0/300 (0.0%)	RR 2.98 (0.31 to 28.52)	0 fewer per 1,000 (from 0 fewer to 0 fewer)*	Very low	IMPORTANT

CI: confidence interval; RR: risk ratio.

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level.

b. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels.

c. I2 was >60%, outcome was downgraded two levels.

d. I2 was between 40% and 60%, outcome was downgraded one level.

* Absolute effects could not be estimated because there were 0 events in one of the arms.

Adherence to / completion of treatment

Table 16 Adherence to / completion of treatment

Certainty assessment					№ of patients		Effect		Certainty	Importance
№ of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Platinum	non-platinum regimens	Relative (95% CI)	Absolute (95% CI)		
Treatment discontinuation due to adverse event (relative effect less than 1 favours platinum-containing chemotherapy regimen) - RE model (I2 >40%)										
5 (Fan 2012; Liu 2024; Tutt 2018; Yardley 2018 A; Yardley 2018 B; Zhang 2018)	very serious[b]	very serious[c]	not serious	serious[a]	65/551 (11.8%)	53/479 (11.1%)	RR 0.88 (0.41 to 1.88)	14 fewer per 1,000 (from 69 fewer to 103 more)	Very low	IMPORTANT

CI: confidence interval; RR: risk ratio.

Explanations

a. 95% confidence interval for the effect size crossed the line of no effect, outcome was downgraded one level.

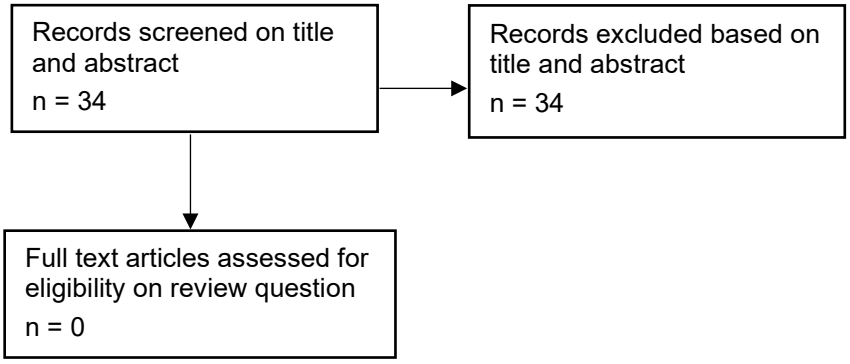
b. Greater than >50% of the weight in a meta-analysis came from studies at high risk of bias, outcome was downgraded two levels.

c. I2 was >60%, outcome was downgraded two levels.

Advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants

There were no studies reporting data on people with advanced breast cancer of any receptor sub-type with germline BRCA1 or BRCA2 pathogenic variants other than triple negative. There was data reported as subgroup analysis of BRCA gene status within the advanced triple negative breast cancer population (see GRADE Table 12 and Table 13 above)

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No evidence was identified which was applicable to this review question.

Appendix I – Health economic model

No de-novo economic analysis was conducted for this review question.

Appendix J – Excluded studies

The systematic review by Egger et al. 2020 included studies that did not meet the inclusion criteria in our protocol. A list of these studies with the reason for exclusion can be seen in the evidence table for Egger et al. 2020.

Effectiveness studies (n= 22)

