National Institute for Health and Care Excellence

Early and locally advanced breast cancer: diagnosis and management

[O] Platinum based neoadjuvant chemotherapy

NICE guideline NG101
Evidence reviews underpinning recommendation 1.11.4 and research recommendations in the NICE guideline

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Draft for consultation

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Platinum based neoadjuvant chemotherapy

1.1 Review question

What is the clinical and cost effectiveness of adding a platinum to a taxane based neoadjuvant chemotherapy regimen with or without an anthracycline in people with invasive breast cancer that is either:

- triple negative, or
- of any receptor subtype with a BRCA germline mutation?

1.1.1 Introduction

The current recommendations in the Early and Locally Advanced Breast Cancer Guideline (NG101) focus on whether to add platinum to anthracycline-containing neoadjuvant chemotherapy regimens for people with triple negative invasive breast cancer. New evidence which supports the existing advice to consider such an addition, and new evidence on overall survival outcomes, has been identified by the 2023 surveillance review. In addition, there is some new evidence about the use of platinum containing neoadjuvant regimens that lack an anthracycline component.

Some, but not all people with triple negative breast cancer (TNBC) will have BRCA germline mutations and some people with BRCA germline mutations will have other subtypes of breast cancer. There are currently no recommendations on the use of platinum in neoadjuvant chemotherapy regimens specifically for people with BRCA germline mutations. Previously, no evidence was identified for this group, but the 2023 surveillance review suggests there may now be some evidence to 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) who have invasive breast cancer that is triple negative and/or who have BRCA germline mutations. **Exclusion:** • Adults (18 and over) who have invasive breast cancer that is not triple negative and do not have BRCA germline mutations. • Adults (18 and over) with newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Adults (18 and over) with Paget's disease of the breast with no invasive component.
Interventions	A neoadjuvant regimen containing a platinum and taxane with or without an anthracycline

Comparator	A neoadjuvant regimen containing a taxane with or without an anthracycline (without platinum)
Outcomes	**Primary outcomes** • Pathological complete response (pCR) • Overall survival (OS) • Disease-free survival (DFS) **Secondary outcomes** • Breast cancer mortality • Quality of life • Adverse events a. treatment-related mortality b. treatment-related morbidity including short -term adverse events and long-term consequences of treatment • Adherence to or completion of treatment regimens (early cessation of treatment) • Local and/or locoregional recurrence • Breast conservation rate
Study type	RCT or systematic reviews of 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 – Review protocols and in Appendix L – Methods.

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 Mason et al. (2023) was partially used as source of evidence for this evidence review. Most of the included studies by Mason et al. (2023) reporting on neoadjuvant chemotherapy regimens met our inclusion criteria (see Table 1 for our inclusion criteria and Table 2 for the included studies in our review).
2) Where data for a non-English language study (Zhao et al. 2014) was presented in the Cochrane review we used their data in our analyses, but otherwise non-English language studies were excluded as per the review protocol.
3) The committee had a discussion about the definition of disease-free survival used by Mason et al. (2023). They concluded that progression-free survival and time-to-progression are not similar to disease-free survival because these 2 outcomes are more appropriate for advanced breast cancer or metastatic breast cancer. Therefore, data for disease-free survival from the NeoCART trial was not included in this review because their definition included disease progression, despite being included in the Cochrane review (see Table 33 for outcome definitions from the included trials). The definitions of pathological complete response (pCR) and overall survival (OS) are as used in the Cochrane review.

4) The committee agreed that some adverse events were likely to be shorter term occurring during treatment or shortly afterwards, while others were likely to be longer term consequences of treatment that could persist after treatment was completed. Adverse events were classified by committee consensus as short term and/ or long term prior to data extraction (see Table 34 for a list of long-term adverse events). All grade 3 and 4 adverse events were reported irrespective of being short term or long term. Grade 2 short term adverse events were only reported if the frequency was 5% or more. Short term adverse events without stating the grade were included with the 5% frequency threshold. Short term adverse events reported as pooled grade 1 and 2 were not extracted. Where a study reported an adverse event at Grade 2 and 3 /4 only the data for Grade 3 / 4 was extracted.

5) Lobaplatin is not licensed in the UK and was not included in the analysis for this review.

6) In the Mason et al. (2023) Cochrane review and the NG101 2018 update (review question 10.5) there were 2 types of studies included and the committee agreed to include both:
   a) studies where the treatments were identical apart from the platinum
   b) studies where one study arm contained a platinum and the other did not and the treatments in each arm were not identical otherwise.

7) The risk of bias was assessed using Cochrane's RoB 1 tool by the Mason et al. (2023) Cochrane review. We took their assessment for the studies included by Mason et al. (2023). We used Cochrane's RoB 2 tool to assess the new included study (de Padua et al. 2023) as this is the preferred checklist listed in Developing NICE guidelines: the manual. Our approach to reach an overall judgement about the risk of bias for each primary study was to:
   a) Low risk of bias: study was judged to be at low risk of bias for all domains or to have some concerns about random sequence generation due to a lack of information provided (as long as allocation concealment was low risk) and/or blinding of participants and personnel. (We agree with Mason et al. (2023) that blinding of participants and personnel is not an issue for the reason they stated in their judgment of the studies: “This may have been associated with some performance bias but it was not judged to be of serious concern given types of outcomes collected”).
   b) Some concerns or moderate risk of bias: study was judged to be at unclear risk of bias for allocation concealment or blinding of outcome assessment or selective reporting or incomplete outcome data.
   c) High risk of bias: study was judged to be at high risk of bias for at least one domain or to have multiple domains at unclear risk of bias.

8) We assessed applicability of the includes studies in Mason et al. (2023) based on our review protocol.

9) We planned to carry out a subgroup analysis for type of platinum used but all of the included studies used carboplatin so this was unnecessary. We also planned to carry out a subgroup analysis for people with male reproductive organs (men, trans women and non-binary people who currently have testes) but we were unable to do this because none of the included studies recruited people with male reproductive organs.

10) 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.

11) In the protocol for all 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. The quality of the outcome was therefore downgraded once for imprecision if either end of the 95% confidence interval crossed the line of no effect.

To be consistent with previous work on this guideline from 2018 we planned to use an event size of 300 events for the second downgrade based on 2018 optimal information size calculations that suggested that at least 300 events were needed to adequately detect an effect. If this information was not readily available, we planned to use sample size instead to ensure that all studies would have the potential to be downgraded twice. Mason et al. (2023) did not report this information for data on hazard ratios and so sample size was used as planned. A minimum sample size of 500 was selected to allow for the possibility of 300 events. As a result, the quality was downgraded a second time if the number of participants for an outcome was less than 500.

12) 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 downgraded 1 level for inconsistency. This meant that data on that adverse event was considered as only available from 1 study. In these situations, the absolute risk was calculated using only data from the study reporting adverse events in either arm.

13) The BrighTNess trial (Loibl at al. 2018) was a 3-arm study. We followed the same approach as Mason et al. (2023) when we extracted additional data from the BrighTNess trial (local/locoregional recurrence and adverse events). This approach was to half the number of participants in the control group (neoadjuvant chemotherapy regimen without platinum) to allow for a comparison with the 2 different neoadjuvant chemotherapy regimens containing platinum. Therefore, the BrighTNess trial was regarded as a single study with 2 comparisons. This meant that funnel plots were not done for outcomes where there were 10 study results with the BrighTNess trial contributing to 2 of these results as the total number of single studies was 9. This also meant that adverse events only reported by the BrighTNess trial were considered to be only available from 1 study and therefore downgraded 1 level for inconsistency (see bullet point above about adverse events and inconsistency).

14) The CALGB 40603 trial (Sikov et al. 2015) was a 4-arm study that was grouped by Mason et al. (2023) into 2 categories according to carboplatin use. We used the same approach as Mason et al. (2023) when we extracted additional data from the this trial. Category 1 (neoadjuvant chemotherapy containing platinum) included arm 3 (paclitaxel plus carboplatin followed by doxorubicin plus cyclophosphamide) and arm 4 (paclitaxel plus carboplatin followed by doxorubicin plus cyclophosphamide plus bevacizumab) in the trial publication. Category 2 (neoadjuvant chemotherapy without platinum) included arm 1 (paclitaxel followed by doxorubicin plus cyclophosphamide) and arm 2 (paclitaxel followed by doxorubicin plus cyclophosphamide plus bevacizumab). Additionally, disease-free survival and overall survival were reported as hazard ratios with 95% confidence intervals by the CALGB trial already combining the arms into categories 1 and 2. Therefore, we were not able to compare the arms separately.

15) People with germline BRCA mutations were listed as a population to be included in the protocol of this evidence review. Evidence for this population was from subgroup data of studies already included for the TNBC part of the review. This data was used to carry out the subgroup analyses by BRCA status for people with TNBC from 5 trials:

    a) BrighTNess (Loibl at al. 2018): disease-free survival and pathological complete response
    b) GeparOcto (Schneeweiss et al. 2019): pathological complete response
    c) GeparOLA (Fasching et al. 2021): pathological complete response
    d) GeparSixto (von Minckwitz et al. 2014) disease-free survival and pathological complete response

e) NACATRINE de Padua Souza (2023): pathological complete response

No additional studies were included that only reported on people with germline BRCA status of all receptor subtypes (this could be any combination of positive or negative oestrogen receptor, progesterone receptor or human epidermal growth factor receptor 2 [HER 2]). However, additional data for all receptor subtypes was available from 2 of the trials already included in the TNBC part of the review:

f) GeparOcto (Schneeweiss et al. 2019): disease-free survival and overall survival

g) GeparOLA trial (Fasching et al. 2021): pathological complete response.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 03 06 2024 and re-run on 24 09 2024. 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). Full search strategies for each database are provided in Appendix B – Literature search strategies.

The searches for the cost effectiveness evidence were run on 06 06 2024 and re-run on 24 09 2024. The following databases were searched: Embase (Ovid); Econlit (Ovid); Health Technology Assessment (HTA) (CRD), International Health Technology Assessment Database (INAHTA), NHS EED (CRD) and Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B – Literature search strategies.

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. The QA procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

The committee noted that current neoadjuvant chemotherapy regimens for people with TNBC contain at least a taxane and an anthracycline, although our review question allowed us to look at data for adding a platinum to a non-anthracycline containing regimen as well. We had carried out a subgroup analysis by anthracycline content with the platinum for outcomes where there was significant heterogeneity but were asked by the committee to look at the effect of only including studies which contained an anthracycline in both arms. To do this we needed to perform subgroup analysis for all relevant outcomes and then carried out a sensitivity analysis removing studies that lacked an anthracycline in both arms.

The committee were also interested in the other subgroups, regardless of the presence of significant heterogeneity. These were carried out where data allowed.

Data for a non-English language study (Zhao 2014) was presented in the Cochrane review and we used their data in our analyses, but otherwise non-English language studies were excluded as per the review protocol.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 731 references (see Appendix B for the literature search strategy). Evidence from the NG101 2018 update (5 references), evidence identified from the list of references of included studies (9 references) was also reviewed.

In total 745 references were screened at title and abstract level against the review protocol, with 692 excluded at this level. 10% of references were screened separately by two reviewers with 98% agreement. Discrepancies were resolved by discussion.

The full texts of 14 systematic reviews and 39 trials were ordered for closer inspection. One systematic review and 13 trials (published in 18 articles) met the criteria specified in the review protocol (Appendix A). For a summary of the included studies see tables Table 2 and Table 3. Included studies reported data on most of the outcomes listed in the review protocol (Appendix A) apart from quality of life.

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

A second search was conducted at the end of the guideline development process for this review question using the original search strategy to capture papers published whilst the guideline was being developed. This search returned 49 references, and all were screened on title and abstract. One reference was ordered for full text screening. This reference was not included because it did not meet the criteria specified in the review protocol (Appendix A).

See section 1.1.14 References 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 Mason et al. 2023)

Author (year)	Primary studies from Mason et al. 2023, included in the NICE review	Population covered by systematic review	Intervention	Comparison	Outcomes	Risk of bias/Applicability of the systematic review
Mason (2023)	• ADAPT-TN (Gluz et al. 2018) • Ando et al. 2014 • BrighTNess (Loibl et al. 2018) • CALGB 40603 (Sikov et al. 2015) • GEICAM 2006-03 (Alba et al. 2012) • GeparOcto (Schneeweiss et al. 2019) • GeparOLA (Fasching et al. 2021) • GeparSixto (von Minckwitz et al. 2014) • Gigolaeva et al. 2019 • NeoCART (Zhang et al. 2022)	**Inclusion criteria:** Types of studies • RCTs examining platinum-based chemotherapy for neoadjuvant or adjuvant treatment for people with early TNBC Types of participants • age 18 years or older with early TNBC • trials from all study locations • participants of all ethnicities **Exclusion criteria:**	Platinum chemotherapy • Any chemotherapy regimen that contained platinum chemotherapy	Non-platinum chemotherapy • Regimens without platinum chemotherapy	• Disease-free survival • Overall survival • Pathological complete response • Completion of regimens • Any grade III/IV toxicity • Quality of life	Low Partially applicable

Author (year)	Primary studies from Mason et al. 2023, included in the NICE review	Population covered by systematic review	Intervention	Comparison	Outcomes	Risk of bias/Applicability of the systematic review
	• Zhang et al. 2016 • Zhao et al. 2014	Types of studies • not reporting their findings for participants with TNBC separately from other participants • included 20% or more participants with non-TNBC Types of participants • trials that did not assess women for HER2 status				

Abbreviations: HER2: human epidermal growth factor receptor 2; RCT: randomised controlled trial; TNBC: triple negative breast cancer

See Appendix D for full evidence tables

Table 3 Randomised controlled trials

Some of these studies published their results in more than 1 publication. We refer to the main publication in this table, but data could have been extracted from more than 1 publication and these are listed in the included studies section (see 1.1.13 References – included studies.

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
ADAPT-TN Gluz (2018)	Location: Germany Total sample size: 336 Follow up time: not reported	Median age: 50 years ranging from 26 to 75 years Key inclusion criteria: • women with previously untreated, operable, unilateral, primary invasive noninflammatory early TNBC (ER and PR < 1%, HER2-negative) • age 18 years or older with good performance status (0/1) • adequate hematologic, cardiac, renal, and hepatic function • negative pregnancy test was required in premenopausal women with childbearing potential Key exclusion criteria: • grade ≥2 peripheral polyneuropathy or known incorporated hypersensitivity reaction to the therapy compounds	Nab-paclitaxel 125 mg/m2 + carboplatin AUC2 days 1 and 8 every 3 weeks for 4 cycles Platinum agent: carboplatin	Nab-paclitaxel 125 mg/m2 + gemcitabine 1000 mg/m2 days 1 and 8 every 3 weeks for 4 cycles Same backbone: No	• Pathological complete response • Overall survival • Disease-free survival • Adverse events: treatment-related mortality • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens	Moderate Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• prior malignancies with a disease-free interval <10 years, except curatively treated skin basalioma or cervix carcinoma in situ, as well as sequential breast cancer				
Ando (2014)	Location: Japan Total sample size: 75 Follow up time: 12 months	Median age: 47 years ranging from 30 to 70 years Key inclusion criteria: • previously untreated, unilateral, histologically confirmed, invasive, non-inflammatory, breast carcinoma, HER2-negative, tumour >2.0 cm at the largest dimension by ultrasonography, or ≤2.0 cm with axillary lymph node metastasis clinically diagnosed as positive (clinical stage II and IIIA) Key exclusion criteria: • T4, N3, (supraclavicular lymph node)	Carboplatin AUC5 every 3 weeks for 4 cycles + paclitaxel 80 mg/m2days 1, 8, 15 for 4 cycles, followed by 4 cycles of cyclophosphamide500 mg/m2, epirubicin 100 mg/m2 and fluorouracil 500 mg/m2every 3 weeks Platinum agent: carboplatin	Paclitaxel 80 mg/m2 days 1, 8,15 for 4 cycles followed by 4cycles of cyclophosphamide500 mg/m2, epirubicin 100mg/m2 and fluorouracil 500mg/m2 every 3 weeks Same backbone: Yes	• Pathological complete response • Overall survival • Disease-free survival • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens • Local and/or locoregional recurrence • Breast conservation rate	Low Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• distant metastatic disease				
BrighTNess Loibl (2018)	Location: Germany, Spain, USA, Korean, France, Czech Republic, Russia, Belgium, Australia, Hungary, Italy, UK, Canada, Taiwan, Netherlands Total sample size: 634 Follow up time: median 4.5 years	Median age: 50 years (IQR 41 to 59 years) Key inclusion criteria: • women 18 years of age or older • histologically or cytologically confirmed invasive triple-negative breast cancer • clinical stage II–III (T1N1–2 or T2–4N0–2) • an ECOG performance status of 0 or 1 • adequate haematological, renal, and hepatic function, candidates for potentially curative surgery by surgeon's assessment at presentation • documented gBRCA mutation testing Key exclusion criteria:	Intervention 1: Paclitaxel 80 mg/m2 weekly + carboplatin AUC6 every 3 weeks for 12 weeks + veliparib 50 mg twice a day, followed by doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 every 2 or 3 weeks for 4 cycles Intervention 2: Paclitaxel 80 mg/m2 weekly + carboplatin AUC6 every 3 weeks for 12 weeks, followed by doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 every 2 or 3 weeks for 4 cycles Platinum agent: carboplatin	Paclitaxel 80 mg/m2 weekly for 12 weeks, followed by doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2 every 2 or 3 weeks for 4 cycles Same backbone: Yes	• Pathological complete response • Overall survival • Disease-free survival • Adverse events: treatment-related mortality • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens • Local and/or locoregional recurrence • Breast conservation rate	Low Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• received previous anti-cancer treatment • receiving ovarian hormonal replacement therapy • history of seizure within 1 year before study entry • pre-existing neuropathy • allergy to cremophor-containing medications • any clinically uncontrolled conditions • previous or concurrent cancer • pregnant or breastfeeding				
CALGB 40603 Sikov (2015)	Location: US Total sample size: 443 Follow up time: median 7.9 years	Most participants were 40 to 59 years old (median or mean age not reported) Key inclusion criteria: • clinical stage II-III TNBC (oestrogen receptor and progesterone receptor ≤10% and human epidermal growth factor receptor 2–negative)	Paclitaxel 80 mg/m2 weekly +carboplatin AUC6 every 3 weeks for 12 weeks followed by doxorubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 2weeks for 4 cycles ± bevacizumab10 mg/kg every 2 weeks for 9 cycles	Paclitaxel 80 mg/m2 weekly for 12 weeks followed by doxorubicin 60 mg/m2 + cyclophosphamide 600 mg/m2every 2 weeks for 4 cycles ±bevacizumab 10 mg/kg every2 weeks for 9 cycles	• Pathological complete response • Overall survival • Disease-free survival • Adverse events: treatment-related mortality • Adverse events: treatment-related morbidity	Moderate Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		Key exclusion criteria: • none reported	Platinum agent: carboplatin	Same backbone: Yes	• Adherence to or completion of treatment regimens • Local and/or locoregional recurrence • Breast conservation rate	
GEICAM 2006-03 Alba (2012)	Location: Spain Total sample size: 94 Follow up time: not reported	Median age: 47 years ranging from 27 to 75 years Key inclusion criteria: • 18-years old • histologically confirmed basal-like breast cancer, ER negative, PR negative, HER2 negative • cytokeratin 5/6 or epidermal growth factor receptor positive by immunohistochemistry, tumour size 2 cm or less if there was axillary involvement • ECOG performance status B1	Epirubicin 90 mg/m2 + cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles followed by docetaxel 75 mg/m2 + carboplatin AUC6 every 3 weeks for 4 cycles Platinum agent: carboplatin	Epirubicin 90 mg/m2 + cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles followed by docetaxel 75 mg/m2 every 3 weeks for 4 cycles Same backbone: Yes	• Pathological complete response • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens • Breast conservation rate	Low Partially applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• normal cardiac function • adequate bone marrow reserve and liver and renal functions • adequate contraception and a negative pregnancy test for women with child-bearing potential Key exclusion criteria: • previous treatment for the present disease • previous anthracycline and/or taxane administration • concurrent treatment with corticosteroids, selective oestrogen-receptor modulators or hormonal replacement therapy • inflammatory, bilateral invasive, or metastatic breast cancer • any other severe or uncontrolled systemic disease				

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• previous history of cancer other than skin (no-melanoma), or cervix tumours adequately treated and other cancers treated more than 10 years before the study entry				
GeparOcto Schneeweiss (2019)	Location: Germany Total sample size: 403 Follow up time: not reported	Median age: 48 years ranging from 21 to 76 years Key inclusion criteria: • previously untreated, unilateral or bilateral, non-metastatic invasive breast cancer • aged ≥18 years • a Karnofsky index of ≥90% • clinical stage T1c-T4a-d tumours • central pathology assessment of oestrogen receptor, progesterone receptor, HER2 status, Ki67 and lymphocyte-predominant breast cancer	Paclitaxel 80 mg/m2 + non-pegylated liposomal doxorubicin20 mg/m2 + carboplatin AUC1.5 weekly for 18 weeks Platinum agent: carboplatin	Epirubicin 150 mg/m2 + paclitaxel 225 mg/m2 + cyclophosphamide 2000 mg/m2 every 2weeks for 3 cycles Same backbone: No	• Overall survival • Pathological complete response • Disease-free survival • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens • Local and/or locoregional recurrence • Breast conservation rate	Moderate Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		on pre-treatment core biopsy Key exclusion criteria: • none reported.				
GeparOLA Fasching (2021)	Location: Germany Total sample size: 77 Follow up time: not reported	Median age: 47 years ranging from 25 to 71 years Key inclusion criteria: • previously untreated unilateral or bilateral primary, non-metastatic invasive HER2-negative breast cancer and homologous recombination deficiency with stages cT2-cT4a-d or cT1c and cN+ or cT1c and pNSLN+ or cT1c and TNBC or cT1c and Ki-67 >20% • normal cardiac function (left ventricular ejection fraction ≥55%) • no evidence of current infection	Paclitaxel 80 mg/m2 + carboplatin AUC2 weekly for 12 weeks followed by epirubicin 90 mg/m2+ cyclophosphamide 600 mg/m2every 2 or 3 weeks for 4 cycles Platinum agent: carboplatin	Paclitaxel 80 mg/m2 weekly + Olaparib 100 mg twice a day for 12 weeks followed by epirubicin 90 mg/m2 + cyclophosphamide 600 mg/m2every 2 or 3 weeks for 4 cycles Same backbone: No	• Pathological complete response • Adverse events: treatment-related mortality • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens • Breast conservation rate	Moderate Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• no concurrent treatment with other anticancer or investigational agents as well as no prior use of poly[adenosine diphosphate (ADP)-ribose] polymerase inhibitor Key exclusion criteria: • none reported.				
GeparSixto von Minckwitz (2014)	Location: Germany Total sample size: 315 Follow up time: median 47.3 months	Median age: 47 years ranging from 21 to 78 years Key inclusion criteria: • women with previously untreated, unilateral or bilateral, non-metastatic primary invasive triple-negative or HER2- positive breast carcinoma • older than 18 years • a Karnofsky performance status index 80 or greater • clinical stage T2–T4a-d tumours or T1c tumours with either clinical or	Carboplatin AUC2 or 1.5 + paclitaxel 80 mg/m2 + non-pegylated liposomal doxorubicin 20 mg/m2 + bevacizumab 15 mg/kg every 3 weeks for 18 weeks Platinum agent: carboplatin	Paclitaxel 80 mg/m2 + non-pegylated liposomal doxorubicin 20 mg/m2 weekly + bevacizumab 15 mg/kg every 3 weeks for 18 weeks Same backbone: Yes	• Pathological complete response • Overall survival • Disease-free survival • Adverse events: treatment-related mortality • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens	Moderate Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		histological stage N+ disease Key exclusion criteria: • none reported.			• Local and/or locoregional recurrence • Breast conservation rate	
Gigolaeva (2019)	Location: Russia Total sample size: 192 Follow up time: not reported	Median age: 47 years ranging from 32 to 62 years Key inclusion criteria: • not reported Key exclusion criteria: • not reported	Doxorubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles followed by carboplatin AUC2 weekly + eribulin 1.4 mg/m2 or paclitaxel 175 mg/m2 every 3 weeks for 12 weeks Platinum agent: carboplatin	Doxorubicin 60 mg/m2 + cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m2 for 12 weeks Same backbone: No	• Pathological complete response	High Directly applicable
NACATRINE de Padua Souza (2023)	Location: Brazil Total sample size: 146 Follow up time: median 47.7 months	Median age: 45 years and 70% were younger than 50 years Key inclusion criteria: • more than 18 years old	Chemotherapy protocol consisted of doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2) both intravenously (i.v.) once every 21 days	Chemotherapy protocol consisted of doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2) both intravenously (i.v.) once every 21 days	• Pathological complete response • Overall survival • Disease-free survival • Breast conservation rate	Moderate Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		• ECOG performance status 0 or 1 • adequate organ function with newly diagnosed stage II–III TNBC • no evidence of distant metastases • gBRCA1/2 mutational status Key exclusion criteria: • history of grade >/2 neuropathy • previous treatment for breast cancer • pregnant or breastfeeding	for four cycles for all patients. Patients were then randomised for additional treatment with paclitaxel (80 mg/m2 i.v.) once every 7 days for 12 cycles with carboplatin AUC 1.5 once every 7 days for 12 cycles Platinum agent: carboplatin	for four cycles for all patients. Patients were then randomised for additional treatment with paclitaxel (80 mg/m2 i.v.) once every 7 days for 12 cycles without carboplatin Same backbone: Yes	• Adherence to or completion of treatment regimens	
NeoCART Zhang (2022)	Location: China Total sample size: 88 Follow up time: median 37 months	Median age: 50 years ranging from 19 to 69 years Key inclusion criteria: • ECOG performance status of 0–1 • age ≥18 years • cytologically or histologically confirmed	Docetaxel 75 mg/m2 + carboplatin AUC6 every 3 weeks for 6 cycles Platinum agent: carboplatin	Epirubicin 90 mg/m2 + cyclophosphamide 600 mg/m2 every 3 weeks for 4 cycles followed by docetaxel 100 mg/ m2 every 3 weeks for 4 cycles Same backbone: No	• Pathological complete response • Overall survival • Disease-free survival • Adverse events: treatment-related morbidity	Low Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		noninflammatory invasive TNBC • a clinical stage of II–III (T1cN1-2 or T2-4N0-2) and previously untreated • patients with a history of malignancy at another site (except for basal cell or squamous cell carcinoma of the skin and cervical carcinoma in situ) that had been fully treated were included if no disease was present for more than 5 years Key exclusion criteria: • patients with metastatic disease or who had received anticancer treatment			• Adherence to or completion of treatment regimens • Breast conservation rate	
Zhang (2016)	Location: China Total sample size: 87	Median age: 46 years ranging from 24 to 73 years Key inclusion criteria:	Paclitaxel 175 mg/m2 + carboplatin AUC5 every 3 weeks for 4–6 cycles	Epirubicin 75 mg/m2 + paclitaxel 175 mg/m2 every 3 weeks for 4–6 cycles	• Pathological complete response • Overall survival • Disease-free survival	High Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
	Follow up time: median 55 months	• 1) women aged 18-75 years • 2) ECOG score 0-1 • 3) pathologically confirmed breast invasive ductal cancer by core needle biopsy, ER/PR/HER2 negative by immunohistochemistry • 4) clinical stage IIA-IIIC with neoadjuvant chemotherapy indication • 5) measurable lesions • 6) normal cardiac, hepatic and marrow function Key exclusion criteria: • history of invasive cancer or prior exposure to chemotherapy/radiotherapy	Platinum agent: carboplatin	Same backbone: No	• Breast cancer mortality • Adverse events: treatment-related mortality • Adverse events: treatment-related morbidity • Adherence to or completion of treatment regimens • Local and/or locoregional recurrence	
Zhao (2014)	Location: China Total sample size: 80 Follow up time: not reported	Median age: 52 years (range not reported by Mason et al. 2023)	Paclitaxel 175 mg/m2 day 1, carboplatin AUC5 day 2, every 3 weeks for 2 cycles	Epirubicin 75 mg/m2 day 1, paclitaxel 175 mg/m2 day 2, every 3 weeks for 2 cycles	• Pathological complete response • Adverse events: treatment-related mortality	High Directly applicable

Study details	Location Total sample size Follow-up time	Median age Population: Key inclusion/exclusion criteria	Intervention	Comparator	Outcomes	Risk of bias Applicability
		Full text in Chinese (outcome data extracted from the Mason et al. 2023)	Platinum agent: carboplatin	Same backbone: No	• Adverse events: treatment-related morbidity	

AUC: area under the plasma concentration/time curve; ECOG: Eastern Cooperative Oncology Group; ER: oestrogen receptor; gBRCA: BRCA germline mutation; HER2: human epidermal growth factor receptor 2; IQR: interquartile range; Ki67: protein Ki67; PR: progesterone receptor; TNBC: triple negative breast cancer

See Appendix D for full evidence tables

1.1.6 Summary of the effectiveness evidence

Assessing publication bias

Funnel plots were constructed for outcomes contributed to by ten or more studies (see the methods chapter for more details and see Appendix E for funnel plots alongside the relevant forest plot (Figure 9 and Figure 16). No risk of bias is suspected based on the distribution of individual studies in the funnel plot.

Interpreting the effectiveness evidence

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 from the evidence to differentiate between comparators if the 95% CI crosses the line of no effect (shortened to 'could not differentiate').

Triple negative breast cancer analyses

Disease-free survival

Table 4 Disease-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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Disease-free survival	Not estimable	Not estimable	HR 0.67 (0.58 to 0.79)	2515 (9 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy

*Absolute effects could not be estimated because number of events were not reported. ** See full GRADE tables in appendix F for reasons for downgrading. CI: confidence interval; HR: hazard ratio. See full GRADE tables (appendix F) for reasons for downgrading the evidence.

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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Overall survival	Not estimable	Not estimable	HR 0.72 (0.59 to 0.88)	2522 (9 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy

*Absolute effects could not be estimated because number of events were not reported. ** See full GRADE tables in appendix F for reasons for downgrading. CI: confidence interval; HR: hazard ratio. See full GRADE tables (appendix F) for reasons for downgrading the evidence.

Pathological complete response

Table 6 Pathological complete response

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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Pathological complete response	316 per 1,000	467 per 1,000 (401 to 546)	RR 1.48 (1.27 to 1.73)	2947 (13 RCTs)	Low	Effect favours platinum based neoadjuvant chemotherapy

*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). **Absolute effects could not be estimated because number of events were not reported. *** See full GRADE tables in appendix F for reasons for downgrading. CI: confidence interval; OR: odds ratio; RR: risk ratio. See full GRADE tables (appendix F) for reasons for downgrading the evidence.

Breast cancer mortality

Table 7 Breast cancer mortality

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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Breast cancer mortality	250 per 1,000	10 per 1,000 (0 to 168)	RR 0.04 (0.00 to 0.67)	91 (1 RCT)	Very low	Effect favours platinum based neoadjuvant chemotherapy

*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. CI: confidence interval; RR: risk ratio. See full GRADE tables (appendix F) for reasons for downgrading the evidence.

Local and/or locoregional recurrence

Table 8 Local and/or locoregional recurrence

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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Local and/or locoregional recurrence	121 per 1,000	75 per 1,000 (54 to 103)	RR 0.62 (0.45 to 0.85)	1550 (5 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy

*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. CI: confidence interval; RR: risk ratio. See full GRADE tables (appendix F) for reasons for downgrading the evidence.

Breast conservation rate

Table 9 Breast conservation 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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Breast conservation rate	477 per 1,000	515 per 1,000 (444 to 592)	RR 1.08 (0.93 to 1.24)	931 (4 RCTs)	Moderate	Could not differentiate

*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. CI: confidence interval; RR: risk ratio. See full GRADE tables (appendix F) for reasons for downgrading the evidence.

Treatment adherence

Table 10 Treatment adherence

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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Treatment adherence: early cessation of treatment	178 per 1,000	210 per 1,000 (179 to 247)	RR 1.18 (1.01 to 1.39)	2545 (9 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy

*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. CI: confidence interval; RR: risk ratio.