Study	Reason for exclusion
Bhattacharyya, G.S., Basu, S., Agarwal, V. et al. (2009) 41LBA Single institute phase II study of weekly cisplatinum and metronomic dosing of endoxan and methotrexate in second line metastatic breast cancer triple-negative. European Journal of Cancer Supplements 7(3): 18-19	- Comparator in study does not match that specified in protocol *Endoxan alone not used in UK routine practice to treat breast cancer.*
Carey, Lisa A, Rugo, Hope S, Marcom, P Kelly et al. (2012) TBCRC 001: randomized phase II study of cetuximab in combination with carboplatin in stage IV triple-negative breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 30(21): 2615-23	- Study does not contain a relevant intervention *Cetuximab not used in UK routine practice to treat breast cancer.*
Gao, C, Zhao, Z, Liu, W et al. (2022) Evaluation of clinical efficacy and toxicities of GP or NX regimen in patients with recurrent metastatic triple negative breast cancer. Anti-tumor pharmacy 12(1): 60-64	- Study not reported in English *Chinese*
Han, H S, Dieras, V, Robson, M et al. (2018) Veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/metastatic breast cancer: randomized phase II study. Annals of oncology : official journal of the European Society for Medical Oncology 29(1): 154-161	- Comparator in study does not match that specified in protocol *Temozolomide not used in UK routine practice to treat breast cancer.*
Icli F, Akbulut H, Uner A et al. (2005) Cisplatin plus oral etoposide (EoP) combination is more effective than paclitaxel in patients with advanced breast cancer pretreated with anthracyclines: a randomised phase III trial of Turkish Oncology Group. British journal of cancer 92(4): 639-644	- Study does not contain a relevant intervention *Etoposide not used in UK routine practice to treat breast cancer.*
Isakoff, Steven J, Puhalla, Shannon, Domchek, Susan M et al. (2017) A randomized Phase II study of veliparib with	- Comparator in study does not match that specified in protocol

Study	Reason for exclusion
temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in BRCA1/2 metastatic breast cancer: design and rationale. Future oncology (London, England) 13(4): 307-320	*Temozolomide not used in UK routine practice to treat breast cancer.*
Jia, X, Wang, K, Xu, L et al. (2022) A systematic review and meta-analysis of BRCA1/2 mutation for predicting the effect of platinum-based chemotherapy in triple-negative breast cancer. Breast (Edinburgh, Scotland) 66: 31-39	- Systematic review used as source of primary studies
Jiang, Y, Meng, XY, Deng, NN et al. (2021) Effect and Safety of Therapeutic Regimens for Patients With Germline BRCA Mutation-Associated Breast Cancer: A Network Meta-Analysis. Frontiers in oncology 11: 718761	- Systematic review used as source of primary studies
Li, T, Zhu, YH, Zhang, J et al. (2020) Objective response of first-line chemotherapy of triple-negative breast cancer translates into survival benefit: an analysis in an independent, prospective clinical trial and a real-world setting. Neoplasma 67(6): 1400-1408	- Not a relevant study design *Data from randomised trial used for prognostic study*
Liu, MC, Janni, W, Georgoulias, V et al. (2019) First-line doublet chemotherapy for metastatic triple-negative breast cancer: circulating tumor cell analysis of the tnAcity trial. Cancer management and research 11: 10427-10433	- Secondary publication of an included study that does not provide any additional relevant information *Correlation analysis of circulating tumour cell levels and efficacy outcomes (overall response rate, progression-free survival and overall survival) of the tnAcity trial*
Lu, Fei, Hou, Yu, Chen, Zhengting et al. (2021) Efficacy and Safety of Platinum-Based Chemotherapy as First-Line Therapy for Metastatic Triple-Negative Breast Cancer: A Meta-Analysis of Randomized Controlled Trials. Technology in cancer research & treatment 20: 15330338211016369	- Systematic review used as source of primary studies
Qian, Y.; Wu, H.; Gao, L. (2024) Efficacy and safety of anlotinib combined with chemotherapy in the treatment of metastatic triple negative breast cancer. European Journal of Gynaecological Oncology 45(3): 68	- Comparator in study does not match that specified in protocol *Cisplatin was included in the intervention and comparator*