Shorter term adverse events

Table 11 Shorter term 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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Anaemia – Random effects model (I2 56%)	15 per 1,000	95 per 1,000 (34 to 263)	RR 6.21 (2.24 to 17.23)	1954 (7 RCTs)	Low	Effect favours non-platinum based neoadjuvant chemotherapy
Febrile neutropenia	39 per 1,000	77 per 1,000 (52 to 117)	RR 1.98 (1.32 to 2.98)	1786 (5 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy
Leukopenia	55 per 1,000	91 per 1,000 (61 to 137)	RR 1.67 (1.11 to 2.51)	1497 (4 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy
Neutropenia – Random effects model (I2 90%)	175 per 1,000	330 per 1,000 (191 to 567)	RR 1.88 (1.09 to 3.23)	2376 (9 RCTs)	Very low	Effect favours non-platinum based neoadjuvant chemotherapy
Thrombocytopenia	11 per 1,000	80 per 1,000 (45 to 143)	RR 7.01 (3.93 to 12.48)	2150 (7 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy
Alanine aminotransferase increased	49 per 1,000	23 per 1,000 (12 to 45)	RR 0.47 (0.24 to 0.92)	1403 (3 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy
Aspartate aminotransferase increased	6 per 1,000	10 per 1,000 (2 to 38)	RR 1.61 (0.40 to 6.38)	960 (2 RCTs)	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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Constipation	8 per 1,000	2 per 1,000 (0 to 20)	RR 0.32 (0.04 to 2.63)	723 (2 RCTs)	Moderate	Could not differentiate
Dehydration	Not estimable**	Not estimable**	RR 1.51 (0.06 to 36.64)	237 (1 RCT)	Very low	Could not differentiate
Diarrhoea	12 per 1,000	17 per 1,000 (7 to 42)	RR 1.48 (0.61 to 3.60)	1491 (4 RCTs)	Low	Could not differentiate
Dizziness	Not estimable**	Not estimable**	RR 1.51 (0.06 to 36.64)	237 (1 RCT)	Very low	Could not differentiate
Dyspnoea	13 per 1,000	1 per 1,000 (0 to 26)	RR 0.08 (0.00 to 2.07)	392 (1 RCT)	Very low	Could not differentiate
Gamma-glutamyltransferase increased	11 per 1,000	20 per 1,000 (3 to 117)	RR 1.79 (0.30 to 10.56)	331 (1 RCT)	Very low	Could not differentiate
Hyperglycaemia	13 per 1,000	14 per 1,000 (3 to 67)	RR 1.10 (0.23 to 5.27)	629 (1 RCT)	Low	Could not differentiate
Hypersensitivity	43 per 1,000	21 per 1,000 (2 to 227)	RR 0.49 (0.05 to 5.21)	93 (1 RCT)	Very low	Could not differentiate
Hypertension	32 per 1,000	20 per 1,000 (10 to 39)	RR 0.61 (0.31 to 1.20)	1403 (3 RCTs)	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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Hypokalaemia	13 per 1,000	21 per 1,000 (8 to 56)	RR 1.57 (0.59 to 4.18)	1072 (2 RCTs)	Low	Could not differentiate
Hyponatraemia	Not estimable**	Not estimable**	RR 1.78 (0.09 to 34.18)	392 (1 RCT)	Very low	Could not differentiate
Increased ALT/AST ratio	Not estimable**	Not estimable**	RR 3.00 (0.13 to 71.70)	88 (1 RCT)	Very low	Could not differentiate
Infection	87 per 1,000	85 per 1,000 (23 to 320)	RR 0.98 (0.26 to 3.68)	93 (1 RCT)	Very low	Could not differentiate
Liver function test increased	44 per 1,000	5 per 1,000 (0 to 86)	RR 0.11 (0.01 to 1.94)	331 (1 RCT)	Very low	Could not differentiate
Lymphopenia – Random effects model (I2 59%)	15 per 1,000	7 per 1,000 (1 to 91)	RR 0.48 (0.04 to 6.21)	722 (2 RCTs)	Low	Could not differentiate
Nausea	22 per 1,000	31 per 1,000 (17 to 56)	RR 1.45 (0.81 to 2.60)	1814 (6 RCTs)	Low	Could not differentiate
Oral mucositis	8 per 1,000	12 per 1,000 (3 to 47)	RR 1.61 (0.41 to 6.23)	774 (2 RCTs)	Low	Could not differentiate
Pneumonia	6 per 1,000	8 per 1,000 (2 to 32)	RR 1.28 (0.30 to 5.48)	960 (2 RCTs)	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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Pruritus	Not estimable**	Not estimable**	RR 3.00 (0.12 to 72.45)	146 (1 RCT)	Very low	Could not differentiate
Pyrexia	6 per 1,000	3 per 1,000 (0 to 15)	RR 0.40 (0.07 to 2.35)	629 (1 RCT)	Low	Could not differentiate
Sinusitis	Not estimable**	Not estimable**	RR 1.27 (0.06 to 26.27)	392 (1 RCT)	Very low	Could not differentiate
Stomatitis	6 per 1,000	3 per 1,000 (0 to 86)	RR 0.48 (0.02 to 13.59)	629 (1 RCT)	Low	Could not differentiate
Syncope	6 per 1,000	7 per 1,000 (1 to 44)	RR 1.16 (0.19 to 6.94)	629 (1 RCT)	Low	Could not differentiate
Vomiting	24 per 1,000	22 per 1,000 (10 to 49)	RR 0.92 (0.42 to 2.05)	1251 (4 RCTs)	Low	Could not differentiate
Treatment-related death	Not estimable**	Not estimable**	RR 1.60 (0.19 to 13.74)	835 (2 RCTs)	Moderate	Could not differentiate

*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). **Absolute effects could not be estimated because there were 0 events in one of the arms. *** See full GRADE tables in appendix F for reasons for downgrading. CI: confidence interval; RR: risk ratio.

Longer term adverse events

Table 12 Longer term 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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Fatigue	59 per 1,000	74 per 1,000 (47 to 115)	RR 1.26 (0.80 to 1.97)	1311 (4 RCTs)	Low	Could not differentiate
Neuropathy	31 per 1,000	37 per 1,000 (23 to 59)	RR 1.18 (0.73 to 1.89)	2024 (6 RCTs)	Low	Could not differentiate
Pain	23 per 1,000	35 per 1,000 (18 to 70)	RR 1.54 (0.78 to 3.05)	1254 (4 RCTs)	Low	Could not differentiate
Pulmonary embolism	6 per 1,000	6 per 1,000 (1 to 35)	RR 0.92 (0.15 to 5.51)	629 (1 RCT)	Low	Could not differentiate

*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. CI: confidence interval; RR: risk ratio.

Triple negative breast cancer sensitivity analyses removing studies where an anthracycline is not included in one or both arms – summary GRADE table

See information at the top of this section for full details of the interpretation of effect for RRs and HRs.

In summary, the interpretation of effect is divided into 2 groups: 1) the evidence showed that there is an effect if the 95% CI does not cross the line of no effect and 2) it was not possible from the evidence to differentiate between comparators if the 95% CI crosses the line of no effect (shortened to 'could not differentiate').

For context we have added information about whether the result or quality has changed from the main analysis. Interpretations or quality ratings that are highlighted green are where the analysis has moved from an 'effect' to 'could not differentiate' or from 'could not differentiate' to an 'effect', or where the quality of the evidence has changed.

Outcomes	Main analysis				Sensitivity analysis			
	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Interpretation of effect
Disease-free survival	HR 0.67 (0.58 to 0.79)	2515 (9 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy	HR 0.72 (0.61 to 0.86)	2006 (6 RCTs)	Low	No change
Overall survival	HR 0.72 (0.59 to 0.88)	2522 (9 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy	HR 0.78 (0.63 to 0.96)	2003 (6 RCTs)	Moderate	No change
Pathological complete response	RR 1.48 (1.27 to 1.73)	2947 (13 RCTs)	Low	Effect favours platinum based neoadjuvant chemotherapy	RR 1.44 (1.20 to 1.73)	2368 (9 RCTs)	Very low	No change

Local or locoregional recurrence	RR 0.62 (0.45 to 0.85)	1550 (5 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy	RR 0.61 (0.44 to 0.85)	1459 (4 RCTs)	Moderate	No change
Breast conservation rate	RR 1.08 (0.93 to 1.24)	931 (4 RCTs)	Moderate	Could not differentiate	RR 1.09 (0.94 to 1.26)	843 (3 RCTs)	Moderate	No change
Treatment adherence: early cessation of treatment	RR 1.18 (1.01 to 1.39)	2545 (9 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy	RR 1.21 (1.03 to 1.43)	2035 (6 RCTs)	Moderate	No change
Anaemia	RR 6.21 (2.24 to 17.23)	1954 (7 RCTs)	Low	Effect favours non-platinum based neoadjuvant chemotherapy	RR 8.91 (3.58 to 22.22)	1786 (5 RCTs)	Moderate	No change
Febrile neutropenia	RR 1.98 (1.32 to 2.98)	1786 (5 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy	RR 1.98 (1.32 to 2.98)	1786 (5 RCTs)	Moderate	No change
Leukopenia	RR 1.67 (1.11 to 2.51)	1497 (4 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy	RR 1.71 (1.12 to 2.61)	1165 (3 RCTs)	Moderate	No change
Neutropenia	RR 1.88 (1.09 to 3.23)	2376 (9 RCTs)	Very low	Effect favours non-platinum based neoadjuvant chemotherapy	RR 3.23 (1.65 to 6.33)	1786 (5 RCTs)	Very low	No change
Thrombocytopenia	RR 7.01 (3.93 to 12.48)	2150 (7 RCTs)	Moderate	Effect favours non-platinum based neoadjuvant chemotherapy	RR 9.09 (4.65 to 17.77)	1640 (4 RCTs)	Moderate	No change

Alanine aminotransferase increased	RR 0.47 (0.24 to 0.92)	1403 (3 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy	RR 0.95 (0.35 to 2.58)	1072 (2 RCTs)	Moderate	Could not differentiate
Aspartate aminotransferase increased	RR 1.61 (0.40 to 6.38)	960 (2 RCTs)	Low	Could not differentiate	RR 1.38 (0.15 to 12.38)	629 (1 RCT)	Low	No change
Constipation	RR 0.32 (0.04 to 2.63)	723 (2 RCTs)	Moderate	Could not differentiate	RR 0.25 (0.02 to 3.99)	392 (1 RCT)	Low	No change
Diarrhoea	RR 1.48 (0.61 to 3.60)	1491 (4 RCTs)	Low	Could not differentiate	RR 2.05 (0.63 to 6.64)	1072 (2 RCTs)	Low	No change
Hypertension	RR 0.61 (0.31 to 1.20)	1403 (3 RCTs)	Low	Could not differentiate	RR 0.59 (0.29 to 1.17)	1072 (2 RCTs)	Low	No change
Pneumonia	RR 1.28 (0.30 to 5.48)	960 (2 RCTs)	Low	Could not differentiate	RR 1.38 (0.15 to 12.38)	629 (1 RCT)	Low	No change
Nausea	RR 1.45 (0.81 to 2.60)	1814 (6 RCTs)	Low	Could not differentiate	RR 1.48 (0.75 to 2.94)	1403 (4 RCTs)	Low	No change
Oral mucositis	RR 1.61 (0.41 to 6.23)	774 (2 RCTs)	Low	Could not differentiate	RR 2.42 (0.47 to 12.35)	443 (1 RCT)	Very low	No change
Vomiting	RR 0.92 (0.42 to 2.05)	1251 (4 RCTs)	Low	Could not differentiate	RR 1.58 (0.53 to 4.67)	1072 (2 RCTs)	Low	No change

Treatment related death	RR 1.60 (0.19 to 13.74)	835 (2 RCTs)	Moderate	Could not differentiate	RR 1.60 (0.19 to 13.74)	835 (2 RCTs)	Moderate	No change
Fatigue	RR 1.26 (0.80 to 1.97)	1311 (4 RCTs)	Low	Could not differentiate	RR 1.26 (0.80 to 1.97)	1311 (4 RCTs)	Low	No change
Neuropathy	RR 1.18 (0.73 to 1.89)	2024 (6 RCTs)	Low	Could not differentiate	RR 1.14 (0.70 to 1.85)	1693 (4 RCTs)	Low	No change
Pain	RR 1.54 (0.78 to 3.05)	1254 (4 RCTs)	Low	Could not differentiate	RR 1.57 (0.71 to 3.45)	835 (2 RCTs)	Low	No change

CI: confidence interval; RR: risk ratio. See full GRADE tables (appendix F) for reasons for downgrading the evidence.

Germline BRCA mutation analyses

Table 13 Germline BRCA mutation analyses

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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Disease-free survival - BRCA wildtype (TNBC)	Not estimable**	Not estimable**	HR 0.60 (0.43 to 0.84)	647 (2 RCTs)	High	Effect favours platinum based neoadjuvant chemotherapy

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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Disease-free survival - BRCA1 or BRCA2 mutation (all receptor subtypes, including triple negative)	Not estimable**	Not estimable**	HR 0.64 (0.35 to 1.18)	118 (3 RCTs)	Very low	Could not differentiate
Disease-free survival - total	Not estimable**	Not estimable**	HR 0.61 (0.46 to 0.82)	765 (3 RCTs)	High	Effect favours platinum based neoadjuvant chemotherapy
Overall survival - BRCA1 or BRCA2 mutation (all receptor subtypes, including triple negative)	Not estimable**	Not estimable**	HR 0.98 (0.28 to 3.38)	(1 RCT)	Very low	Could not differentiate
Pathological complete response - BRCA 1/2 wildtype (all receptor subtypes, including triple negative) – Random effects model (I2 68%)	380 per 1,000	543 per 1,000 (410 to 718)	RR 1.43 (1.08 to 1.89)	1193 (5 RCTs)	Very low	Effect favours platinum based neoadjuvant chemotherapy
Pathological complete response - BRCA 1/2 mutation (all receptor subtypes, including triple negative) – Fixed effects model	595 per 1,000	660 per 1,000 (541 to 815)	RR 1.11 (0.91 to 1.37)	271 (4 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 based neoadjuvant chemotherapy	Risk with Platinum based neoadjuvant chemotherapy				
Pathological complete response - total – Random effects model (I2 50%)	424 per 1,000	547 per 1,000 (458 to 653)	RR 1.29 (1.08 to 1.54)	1464 (5 RCTs)	Low	Effect favours platinum based neoadjuvant chemotherapy

*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). ** Absolute effects could not be estimated because number of events were not reported. *** See full GRADE tables in appendix F for reasons for downgrading. CI: confidence interval; HR: hazard ratio; RR: risk ratio.

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A search was performed to identify published economic evaluations of relevance to this guideline update (see Appendix G). This search retrieved 1,314 studies. After title and abstract screening, 1,308 of the studies were excluded for this question. Following the full-text review, we excluded the remaining 6 studies. Thus, no studies were included in this review.

1.1.7.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.9 Economic model

This question was not prioritised for original economic analysis.

1.1.10 Unit costs

Costs for a cycle of treatment were presented to the committee to help inform decision making.

Table 14 Cost of chemotherapy regimens

Regimen*	Dosing	Cost per cycle	Total cost
Paclitaxel and carboplatin	Paclitaxel: 80mg/m^2 on days 1,8 and 15; carboplatin AUC 5 on day 1 Cycle every 28 days, up to 6 cycles	£167	£1,002.96
Epirubicin & cyclophosphamide (EC) / carboplatin + weekly paclitaxel	Cycle 1-3: EC on day 1, every 21 days. Epirubicin: 100mg/m^2; cyclophosphamide: 500mg/m^2. Cycle 4-7: carboplatin + paclitaxel weekly every 21 days. Carboplatin: AUC 5 on day 1. Paclitaxel: 80mg/m^2 on days 1,8 and 15.	Cycle A: £38.94 Cycle B: £167.16	£785.46
Epirubicin & cyclophosphamide & paclitaxel (EC-Paclitaxel)	Cycle 1-3: EC on day 1, every 21 days. Epirubicin: 100mg/m^2; cyclophosphamide: 500mg/m^2. Cycle 4-7: weekly paclitaxel every 21 days. Paclitaxel: 80mg/m^2 on days 1,8 and 15.	Cycle A: £38.94 Cycle B: £50.76	£319.86
Epirubicin & cyclophosphamide & docetaxel (EC-T)	Cycle 1-3: EC on day 1, every 21 days. Epirubicin: 100mg/m^2; cyclophosphamide: 500mg/m^2. Cycle 4-6: docetaxel on day 1, every 21 days. Docetaxel: 100mg/m^2.	Cycle A: £38.94 Cycle B: £21.68	£181.86
Fluorouracil, Epirubicin and Cyclophosphamide and Docetaxel (FEC-T)	Cycle 1-3: FEC100 on day 1, every 21 days. Epirubicin: 100mg/m^2; fluorouracil: 500mg/m^2, cyclophosphamide: 500mg/m^2. Cycle 4-6: docetaxel on day 1, every 21 days. Docetaxel: 100mg/m^2.	Cycle A: £41.98 Cycle B: £21.68	£190.98
Fluorouracil, Epirubicin + Cyclophosphamide and Docetaxel + Carboplatin (FEC-T + Carboplatin)	Cycle 1-3: FEC100 on day 1, every 21 days. Epirubicin: 100mg/m^2; fluorouracil: 500mg/m^2, cyclophosphamide: 500mg/m^2. Cycle 4-7: Docetaxel + carboplatin, on day 1, every 21 days. Docetaxel: 100mg/m^2, carboplatin AUC 6.	Cycle A: £41.98 Cycle B: £162.28	£775.06

* Platinum chemotherapy: carboplatin. Taxane chemotherapy: paclitaxel, docetaxel. Anthracycline chemotherapy: epirubicin.

1 Source of drug costs: eMIT (accessed 20/06/24); Source of dosing regimens: Protocols Archive - SWAG Cancer Alliance. Costs assume no vial sharing.

Cost of adverse events and recurrences were estimated using data from the NICE Technology Appraisal on olaparib and treatment information from the National Disease Registration Service (NDRS).

Table 15 Cost of adverse events

Adverse event	Costs	Source
Anaemia	£533	NHS Reference Costs 2019/2020; SA04G-SA04L – Iron Deficiency Anaemia - non-elective short stay – average cost estimated
Neutropenia	£127	NHS Reference Costs 2015/2016; XD25Z Neutropenia drugs band 1; uplifted to 2021 prices using the PSSRU 2021 NHSCII price index as XD25Z has been excluded from the current NHS Reference Costs 2019/2020
Febrile neutropenia	£3,747	NHS Reference Costs 2019/2020; SA35A Agranulocytosis with CC Score 13+ [a]

a) Febrile neutropenia not reported in in NHS Reference Costs, assumed equivalent to agranulocytosis as per NICE TA851

Table 16 Cost of a recurrence

Treatment	Unit cost	Non-metastatic recurrence	Metastatic recurrence
Radiotherapy	£3,115[a]	67%[d]	35%[d]
Surgery for non-metastatic BC	£5,383[a]	89%[d]	0%[d]
Surgery for metastatic BC	£2,122[a]	0%[d]	19%[d]
Drug therapy for locoregional disease recurrence	£1,003[b]	34%[d]	0%[d]
Drug therapy for distant recurrence	£7,610[c]	0%[d]	56%[d]
Average		**£7,219**	**£2,055**[e]

a) NICE TA886
b) Assumed to be paclitaxel and carboplatin for non-metastatic recurrence, as per NICE TA886
c) Assumed to be 30% atezolizumab + nab-paclitaxel, 70% capecitabine, as per NICE TA886. Cost does not include confidential discount for atezolizumab.
d) National Disease Registration Service (NDRS)
e) End-of-life care costs not included

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

Neoadjuvant chemotherapy aims to reduce tumour size before surgery and to improve survival in the long term. As a result, the committee agreed that the critical outcomes for this review were pathological complete response (pCR, as a direct measure of the effectiveness of the neoadjuvant intervention that can be assessed after surgery or biopsy), disease-free survival and overall survival. In addition, pCR can be used by clinicians to make decisions about whether further treatment is necessary, for example, further chemotherapy.

In addition, the committee acknowledged the importance of other outcomes including mortality due to breast cancer, local and/or locoregional recurrence, and quality of life in decision making. Breast cancer mortality 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 neoadjuvant chemotherapy. The risk of local and/or locoregional recurrence may be expected to be reduced after neoadjuvant chemotherapy if it is effective.

The committee also noted that the risk of adverse events and types of adverse events that people with TNBC may experience with platinum-based chemotherapy play an important role in their decision making about whether to accept this treatment and whether to continue taking it. Therefore, they agreed that adverse events (both shorter term on treatment and longer term) and cessation of treatment 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.

Breast conservation rate was considered to be an important outcome because it represents the number of people undergoing breast conserving surgery. However, the committee noted that the decision to undergo breast conserving surgery or mastectomy is made before pCR is known, which complicates interpretation of this outcome.

1.1.11.2 The quality of the evidence

Triple negative breast cancer

Overall, the outcomes ranged from high to very low quality with the main reasons for downgrading being due to risk of bias, inconsistency and imprecision of the evidence. Some studies were judged to be at moderate or high risk of bias due to poor reporting. There was variability in the results of some outcomes within studies or evidence came from a single study. Some of the evidence was 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). Studies with a sample size of less than 500 participants were also downgraded for imprecision as there were likely to be too few participants to reliably detect an effect.

The majority of the outcome data related to the critical outcomes: pathological complete response (pCR), disease-free survival (DFS) and overall survival (OS). Treatment adherence was the second most reported outcome. There was less evidence for individual adverse events, local/locoregional recurrence, and breast conservation rate. Breast cancer mortality was only reported by one study. There was no evidence at all on quality of life.

The committee had specified that a number of subgroup analyses be carried out to help them with drafting recommendations. Subgroup analyses by type of platinum agent was not necessary because all included studies used the same platinum agent (carboplatin). We were unable to carry out the subgroup analyses for people with male reproductive organs (men, trans women and non-binary people who currently have testes) as none of the trials reported data separately for these people. Many of the trials specified that participants were women and it is likely that even those that did not specify this predominantly or solely recruited people with female reproductive organs (women, trans men and non-binary people). The committee acknowledge that people with male reproductive organs are also at risk of having TNBC but are often excluded from trials or only form a small proportion of the population due to limited numbers of people with male reproductive organs who have breast cancer.

The committee highlighted that evidence came from studies recruiting young women (median age in the included studies ranged from 45 to 52 years with the majority of participants being 40 to 60 years old). The committee acknowledged that women under 40 years old are more likely to have TNBC, but older people can also have TNBC and it is important to gather evidence for neoadjuvant chemotherapy on all ages. There was sufficient evidence to carry out planned subgroup analyses by age. Three studies (CALGB 40603 [Sikov et al. 2015]; NeoCART [Zhang et al. 2022]; and Zhang et al. 2016) reported data for this subgroup analysis. No subgroup differences were detected between the age groups for the critical outcomes pCR, DFS and OS.

Lymph node status was another planned subgroup analysis with limited data. Three studies reported this subgroup (CALGB 40603 [Sikov et al. 2015]; BrighTNess [Loibl et al. 2018]; and Zhang et al. 2016) but they did not report data for all 3 critical outcomes. CALGB 40603 [Sikov et al. 2015]) reported lymph node status by stage (rather than by the lymph node status being positive or negative) for DFS and OS. The committee agreed that this could be analysed in this format rather than being reclassified as lymph node positive or negative because it was more informative to retain the separate groups. In addition, this study did not provide data for pCR which was reported by 2 studies (BrighTNess [Loibl et al. 2018]; Zhang et al. 2016) and so could not be included in a meta-analysis with them. No subgroup differences were detected between the groups based on lymph node status for the critical outcomes pCR, DFS and OS.

Subgroup analyses by germline BRCA status in people with TNBC was limited to DFS and pCR with no data available for OS. In addition, the number of people included in these subgroups was small, ranging from 118 to 250, which may have limited the ability of our analyses to detect any differences in treatment effect between people with TNBC that have germline BRCA mutations and those without. No subgroup differences were detected based on germline BRCA mutation status for the critical outcomes pCR and DFS.

The committee highlighted that in current practice neoadjuvant chemotherapy regimens contain at least a taxane and an anthracycline. As part of the subgroup analyses, we had already looked at whether there were differences in effect between studies that had a platinum with an anthracycline in the intervention arm for pCR, DFS and OS, and in all cases, there were no detectable subgroup differences (p value of the test for subgroup differences was ≥ 0.05). However, the subgroup analyses were limited to the critical outcomes only. In a protocol deviation, a sensitivity analysis was carried out removing 3 studies without an anthracycline in the intervention arm (NeoCART [Zhang et al. 2022]; Zhang et al. 2016; and Zhao et al. 2014) and 1 study without an anthracycline in neither the intervention arm and the control arm (ADAPT-TN [Gluz et al. 2018]) from all outcomes where data was reported by these studies. The evidence changed from being statistically significant

(RR 0.47 [95% CI 0.24 to 0.92], moderate quality evidence, favouring the platinum containing treatment) to crossing the line of no effect (RR 0.95 [95% CI 0.35 to 2.58], moderate quality evidence) for the adverse event of increased alanine aminotransferase levels. The quality of the evidence changed in the sensitivity analysis for 2 of the critical outcomes: DFS (from moderate quality to low quality evidence) and pCR (from low quality to very low quality evidence); and for 3 of the adverse events: anaemia (from low quality to moderate quality evidence), constipation (from moderate quality to low quality evidence), and oral mucositis (from low quality to very low quality evidence). The rest of the outcomes remained the same in interpretation of effect, or lack of detectable effect, and quality.

There were 2 types of studies included in this evidence review which were also included in the 2018 update of this NICE guideline (NG101, see evidence review J for more details) and in the Cochrane systematic review by Mason et al. (2023). These were firstly, studies with identical treatments in both arms, apart from the platinum, and secondly, studies with one arm containing a platinum and the other without a platinum but the rest of treatments in each arm were not identical otherwise. 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 pCR, DFS and OS and in all cases, there were no detectable subgroup differences.

Many of the studies also included additional treatments in one or both of the trial arms (CALGB 40603 [Shepherd et al. 2022], ADAPT-TN [Gluz et al. 2018], Brightness [Loibl et al. 2018], GeparOLA [Fasching et al. 2021], GeparSixto [von Minckwitz et al. 2014] and Gigolaeva et al. 2019). For example, CALGB 40603 (Shepherd et al. 2022) included bevacizumab in both arms; ADAPT-TN (Gluz et al. 2018) included gemcitabine in the non-platinum arm. The committee agreed that all trials should be included. They noted that in trials with additional treatments in both arms, the effect of platinum compared to non-platinum was likely to be balanced between arms. For trials with additional treatments in one arm (like ADAPT-TN), subgroup analyses did not show detectable subgroup differences (see previous paragraph for more details on this subgroup analysis).

One study (GEICAM 2006-3 [Alba et al. 2012]) restricted recruitment to patients with basal like breast cancer which was downgraded for indirectness in the 2018 update of the guideline. The committee downgraded this study once for indirectness based on the population. This agreed with the decision made by the committee in 2018.

The committee noted that the evidence was mainly from studies including younger people (the median age of participants being from 45 to 52 years old), limited evidence was available for older people (people aged 65 years and over) and no evidence was available for pregnant people, or people with male reproductive organs. The committee acknowledged that these people are also at risk of having TNBC but are often excluded from trials or only form a small proportion of the population due to concerns about potential frailty and comorbidities (older people), the risk of causing problems during development of the baby (pregnant women) and limited numbers of people with male reproductive organs who have breast cancer. However, they could be candidates for treatment with neoadjuvant chemotherapy. The committee also highlighted that real world evidence (RWE) is available that could fill in these gaps for groups of people not recruited to participate in RCTs. For example, the SAIL databank in Wales and the Systemic Anti-Cancer Therapy Dataset (SACT) could be used as sources of real world evidence (RWE) for outcomes following platinum based neoadjuvant chemotherapy use. Therefore, the committee made a recommendation for research using RWE (see Appendix K– Research recommendations – full details) to include these populations usually excluded by RCTs.

Germline BRCA status – all receptor subtypes

The overall quality of the evidence was similar to the data on TNBC with similar reasons for downgrading the evidence. No additional studies were included that only reported on people with germline BRCA status of all receptor subtypes. Most of the evidence was from subgroup data of studies already included for the TNBC part of the review (Figure 2, Figure 17). This was combined with additional data for all receptor subtypes from the GeparOcto trial (Schneeweiss et al. 2019) reporting on DFS and OS (n=96) and the GeparOLA trial (Fasching et al. 2021) reporting on pathological complete response (n=59) (Figure 90, Figure 91 and Figure 92). These small sample sizes may have led to there not being a high enough number of events to detect a difference between the effects of platinum containing and non-platinum containing neoadjuvant chemotherapy regimens for DFS, OS and pCR in people with germline BRCA mutation of all receptor subtypes. However, where there was data for people with both wildtype BRCA and germline BRCA mutations of all receptor subtypes (for DFS and pCR) no subgroup differences were detected between the groups based on their germline BRCA status. The interpretation of this result is complicated by the fact that both groups included people who have TNBC, making it hard to separate the effects of using a platinum based neoadjuvant chemotherapy based on their TN status from any effects based on their BRCA status.

As mentioned above, for people who have TNBC and have germline BRCA mutations no subgroup differences were detected based on gBRCA mutation status for the critical outcomes of pCR and DFS (Figure 2, Figure 17). There was no data for OS. Therefore, the committee agreed that when considering type of chemotherapy, they would not treat people with germline BRCA mutations who had TNBC differently from people with TNBC who did not have these germline BRCA mutations.

The committee noted the limited evidence on the effectiveness of neoadjuvant chemotherapy for people with germline BRCA mutations in general, and in particular for those people who did not also have TNBC. They did not think that this supported making separate recommendations for people with germline BRCA mutations who do not have TNBC. However, the committee agreed that this was an important topic for further research and made a recommendation for research for this population (see appendix K).

1.1.11.3 Benefits and harms

Triple negative breast cancer

The committee discussed the evidence for neoadjuvant chemotherapy regimens for people with triple negative breast cancer (TNBC) and noted that there was a statistically significant improvement in pathological complete response (pCR), disease-free survival (DFS) and overall survival (OS) with regimens containing platinum agents compared to regimens without platinum agents. They agreed that these improvements were large enough to be clinically meaningful and they were more convinced by the quality of the evidence (moderate quality evidence for DFS and OS.

Subgroup analyses were carried out where there was data, but no subgroup differences were detected for any of the analyses (see quality of the evidence for more about the subgroup analyses.) These included germline BRCA mutation status (Figure 2, Figure 10, Figure 17, Figure 18, and Figure 19), same or different backbone chemotherapy (Figure 3, Figure 4, Figure 11, Figure 20, and Figure 21), lymph node status (

Figure 5, Figure 12, and Figure 22), anthracycline content (Figure 6, Figure 13, Figure 23, and Figure 24) and age (Figure 7, Figure 14, and Figure 25).

There was limited evidence for breast cancer mortality with data from a single study showing that breast cancer mortality was statistically significantly reduced with neoadjuvant chemotherapy containing platinum compared to neoadjuvant chemotherapy not containing platinum (RR 0.04 [95% CI 0.00 to 0.67], 4.5 years follow-up). This was also judged to be a clinically meaningful effect. However, they noted that the numbers of events and participants in this study were very low (91 people in total, 11 events in the non-platinum containing arm, 0 events in the platinum containing arm) and that the evidence was very low quality leading to reduced confidence in this outcome.

Local/locoregional recurrence was statistically significantly reduced with neoadjuvant chemotherapy regimens containing platinum compared to neoadjuvant chemotherapy regimens not containing platinum (RR 0.62 [95% CI 0.45 to 0.85], up to 8 years follow-up). Again, this was judged to be a clinically meaningful effect with moderate quality evidence.

For breast conservation rate, it was not possible from the evidence to differentiate between neoadjuvant chemotherapy regimens containing platinum agents and neoadjuvant chemotherapy regimens not containing platinum agents (RR 1.08 [95% CI 0.93 to 1.24]). The committee were clear that there was an associated degree of uncertainty with the interpretation of these results because this covers 2 scenarios. In the first situation, there may be no difference between the effects of the 2 neoadjuvant chemotherapy regimens (this means that they may be clinically and/or statistically equivalent). In the second situation, there may be differences between the effects of the 2 neoadjuvant chemotherapy regimens, but the differences may not be detectable because there are too few people and events to see the difference.

In the 2018 update of this NICE guideline (NG101, see evidence review J for more details), evidence was reported for breast conservation rate with a statistically significant difference favouring neoadjuvant chemotherapy regimens containing a platinum agent, however, this result was driven by a study defining breast conservation rate as the number of people who were judged ineligible for breast conserving surgery at baseline and became eligible after treatment rather than the number of people who actually underwent breast conserving surgery after neoadjuvant chemotherapy. For our current analyses, we have excluded this study as we decided to only include those studies reporting actual breast conservation rates.

Neoadjuvant chemotherapy aims to reduce the size of the tumour, which may allow people to choose breast conserving surgery over mastectomy. The committee were not surprised that an improved pCR was not associated with an increase in breast conserving surgery or no surgery because in current clinical practice, pCR is measured after surgery takes place. This information is therefore not available at an individual level for patients when they are choosing between breast conserving surgery, mastectomy or no further surgery. The committee noted that choice of surgery will ultimately be decided upon through discussion between the surgeon and the individual patient.

The committee were aware of ongoing research (for example, the NOSTRA trial) in other breast cancer receptor subtypes looking at biopsy after neoadjuvant chemotherapy. The aim of the ongoing research is to determine whether people with residual cancer can be identified using this procedure, which may help with decisions around choice of surgery. The committee also highlighted that some people (regardless of BRCA status) may choose mastectomy even if they are eligible for breast conserving surgery (see evidence review N on further surgery after breast-conserving surgery based on tissue margins for more discussion

about surgical margins and some of the factors that patients take into account during their decision making around surgery).

The committee discussed the evidence for harms from neoadjuvant chemotherapy and noted that there were statistically significant and clinically meaningful increased risk of neutropenia, febrile neutropenia, anaemia, thrombocytopenia, and leukopenia with neoadjuvant chemotherapy containing a platinum agent compared to neoadjuvant chemotherapy without a platinum. They agreed that there should be a consideration of the increased risk of these adverse events when discussing the balance between the benefits and risks of using these regimens. The committee also produce a table in the recommendations to help with these discussions.

There was also a statistically significant decrease in the risk of increased alanine aminotransferase levels with neoadjuvant chemotherapy containing a platinum agent compared to neoadjuvant chemotherapy without platinum (RR 0.47 [95% CI 0.24 to 0.92]). This result ceased to be statistically significant in the sensitivity analysis described above when ADAPT-TN [Gluz et al. 2018] was removed (see the section on quality of the evidence). The committee noted that this adverse event is not a key outcome for decision making in clinical practice as is expected with these treatments.

Drafting the recommendations

In 2018 the committee made a weak recommendation to consider a neoadjuvant chemotherapy regimen that contained both a platinum and an anthracycline for people with TNBC and to discuss the benefits and risks of this regimen, in particular the risk of increased toxicity. (They listed the benefits and risks in a table next to the recommendation). There was no evidence for an improvement in OS.

The current committee were confident that the evidence in 2024 was stronger as there were more included studies and evidence for an improvement in OS. They therefore made a recommendation to offer a platinum, a taxane and anthracycline based neoadjuvant chemotherapy regimen. They noted that there might be people for whom neoadjuvant chemotherapy is not indicated, for example if the treatments are contraindicated due to existing comorbidities or frailty and included reference to this in the recommendation.

Although this review looked at the evidence for adding a platinum to a taxane based neoadjuvant chemotherapy regimen with or without an anthracycline, the committee decided to specify in their recommendation that the regimen included an anthracycline. This was because this review was not designed to examine the role of anthracyclines (whether to include them or not) and current practice for people with TNBC includes an anthracycline component in the neoadjuvant chemotherapy regimen along with a taxane.

The committee agreed that there should be a balance between clinical outcomes and patient reported outcomes when making decisions about neoadjuvant 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. In particular, they supported the view of the clinicians that a discussion should take place about the benefits and risks of adding a platinum to neoadjuvant chemotherapy for people with TNBC. The need for a discussion of the benefits and risks was also included in the recommendation because of this.

The committee updated the table of benefits and risks of adding a platinum to neoadjuvant chemotherapy based on the new evidence that there were clinical meaningful improvements for critical outcomes (pCR, DFS, and OS) with neoadjuvant chemotherapy regimens containing platinum. They agreed that this should be balanced by consideration of the increased risk of adverse events (neutropenia, febrile neutropenia, anaemia, thrombocytopenia, and leukopenia) using these regimens.

Studies reported febrile neutropenia as one of the most common adverse events in people undergoing neoadjuvant chemotherapy with regimens containing a taxane, an anthracycline and a platinum. The data recorded in the trials was for febrile neutropenia and no data was identified specifically for neutropenic sepsis. The committee noted the partial overlap of this outcome with that of neutropenic sepsis and agreed that the potential for an increased risk of neutropenic sepsis (as a result of the detected increased risk of febrile neutropenia) was important to highlight as this could have a very severe outcome if left untreated. However, some people with febrile neutropenia will not have sepsis and not everyone with neutropenic sepsis will have a fever. (See the NICE clinical knowledge summary on neutropenic sepsis for more information and see also the NICE guideline on Neutropenic sepsis: prevention and management in people with cancer.)

1.1.11.4 Cost effectiveness and resource use

No health economic studies were identified and *de novo* economic modelling was not undertaken for this review question.

The committee were presented with unit costs and costs of different treatment regimens. Platinum-based regimens were found to be, on average, more expensive than non-platinum regimens. For instance, a regimen including epirubicin, cyclophosphamide & paclitaxel (EC-Paclitaxel) was estimated to cost around £320, whereas the same regimen including carboplatin was estimated to cost around £775.

The clinical review found that neoadjuvant chemotherapy containing a platinum agent would increase the risk of various adverse events, including neutropenia and anaemia, which could lead to hospitalisation. The NICE technology appraisal on olaparib for adjuvant treatment of BRCA mutation-positive high-risk early breast cancer (TA886) estimated that a hospitalisation would cost around £127 for neutropenia and £533 for anaemia. However, platinum-based therapy was found to improve pathological response and reduce the risk of recurrence as well as mortality. Data from TA886 on olaparib and the National Disease Registration Service (NDRS) were utilised to estimate the average cost of non-metastatic and a metastatic recurrence in the UK, which are £7,219 and £2,055, respectively. The committee acknowledged that these are likely underestimations due to the exclusion of end-of-life care from the cost calculations and the application of the same pharmaceutical cost to both non-metastatic and metastatic recurrences.

The committee agreed that the benefits of platinum-based regimens are likely to offset any initial costs or negative impacts caused by adverse events. In particular, the lower rate of recurrence is expected to lead to significant NHS saving in the long-term and to increase people quality of life and survival. Therefore, the committee decided to strengthen the previous recommendation and made an offer recommendation for platinum-based neoadjuvant chemotherapy for people with TNBC.

The committee consider that neoadjuvant chemotherapy including a platinum-based chemotherapy is already current practice in the UK. The recommendation may increase this

figure and might lead to an initial increase in NHS spending. However, downstream savings caused by less recurrences will likely offset the higher pharmaceutical costs.

1.1.11.5 Other factors the committee took into account

The committee noted that the equality and health inequalities assessment that accompanies this review highlighted a large number of issues that could act as barriers to people with TNBC with or without BRCA germline mutations constraining their decisions about whether to have neoadjuvant chemotherapy with regimens containing a taxane, an anthracycline and a platinum. 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 hours that may help those who require this type of support.

Some of the 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). To facilitate the decision-making process and ensure that patients are able to fully participate the committee included cross references to relevant sections of some core NICE guidelines in the overarching section of the guideline that covers systemic anti-cancer therapy planning. These were the sections on enabling patients to actively participate in their care in the NICE guideline on patient experience in adult NHS services, and communicating risks, benefits and consequences in the NICE guideline on shared decision making.

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 noted the importance of discussing the person's preferences and asking about their personal circumstances when health professionals explain the benefits and risks of having a neoadjuvant chemotherapy regimen which includes a taxane, an anthracycline and a platinum. They were aware that, in addition to clinical factors (including effects on OS, breast conservation rate, pCR and the risk of adverse events), there are a range of factors that will influence a person's choice of whether to have neoadjuvant chemotherapy and the type of neoadjuvant chemotherapy regimen. This could include the number of cycles of neoadjuvant 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 regimes or decline this treatment.

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 neoadjuvant chemotherapy regimen that includes a taxane and an anthracycline, with or without a platinum. However, they acknowledged that these people may need additional support to overcome any barriers they face when deciding what it is the right option for them and to help them access treatment. They therefore recommended that the person's circumstances, needs and preferences should form part of the decision-making process to ensure that the

realities of people's lives are taken into account and to help identify and minimise the impact of health inequalities, where possible.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendation 1.11.4 and the research recommendation on real-world evidence for people who are often excluded from clinical trials and the research recommendation on people with invasive breast cancer who have a germline BRCA mutation but who do not have triple-negative breast cancer.

1.1.13 References – included studies

1.1.13.1 Effectiveness evidence

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Mason, Sofia Re, Willson, Melina L, Egger, Sam J et al. (2023) Platinum-based chemotherapy for early triple-negative breast cancer. The Cochrane database of systematic reviews 9: cd014805

Schneeweiss A, Möbus V, Tesch H et al. (2019) Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto-GBG 84): A randomised phase III trial. European journal of cancer (Oxford, England : 1990) 106: 181-192

Schneeweiss, A, Michel, LL, Möbus, V et al. (2022) Survival analysis of the randomised phase III GeparOcto trial comparing neoadjuvant chemotherapy of intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for patients with high-risk early breast cancer. European journal of cancer (Oxford, England : 1990) 160: 100-111

Shepherd, Jonathan H, Ballman, Karla, Polley, Mei-Yin C et al. (2022) CALGB 40603 (Alliance): Long-Term Outcomes and Genomic Correlates of Response and Survival After Neoadjuvant Chemotherapy With or Without Carboplatin and Bevacizumab in Triple-Negative Breast Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 40(12): 1323-1334

Sikov WM, Berry DA, Perou CM et al. (2015) Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). Journal of clinical oncology : official journal of the American Society of Clinical Oncology 33(1): 13-21

von Minckwitz G, Schneeweiss A, Loibl S et al. (2014) Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. The Lancet. Oncology 15(7): 747-756

Zhang P, Yin Y, Mo H et al. (2016) Better pathologic complete response and relapse-free survival after carboplatin plus paclitaxel compared with epirubicin plus paclitaxel as neoadjuvant chemotherapy for locally advanced triple-negative breast cancer: a randomized phase 2 trial. Oncotarget 7(37): 60647-60656

Zhang, L., Wu, Z.-Y., Lin, Y. et al. (2022) Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): Results from a multicenter, randomized controlled, open-label phase II trial. International Journal of Cancer 150(4): 654-662

Zhang, Liulu, Wu, Zhiyong, Li, Jie et al. (2023) Impact of Homologous Recombination Deficiency on Outcomes in Patients With Triple-Negative Breast Cancer Treated With Carboplatin-Based Neoadjuvant Chemotherapy: Secondary Analysis of the NeoCART Randomized Clinical Trial. JCO precision oncology 7: e2200337

Zhao, Yue; Li, Jin-feng; Chu, Gui-wei (2014) Neoadjuvant chemotherapy regimens for patients with triple-negative breast cancer:TE versus TC. Journal of Practical Oncology: 576-579

1.1.13.2 Economic

None.

Appendices

Appendix A – Review protocols

Review protocol for platinum based neoadjuvant chemotherapy in people with invasive breast cancer that is triple negative and/or who have BRCA germline mutations.

ID	Field	Content
1.	Review title	RQ1.1 Platinum based neoadjuvant chemotherapy in people with invasive breast cancer that is triple negative and/or who have BRCA germline mutations.
2.	Review question	RQ 1.1 What is the clinical and cost effectiveness of adding a platinum to a taxane based neoadjuvant chemotherapy regimen with or without an anthracycline in people with invasive breast cancer that is either: • triple negative, or • of any receptor subtype with a BRCA germline mutation?
3.	Objective	To assess whether it is clinically and cost effective adding a platinum to a taxane based neoadjuvant chemotherapy regimen with or without an anthracycline in people with invasive breast cancer that is either: • triple negative, or • of any receptor subtype with a BRCA germline mutation.
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 • Econlit • INAHTA • HTA (Health Technology Assessment)

		• NHS EED Searches will be restricted by: • Date of last search (BRCA September 2017) and Cochrane Review (TNBC April 2022) • English language • Human studies • Abstracts, conference presentations, and theses will be excluded. • Systematic reviews and RCTs Cochrane review reference: Mason SRE, Willson ML, Egger SJ, Beith J, Dear RF, Goodwin A. Platinum-based chemotherapy for early triple-negative breast cancer. Cochrane Database of Systematic Reviews 2023, Issue 9. Art. No.: CD014805. DOI: 10.1002/14651858.CD014805.pub2. Accessed 30 May 2024. The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Invasive breast cancer that is triple negative or of any receptor subtype with a germline BRCA mutation.
6.	Population	Inclusion: • Adults (18 and over) who have invasive breast cancer that is triple negative and/or who have BRCA germline mutations. Exclusion: • Adults (18 and over) who have invasive breast cancer that is not triple negative and do not have BRCA germline mutations. • Adults (18 and over) with newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Adults (18 and over) with Paget's disease of the breast with no invasive component.
7.	Intervention	A neoadjuvant regimen containing a platinum and taxane with or without an anthracycline
8.	Comparator	A neoadjuvant regimen containing an a taxane with or without an anthracycline (without platinum) This will include studies where one study arm contains a platinum and the other doesn't but the treatments in each

		arm are not identical otherwise, as well as studies where the treatments are identical across the study arms apart from the platinum.
9.	Types of study to be included	• Systematic reviews/meta-analyses 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 have triple negative breast cancer (for the triple negative analyses) or where subgroup data is not available. • Studies where more than 20% of the participants do not BRCA germline mutations (for the BRCA analyses) or where subgroup data is not available. • Studies where data on neoadjuvant and adjuvant platinum-based chemotherapy are not reported separately.
11.	Context	The current recommendations focus on whether to add platinum to anthracycline-containing neoadjuvant chemotherapy regimens for people with triple negative invasive breast cancer. New evidence has been identified by the 2023 surveillance review. (We will use the recent Cochrane review: Platinum-based chemotherapy for early triple-negative breast cancer, Mason et al., 2023 as a basis for this work.) Some people with triple negative breast cancer will also have BRCA germline mutations. However, people with invasive breast cancer of other receptor subtypes may also have BRCA germline mutations. There are currently no recommendations on the use of platinum containing neoadjuvant chemotherapy regimens specifically for people with BRCA germline mutations. The 2023 surveillance review suggests there may now be some evidence to support the development of advice in this area.
12.	Primary outcomes (critical outcomes)	• Pathological complete response (dichotomous outcome) • Overall survival (time to event data) • Disease-free survival (time to event data) **Minimal important differences** Any statistically significant difference will be used for all critical outcomes. **Time points**

		The longest follow-up periods will be prioritised if multiple time points are reported.

13.	Secondary outcomes (important outcomes)	• Breast cancer mortality (time to event data)
		• Quality of life (using validated measures such as the EQ-5D; continuous outcome)
		• Adverse events (dichotomous outcome)
		  ○ treatment-related mortality
		  ○ treatment-related morbidity including short - term adverse events and long-term consequences of treatment
		• Adherence to or completion of treatment regimens (early cessation of treatment; dichotomous outcome)
		• Local and/or locoregional recurrence (dichotomous outcome)
		• Breast conservation rate (dichotomous outcome)
		
		Minimal important differences
		
		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
		• WHOQOL-100: 1 point
		
		Any statistically significant difference will be used for the rest of the important outcomes.
		
		Process for assessing treatment-related morbidity:
		
		1. With committee input determine whether the adverse event will be short or long term.
		
		For short term adverse events:
		
		• We will report any grade III/IV adverse events
		
		• We will report any other adverse events at Grade II if the frequency is 5% or more. (This threshold was agreed by the committee to exclude very rare events.)
		
		If the study only reports adverse events without stating the grade we will include them but apply the 5% threshold.
		
		For long term adverse events: no threshold will be used and all will be reported.

		We will use different thresholds to report these because although fewer people may experience the longer-term adverse events, they may have a very large impact on quality of life for the individual and we do not expect that this will be covered by other outcomes as quality of life is unlikely to be reported. **Time points** 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 reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	Risk of bias for RCTs and systematic reviews will be assessed using the Cochrane Risk of Bias v.2.0 or ROBIS respectively, as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions. Hazard ratios will be pooled using the generic inverse-variance method. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met:

		• Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%. GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. 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 subgroups	For critical outcomes only, where there is significant heterogeneity and disambiguation of the results using the following subgroups reduces this then these analyses will be carried out: • Subgroups for triple negative analyses only: triple negative breast cancer with/without BRCA • Subgroup for BRCA germline mutations analyses only: all receptor subtypes (including triple negative) Subgroups for both triple negative and BRCA analyses: • Type of platinum agent used in the platinum arm • Types of chemotherapy backbone (same or different) • Anthracycline content of chemotherapy (platinum with or without anthracycline) • Lymph node status (positive/negative) • Age (under 50, 50 to 70, over 70; if these subgroups are not reported then under 50 and 50 plus will be used; age and range will be added to evidence tables) • Male breast cancer (people with male reproductive organs) or female breast cancer (people with female reproductive organs) Where we look at gBRCA mutations we will note/ do additional subgrouping for BRCA1 or BRCA2 status as appropriate. We will check with committee whether lymph node status is reported before chemo (clinically) or after chemo (pathologically).

1

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 searches were run on 3rd June 2024 and re-run on 24th September 2024.

This search report is compliant with 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).

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).

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.

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 for the BRCA part of the search was based on the strategies used for NG101 and CG81. The search strategy for the TNBC part of the search was based on the strategies in a Cochrane Review (Mason SRE et al. Platinum-based chemotherapy for early triple-negative breast cancer. *Cochrane Database of Systematic Reviews* 2023, Issue 9).

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and 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

A date limit of April 2022 to June 2024 was applied for the TNBC part of the effectiveness search and September 2017 to June 2024 for the BRCA part of the effectiveness search, as stated in the review protocol, because these searches were updating a NICE evidence review and Cochrane Review (see above). A date limit of 2000 to date was applied for the cost-effectiveness search because there had been no cost effectiveness search for the previous NICE Evidence review or the Cochrane Review.

Search filters and classifiers

Effectiveness searches

Randomised controlled trials filter

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

The standard NICE modifications were used: the MeSH heading *randomized controlled trial/*, which is equivalent *to randomized controlled trial.pt* was exploded to capture newer, narrower *terms equivalence trial/ and pragmatic clinical trial*. The free-text term *randomized.mp* was also changed to the (more inclusive) alternative *randomi?ed.mp.* to capture both UK and US spellings.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

Systematic reviews filters:

Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. BMC Medical Research Methodology, 12(1), 51.

- In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.
- In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

> Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

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

1 **Effectiveness searches**

Database results

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	03/06/2024	Wiley	Cochrane Central Register of Controlled Trials Issue 5 of 12, May 2024	194
Cochrane Database of Systematic Reviews (CDSR)	03/06/2024	Wiley	Cochrane Database of Systematic Reviews Issue 6 of 12, June 2024	3
Embase	03/06/2024	Ovid	Embase <1974 to 2024 May 31>	628
Epistemonikos	03/06/2024	Epistemonikos		93 (53 and 40)
MEDLINE ALL	03/06/2024	Ovid	Ovid MEDLINE(R) ALL <1946 to May 30, 2024>	289

2 **Re-run search database results**

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	24/09/24	Wiley	Cochrane Central Register of Controlled Trials Issue 8 of 12, August 2024	35
Cochrane Database of Systematic Reviews (CDSR)	24/09/24	Wiley	Cochrane Database of Systematic Reviews Issue 9 of 12, September 2024	0
Embase	24/09/24	Ovid	Embase <1974 to 2024 September 23>	52

Epistemonikos	24/09/24	Epistemonikos	Ovid MEDLINE(R) ALL <1946 to September 23, 2024>	12 (9 and 3)

1

2 **Search strategy history**

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

Searches
#1 MeSH descriptor: [Breast Neoplasms] explode all trees 20230
#2 MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 1012
#3 MeSH descriptor: [Carcinoma, Lobular] this term only 219
#4 MeSH descriptor: [Carcinoma, Medullary] this term only 21
#5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 309
#6 {OR #1-#5} 20536
#7 MeSH descriptor: [Breast] explode all trees 1154
#8 breast*:ti,ab 61434
#9 #7 or #8 61543
#10 (breast NEXT milk):ti,ab 2772
#11 (breast NEXT tender*):ti,ab 268
#12 #10 or #11 3039
#13 #9 not #12 58504
#14 MeSH descriptor: [Neoplasms] explode all trees 125042
#15 #13 and #14 20572
#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 43962
#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 283
#18 {OR #15-#17} 44986
#19 #6 or #18 46403
#20 (duct* carcinoma* in situ or DCIS):ti,ab 899
#21 #19 or #20 46474
#22 MeSH descriptor: [Triple Negative Breast Neoplasms] this term only 529
#23 (triple near/3 negativ*):ti,ab 2071
#24 TNBC:ti,ab 1284
#25 (basal* next (like* or type* or subtype*)):ti,ab 216
#26 {OR #22-#25} 2407
#27 MeSH descriptor: [BRCA1 Protein] this term only 190
#28 MeSH descriptor: [BRCA2 Protein] this term only 150
#29 MeSH descriptor: [Genes, BRCA1] this term only 158

Searches
#30 MeSH descriptor: [Genes, BRCA2] this term only 129 #31 (BRCA* near/3 (mutat* or alter* or positive* or gene* or protein*)):ti,ab 1528 #32 FANCD1*:ti,ab 0 #33 (D1 NEXT protein*):ti,ab 11 #34 (ring finger near/2 (protein* or domain*)):ti,ab 15 #35 {OR #27-#34} 1629 #36 #21 and #26 2310 #37 #21 and #35 839 #38 MeSH descriptor: [Neoadjuvant Therapy] this term only 2630 #39 (neoadjuvant* or neo-adjuvant* or neo* NEXT adjuvant*):ti,ab 12088 #40 (primary near/3 (chemotherap* or therap* or treatment*)):ti,ab 30145 #41 (induct* near/3 (chemotherap* or therap* or treatment*)):ti,ab 10480 #42 ((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) near/3 (chemotherap* or therap* or treatment*)):ti,ab 5736 #43 {OR #38-#42} 55700 #44 MeSH descriptor: [Cisplatin] this term only 6380 #45 MeSH descriptor: [Carboplatin] this term only 3289 #46 MeSH descriptor: [Platinum Compounds] this term only 145 #47 MeSH descriptor: [Platinum] this term only 385 #48 (platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*):ti,ab 27872 #49 (nsc-119875 or nsc-241240 or cbdca or jm-8):ti,ab 263 #50 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum):ti,ab 78 #51 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum):ti,ab 306 #52 {OR #44-#51} 29193 #53 MeSH descriptor: [Taxoids] explode all trees 7831 #54 (taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*):ti,ab 20602 #55 MeSH descriptor: [Anthracyclines] explode all trees 7100 #56 (anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*):ti,ab 15250 #57 {OR #53-#56} 34132 #58 #43 or #52 or #57 97076 #59 #36 and #58 with Cochrane Library publication date Between Apr 2022 and May 2024, in Cochrane Reviews, Cochrane Protocols 1 #60 #36 and #58 with Publication Year from 2022 to 2024, in Trials 371 #61 #37 and #58 with Cochrane Library publication date Between Sep 2017 and May 2024, in Cochrane Reviews, Cochrane Protocols 3 #62 #37 and #58 with Publication Year from 2017 to 2024, in Trials 254 #63 #59 or #61 3 #64 #60 or #62 584 #65 ((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*

Searches
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 510929 #66 "conference":pt 244130 #67 #65 or #66 755059 #68 #64 not #67 194

1 **Database name: Cochrane Database of Systematic Reviews (CDSR)**

Searches
#1 MeSH descriptor: [Breast Neoplasms] explode all trees 20230 #2 MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 1012 #3 MeSH descriptor: [Carcinoma, Lobular] this term only 219 #4 MeSH descriptor: [Carcinoma, Medullary] this term only 21 #5 MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 309 #6 {OR #1-#5} 20536 #7 MeSH descriptor: [Breast] explode all trees 1154 #8 breast*:ti,ab 61434 #9 #7 or #8 61543 #10 (breast NEXT milk):ti,ab 2772 #11 (breast NEXT tender*):ti,ab 268 #12 #10 or #11 3039 #13 #9 not #12 58504 #14 MeSH descriptor: [Neoplasms] explode all trees 125042 #15 #13 and #14 20572 #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 43962 #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 283 #18 {OR #15-#17} 44986 #19 #6 or #18 46403 #20 (duct* carcinoma* in situ or DCIS):ti,ab 899 #21 #19 or #20 46474 #22 MeSH descriptor: [Triple Negative Breast Neoplasms] this term only 529 #23 (triple near/3 negativ*):ti,ab 2071 #24 TNBC:ti,ab 1284 #25 (basal* next (like* or type* or subtype*)):ti,ab 216 #26 {OR #22-#25} 2407 #27 MeSH descriptor: [BRCA1 Protein] this term only 190 #28 MeSH descriptor: [BRCA2 Protein] this term only 150 #29 MeSH descriptor: [Genes, BRCA1] this term only 158 #30 MeSH descriptor: [Genes, BRCA2] this term only 129 #31 (BRCA* near/3 (mutat* or alter* or positive* or gene* or protein*)):ti,ab 1528

Searches
#32 FANCD1*:ti,ab 0 #33 (D1 NEXT protein*):ti,ab 11 #34 (ring finger near/2 (protein* or domain*)):ti,ab 15 #35 {OR #27-#34} 1629 #36 #21 and #26 2310 #37 #21 and #35 839 #38 MeSH descriptor: [Neoadjuvant Therapy] this term only 2630 #39 (neoadjuvant* or neo-adjuvant* or neo* NEXT adjuvant*):ti,ab 12088 #40 (primary near/3 (chemotherap* or therap* or treatment*)):ti,ab 30145 #41 (induct* near/3 (chemotherap* or therap* or treatment*)):ti,ab 10480 #42 ((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) near/3 (chemotherap* or therap* or treatment*)):ti,ab 5736 #43 {OR #38-#42} 55700 #44 MeSH descriptor: [Cisplatin] this term only 6380 #45 MeSH descriptor: [Carboplatin] this term only 3289 #46 MeSH descriptor: [Platinum Compounds] this term only 145 #47 MeSH descriptor: [Platinum] this term only 385 #48 (platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*):ti,ab 27872 #49 (nsc-119875 or nsc-241240 or cbdca or jm-8):ti,ab 263 #50 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum):ti,ab 78 #51 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum):ti,ab 306 #52 {OR #44-#51} 29193 #53 MeSH descriptor: [Taxoids] explode all trees 7831 #54 (taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*):ti,ab 20602 #55 MeSH descriptor: [Anthracyclines] explode all trees 7100 #56 (anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*):ti,ab 15250 #57 {OR #53-#56} 34132 #58 #43 or #52 or #57 97076 #59 #36 and #58 with Cochrane Library publication date Between Apr 2022 and May 2024, in Cochrane Reviews, Cochrane Protocols 1 #60 #36 and #58 with Publication Year from 2022 to 2024, in Trials 371 #61 #37 and #58 with Cochrane Library publication date Between Sep 2017 and May 2024, in Cochrane Reviews, Cochrane Protocols 3 #62 #37 and #58 with Publication Year from 2017 to 2024, in Trials 254 #63 #59 or #61 3

1 **Database name: Embase**

Searches
1 exp breast cancer/ 598974 2 exp breast carcinoma/ 99951 3 exp medullary carcinoma/ 13022

Searches
4 ductal breast carcinoma in situ/ 3328 5 exp breast tumor/ 680797 6 lobular carcinoma/ 3548 7 or/1-6 692254 8 exp breast/ 129933 9 breast*.ti,ab,kw. 805130 10 8 or 9 838204 11 (breast adj milk).ti,ab,kw. 20713 12 (breast adj tender*).ti,ab,kw. 780 13 11 or 12 21487 14 10 not 13 816717 15 exp neoplasm/ 5768127 16 14 and 15 621980 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,kw. 621113 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,kw. 44331 19 16 or 17 or 18 697482 20 7 or 19 824314 21 (duct* carcinoma* in situ or DCIS).ti,ab,kw. 16805 22 20 or 21 825238 23 triple negative breast cancer/ 40717 24 (triple adj3 negativ*).ti,ab. 45969 25 TNBC.ti,ab. 23257 26 (basal* adj (like* or type* or subtype*)).ti,ab. 7755 27 or/23-26 60221 28 BRCA2 protein/ or BRCA1 protein/ 31965 29 (BRCA* adj3 (mutat* or alter* or positive* or gene* or protein*)).ti,ab. 30647 30 FANCD1*.ti,ab. 215 31 D1 protein*.ti,ab. 2450 32 (ring finger adj2 (protein* or domain*)).ti,ab. 3346 33 or/28-32 52062 34 22 and 27 57529 35 22 and 33 28021 36 exp neoadjuvant therapy/ 58704 37 (neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 100599 38 (primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 126714 39 (induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 62298 40 ((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 42821 41 or/36-40 327691 42 cisplatin/ or cisplatin derivative/ 228527 43 carboplatin/ 91341 44 platinum derivative/ or platinum/ 53515 45 (platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*).ti,ab. 217571

Searches
46 (nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 1419 47 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 3100 48 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 5235 49 or/42-48 370524 50 taxoid/ 2743 51 paclitaxel/ or docetaxel/ or taxane derivative/ 196723 52 (taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 110540 53 exp anthracycline antibiotic agent/ 308317 54 (anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab. 139127 55 or/50-54 477222 56 or/41,49,55 964892 57 34 and 56 18761 58 35 and 56 4724 59 (MEDLINE or pubmed).tw. 447328 60 exp systematic review/ or systematic review.tw. 556195 61 meta-analysis/ 317470 62 intervention*.ti. 282563 63 or/59-62 1044208 64 random:.tw. 2074921 65 placebo:.mp. 539505 66 double-blind:.tw. 252495 67 or/64-66 2358404 68 63 or 67 3081034 69 57 and 68 2782 70 limit 69 to dc=20220401-20240603 822 71 58 and 68 690 72 limit 71 to dc=20170901-20240603 420 73 70 or 72 1141 74 limit 73 to english language 1129 75 nonhuman/ not human/ 5456142 76 74 not 75 1107 77 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5959494 78 case report/ 3004770 79 77 or 78 8578266 80 76 not 79 628

1 **Database name: Epistimonikos - TNBC**

Searches
(title:((breast* AND (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*)) OR (mammar* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR

Searches
adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR dcis OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (duct* carcinoma* in situ OR dcis)) OR abstract:((breast* AND (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*)) OR (mammar* AND (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*)) OR (duct* carcinoma* in situ OR dcis))) AND (title:((brca* AND (mutat* OR alter* OR positive* OR gene* OR protein*)) OR fancd1* OR (d1 AND protein*) OR (ring finger AND (protein* OR domain*))) OR abstract:((brca* AND (mutat* OR alter* OR positive* OR gene* OR protein*)) OR fancd1* OR (d1 AND protein*) OR (ring finger AND (protein* OR domain*)))) AND (title:((neoadjuvant* OR neo-adjuvant* OR neo* AND adjuvant*) OR (primary AND (chemotherap* OR therap* OR treatment*)) OR (induct* AND (chemotherap* OR therap* OR treatment*)) OR ((perioperat* OR peri-operat* OR perisurg* OR peri-surg* OR preoperat* OR pre-operat* OR presurg* OR pre-surg*) AND (chemotherap* OR therap* OR treatment*)) OR (platin* OR cisplatin* OR platinol* OR carboplatin* OR paraplatin* OR platidiam*) OR (nsc-119875 OR nsc-241240 OR cbdca OR jm-8) OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR cis-platinum) OR (taxane* OR taxoid* OR docetaxel* OR taxotere* OR paclitaxel* OR taxol*) OR (anthracycline* OR daunorubicin* OR cerubidine* OR daunoxome* OR doxorubicin* OR adriamycin* OR doxil* OR epirubicin* OR ellence* OR idarubicin* OR idamycin* OR mitoxantrone* OR valrubicin*)) OR abstract:((neoadjuvant* OR neo-adjuvant* OR neo* AND adjuvant*) OR (primary AND (chemotherap* OR therap* OR treatment*)) OR (induct* AND (chemotherap* OR therap* OR treatment*)) OR ((perioperat* OR peri-operat* OR perisurg* OR peri-surg* OR preoperat* OR pre-operat* OR presurg* OR pre-surg*) AND (chemotherap* OR therap* OR treatment*)) OR (platin* OR cisplatin* OR platinol* OR carboplatin* OR paraplatin* OR platidiam*) OR (nsc-119875 OR nsc-241240 OR cbdca OR jm-8) OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR cis-platinum) OR (taxane* OR taxoid* OR docetaxel* OR taxotere* OR paclitaxel* OR taxol*) OR (anthracycline* OR daunorubicin* OR cerubidine* OR daunoxome* OR doxorubicin* OR adriamycin* OR doxil* OR epirubicin* OR ellence* OR idarubicin* OR idamycin* OR mitoxantrone* OR valrubicin*))) + Date limit: 2022-2024 + Publication limit - Systematic Reviews

1 **Database name: Epistimonikos - BRCA**

Searches
(title:((breast* AND (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*)) OR

Searches
(mammar* AND (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*)) OR (duct* carcinoma* in situ OR dcis)) OR abstract:((breast* AND (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*)) OR (mammar* AND (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*)) OR (duct* carcinoma* in situ OR dcis))) AND (title:((triple AND negativ*) OR tnbc OR (basal* AND (like* OR type* OR subtype*))) OR abstract:((triple AND negativ*) OR tnbc OR (basal* AND (like* OR type* OR subtype*)))) AND (title:((neoadjuvant* OR neo-adjuvant* OR neo* AND adjuvant*) OR (primary AND (chemotherap* OR therap* OR treatment*)) OR (induct* AND (chemotherap* OR therap* OR treatment*)) OR ((perioperat* OR peri-operat* OR perisurg* OR peri-surg* OR preoperat* OR pre-operat* OR presurg* OR pre-surg*) AND (chemotherap* OR therap* OR treatment*)) OR (platin* OR cisplatin* OR platinol* OR carboplatin* OR paraplatin* OR platidiam*) OR (nsc-119875 OR nsc-241240 OR cbdca OR jm-8) OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR cis-platinum) OR (taxane* OR taxoid* OR docetaxel* OR taxotere* OR paclitaxel* OR taxol*) OR (anthracycline* OR daunorubicin* OR cerubidine* OR daunoxome* OR doxorubicin* OR adriamycin* OR doxil* OR epirubicin* OR ellence* OR idarubicin* OR idamycin* OR mitoxantrone* OR valrubicin*)) OR abstract:((neoadjuvant* OR neo-adjuvant* OR neo* AND adjuvant*) OR (primary AND (chemotherap* OR therap* OR treatment*)) OR (induct* AND (chemotherap* OR therap* OR treatment*)) OR ((perioperat* OR peri-operat* OR perisurg* OR peri-surg* OR preoperat* OR pre-operat* OR presurg* OR pre-surg*) AND (chemotherap* OR therap* OR treatment*)) OR (platin* OR cisplatin* OR platinol* OR carboplatin* OR paraplatin* OR platidiam*) OR (nsc-119875 OR nsc-241240 OR cbdca OR jm-8) OR (biocisplatinum OR dichlorodiammineplatinum OR diamminedichloroplatinum) OR (cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR cis-platinum) OR (taxane* OR taxoid* OR docetaxel* OR taxotere* OR paclitaxel* OR taxol*) OR (anthracycline* OR daunorubicin* OR cerubidine* OR daunoxome* OR doxorubicin* OR adriamycin* OR doxil* OR epirubicin* OR ellence* OR idarubicin* OR idamycin* OR mitoxantrone* OR valrubicin*))) + Date limit: 2017-2024 + Publication limit - Systematic Reviews

1

2

3 **Database name: MEDLINE ALL**

Searches		
1	exp Breast Neoplasms/	354248
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/	48135

Searches
3 Carcinoma, Lobular/ 6169
4 Carcinoma, Medullary/ 3422
5 Carcinoma, Intraductal, Noninfiltrating/ 10853
6 or/1-5 374452
7 exp Breast/ 54727
8 breast*.ti,ab,kw. 581082
9 7 or 8 591083
10 (breast adj milk).ti,ab,kw. 16275
11 (breast adj tender*).ti,ab,kw. 595
12 10 or 11 16867
13 9 not 12 574216
14 exp Neoplasms/ 3977434
15 13 and 14 371850
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,kw. 432262
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,kw. 37174
18 or/15-17 488742
19 6 or 18 546594
20 (duct* carcinoma* in situ or DCIS).ti,ab,kw. 9749
21 19 or 20 546844
22 Triple Negative Breast Neoplasms/ 11464
23 (triple adj3 negativ*).ti,ab. 24992
24 TNBC.ti,ab. 12606
25 (basal* adj (like* or type* or subtype*)).ti,ab. 4290
26 or/22-25 28900
27 BRCA1 Protein/ or BRCA2 Protein/ 10051
28 Genes, BRCA1/ or Genes, BRCA2/ 7132
29 (BRCA* adj3 (mutat* or alter* or positive* or gene* or protein*)).ti,ab. 18142
30 FANCD1*.ti,ab. 136
31 D1 protein*.ti,ab. 2151
32 (ring finger adj2 (protein* or domain*)).ti,ab. 2881
33 or/27-32 28143
34 21 and 26 27618
35 21 and 33 15825
36 Neoadjuvant Therapy/ 30468
37 (neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 52729
38 (primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 83112
39 (induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 32100
40 ((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 28442
41 or/36-40 192600
42 Cisplatin/ 59923
43 Carboplatin/ 13309
44 Platinum Compounds/ or Platinum/ 14105

Searches
45 (platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*).ti,ab. 151943
46 (nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 967
47 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 2880
48 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 4637
49 or/42-48 168156
50 exp Taxoids/ 44859
51 (taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 64880
52 exp Anthracyclines/ 80031
53 (anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab. 95947
54 or/50-53 178689
55 or/41,49,54 482387
56 34 and 55 6120
57 35 and 55 1324
58 (MEDLINE or pubmed).tw. 361191
59 systematic review.tw. 303356
60 systematic review.pt. 262334
61 meta-analysis.pt. 201591
62 intervention*.ti. 215272
63 or/58-62 750010
64 exp Randomized Controlled Trial/ 615611
65 randomi?ed.mp. 1122426
66 placebo.mp. 256843
67 or/64-66 1190232
68 63 or 67 1746202
69 56 and 68 680
70 limit 69 to ed=20220401-20240603 138
71 limit 69 to dt=20220401-20240603 174
72 70 or 71 192
73 57 and 68 181
74 limit 73 to ed=20170901-20240603 94
75 limit 73 to dt=20170901-20240603 114
76 74 or 75 123
77 72 or 76 291
78 limit 77 to english language 290
79 Animals/ not (Animals/ and Humans/) 5192576
80 78 not 79 289
81 limit 80 to (case reports or clinical conference or comment or editorial or letter) 9
82 80 not 79 289

1

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	06/06/2024	OVID	Embase <1974 to 2024 June 05>	1115
Econlit	06/06/2024	Ovid	Econlit <1886 to May 30, 2024>	1
HTA		CRD		30
INAHTA	06/06/2024			57
NHS EED	06/06/2024	CRD		26
Medline ALL	06/06/2024	Ovid	Ovid MEDLINE(R) ALL <1946 to June 05, 2024>	336

Re-run search database results

INAHTA and NHS EED were not searched because both databases are now legacy databases and do not contain up to date records.