Study	Reason for exclusion
Shi, Mingqiang, Li, Zhoujuan, Shen, Guoshuang et al. (2024) Efficacy and safety of first-line treatment for metastatic triple-negative breast cancer: A network meta-analysis. Cancer pathogenesis and therapy 2(2): 81-90	- Systematic review used as source of primary studies
Sun, W, Wu, Y, Ma, F et al. (2023) Efficacy of PARP Inhibitor, Platinum, and Immunotherapy in BRCA-Mutated HER2-Negative Breast Cancer Patients: A Systematic Review and Network Meta-Analysis. Journal of clinical medicine 12(4)	- Systematic review used as source of primary studies
Tovey, H, Sipos, O, Parker, JS et al. (2023) Integrated Multimodal Analyses of DNA Damage Response and Immune Markers as Predictors of Response in Metastatic Triple-Negative Breast Cancer in the TNT Trial (NCT00532727). Clinical cancer research 29(18): 3691-3705	- Secondary publication of an included study that does not provide any additional relevant information *Exploratory study of DNA and immune markers (TNT trial)*
van Rossum, Annelot G J, Mandjes, Ingrid A M, van Werkhoven, Erik et al. (2021) Carboplatin-Cyclophosphamide or Paclitaxel without or with Bevacizumab as First-Line Treatment for Metastatic Triple-Negative Breast Cancer (BOOG 2013-01). Breast care (Basel, Switzerland) 16(6): 598-606	- Study does not contain a relevant intervention *Carboplatin combined with cyclophosphamide is not used in UK practice*
Xu, Binghe, Jiang, Zefei, Kim, Sung-Bae et al. (2011) Biweekly gemcitabine–paclitaxel, gemcitabine–carboplatin, or gemcitabine–cisplatin as first-line treatment in metastatic breast cancer after anthracycline failure: a phase II randomized selection trial. Breast Cancer 18(3): 203-212	- Does not contain a population of people with triple negative breast cancer or BRCA 1/2 gene pathogenic variants *More than 40% of participants had positive oestrogen receptor breast cancer; study did not report subgroup analysis for people with triple negative breast cancer; there was no information about participants BRCA gene status*
Yang, Rui, Shi, You-Yang, Han, Xiang-Hui et al. (2021) The Impact of Platinum-Containing Chemotherapies in Advanced Triple-Negative Breast Cancer: Meta-Analytical Approach to Evaluating Its Efficacy and Safety. Oncology research and treatment 44(6): 333-343	- Systematic review used as source of primary studies
Yardley, D.A., Brufsky, A., Coleman, R.E. et al. (2016) Erratum to 'Phase II/III weekly nab-paclitaxel plus gemcitabine or carboplatin versus gemcitabine/carboplatin	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reason for exclusion
as first-line treatment of patients with metastatic triple-negative breast cancer (the tnAcity study): Study protocol for a randomized controlled trial. [Trials (2015), 16, 575] DOI: 10.1186/s13063-016-1195-6. Trials 17(1): 63	*Erratum related to tnAcity trial without any changes to data or analyses*
Yardley, Denise A, Brufsky, Adam, Coleman, Robert E et al. (2016) Erratum to: 'Phase II/III weekly nab-paclitaxel plus gemcitabine or carboplatin versus gemcitabine/carboplatin as first-line treatment of patients with metastatic triple-negative breast cancer (the tnAcity study): study protocol for a randomized controlled trial. Trials 17: 63	- Duplicate reference
Yardley, Denise A, Brufsky, Adam, Coleman, Robert E et al. (2015) Phase II/III weekly nab-paclitaxel plus gemcitabine or carboplatin versus gemcitabine/carboplatin as first-line treatment of patients with metastatic triple-negative breast cancer (the tnAcity study): study protocol for a randomized controlled trial. Trials 16: 575	- Protocol
Yuan, Y, Yost, SE, Cui, Y et al. (2023) Phase I Trial of Ipatasertib Plus Carboplatin, Carboplatin/Paclitaxel, or Capecitabine and Atezolizumab in Metastatic Triple-Negative Breast Cancer. Oncologist 28(7): e498-e507	- Study does not contain a relevant intervention *Ipatasertib is not licensed in the UK for any indication.*

Cost-effectiveness studies

No studies were considered at full text stage.