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	24/09/2024	OVID	Embase <1974 to 2024 September 23>	71
Econlit	24/09/2024	Ovid	Econlit <1886 to September 12, 2024>	0
INAHTA	24/09/2024			3
Medline ALL	24/09/2024	Ovid	Ovid MEDLINE(R) ALL <1946 to September 23, 2024>	27

1 Search strategy history

2 Database name: Embase

Searches		
1	exp breast cancer/	599206
2	exp breast carcinoma/	99975
3	exp medullary carcinoma/	13026
4	ductal breast carcinoma in situ/	3336
5	exp breast tumor/	681074
6	lobular carcinoma/	3549
7	or/1-6	692535
8	exp breast/	129957
9	breast*.ti,ab,kw.	805521
10	8 or 9	838600
11	(breast adj milk).ti,ab,kw.	20720
12	(breast adj tender*).ti,ab,kw.	780
13	11 or 12	21494
14	10 not 13	817106
15	exp neoplasm/	5770621
16	14 and 15	622281
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,kw.	621401
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,kw.	44345
19	16 or 17 or 18	697800
20	7 or 19	824638
21	(duct* carcinoma* in situ or DCIS).ti,ab,kw.	16813
22	20 or 21	825562
23	triple negative breast cancer/	40744
24	(triple adj3 negativ*).ti,ab.	46003
25	TNBC.ti,ab.	23276
26	(basal* adj (like* or type* or subtype*)).ti,ab.	7760
27	or/23-26	60257
28	BRCA2 protein/ or BRCA1 protein/	31968
29	(BRCA* adj3 (mutat* or alter* or positive* or gene* or protein*)).ti,ab.	30665
30	FANCD1*.ti,ab.	215
31	D1 protein*.ti,ab.	2450
32	(ring finger adj2 (protein* or domain*)).ti,ab.	3349
33	or/28-32	52083
34	27 or 33	107746
35	22 and 34	81017
36	exp neoadjuvant therapy/	58751

Searches
37 (neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 100671
38 (primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 126777
39 (induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 62313
40 ((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 42844
41 or/36-40 327857
42 cisplatin/ or cisplatin derivative/ 228568
43 carboplatin/ 91357
44 platinum derivative/ or platinum/ 53537
45 (platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*).ti,ab. 217675
46 (nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 1419
47 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 3100
48 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 5235
49 or/42-48 370629
50 taxoid/ 2743
51 paclitaxel/ or docetaxel/ or taxane derivative/ 196748
52 (taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 110572
53 exp anthracycline antibiotic agent/ 308364
54 (anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab. 139175
55 or/50-54 477297
56 or/41,49,55 965207
57 35 and 56 21635
58 exp Health Economics/ 1076174
59 exp "Health Care Cost"/ 353622
60 exp Pharmacoeconomics/ 242749
61 Monte Carlo Method/ 53770
62 Decision Tree/ 24620
63 econom$.tw. 526229
64 cba.tw. 14560
65 cea.tw. 43116
66 cua.tw. 1980
67 markov$.tw. 41853
68 (monte adj carlo).tw. 64305
69 (decision adj3 (tree$ or analys$)).tw. 42721
70 (cost or costs or costing$ or costly or costed).tw. 1048483
71 (price$ or pricing$).tw. 76909
72 budget$.tw. 49452
73 expenditure$.tw. 94568
74 (value adj3 (money or monetary)).tw. 4499

Searches	
75	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. 9918
76	or/58-75 2368224
77	"Quality of Life"/ 668288
78	Quality Adjusted Life Year/ 37511
79	Quality of Life Index/ 3290
80	Short Form 36/ 41963
81	Health Status/ 158109
82	quality of life.tw. 629716
83	quality adjusted life.tw. 27975
84	(qaly$ or qald$ or qale$ or qtime$).tw. 28411
85	disability adjusted life.tw. 7293
86	daly$.tw. 7006
87	(sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 51632
88	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 3093
89	(sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 12763
90	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 73
91	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 542
92	(euroqol or euro qol or eq5d or eq 5d).tw. 32541
93	(qol or hql or hqol or hrqol).tw. 139285
94	(hye or hyes).tw. 191
95	health$ year$ equivalent$.tw. 41
96	utilit$.tw. 398556
97	(hui or hui1 or hui2 or hui3).tw. 3327
98	disutili$.tw. 1361
99	rosser.tw. 144
100	quality of wellbeing.tw. 78
101	quality of well-being.tw. 586
102	qwb.tw. 274
103	willingness to pay.tw. 13919
104	standard gamble$.tw. 1214
105	time trade off.tw. 2138
106	time tradeoff.tw. 321
107	tto.tw. 2347
108	or/77-107 1377270
109	76 or 108 3526035
110	57 and 109 1984
111	limit 110 to dc=20000101-20240606 1983
112	limit 111 to english language 1946
113	nonhuman/ not human/ 5458292

Searches		
114	112 not 113	1900
115	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.	5960232
116	case report/	3005635
117	115 or 116	8579838
118	114 not 117	1115

Database name: Econlit

Searches		
1	(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,kw.	401
2	(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,kw.	1
3	(duct* carcinoma* in situ or DCIS).ti,ab,kw.	3
4	or/1-3	403
5	(triple adj3 negativ*).ti,ab,kw.	2
6	TNBC.ti,ab,kw.	0
7	(basal* adj (like* or type* or subtype*)).ti,ab,kw.	0
8	or/5-7	2
9	(BRCA* adj3 (mutat* or alter* or positive* or gene* or protein*)).ti,ab,kw.	21
10	FANCD1*.ti,ab,kw.	0
11	D1 protein*.ti,ab,kw.	0
12	(ring finger adj2 (protein* or domain*)).ti,ab,kw.	0
13	or/9-12	21
14	8 or 13	23
15	4 and 14	17
16	(neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab,kw.	2
17	(primary adj3 (chemotherap* or therap* or treatment*)).ti,ab,kw.	42
18	(induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab,kw.	5
19	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab,kw.	1
20	or/16-19	50
21	(platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*).ti,ab,kw.	343
22	(nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab,kw.	0
23	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab,kw.	0
24	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab,kw.	0
25	or/21-24	343
26	(taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab,kw.	17

Searches		
27	(anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab,kw.	6
28	26 or 27	21
29	or/20,25,28	409
30	15 and 29	1
31	limit 30 to yr="2000 -Current"	1
32	limit 31 to english	1

1 **Database name: HTA**

Searches
1 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2 MeSH DESCRIPTOR Carcinoma, Ductal, Breast
3 MeSH DESCRIPTOR Carcinoma, Lobular
4 MeSH DESCRIPTOR Carcinoma, Medullary
5 MeSH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating
6 #1 OR #2 OR #3 OR #4 OR #5
7 MeSH DESCRIPTOR breast EXPLODE ALL TREES
8 (breast*)
9 #7 OR #8
10 ((breast adj milk))
11 ((breast adj tender*))
12 #10 OR #11
13 #9 NOT #12
14 MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES
15 #13 AND #14
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 malignanc*)))
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 malignanc*)))
18 MeSH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES
19 ((paget* and (breast* or mammary or nipple*)))
20 #15 OR #16 OR #17 OR #18 OR #19
21 #6 OR #20
22 (duct* carcinoma* in situ or DCIS)
23 #21 OR #22
24 MeSH DESCRIPTOR Triple Negative Breast Neoplasms
25 (triple adj3 negativ*)
26 (TNBC)
27 (basal*) AND (like* or type* or subtype*)
28 #24 OR #25 OR #26 OR #27
29 MeSH DESCRIPTOR BRCA1 Protein

Searches
30 MeSH DESCRIPTOR BRCA2 Protein
31 MeSH DESCRIPTOR Genes, BRCA1 EXPLODE ALL TREES
32 MeSH DESCRIPTOR Genes, BRCA2 EXPLODE ALL TREES
33 (BRCA* adj3 (mutat* or alter* or positive* or gene* or protein*))
34 (FANCD1*)
35 (D1 protein*)
36 ((ring finger adj2 (protein* or domain*)))
37 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38 #28 OR #37
39 #23 AND #38
40 (#39) IN NHSEED, HTA FROM 2000 TO 2024
41 (#39) IN NHSEED FROM 2000 TO 2024
42 (#39) IN HTA FROM 2000 TO 2024

1 **Database name: INAHTA**

Searches
((((ring finger) AND (protein* or domain*)) OR ((D1 protein*)) OR ((FANCD1*)) OR ((BRCA*) AND (mutat* or alter* or positive* or gene* or protein*)) OR ("Genes, BRCA2"[mh]) OR ("Genes, BRCA1"[mh]) OR ("BRCA2 Protein"[mh]) OR ("BRCA1 Protein"[mh])) OR (((basal*) AND (like* or type* or subtype*)) OR ((TNBC)) OR ((triple) AND (negativ*)) OR ("Triple Negative Breast Neoplasms"[mh]))) AND ((((duct* carcinoma* in situ or DCIS)) OR ((mammar* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ((breast* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ("Carcinoma, Intraductal, Noninfiltrating"[mh]) OR ("Carcinoma, Medullary"[mh]) OR ("Carcinoma, Lobular"[mh]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR ("Breast Neoplasms"[mhe])))

2 **Database name: NHS EED**

Searches
1 MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2 MeSH DESCRIPTOR Carcinoma, Ductal, Breast
3 MeSH DESCRIPTOR Carcinoma, Lobular
4 MeSH DESCRIPTOR Carcinoma, Medullary
5 MeSH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating
6 #1 OR #2 OR #3 OR #4 OR #5
7 MeSH DESCRIPTOR breast EXPLODE ALL TREES
8 (breast*)
9 #7 OR #8
10 ((breast adj milk))
11 ((breast adj tender*))

Searches
12 #10 OR #11
13 #9 NOT #12
14 MeSH DESCRIPTOR Neoplasms EXPLODE ALL TREES
15 #13 AND #14
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 malignanc*)))
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 malignanc*)))
18 MeSH DESCRIPTOR Paget's Disease, Mammary EXPLODE ALL TREES
19 ((paget* and (breast* or mammary or nipple*)))
20 #15 OR #16 OR #17 OR #18 OR #19
21 #6 OR #20
22 (duct* carcinoma* in situ or DCIS)
23 #21 OR #22
24 MeSH DESCRIPTOR Triple Negative Breast Neoplasms
25 (triple adj3 negativ*)
26 (TNBC)
27 (basal*) AND (like* or type* or subtype*)
28 #24 OR #25 OR #26 OR #27
29 MeSH DESCRIPTOR BRCA1 Protein
30 MeSH DESCRIPTOR BRCA2 Protein
31 MeSH DESCRIPTOR Genes, BRCA1 EXPLODE ALL TREES
32 MeSH DESCRIPTOR Genes, BRCA2 EXPLODE ALL TREES
33 (BRCA* adj3 (mutat* or alter* or positive* or gene* or protein*))
34 (FANCD1*)
35 (D1 protein*)
36 ((ring finger adj2 (protein* or domain*)))
37 #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38 #28 OR #37
39 #23 AND #38
40 (#39) IN NHSEED, HTA FROM 2000 TO 2024
41 (#39) IN NHSEED FROM 2000 TO 2024

1 **Database name: MEDLINE ALL**

Searches		
1	exp Breast Neoplasms/	354397
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/	48143
3	Carcinoma, Lobular/	6165
4	Carcinoma, Medullary/	3420
5	Carcinoma, Intraductal, Noninfiltrating/	10848

Searches	
6	or/1-5 374611
7	exp Breast/ 54727
8	breast*.ti,ab,kw. 581348
9	7 or 8 591352
10	(breast adj milk).ti,ab,kw. 16284
11	(breast adj tender*).ti,ab,kw. 594
12	10 or 11 16875
13	9 not 12 574477
14	exp Neoplasms/ 3979051
15	13 and 14 372011
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,kw. 432462
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,kw. 37185
18	or/15-17 488965
19	6 or 18 546830
20	(duct* carcinoma* in situ or DCIS).ti,ab,kw. 9743
21	19 or 20 547081
22	Triple Negative Breast Neoplasms/ 11480
23	(triple adj3 negativ*).ti,ab. 25012
24	TNBC.ti,ab. 12621
25	(basal* adj (like* or type* or subtype*)).ti,ab. 4293
26	or/22-25 28921
27	BRCA1 Protein/ or BRCA2 Protein/ 10062
28	Genes, BRCA1/ or Genes, BRCA2/ 7134
29	(BRCA* adj3 (mutat* or alter* or positive* or gene* or protein*)).ti,ab. 18149
30	FANCD1*.ti,ab. 136
31	D1 protein*.ti,ab. 2153
32	(ring finger adj2 (protein* or domain*)).ti,ab. 2881
33	or/27-32 28155
34	26 or 33 55384
35	21 and 34 41777
36	Neoadjuvant Therapy/ 30481
37	(neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 52754
38	(primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 83168
39	(induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 32123
40	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 28456
41	or/36-40 192709
42	Cisplatin/ 59941
43	Carboplatin/ 13314
44	Platinum Compounds/ or Platinum/ 14106

Searches	
45	(platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*).ti,ab. 152012
46	(nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 967
47	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 2880
48	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 4637
49	or/42-48 168227
50	exp Taxoids/ 44883
51	(taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 64916
52	exp Anthracyclines/ 80057
53	(anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab. 95969
54	or/50-53 178745
55	or/41,49,54 482596
56	35 and 55 7008
57	Economics/ 27535
58	exp "Costs and Cost Analysis"/ 270915
59	Economics, Dental/ 1922
60	exp Economics, Hospital/ 25863
61	exp Economics, Medical/ 14435
62	Economics, Nursing/ 4013
63	Economics, Pharmaceutical/ 3138
64	Budgets/ 11816
65	exp Models, Economic/ 16350
66	Markov Chains/ 16194
67	Monte Carlo Method/ 32923
68	Decision Trees/ 12230
69	econom$.tw. 435007
70	cba.tw. 11381
71	cea.tw. 27889
72	cua.tw. 1506
73	markov$.tw. 33308
74	(monte adj carlo).tw. 61591
75	(decision adj3 (tree$ or analys$)).tw. 32245
76	(cost or costs or costing$ or costly or costed).tw. 790511
77	(price$ or pricing$).tw. 56502
78	budget$.tw. 37516
79	expenditure$.tw. 71757
80	(value adj3 (money or monetary)).tw. 3363
81	(pharmacoeconomic$ or (pharmaco adj economic$)).tw. 4630
82	or/57-81 1516937
83	"Quality of Life"/ 289043

Searches
84 quality of life.tw. 402678
85 "Value of Life"/ 5827
86 Quality-Adjusted Life Years/ 16467
87 quality adjusted life.tw. 18465
88 (qaly$ or qald$ or qale$ or qtime$).tw. 15447
89 disability adjusted life.tw. 6108
90 daly$.tw. 5477
91 Health Status Indicators/ 24123
92 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. 31787
93 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. 2759
94 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. 8059
95 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. 41
96 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. 467
97 (euroqol or euro qol or eq5d or eq 5d).tw. 18170
98 (qol or hql or hqol or hrqol).tw. 78568
99 (hye or hyes).tw. 77
100 health$ year$ equivalent$.tw. 40
101 utilit$.tw. 286143
102 (hui or hui1 or hui2 or hui3).tw. 2089
103 disutili$.tw. 681
104 rosser.tw. 111
105 quality of wellbeing.tw. 52
106 quality of well-being.tw. 505
107 qwb.tw. 219
108 willingness to pay.tw. 9349
109 standard gamble$.tw. 916
110 time trade off.tw. 1442
111 time tradeoff.tw. 268
112 tto.tw. 1478
113 or/83-112 798309
114 82 or 113 2204200
115 56 and 114 370
116 limit 115 to ed=20000101-20240606 285
117 limit 115 to dt=20000101-20240606 368
118 116 or 117 368
119 limit 118 to english language 355
120 Animals/ not (Animals/ and Humans/) 5194075
121 119 not 120 352
122 limit 121 to (case reports or clinical conference or comment or editorial or letter) 16

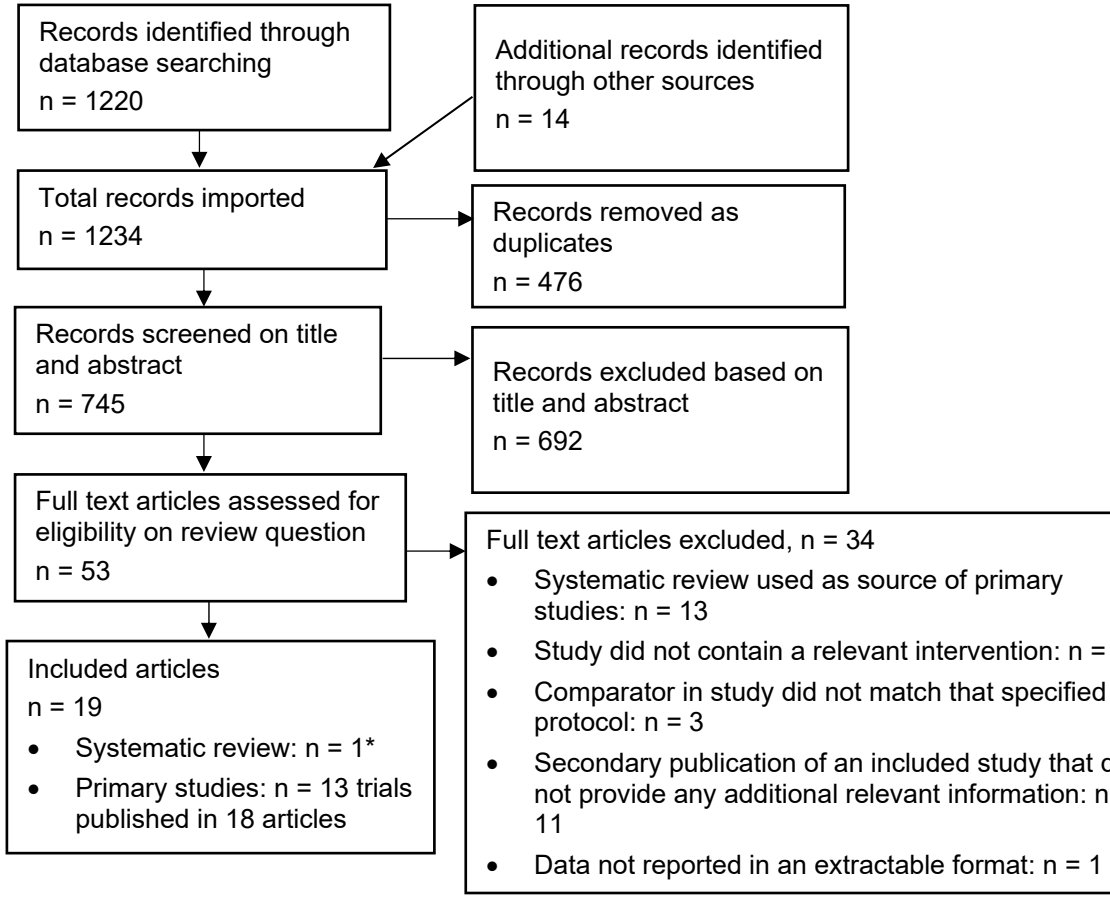
Searches		
123	121 not 122	336

1

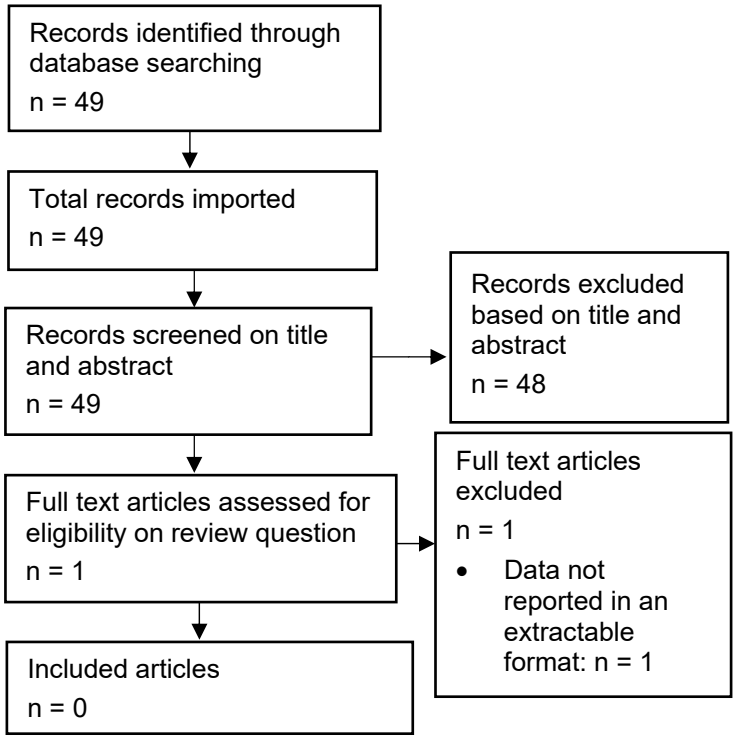
2

Appendix C – Effectiveness evidence study selection

Main study selection



Study selection based on rerun search



* This refers to the Cochrane review by Mason et al. (2023) which was the systematic review that met most of the inclusion criteria listed in this review protocol

1 Appendix D – Effectiveness evidence

2 Systematic review

3 Mason, 2023

Bibliographic Reference	Mason, Sofia Re; Willson, Melina L; Egger, Sam J; Beith, Jane; Dear, Rachel F; Goodwin, Annabel; Platinum-based chemotherapy for early triple-negative breast cancer.; The Cochrane database of systematic reviews; 2023; vol. 9; cd014805

4 Study Characteristics

Study design	Systematic review
Study details	Dates searched The latest search date was 4 April 2022 Databases searched • The Cochrane Breast Cancer Group's (CBCG's) Specialised Register • Cochrane Central Register of Controlled Trials (CENTRAL) • MEDLINE OvidSP • Embase OvidSP • World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal • ClinicalTrials.gov • Sources of funding • NHMRC Clinical Trials Centre, University of Sydney, Australia
Inclusion criteria	**Types of studies** Randomised controlled trials (RCTs) examining platinum-based chemotherapy for neoadjuvant or adjuvant treatment for people with early TNBC. This included trials which added a platinum-based chemotherapy to another standard chemotherapy regimen, or compared a platinum regimen to a nonplatinum regimen. To be included, studies must have reported their findings for participants with TNBC separately from other participants, or only included less than 20% (a minority is less than 50%) of participants with non-TNBC. **Types of participants** Participants aged 18 years or older with early TNBC, defined as breast cancers with disease isolated to the breast and axillary lymph nodes that lack expression of the oestrogen receptor and progesterone receptor (as defined by the trial), and negative for human epidermal receptor 2 (HER2; negative with in situ hybridisation testing; 0 to 1+ with immunohistochemistry (IHC); or 2+ with IHC and negative with fluorescence in situ hybridisation). Trials were included from all study locations, and participants of all ethnicities.
Exclusion criteria	**Types of studies** Studies not reporting their findings for participants with TNBC separately from other participants, or included 20% or more participants with non-TNBC. **Types of participants** Trials that did not assess women for HER2 status.

Intervention(s)	Platinum chemotherapy Any chemotherapy regimen that contained platinum chemotherapy. Non-platinum chemotherapy Regimens without platinum chemotherapy.
Outcome(s)	Disease-free survival Time-to-event outcome defined as time from surgery (in neoadjuvant setting) or randomisation (in adjuvant setting) to first date of a local, regional or distant relapse; diagnosis of a second primary cancer; or death from any cause. Similar outcomes were included, such as progression-free survival and time-to-progression in this section. Overall survival Time-to-event outcome defined as the time from randomisation or study entry until death from any cause. Pathological complete response Dichotomous outcome defined as no invasive carcinoma in the breast or axillary lymph nodes (ypT0/isypN0 TNM [tumour, node, metastasis] staging; Edge 2010) after neoadjuvant therapy. Completion of regimens Dichotomous outcomes assessed by absence of delay in treatment or dose reductions, or both, or early cessation of treatment. Any grade III/IV toxicity Related to chemotherapy (dichotomous outcomes). Quality of life Authors stated that quality of life information is typically not collected in these types of trials and that they aimed to report any quality of life data as measured by the many validated tools available to trialists, and at all reported time points.
Number of studies included in the systematic review	20
Studies from the systematic review that are relevant for use in the current review	**Neoadjuvant studies** • ADAPT-TN (Gluz et al. 2018) • Ando et al. 2014 • BrighTNess (Loibl et al. 2018) • CALGB 40603 (Sikov et al. 2015) • GEICAM 2006-03 (Alba et al. 2012) • GeparOcto (Schneeweiss et al. 2019) • GeparOLA (Fasching et al. 2021) • GeparSixto (von Minckwitz et al. 2014) • Gigolaeva et al. 2019 • NeoCART (Zhang et al. 2022) • Zhang et al. 2016 • Zhao et al. 2014

Studies from the systematic review that are not relevant for use in the current review	**Neoadjuvant studies without a taxane on one of both arms:** • INFORM (Tung et al. 2020) • I-SPY2 (Rugo et al. 2016) • TBCRC 030 (Mayer et al. 2020) **Neoadjuvant and adjuvant studies (only pooled data reported)** • Wu et al. 2018 **Adjuvant studies** • Li et al. 2020 • Nasr et al. 2015 • PATTERN (Yu et al. 2020) • Zheng et al. 2022

Additional comments	We only extracted early cessation of treatment from the data reported by Mason et al. (2023) as completion of treatment regimens.
	The following data was extracted from Mason et al. (2023) for each study:
	• Disease-free survival: ADAPT-TN, Ando et al. 2014, BrighTNess, CALGB 40603, GeparSixto, NeoCART, Zhang et al. 2016
	• Overall survival: ADAPT-TN, Ando et al. 2014, BrighTNess, CALGB 40603, GeparSixto, NeoCART, Zhang et al. 2016
	• Pathological complete response: ADAPT-TN, Ando et al. 2014, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, GeparOLA, GeparSixto, Gigolaeva et al. 2019, NeoCART, Zhang et al. 2016, Zhao et al. 2014
	• Early cessation of treatment: ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, GeparSixto, NeoCART, Zhang et al. 2016
	• Neutropenia: ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NeoCART, Zhang et al. 2016, Zhao et al. 2014
	• Febrile neutropenia: ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto
	• Anaemia: ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NeoCART, Zhao et al. 2014
	• Thrombocytopenia: ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NeoCART, Zhang et al. 2016, Zhao et al. 2014
	• Neuropathy: ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, Zhang et al. 2016
	• Nausea: ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NeoCART, Zhao et al. 2014
	• Renal impairment: Zhao et al. 2014
	• Treatment-related death: ADAPT-TN, Ando et al. 2014, BrighTNess, CALGB 40603, Zhang et al. 2016, Zhao et al. 2014
	• Subgroup data for DFS, OS and pCR:
	  ○ BRCA mutation status: BrighTNess (DFS and pCR), GeparOcto (pCR), GeparOLA (pCR), GeparSixto (DFS and pCR)
	  ○ Lymph node status: BrighTNess (pCR), Zhang et al. 2016 (pCR)
	  ○ Backbone therapy: ADAPT-TN (DFS, OS, pCR), Ando et al. 2014 (DFS, OS, pCR), BrighTNess (DFS, OS, pCR), CALGB 40603 (DFS, OS, pCR), GEICAM 2006-03 (pCR), GeparOcto (pCR), GeparOLA (pCR), GeparSixto (DFS, OS, pCR), Gigolaeva et al. 2019 (pCR), NeoCART

		(DFS, OS, pCR), Zhang et al. 2016 (DFS, OS, pCR), Zhao et al. 2014 (pCR) ○ Anthracycline content of chemotherapy: ADAPT-TN (DFS, OS, pCR), Ando et al. 2014 (DFS, OS, pCR), BrighTNess (DFS, OS, pCR), CALGB 40603 (DFS, OS, pCR), GEICAM 2006-03 (pCR), GeparOcto (pCR), GeparOLA (pCR), GeparSixto (DFS, OS, pCR), Gigolaeva et al. 2019 (pCR), NeoCART (DFS, OS, pCR), Zhang et al. 2016 (DFS, OS, pCR) , Zhao et al. 2014 (pCR)

Study arms

Platinum chemotherapy (N = 1658)

Non-platinum chemotherapy (N = 1425)

Critical appraisal - ROBIS checklist

Overall risk of bias	Low	
Applicability as a source of data	Fully applicable	The Cochrane systematic review included studies that were relevant to the NICE review (neoadjuvant chemotherapy).

Randomised controlled trials included in Mason et al. 2023

For RCTs that were included in Mason et al. (2023) see the evidence tables provided in that review for study characteristics and full risk of bias assessments.

Table 17 Overall risk of bias and applicability for studies included in Mason et al. 2023

Overall risk of bias and applicability for the relevant studies from the Cochrane review was determined by NICE (see section 1.1.3 Methods and process for more details).

Alba, 2012 (GEICAM 2006-03)

Bibliographic Reference	Alba E; Chacon JI; Lluch A; Anton A; Estevez L; Cirauqui B; Carrasco E; Calvo L; Segui MA; Ribelles N; Alvarez R; Sanchez-Muñoz A; Sanchez R; Garcia-Asenjo JA; Rodriguez-Martin C; Escudero MJ; Albanell J; A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006-03, multicenter study.; Breast cancer research and treatment; 2012; vol. 136 (no. 2)

Critical appraisal Cochrane Risk of Bias tool Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low (From Mason:

Section	Question	Answer
		This text was used to support low RoB: bias was low risk apart from random sequence generation and blinding of participants and personnel which were unclear RoB (these 2 issues were not considered to be the most important issues for this review).)
Overall bias and Directness	Overall Directness	Partially applicable (Restricted to patients with basal like breast cancer).

1 Ando, 2014

Bibliographic Reference	Ando M; Yamauchi H; Aogi K; Shimizu S; Iwata H; Masuda N; Yamamoto N; Inoue K; Ohono S; Kuroi K; Hamano T; Sukigara T; Fujiwara Y; Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression.; Breast cancer research and treatment; 2014; vol. 145 (no. 2)

2 Critical appraisal Cochrane Risk of Bias tool Normal RCT

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low (From Mason This text was used to support low RoB: Participants and personnel were aware of treatment allocation. This may have been associated with some performance bias but it was not judged to be of serious concern given types of outcomes collected. The rest of bias was low risk.)
Overall bias and Directness	Overall Directness	Directly applicable

3 Fasching, 2021 (GeparOLA)

Bibliographic Reference	Fasching, P A; Link, T; Hauke, J; Seither, F; Jackisch, C; Klare, P; Schmatloch, S; Hanusch, C; Huober, J; Stefek, A; Seiler, S; Schmitt, W D; Uleer, C; Doering, G; Rhiem, K; Schneeweiss, A; Engels, K; Denkert, C; Schmutzler, R K; Hahnen, E; Untch, M; Burchardi, N; Blohmer, J-U; Loibl, S; Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study).; Annals of oncology : official journal of the European Society for Medical Oncology; 2021; vol. 32 (no. 1); 49-57

1 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (From Mason This text was used to support moderate RoB: Selective reporting: Outcomes prespecified in the trial registry record were reported in the trial publication. Important outcomes of DFS and OS not reported but expected that information would have been collected. The rest of bias was low risk or unclear risk (blinding of participants and personnel).)
Overall bias and Directness	Overall Directness	Directly applicable

2 **Gigolaeva, 2019**

Bibliographic Reference	Gigolaeva, L; Krivorotko, P; Zhiltsova, E; Dashyan, G; Chadjimatova, S; Pesotckiy, R; Emelyanov, A; Semiglazov, V; Neoadjuvant chemotherapy regimens for triple negative breast cancer patients; Breast (Edinburgh, Scotland); 2019; vol. 44; 70

3 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (From Mason This text was used to support high RoB: all bias was unclear risk, main reason was that there was not enough information in abstract.)
Overall bias and Directness	Overall Directness	Directly applicable

4 **Gluz, 2018 (ADAPT-TN)**

Bibliographic Reference	Gluz O; Nitz U; Liedtke C; Christgen M; Grischke EM; Forstbauer H; Braun M; Warm M; Hackmann J; Uleer C; Aktas B; Schumacher C; Bangemann N; Lindner C; Kuemmel S; Clemens M; Potenberg J; Staib P; Kohls A; von Schumann R; Kates R; Kates R; Schumacher J; Wuerstlein R; Kreipe HH; Harbeck N; Comparison of Neoadjuvant Nab-Paclitaxel+Carboplatin vs Nab-Paclitaxel+Gemcitabine in Triple-Negative Breast Cancer: Randomized WSG-ADAPT-TN Trial Results.; Journal of the National Cancer Institute; 2018; vol. 110 (no. 6)

5 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (From Mason This text was used to support moderate RoB: Incomplete outcome data: CONSORT diagram showed that 5/336 randomised participants did not

Section	Question	Answer
		receive treatment and were excluded from analysis. Reasons for exclusions were detailed, including consent withdrawn, and violation of inclusion criteria. Additionally, pCR results for 12 participants were not reported. The rest of bias was low risk or unclear risk (random sequence generation; blinding of participants and personnel).)
Overall bias and Directness	Overall Directness	Directly applicable

1 **Loibl, 2018 (BrighTNess)**

Bibliographic Reference Loibl, Sibylle; O'Shaughnessy, Joyce; Untch, Michael; Sikov, William M; Rugo, Hope S; McKee, Mark D; Huober, Jens; Golshan, Mehra; von Minckwitz, Gunter; Maag, David; Sullivan, Danielle; Wolmark, Norman; McIntyre, Kristi; Ponce Lorenzo, Jose J; Metzger Filho, Otto; Rastogi, Priya; Symmans, W Fraser; Liu, Xuan; Geyer, Charles E Jr; Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial.; The Lancet. Oncology; 2018; vol. 19 (no. 4); 497-509

2 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low (From Mason All bias was low risk.)
Overall bias and Directness	Overall Directness	Directly applicable

3 **Schneeweiss, 2019 (GeparOcto)**

Bibliographic Reference Schneeweiss A; Möbus V; Tesch H; Hanusch C; Denkert C; Lübbe K; Huober J; Klare P; Kümmel S; Untch M; Kast K; Jackisch C; Thomalla J; Ingold-Heppner B; Blohmer JU; Rezai M; Frank M; Engels K; Rhiem K; Fasching PA; Nekljudova V; von Minckwitz G; Loibl S; Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto-GBG 84): A randomised phase III trial.; European journal of cancer (Oxford, England : 1990); 2019; vol. 106

4 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (From Mason This text was used to support moderate RoB: Incomplete outcome data: CONSORT diagram indicates reasons for exclusions across both arms within a higher proportion discontinuing treatment in the platinum arm. Only those who received treatment were included in the analyses. The

Section	Question	Answer
		rest of bias was low risk or unclear risk (blinding of participants and personnel).)
Overall bias and Directness	Overall Directness	Directly applicable

1 **Sikov, 2015 (CALGB 40603)**

Bibliographic Reference	Sikov WM; Berry DA; Perou CM; Singh B; Cirrincione CT; Tolaney SM; Kuzma CS; Pluard TJ; Somlo G; Port ER; Golshan M; Bellon JR; Collyar D; Hahn OM; Carey LA; Hudis CA; Winer EP; Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance).; Journal of clinical oncology : official journal of the American Society of Clinical Oncology; 2015; vol. 33 (no. 1)

2 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (From Mason This text was used to support moderate RoB: Incomplete outcome data: CONSORT diagram showed that 11/454 participants who were randomised but did not receive treatment were not included in the efficacy analysis. Reasons for exclusions were not detailed. The rest of bias was low risk or unclear risk (random sequence generation; blinding of participants and personnel).)
Overall bias and Directness	Overall Directness	Directly applicable

3 **von Minckwitz, 2014 (GeparSixto)**

Bibliographic Reference	von Minckwitz G; Schneeweiss A; Loibl S; Salat C; Denkert C; Rezai M; Blohmer JU; Jackisch C; Paepke S; Gerber B; Zahm DM; Kümmel S; Eidtmann H; Klare P; Huober J; Costa S; Tesch H; Hanusch C; Hilfrich J; Khandan F; Fasching PA; Sinn BV; Engels K; Mehta K; Nekljudova V; Untch M; Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial.; The Lancet. Oncology; 2014; vol. 15 (no. 7)

4 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate (From Mason

Section	Question	Answer
		This text was used to support moderate RoB: Incomplete outcome data: CONSORT diagram showed that 7/595 patients (6 patients in the comparator arm and 1 patient in the intervention arm) did not proceed with treatment due to patient and investigator decisions. Although the numbers were not equal between groups, the reasons were stated. The trial publication stated they conducted an intention-to-treat analysis, however, it used a modified intention-to-treat analysis. Number of exclusions were small and not considered as a concern. The rest of bias was low risk or unclear risk (blinding of participants and personnel).)
Overall bias and Directness	Overall Directness	Directly applicable

1 **Zhang, 2016**

Bibliographic Reference	Zhang P; Yin Y; Mo H; Zhang B; Wang X; Li Q; Yuan P; Wang J; Zheng S; Cai R; Ma F; Fan Y; Xu B; Better pathologic complete response and relapse-free survival after carboplatin plus paclitaxel compared with epirubicin plus paclitaxel as neoadjuvant chemotherapy for locally advanced triple-negative breast cancer: a randomized phase 2 trial.; Oncotarget; 2016; vol. 7 (no. 37)

2 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (From Mason This text was used to support high RoB: Allocation concealment: No information provided about what occurred at single site. Incomplete outcome data: CONSORT diagram outlined reasons for exclusions. For time-to-event outcomes, only those participants who had surgery were included in the analysis (not all those randomised) and for toxicity assessment, all randomised participants were included in analysis irrespective of whether they received treatment or not. There was some concern regarding the analytical approach used when reporting results. The rest of bias was low risk or unclear risk (random sequence generation; blinding of participants and personnel).)
Overall bias and Directness	Overall Directness	Directly applicable

3 **Zhang, 2022 (NeoCART)**

Bibliographic Reference	Zhang, L.; Wu, Z.-Y.; Lin, Y.; Liu, Z.; Cao, Y.; Zhang, G.; Gao, H.-F.; Yang, M.; Yang, C.-Q.; Zhu, T.; Cheng, M.-Y.; Ji, F.; Li, J.; Wang, K.; Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): Results from a multicenter, randomized controlled, open-label phase II trial; International Journal of Cancer; 2022; vol. 150 (no. 4); 654-662

1 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low (From Mason This text was used to support low RoB: bias was low risk apart from blinding of participants and personnel which was unclear RoB (this issue was not considered to be one of the most important issues for this review).)
Overall bias and Directness	Overall Directness	Directly applicable

2 **Zhao, 2014**

Bibliographic Reference	Zhao, Yue; Li, Jin-feng; Chu, Gui-wei; Neoadjuvant chemotherapy regimens for patients with triple-negative breast cancer:TE versus TC; Journal of Practical Oncology; 2014; (no. 6); 576-579

3 **Critical appraisal Cochrane Risk of Bias tool Normal RCT**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (From Mason This text was used to support high RoB: all bias was unclear risk apart from selective reporting which was low RoB.)
Overall bias and Directness	Overall Directness	Directly applicable

4 **Randomised controlled trials not included in Mason et al. 2023**

5 **de Padua Souza, 2023**

Bibliographic Reference	de Padua Souza, Cristiano; Carneiro, Ana Suellen Barroso; de Oliveira Lessa, Ana Cecilia; Lacerda, Domicio Carvalho; Paiva, Carlos Eduardo; Zorzetto, Marina Moreira Costa; de Freitas, Ana Julia Aguiar; Santana, Iara Viana Vidigal; de Oliveira, Marco Antonio; Palmero, Edenir Inez; Marques, Marcia Maria Chiquitelli; Reinert, Tomas; Neoadjuvant carboplatin in triple-negative breast cancer: results from NACATRINE, a randomized phase II clinical trial.; Breast cancer research and treatment; 2023; vol. 202 (no. 1); 57-65

6 **Study details**

Trial registration number and/or trial name	NACATRINE / NCT02978495
Study type	Randomised controlled trial (RCT)

Study location	Brazil
Study setting	Hospital
Study dates	2017 to 2021
Sources of funding	This clinical trial received funding from the Department of Science and Technology—DECIT, Brazilian Ministry of Health (Grant No. 879848/2018).
Inclusion criteria	Key eligibility criteria included patients more than 18 years old, with ECOG PS 0 or 1, adequate organ function with newly diagnosed stage II–III TNBC (ER < 1%, PR < 1%, and HER2 negative according to ASCO/CAP Guidelines in 2014 and no evidence of distant metastases. All patients had known germline BRCA1/2 mutational status. Bilateral TNBC should be confirmed by core biopsy in patients with bilateral tumours.
Exclusion criteria	Patients were excluded if they had a history of grade >/2 neuropathy, had previous treatment for breast cancer, and if pregnant or breastfeeding.
Intervention(s)	Chemotherapy protocol consisted of doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2) both intravenously (i.v.) once every 21 days for four cycles for all patients. Patients were then randomised for additional treatment with paclitaxel (80 mg/m2 i.v.) once every 7 days for 12 cycles with carboplatin AUC 1.5 once every 7 days for 12 cycles. Platinum agent: carboplatin.
Comparator	Chemotherapy protocol consisted of doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2) both intravenously (i.v.) once every 21 days for four cycles for all patients. Patients were then randomised for additional treatment with paclitaxel (80 mg/m2 i.v.) once every 7 days for 12 cycles without carboplatin. Same backbone: Yes
Outcome measures	Pathological complete response Defined as no invasive tumour in the breast and lymph nodes (ypT0ypN0). Overall survival Defined as the interval from random assignment to death from any reason. Disease-free survival Defined as the time from random assignment to invasive disease recurrence or death from any cause. Adherence to or completion of treatment regimens Permanent treatment discontinuation Breast conservation rate
Number of participants	146
Duration of follow-up	Median follow-up of 47.7 months
Loss to follow-up	None
Methods of analysis	Intention-to-treat analysis

Subgroups data	BRCA Type of platinum Chemotherapy backbone

1 **Study arms**

2 **Neoadjuvant regimen containing carboplatin (N = 73)**

3 **Neoadjuvant regimen without carboplatin (N = 73)**

4 **Characteristics**

5 **Arm-level characteristics**

Characteristic	Neoadjuvant regimen containing carboplatin (N = 73)	Neoadjuvant regimen without carboplatin (N = 73)
Age		
<50 years No of events	n = 50 ; % = 68.5	n = 52 ; % = 71.2
50+ No of events	n = 23 ; % = 31.5	n = 21 ; % = 28.8
Clinical stage (TNM) at baseline		
Stage II No of events	n = 24 ; % = 32.9	n = 25 ; % = 34.2
Stage III No of events	n = 49 ; % = 67.1	n = 48 ; % = 65.8
Tumour stage (T)		
cT1 No of events	n = 0 ; % = 0	n = 1 ; % = 1.3
cT2 No of events	n = 24 ; % = 32.9	n = 23 ; % = 31.5
cT3 No of events	n = 29 ; % = 39.7	n = 31 ; % = 42.5
cT4 No of events	n = 20 ; % = 27.4	n = 18 ; % = 24.7
Initial nodal status (N)		
cN0 No of events	n = 34 ; % = 46.6	n = 30 ; % = 41.1
cN+	n = 39 ; % = 53.4	n = 43 ; % = 58.9

Characteristic	Neoadjuvant regimen containing carboplatin (N = 73)	Neoadjuvant regimen without carboplatin (N = 73)
No of events		
BRCA status		
BRCA mutation No of events	n = 15 ; % = 20.5	n = 14 ; % = 19.2
wild type BRCA No of events	n = 58 ; % = 79.5	n = 59 ; % = 80.8
Tumour grade		
Grade 1 No of events	n = 2 ; % = 2.8	n = 2 ; % = 2.8
Grade 2 No of events	n = 20 ; % = 28.2	n = 29 ; % = 40.3
Grade 3 No of events	n = 49 ; % = 69	n = 41 ; % = 56.9

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

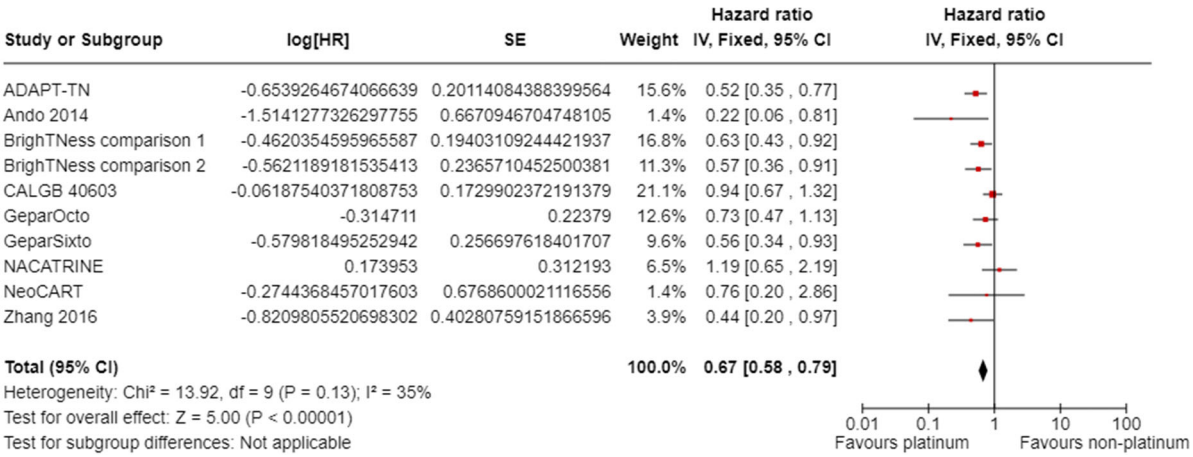
Overall risk of bias	Moderate	All bias was low risk apart from allocation concealment which was not described
Applicability as a source of data	Directly applicable	

Appendix E – Forest plots

Triple negative breast cancer analyses

Disease free survival

Figure 1 Disease free survival: main analysis



Study	Follow-up
ADAPT-TN	3 years
Ando 2014	6.6 years
BrighTNess	4.5 years
CALGB 40603	7.9 years
GeparOcto	4 years
GeparSixto	4 years
NACATRINE	3 years
NeoCART	3 years
Zhang 2016	4.5 years

Figure 2 Disease free survival subgroup analysis: gBRCA mutation status

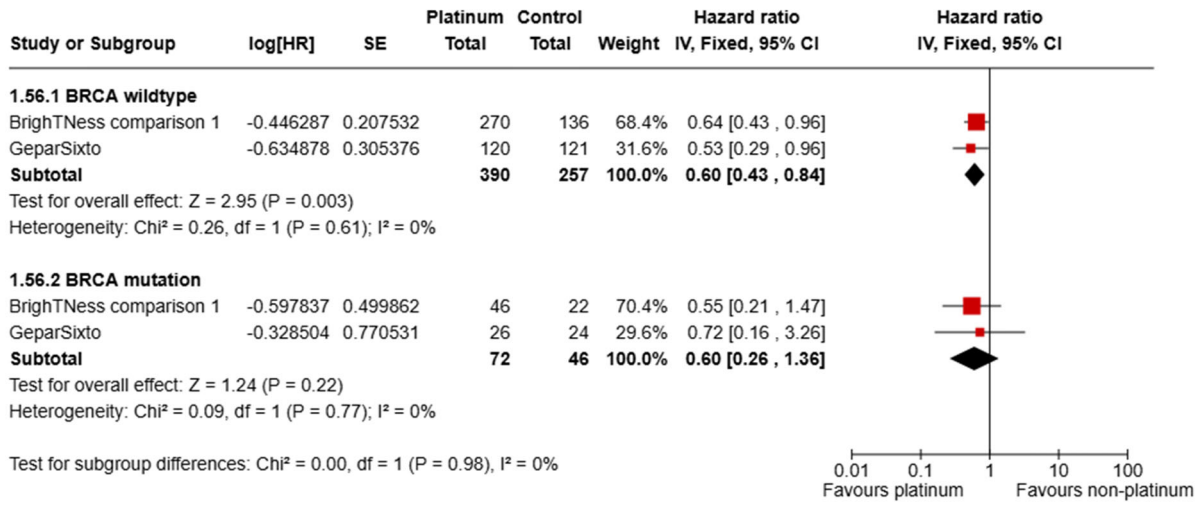


Figure 3 Disease free survival subgroup analysis: chemotherapy backbone (FE model for different backbone subgroup and pooled result)

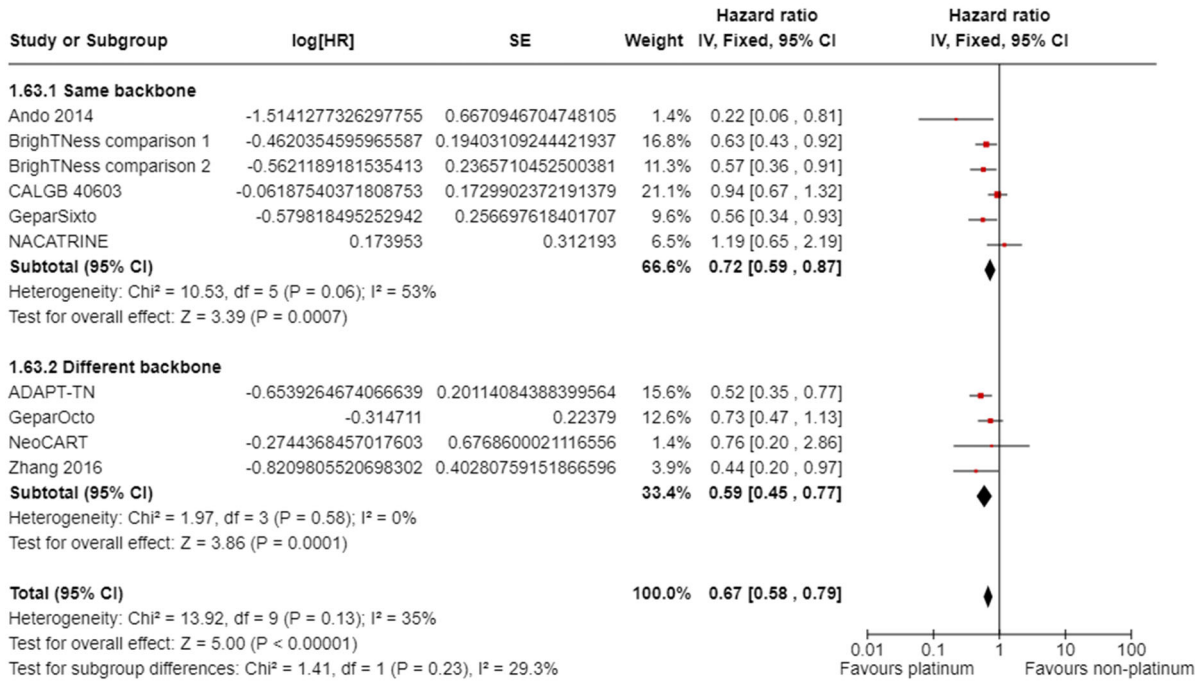


Figure 4 Disease free survival subgroup analysis: chemotherapy backbone RE model for same backbone subgroup

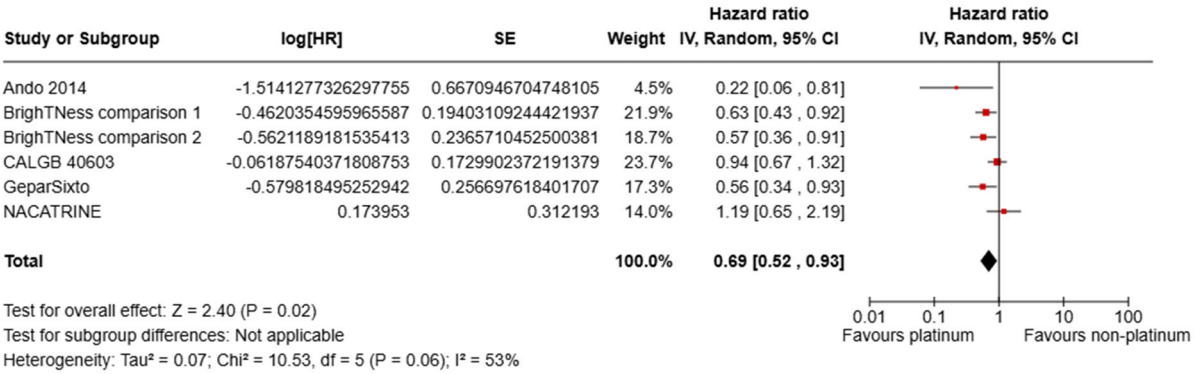


Figure 5 Disease free survival subgroup analysis: lymph node status

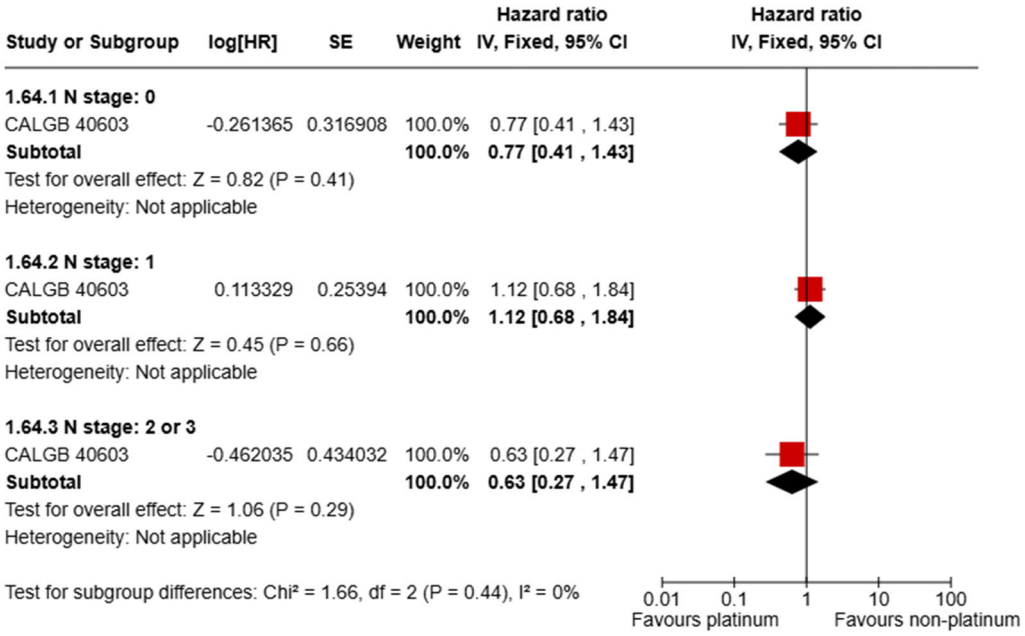


Figure 6 Disease free survival subgroup analysis: anthracycline content of platinum containing chemotherapy

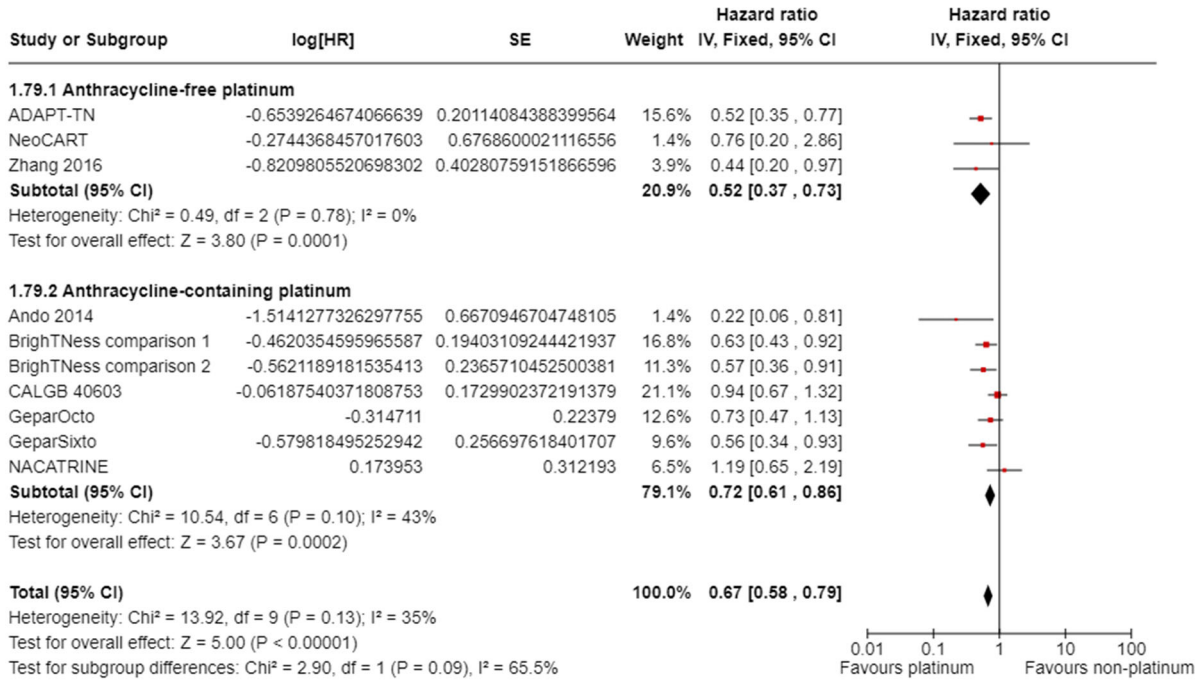
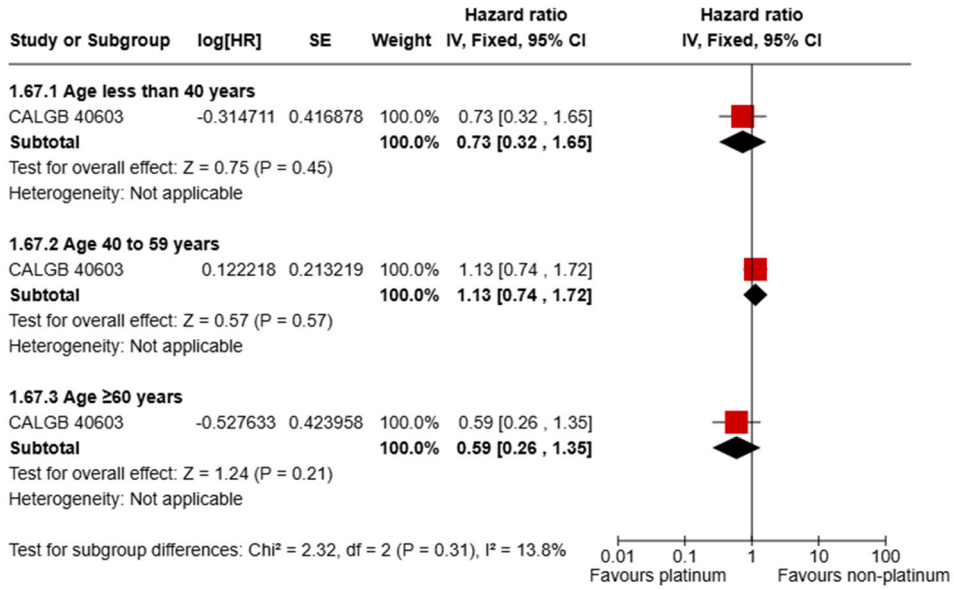
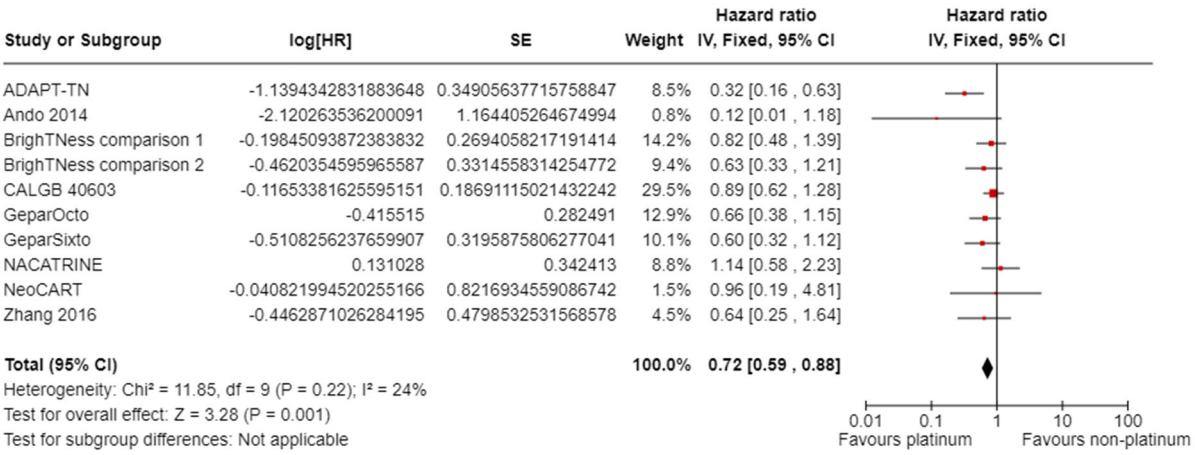


Figure 7 Disease free survival subgroup analysis: age



Overall survival

Figure 8 Overall survival main analysis



Study	Follow-up
ADAPT-TN	3 years
Ando 2014	6.6 years
BrighTNess	4.5 years
CALGB 40603	7.9 years
GeparOcto	4 years
GeparSixto	4 years
NACATRINE	3 years
NeoCART	3 years
Zhang 2016	4.5 years