Appendix K– Research recommendations – full details

K1.1 Research recommendation

What is the clinical and cost effectiveness of a platinum-containing chemotherapy regimen compared to a non-platinum-containing chemotherapy regimen in people with advanced breast cancer who have BRCA 1/2 gene pathogenic variants?

K1.1.1 Why this is important

The committee highlighted that there was limited evidence on platinum-containing chemotherapy regimens for people with advanced breast cancer and BRCA 1/2 gene pathogenic variants and it was insufficient to make any specific recommendations for this group of people. This evidence came from subgroup data from 2 studies with small sample sizes looking at people with advanced triple negative breast cancer with or without BRCA 1/2 gene pathogenic variants (number of people with advanced triple negative breast cancer and BRCA 1/2 gene pathogenic variants: Tutt et al. 2018: n=43; and Zhang et al. 2018: n=14). Therefore, a research recommendation was developed to cover this gap in the evidence.

K1.1.2 Rationale for research recommendation

Table 17: Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the clinical and cost effectiveness of adding a platinum to a chemotherapy regimen in people with advanced breast cancer who have BRCA 1/2 gene pathogenic variants. An improved evidence base will help ensure that the best chemotherapy options are identified and provided to people with advanced breast cancer who BRCA 1/2 gene pathogenic variants.
Relevance to NICE guidance	All of the evidence about the clinical and cost effectiveness of adding a platinum to a chemotherapy regimen considered in this review was in people with advanced breast cancer who had triple-negative breast cancer. Small numbers of these people also had BRCA 1/2 gene pathogenic variants. No evidence was available in people with advanced breast cancer who had BRCA 1/2 gene pathogenic variants but who did not have triple-negative breast cancer. Therefore, all receptor subtypes are of interest for this research recommendation.
Relevance to the NHS	More evidence could help clinicians to offer the best type of chemotherapy to people with advanced breast cancer who have BRCA 1/2 gene pathogenic variants.
National priorities	No specific national priorities.
Current evidence base	Subgroup data from 2 studies with small sample sizes looking at people with advanced triple negative breast cancer and BRCA 1/2 gene pathogenic variants.
Equality considerations	A list of health inequalities issues was identified during the development of recommendations on chemotherapy and listed in the equality and health inequalities assessment. These include age, disability, race, and sex, as well as socioeconomic deprivation.

K1.1.3 Modified PICO table

Table 18: Modified PICO table

Population	**Inclusion:** • Adults (18 and over) who have invasive adenocarcinoma of the breast with distant metastasis (M1) that is of any receptor subtype and who have BRCA 1/2 gene pathogenic variants. **Exclusion:** • Adults (18 and over) who have invasive adenocarcinoma of the breast with distant metastases who do not have BRCA 1/2 gene pathogenic variants. • Adults (18 and over) with newly diagnosed invasive adenocarcinoma of the breast of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0) • Adults (18 and over) with metastases to the breast from other primary tumours • Adults (18 and over) with non-epithelial breast tumours (for example, angiosarcoma, lymphoma) • Adults (18 and over) with benign breast conditions (for example, fibroadenoma, benign phyllodes tumours)
Intervention	Any chemotherapy regimen containing a platinum agent. Platinums of interest: • Carboplatin (all doses and regimens) • Cisplatin (all doses and regimens)
Comparator	Any chemotherapy regimen without a platinum agent
Outcome	**Primary outcomes:** • Overall survival • Progression-free survival • Objective tumour response rate **Secondary outcomes:** • Cancer-specific survival • Adverse events • Adherence to or completion of treatment • Quality of life
Study design	Randomised controlled trial, real world evidence: cohort study
Timeframe	Long term
Additional information	For cohort studies, attempts should be made to reduce confounding either through matching participants or controlling for confounders in the analysis.