Figure 9 Overall survival funnel plot

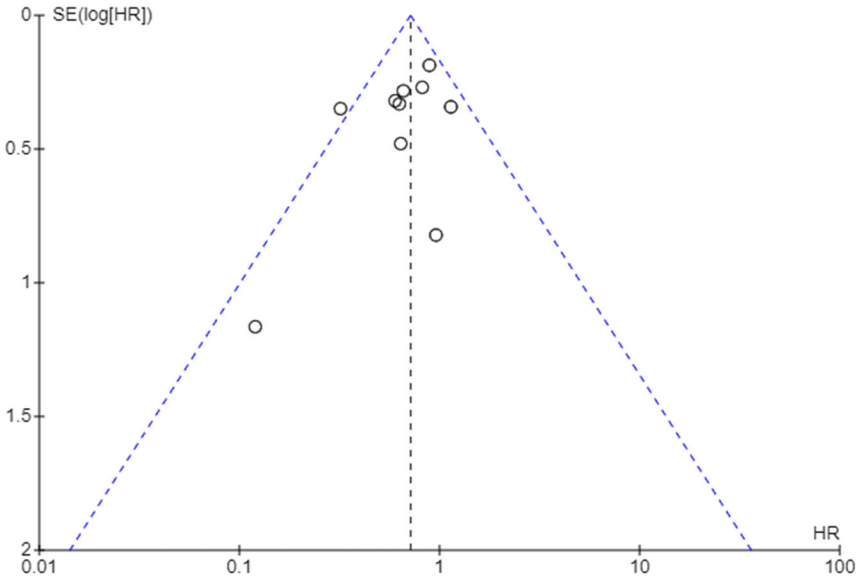


Figure 10 Overall survival subgroup analysis: gBRCA mutation status

No data available

Figure 11 Overall survival subgroup analysis: chemotherapy backbone

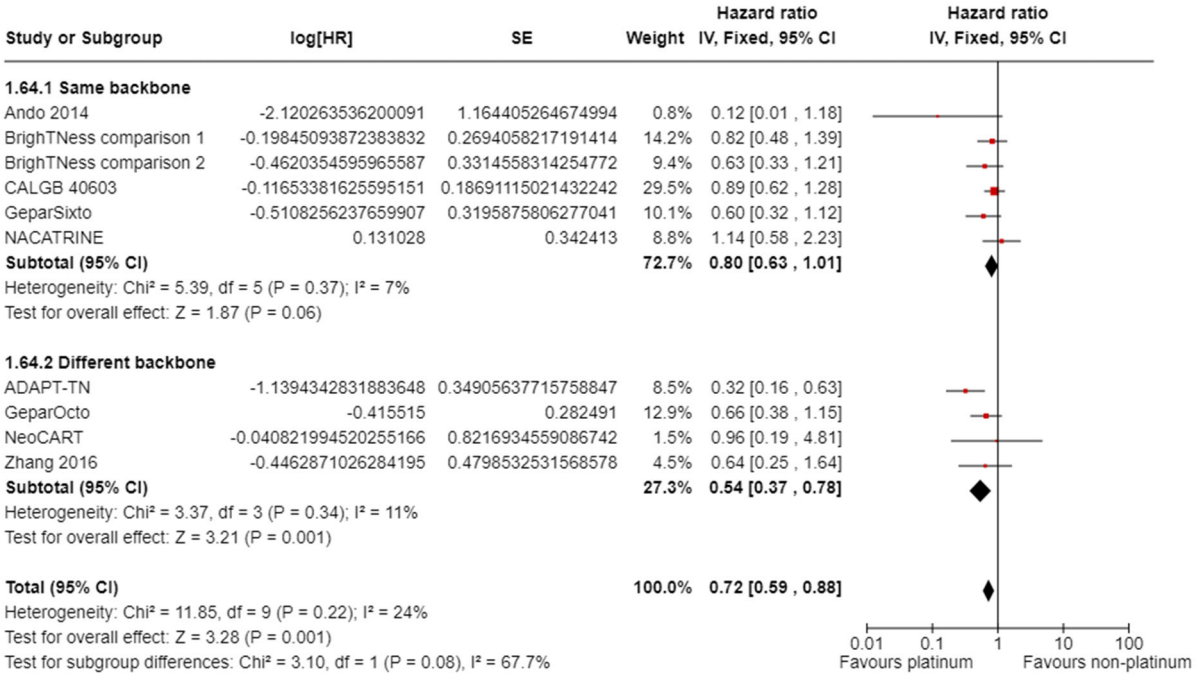


Figure 12 Overall survival subgroup analysis: lymph node status

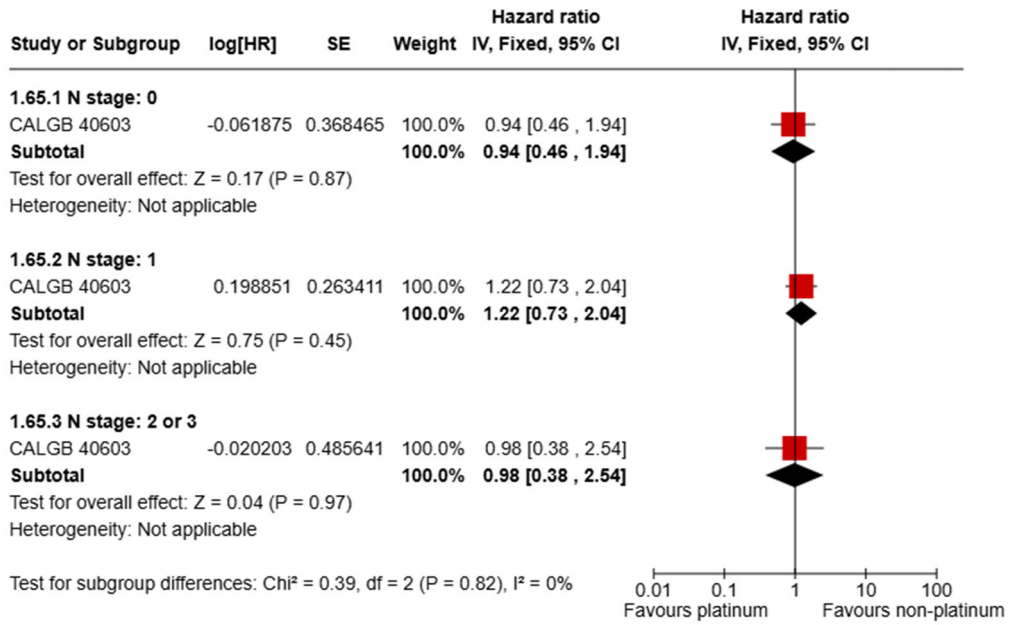


Figure 13 Overall survival subgroup analysis: anthracycline content of platinum containing chemotherapy

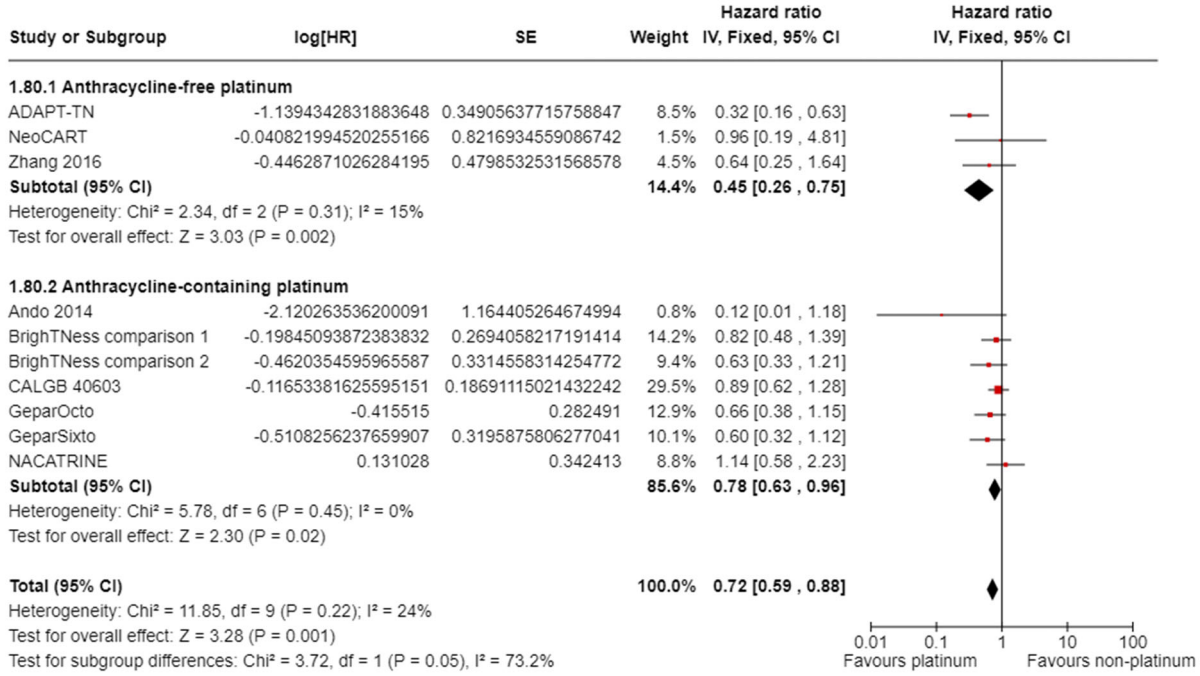
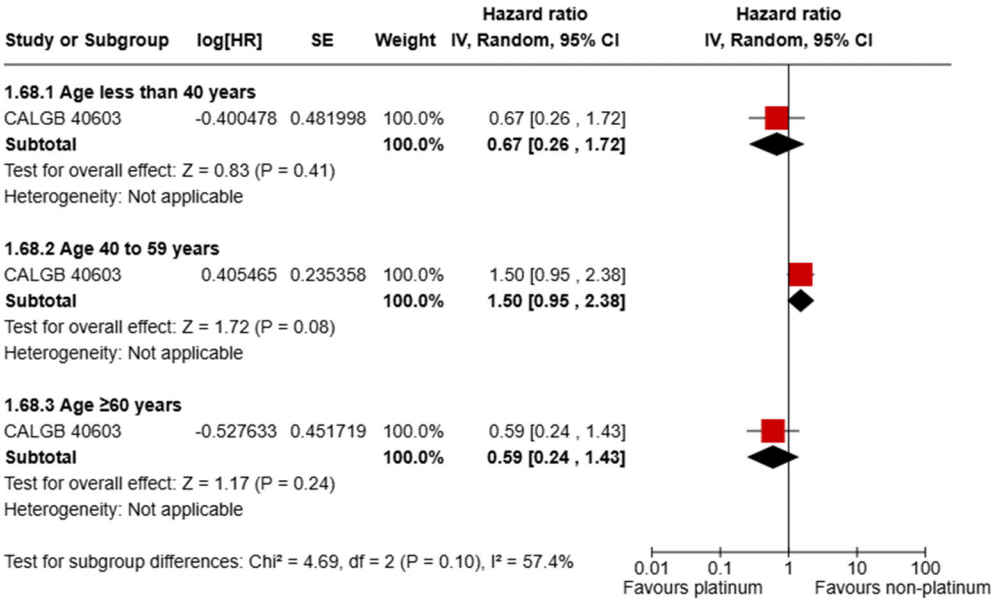


Figure 14 Overall survival subgroup analysis: age



Pathological complete response

Figure 15 Pathological complete response main analysis

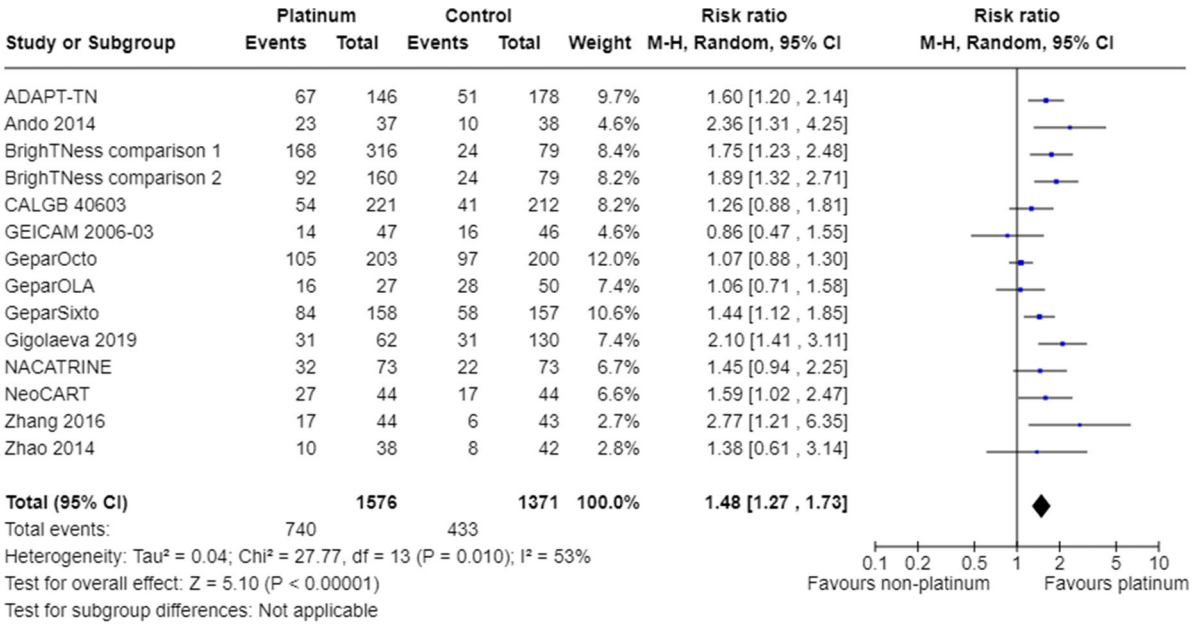


Figure 16 Pathological complete response funnel plot

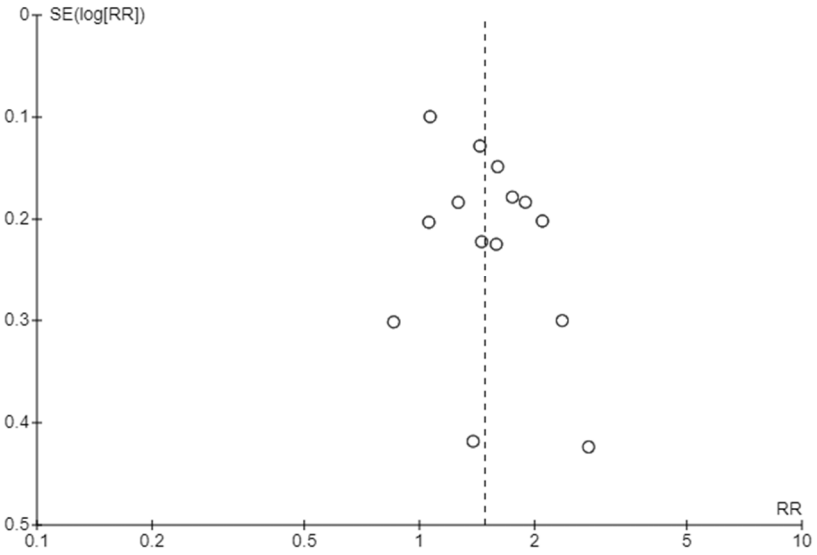


Figure 17 Pathological complete response subgroup analysis: gBRCA mutation status 1 (FE model)

Study or Subgroup	Platinum Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% CI
1.80.1 BRCA wildtype						
BrighTNess comparison 1	142	270	20	68	16.6%	1.79 [1.22 , 2.63]
BrighTNess comparison 2	80	136	20	68	13.8%	2.00 [1.35 , 2.97]
GeparOcto	77	164	72	160	37.8%	1.04 [0.82 , 1.32]
GeparOLA	6	15	13	23	5.3%	0.71 [0.35 , 1.45]
GeparSixto	66	120	44	121	22.7%	1.51 [1.14 , 2.01]
NACATRINE	12	18	8	22	3.7%	1.83 [0.96 , 3.48]
Subtotal		**723**		**462**	**100.0%**	**1.42 [1.23 , 1.64]**
Total events:	383		177			
Test for overall effect: Z = 4.70 (P < 0.00001)						
Heterogeneity: Chi² = 15.22, df = 5 (P = 0.009); I² = 67%						
1.80.2 BRCA mutation						
BrighTNess comparison 1	26	46	5	11	13.0%	1.24 [0.62 , 2.49]
BrighTNess comparison 2	12	24	4	11	8.8%	1.38 [0.57 , 3.31]
GeparOcto	26	36	22	34	36.3%	1.12 [0.81 , 1.54]
GeparOLA	10	12	15	26	15.2%	1.44 [0.95 , 2.19]
GeparSixto	17	26	16	24	26.7%	0.98 [0.66 , 1.46]
Subtotal		**144**		**106**	**100.0%**	**1.17 [0.95 , 1.44]**
Total events:	91		62			
Test for overall effect: Z = 1.48 (P = 0.14)						
Heterogeneity: Chi² = 1.99, df = 4 (P = 0.74); I² = 0%						
Test for subgroup differences: Chi² = 2.22, df = 1 (P = 0.14), I² = 54.9%						

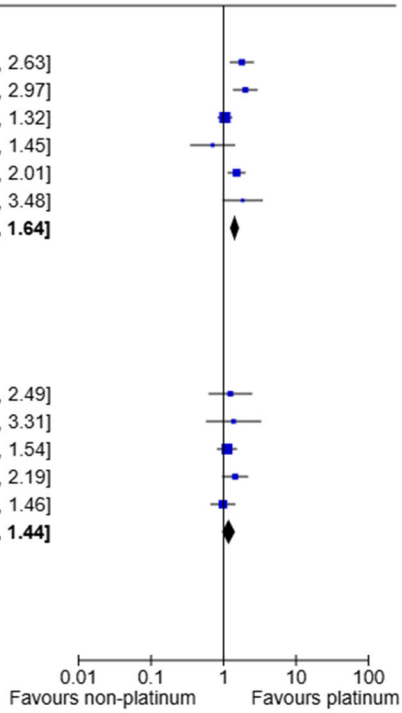


Figure 18 Pathological complete response subgroup analysis: gBRCA mutation status 1 (RE model for BRCA wildtype subgroup)

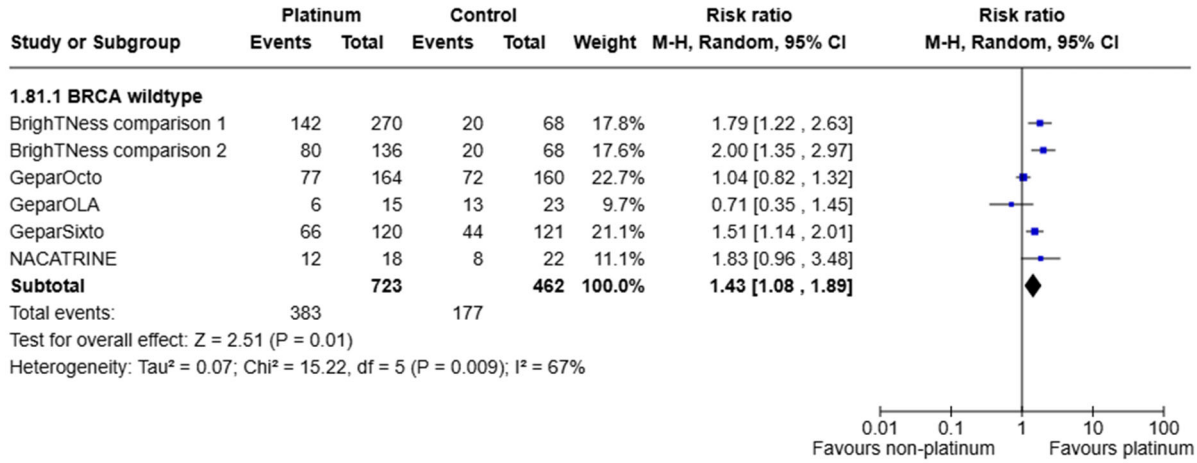


Figure 19 Pathological complete response subgroup analysis: gBRCA mutation status 2

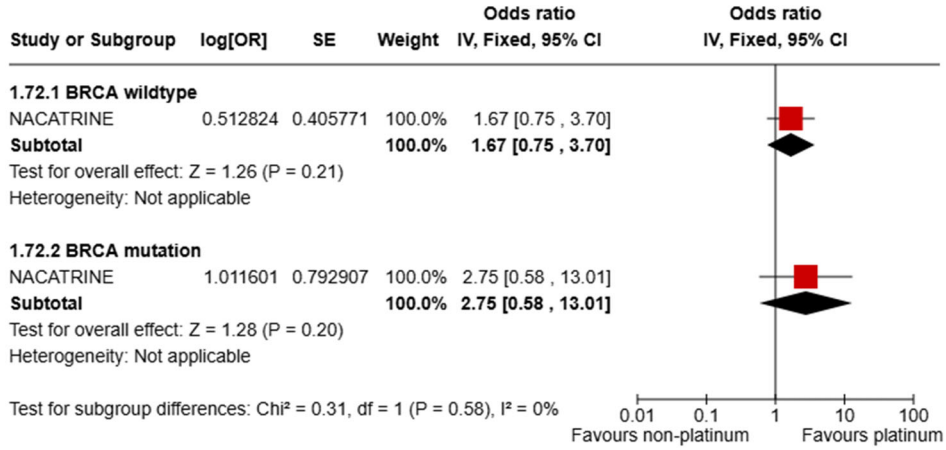


Figure 20 Pathological complete response subgroup analysis: backbone chemotherapy (RE model for different backbone subgroup and pooled result)

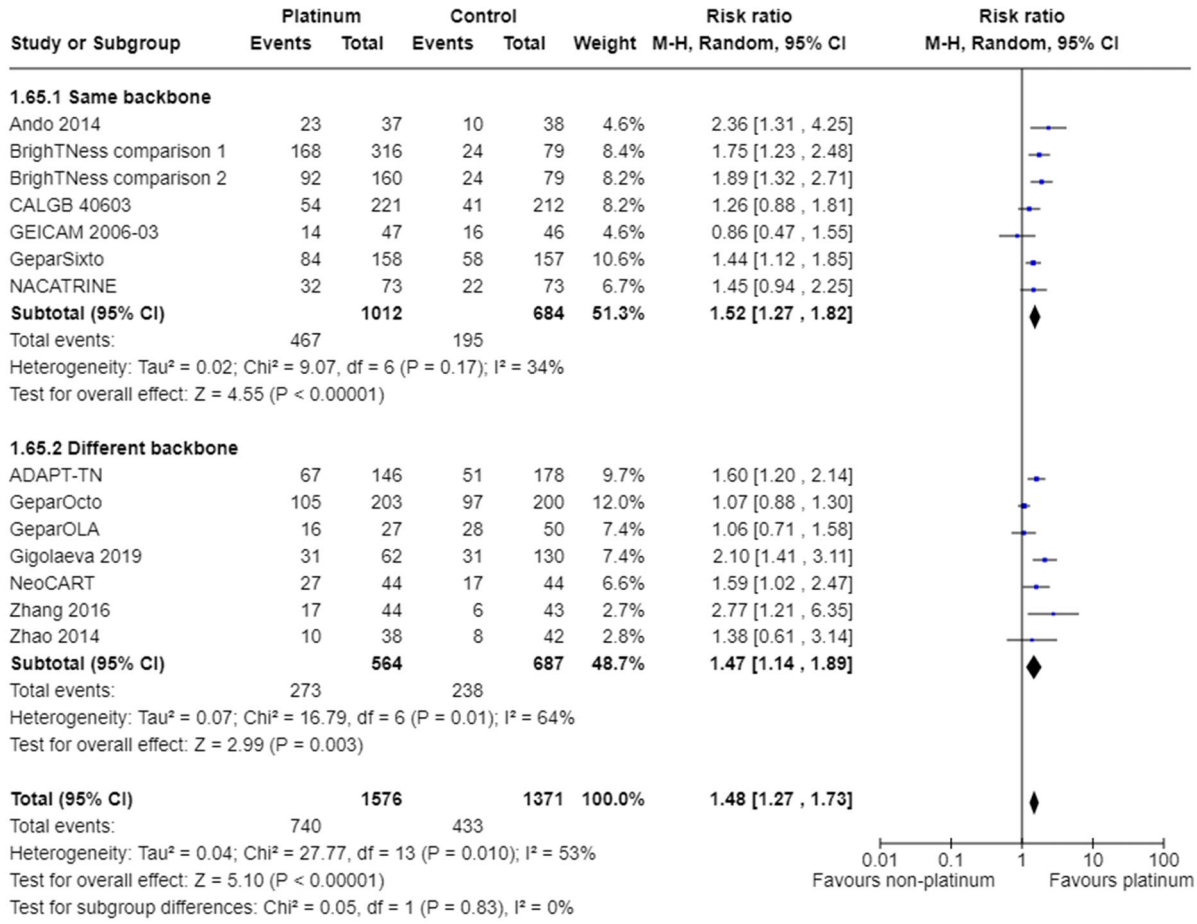


Figure 21 Pathological complete response subgroup analysis: backbone chemotherapy (FE model for same backbone subgroup)

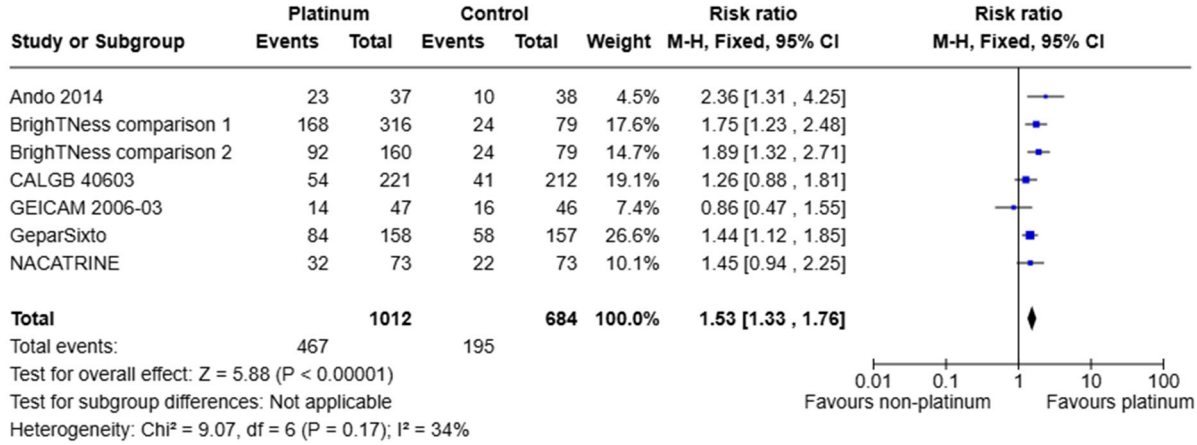


Figure 22 Pathological complete response subgroup analysis: lymph node status

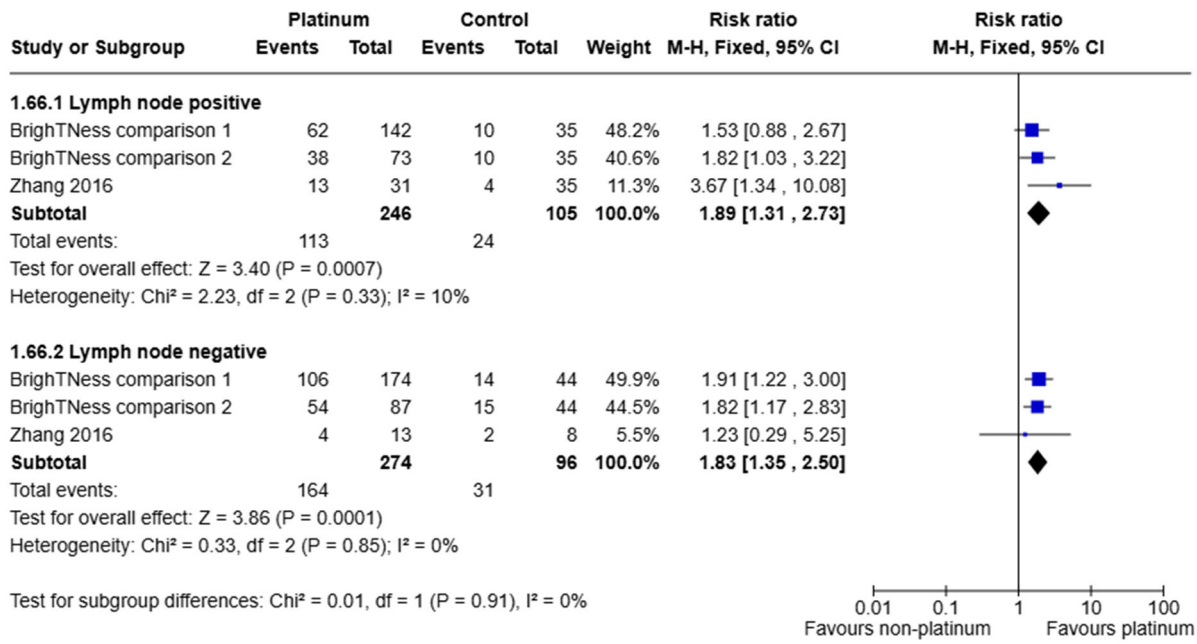


Figure 23 Pathological complete response subgroup analysis: anthracycline content of platinum containing chemotherapy (RE model for anthracycline-containing platinum subgroup and pooled result)

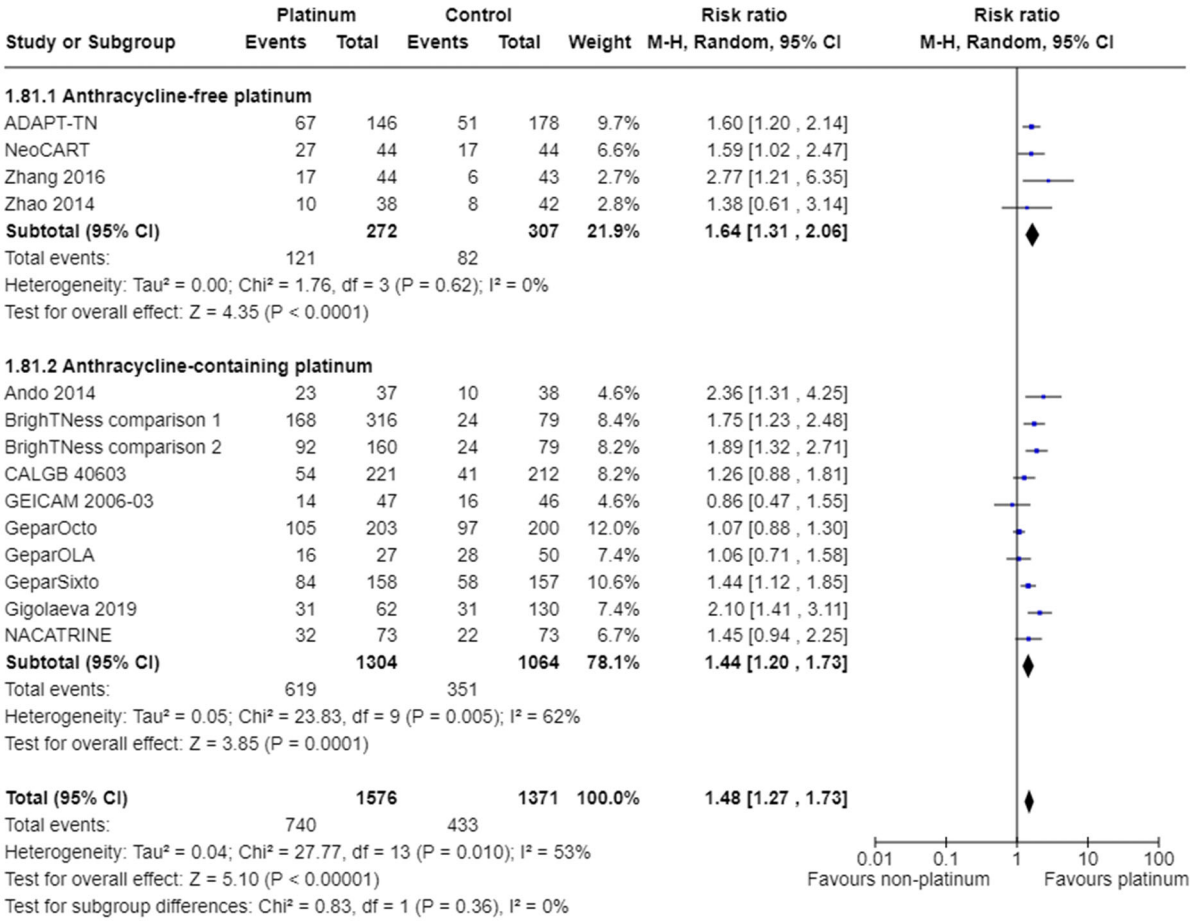


Figure 24 Pathological complete response subgroup analysis: FE model for anthracycline free-platinum containing chemotherapy

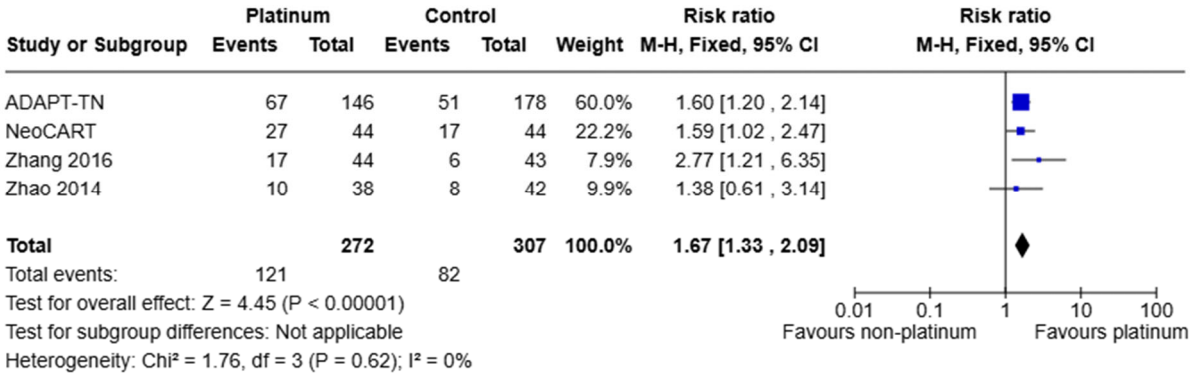
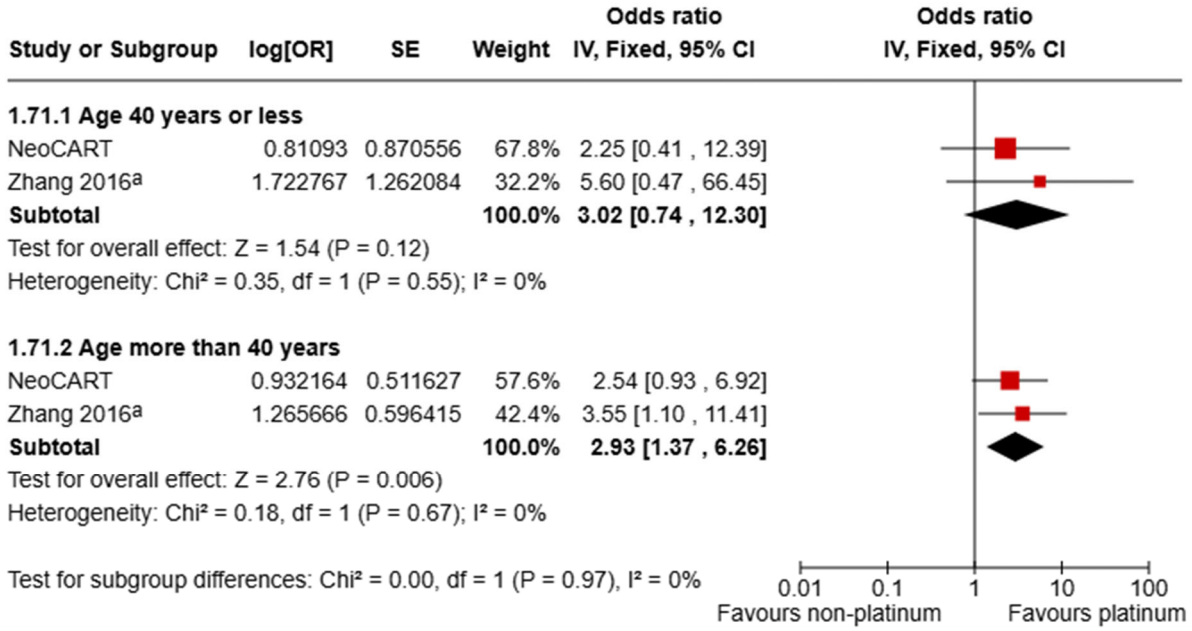


Figure 25 Pathological complete response subgroup analysis: age

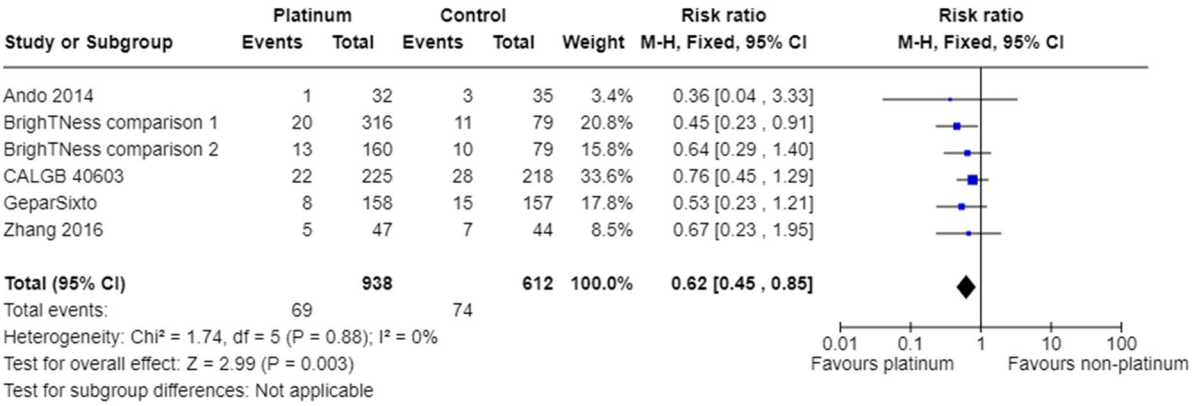


Breast cancer mortality

Figure 26 Breast cancer mortality

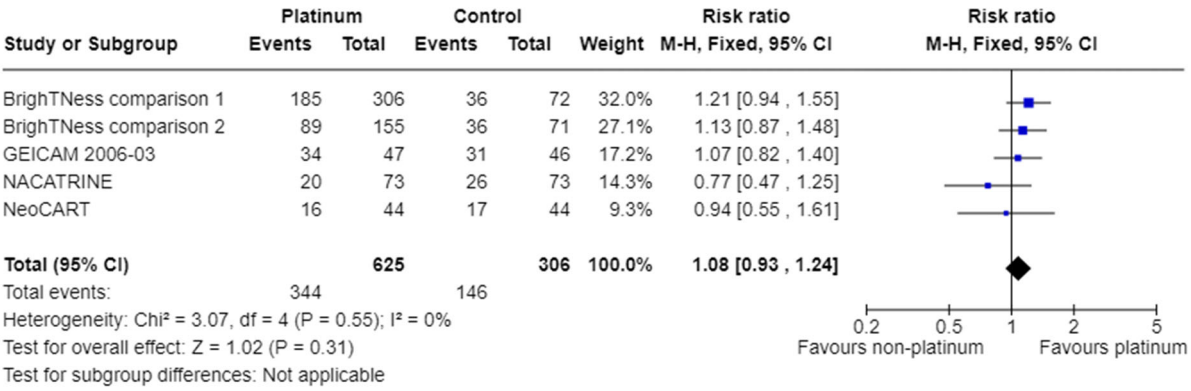
Local and/or locoregional recurrence

Figure 27 Local and/or locoregional recurrence



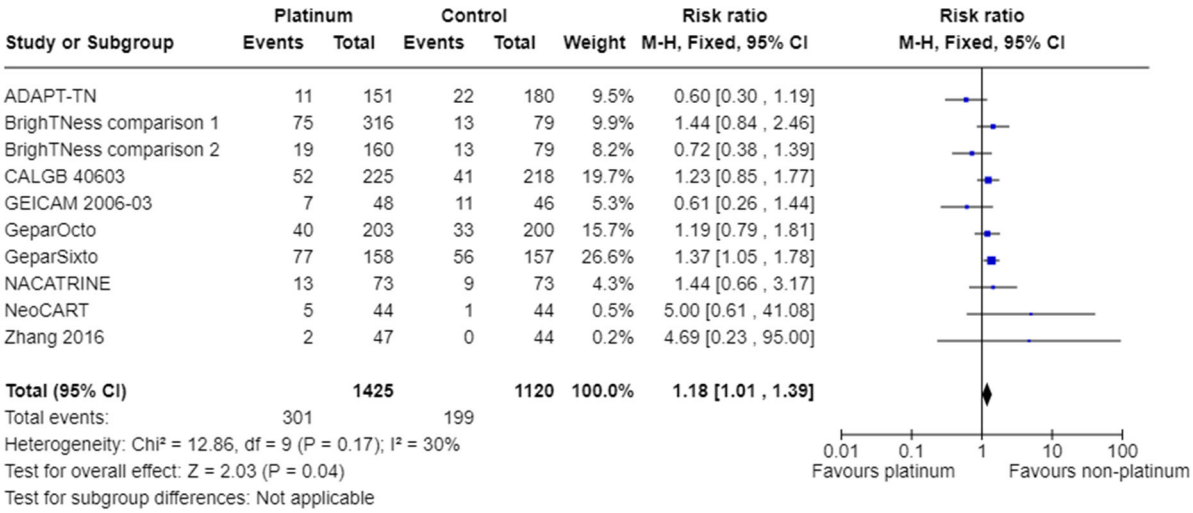
Breast conservation rate

Figure 28 Breast conservation rate



Treatment adherence

Figure 29 Treatment adherence: early cessation of treatment



Adverse events

Shorter term adverse events

Figure 30 Anaemia

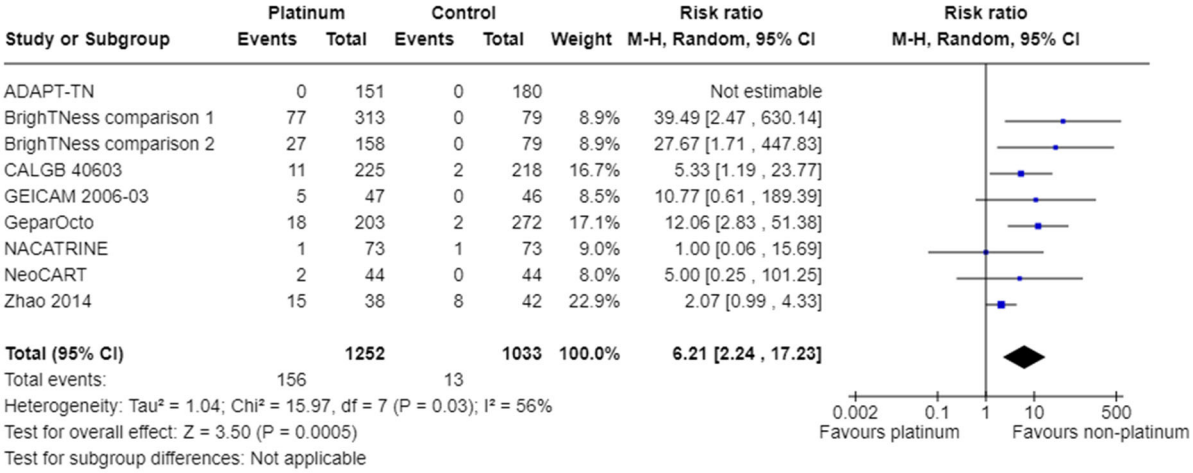


Figure 31 Febrile neutropenia

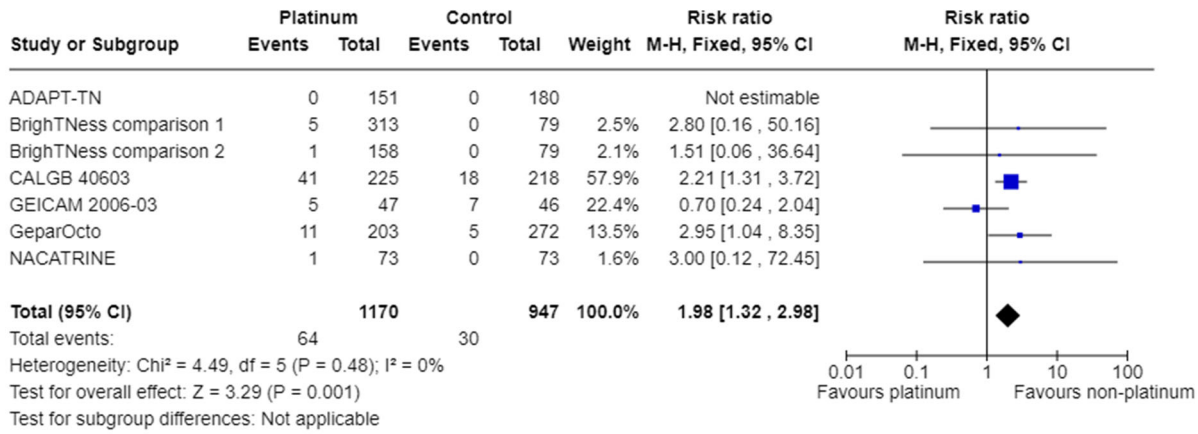


Figure 32 Leukopenia

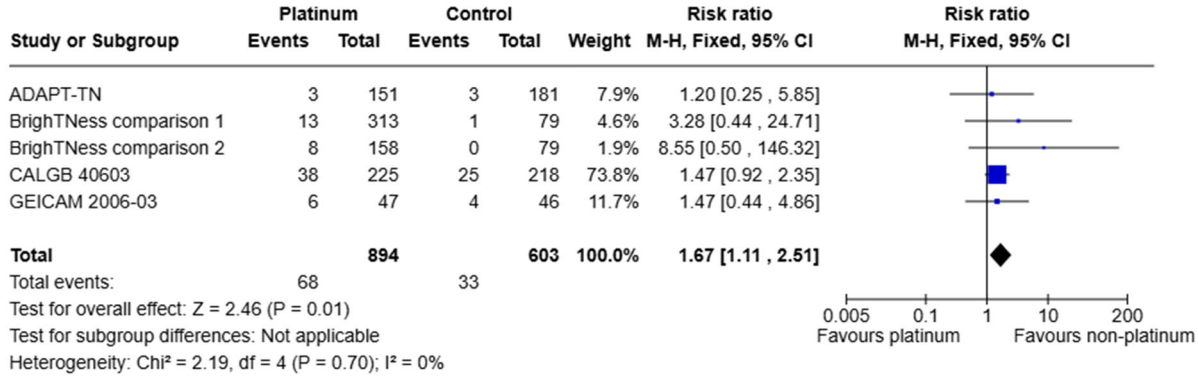


Figure 33 Neutropenia

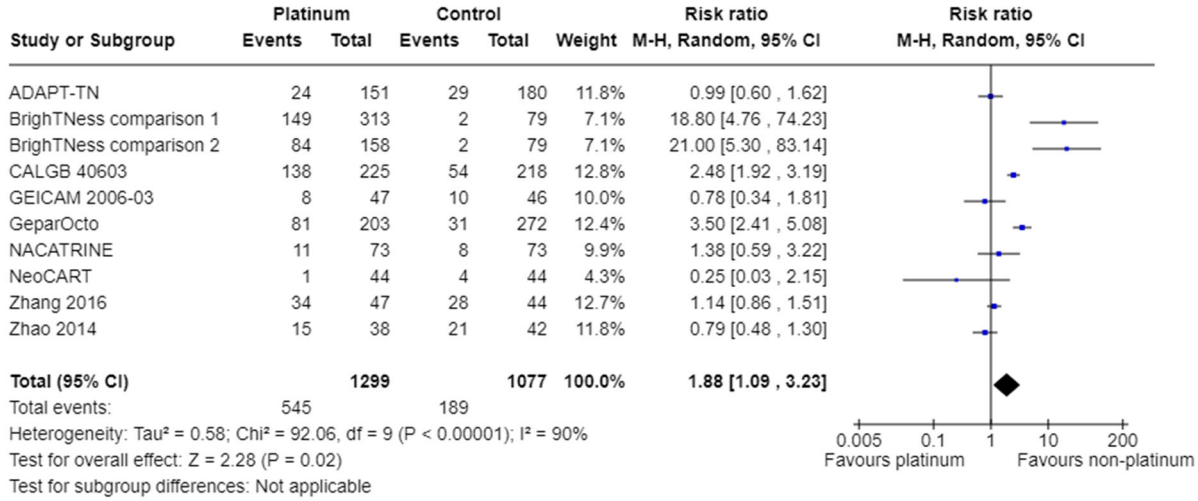


Figure 34 Thrombocytopenia

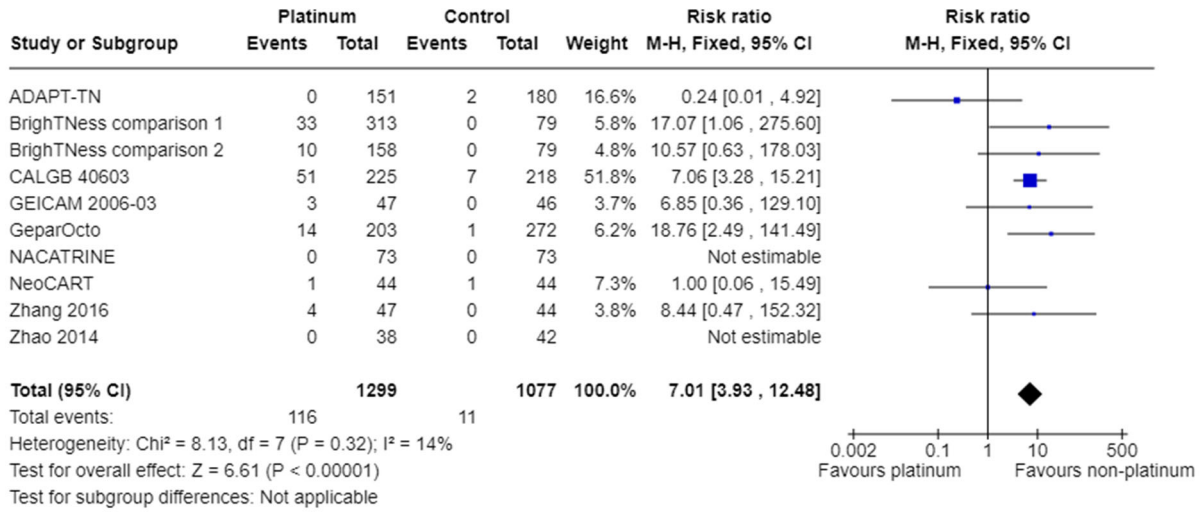


Figure 35 Alanine aminotransferase increased

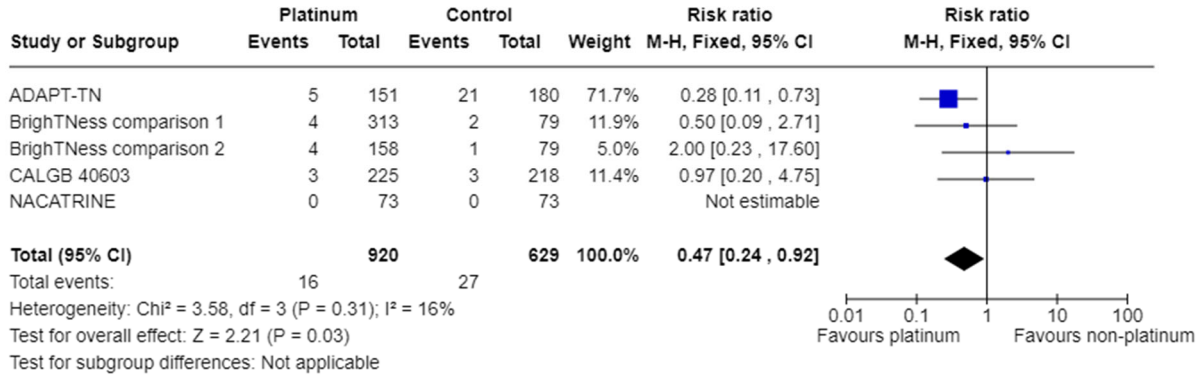


Figure 36 Aspartate aminotransferase increased

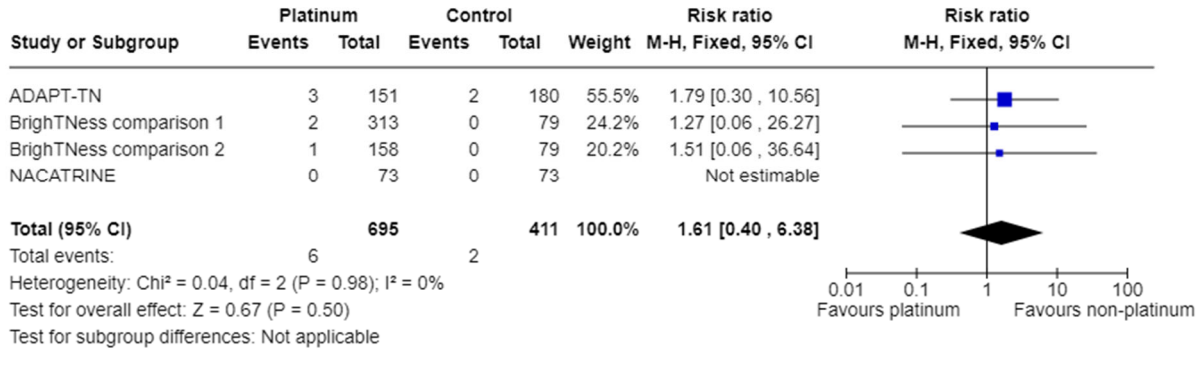


Figure 37 Constipation

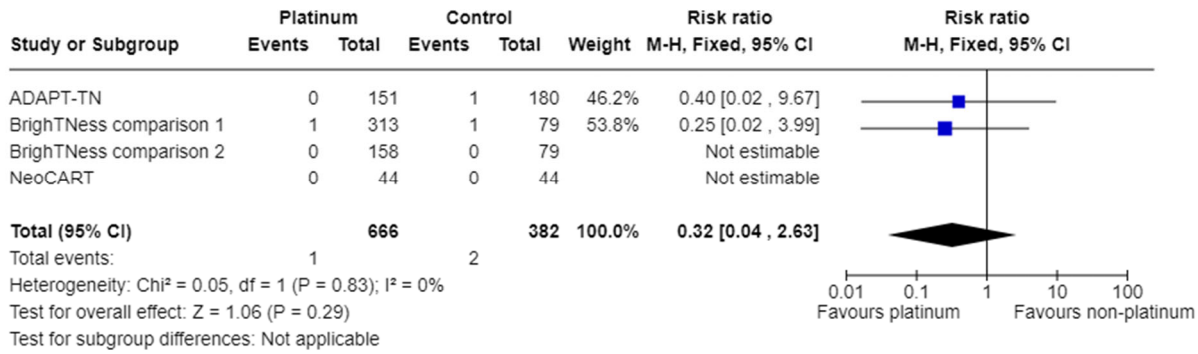


Figure 38 Dehydration

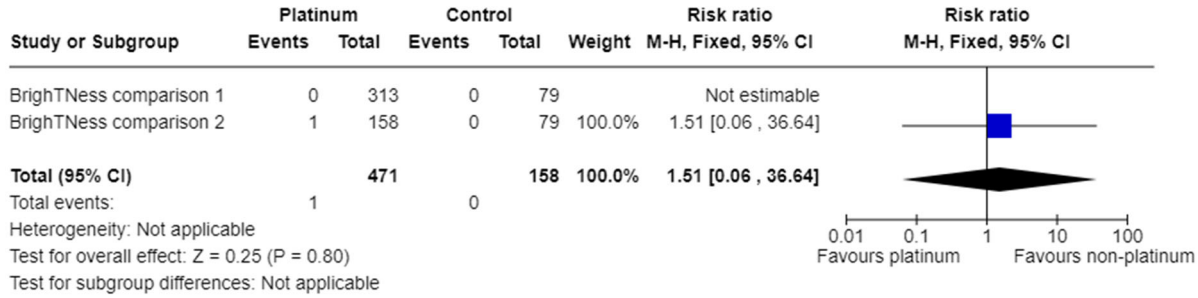


Figure 39 Diarrhoea

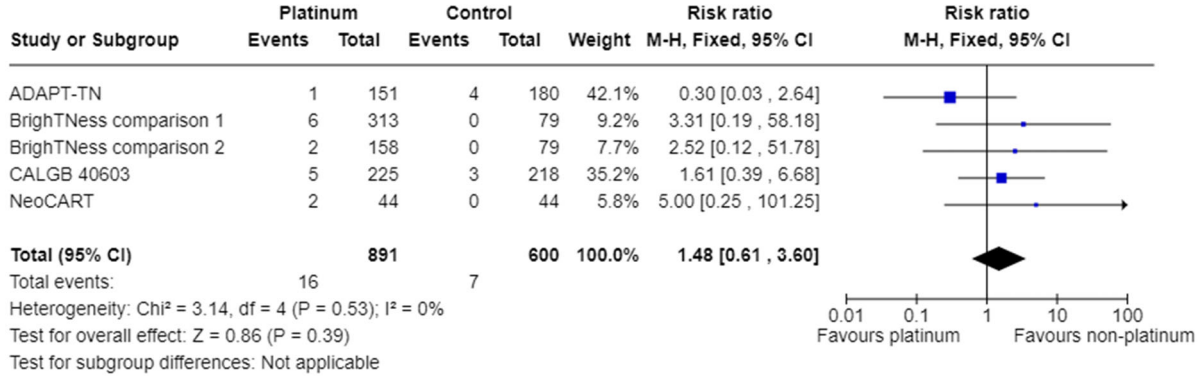


Figure 40 Dizziness

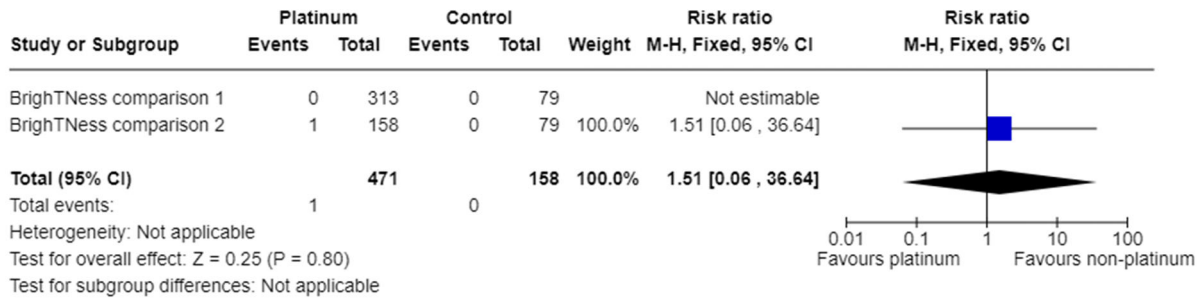


Figure 41 Dyspnoea

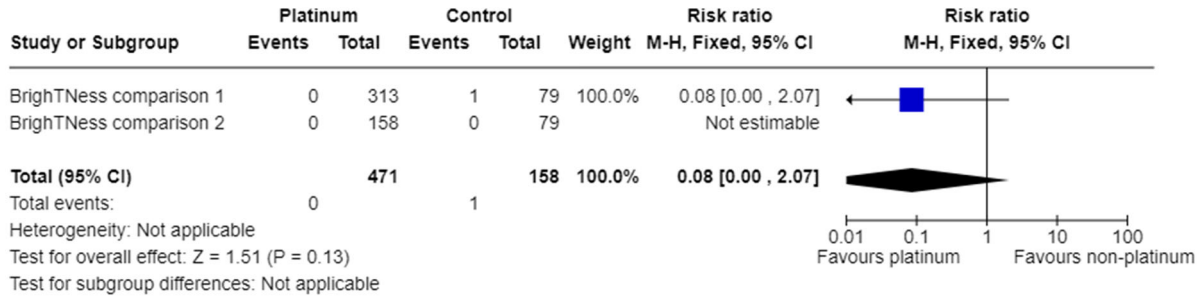


Figure 42 Gamma-glutamyltransferase increased

Figure 43 Hyperglycaemia

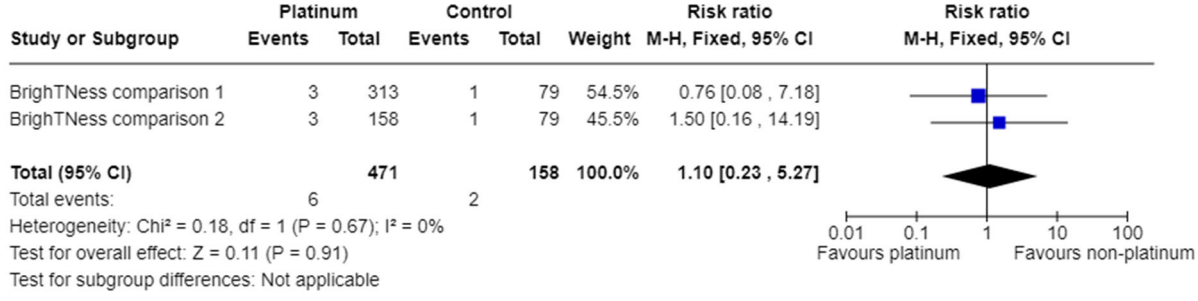


Figure 44 Hypersensitivity

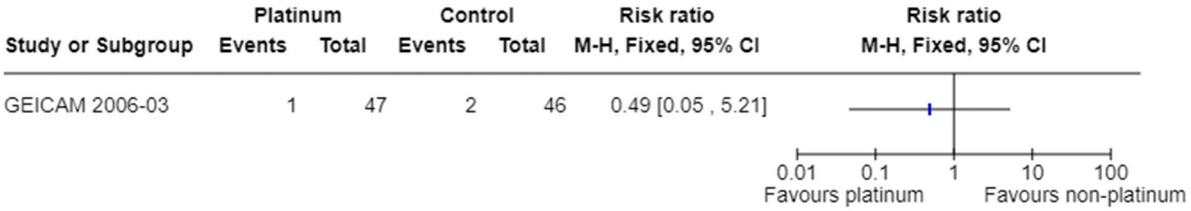


Figure 45 Hypertension

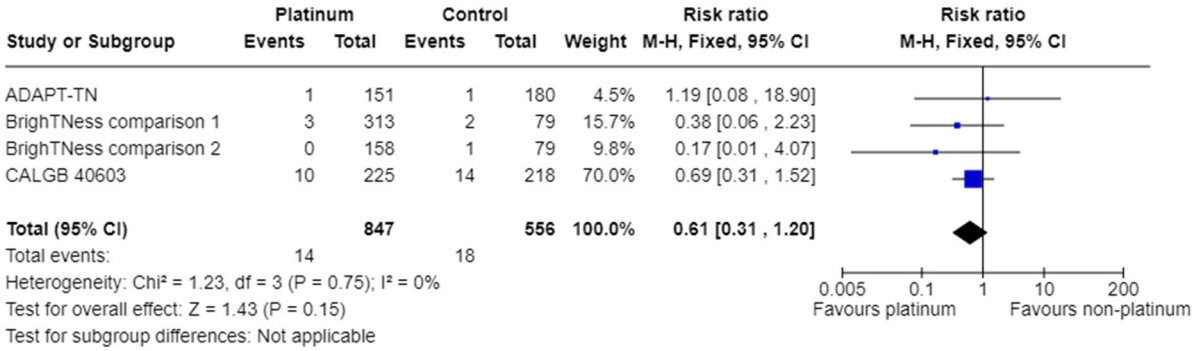


Figure 46 Hypokalaemia

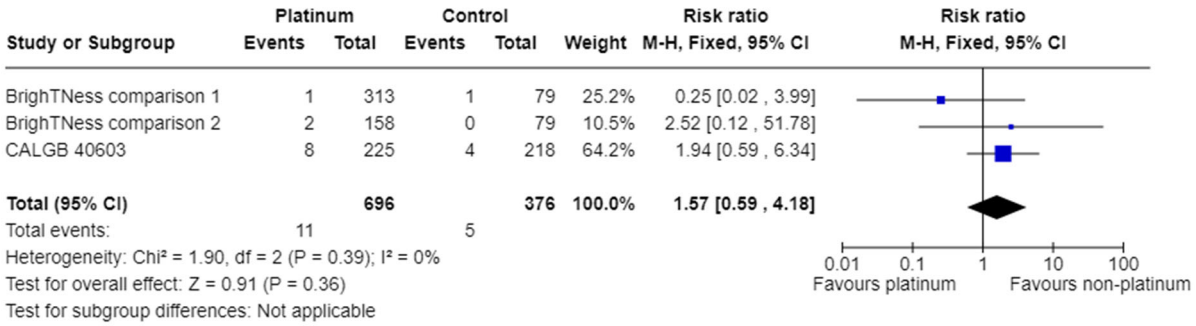


Figure 47 Hyponatraemia

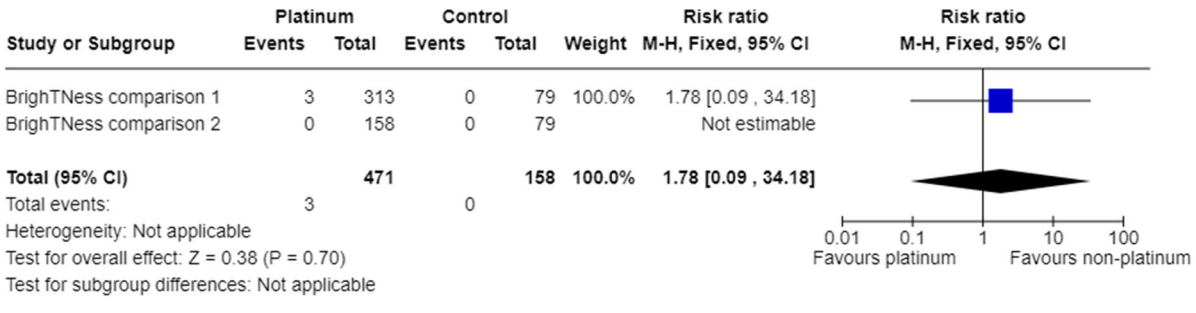


Figure 48 Increased ALT/AST ratio

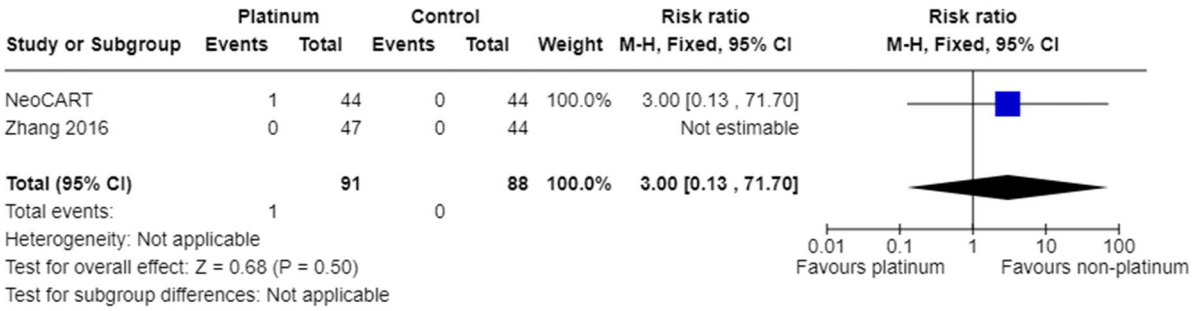


Figure 49 Infection

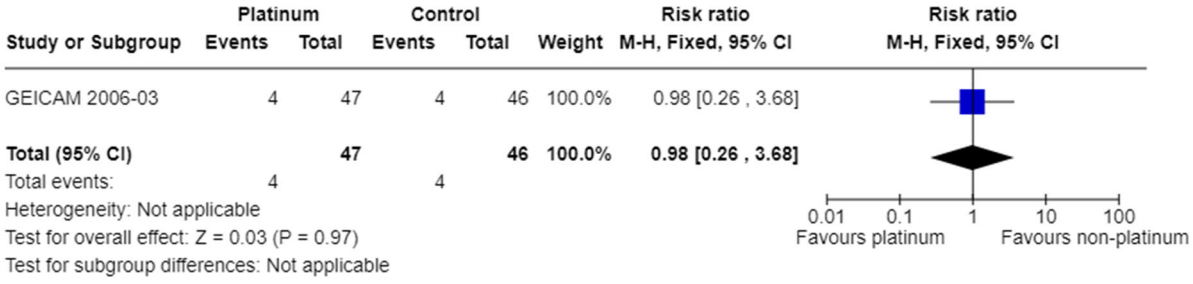


Figure 50 Liver function increased

Figure 51 Lymphopenia

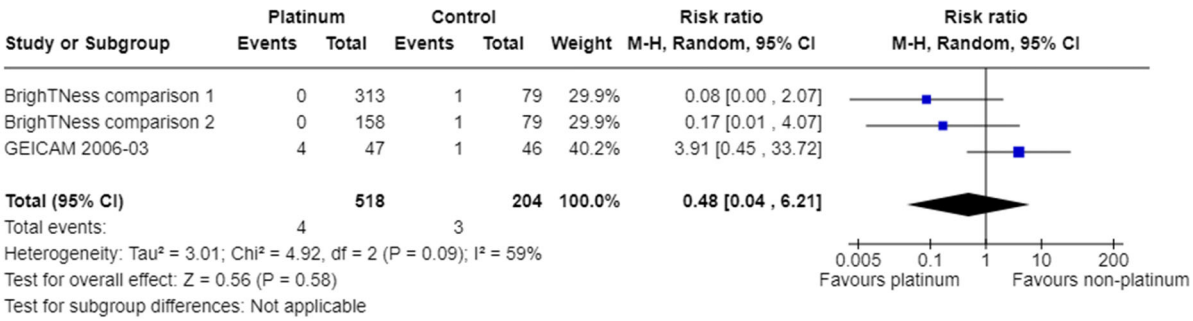


Figure 52 Nausea

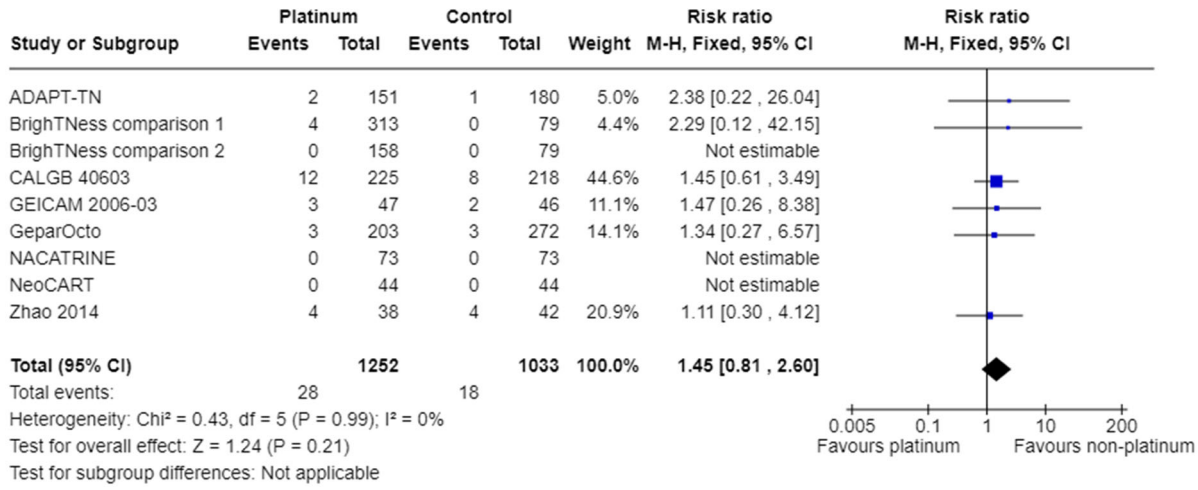


Figure 53 Oral mucositis

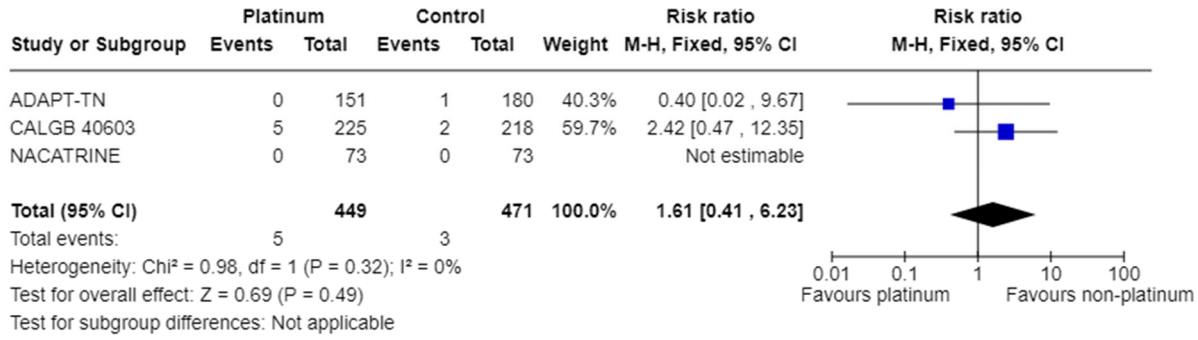


Figure 54 Pneumonia

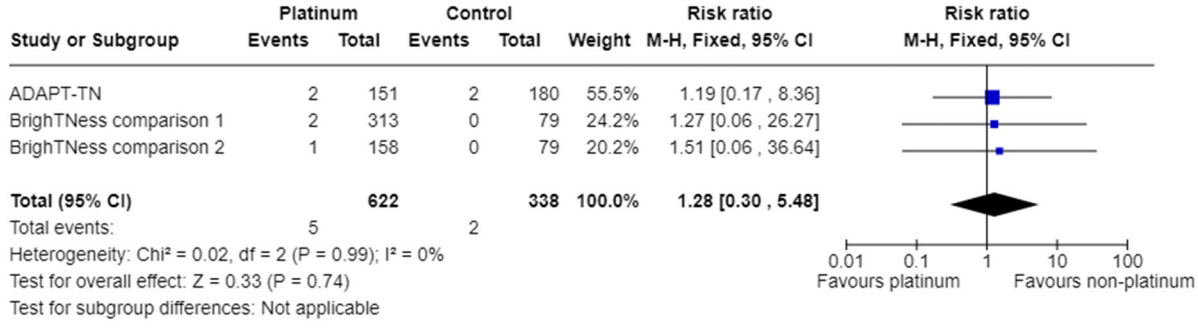


Figure 55 Pruritus

Figure 56 Pyrexia

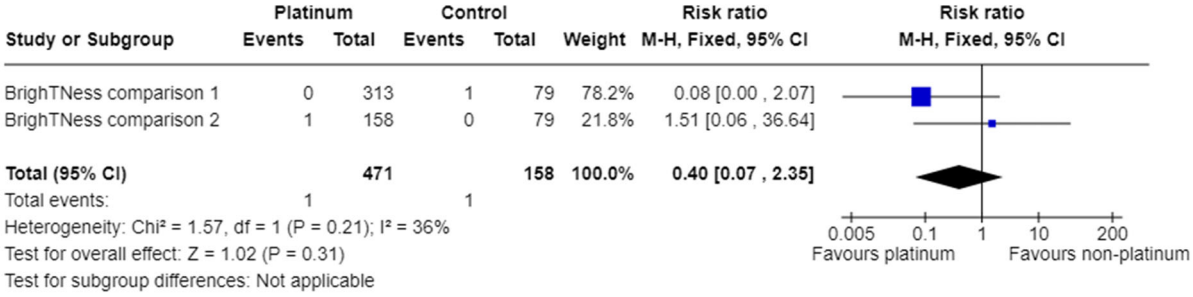


Figure 57 Sinusitis

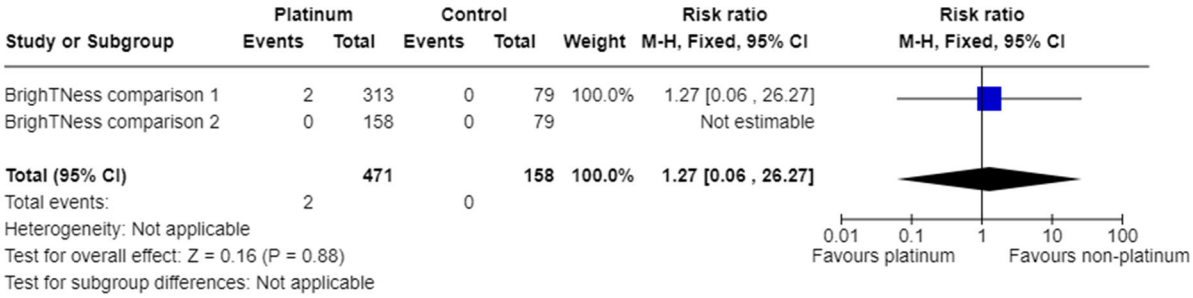


Figure 58 Stomatitis

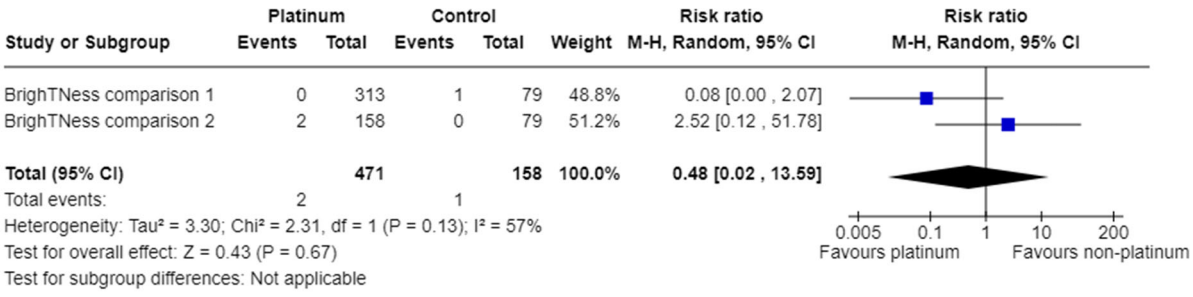


Figure 59 Syncope

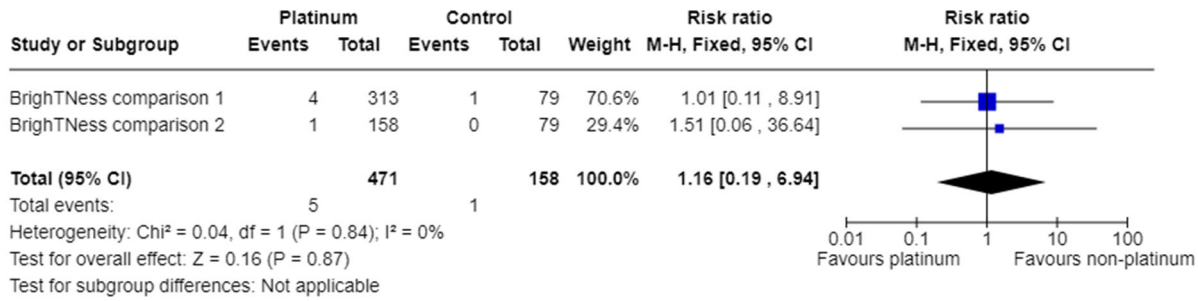


Figure 60 Vomiting

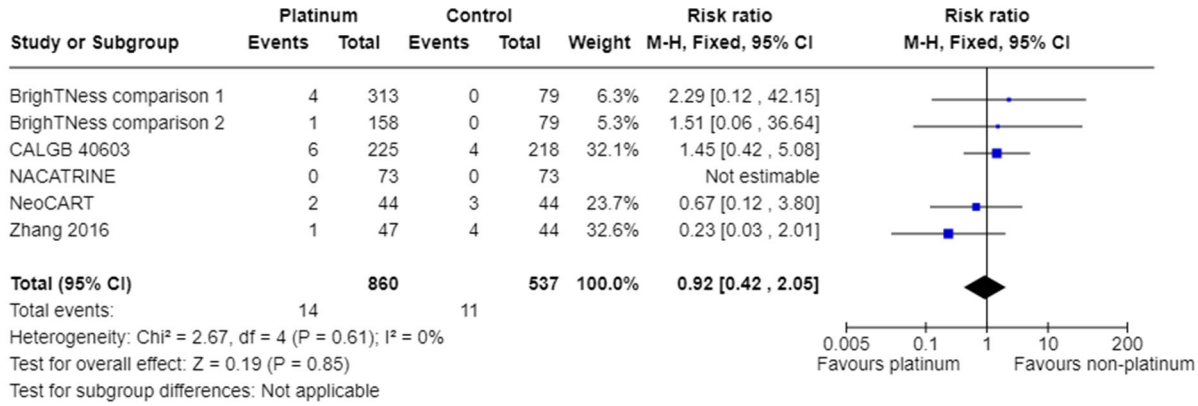
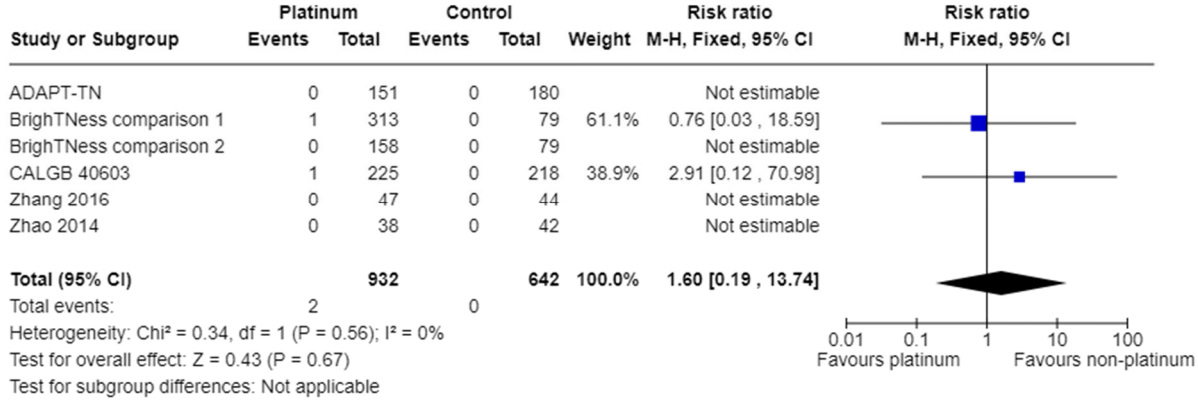


Figure 61 Treatment related death



Longer term adverse events

Figure 62 Fatigue

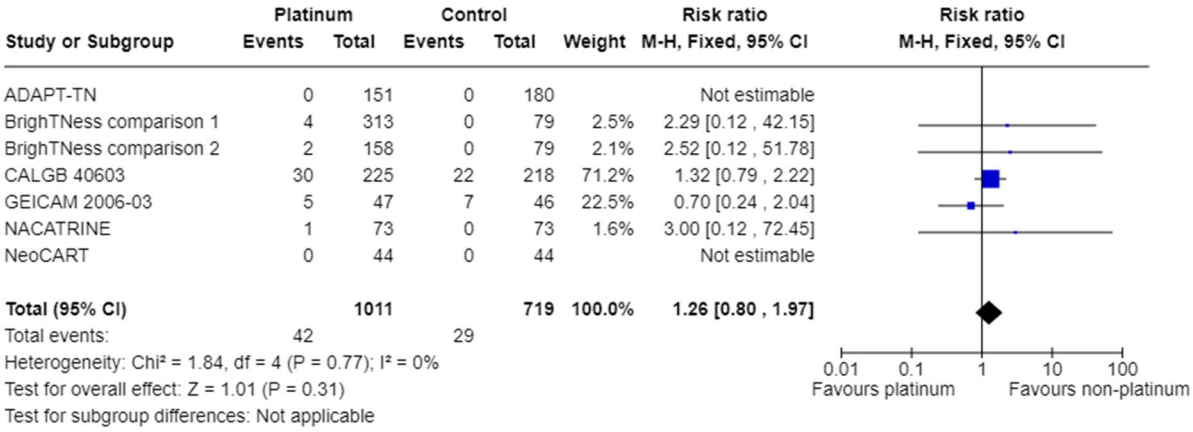


Figure 63 Neuropathy

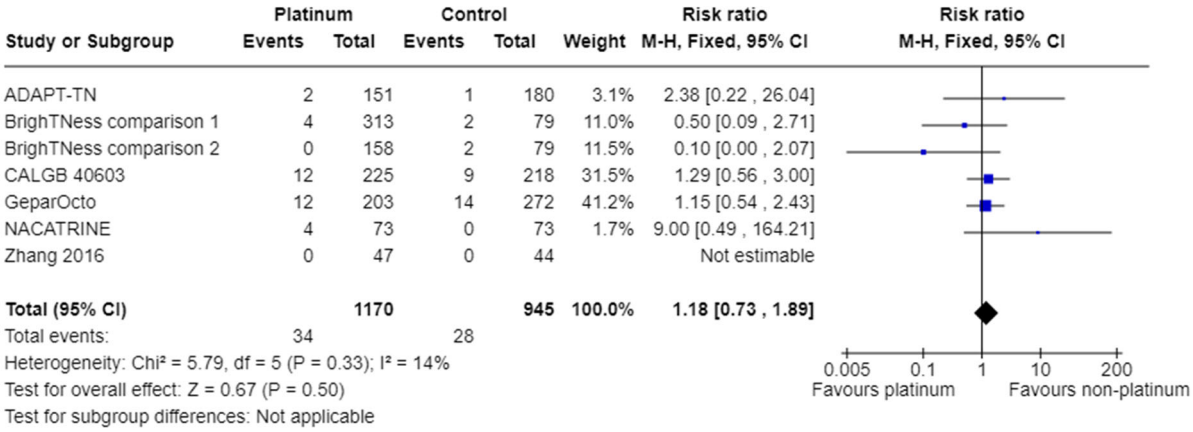


Figure 64 Pain

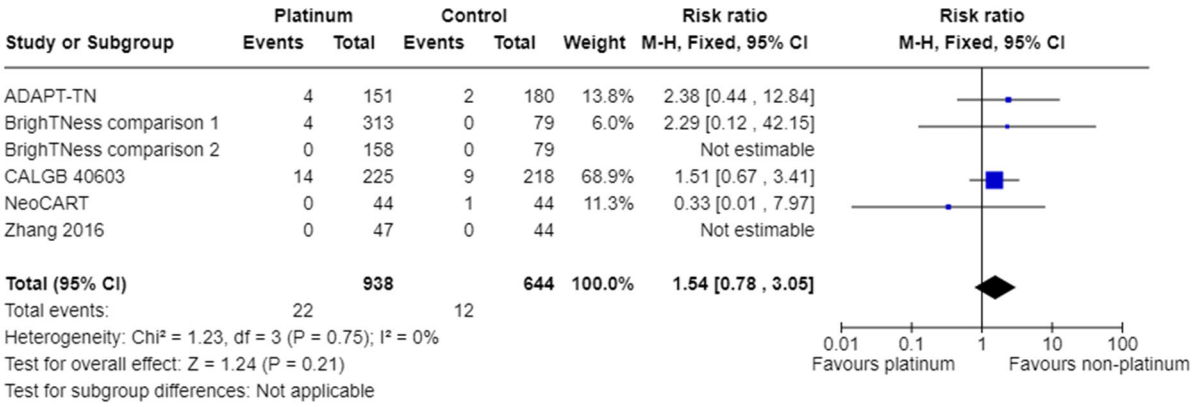
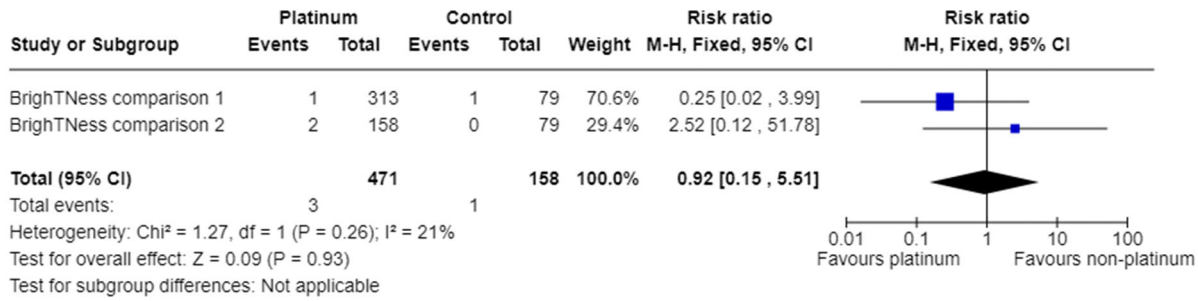


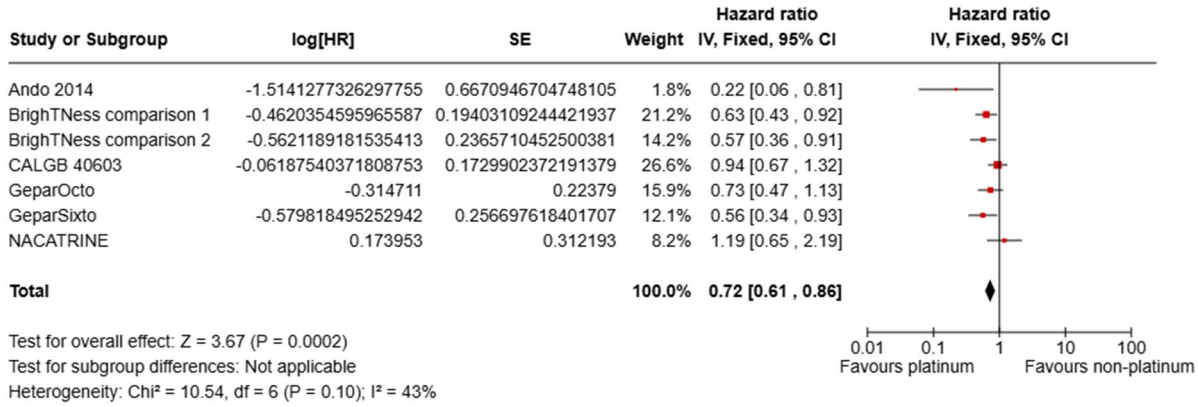
Figure 65 Pulmonary embolism



Triple negative breast cancer sensitivity analyses removing studies where an anthracycline is not included in one or both arms

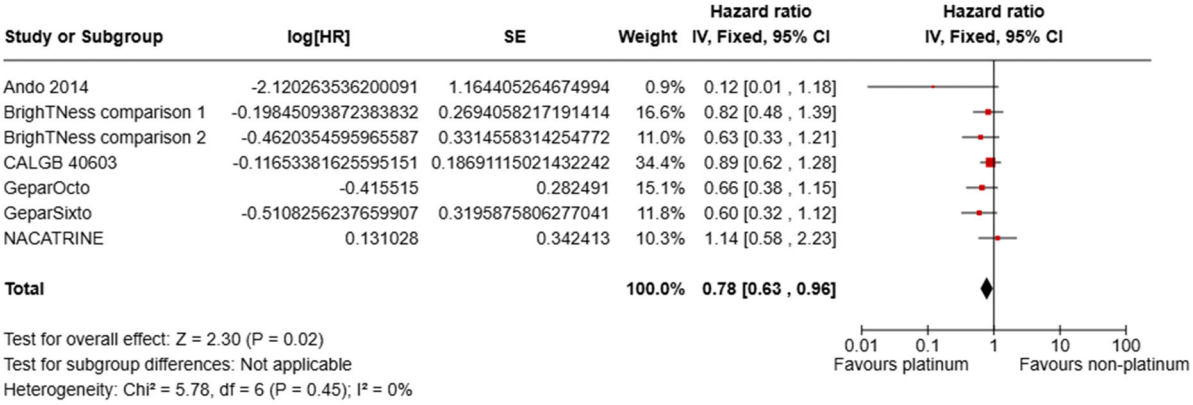
Disease free survival

Figure 66 Disease free survival: sensitivity analysis



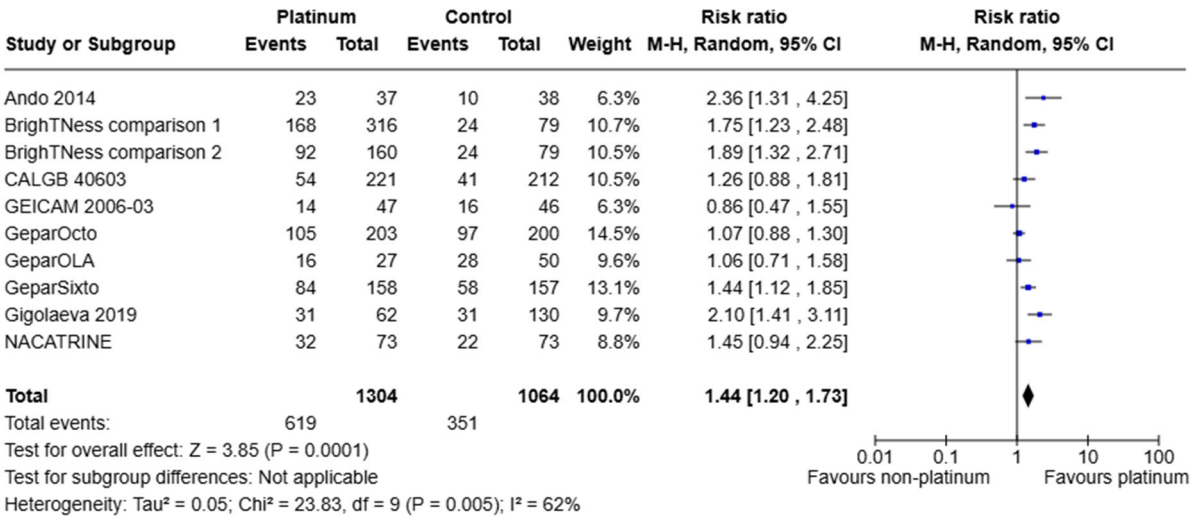
Overall survival

Figure 67 Overall survival: sensitivity analysis



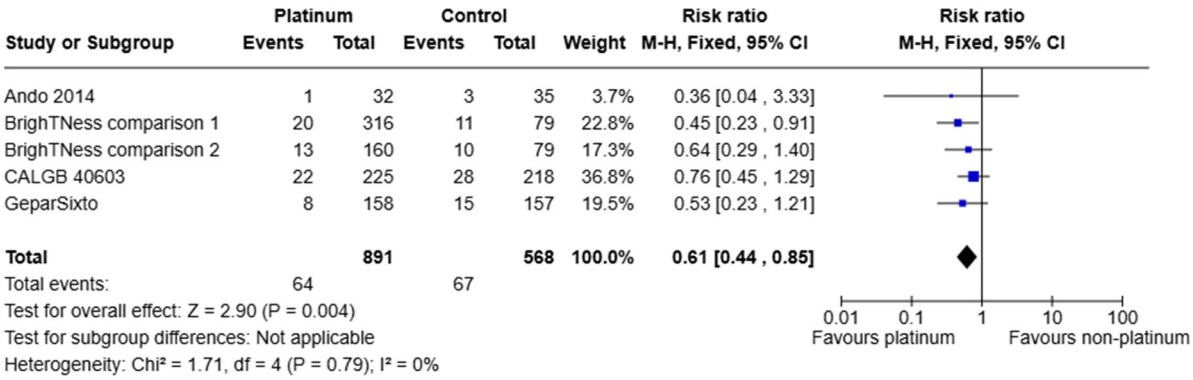
Pathological complete response

Figure 68 Pathological complete response: sensitivity analysis



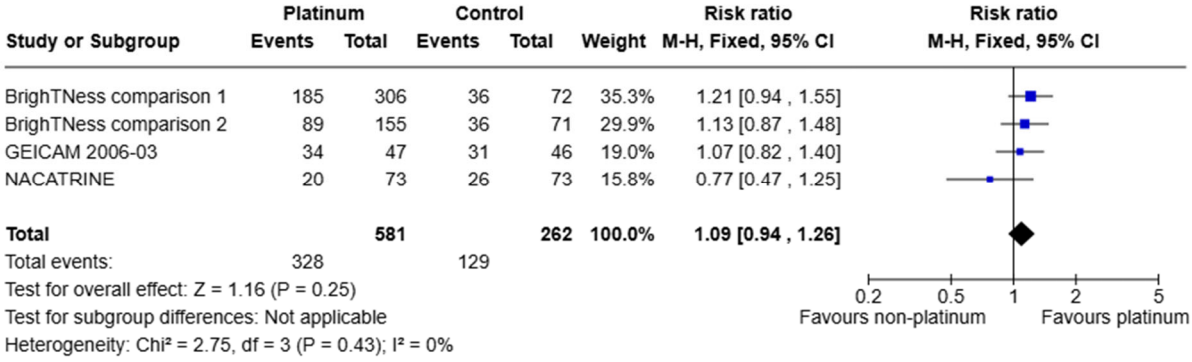
Local and/or locoregional recurrence

Figure 69 Local and/or locoregional recurrence: sensitivity analysis



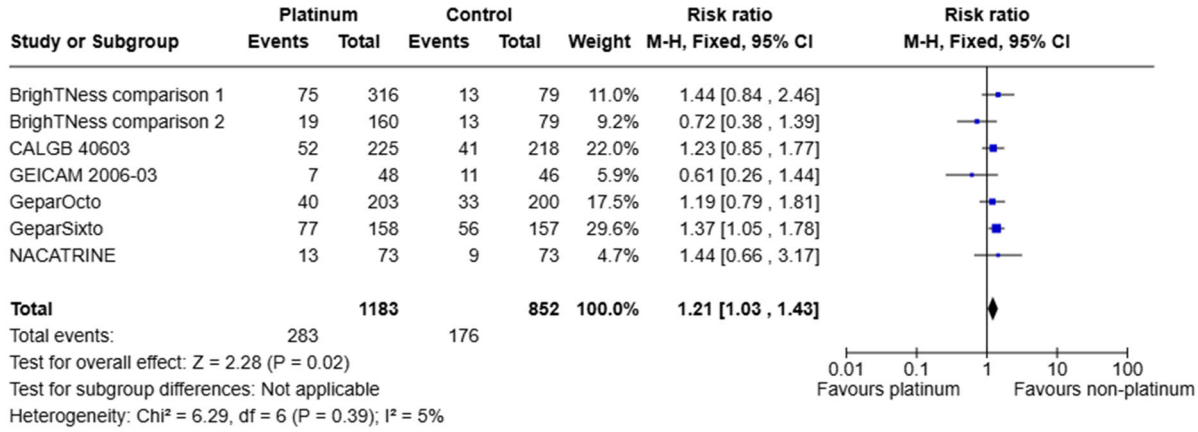
Breast conservation rate

Figure 70 Breast conservation rate: sensitivity analysis



Treatment adherence

Figure 71 Treatment adherence: sensitivity analysis



Short term adverse events

Figure 72 Anaemia: sensitivity analysis

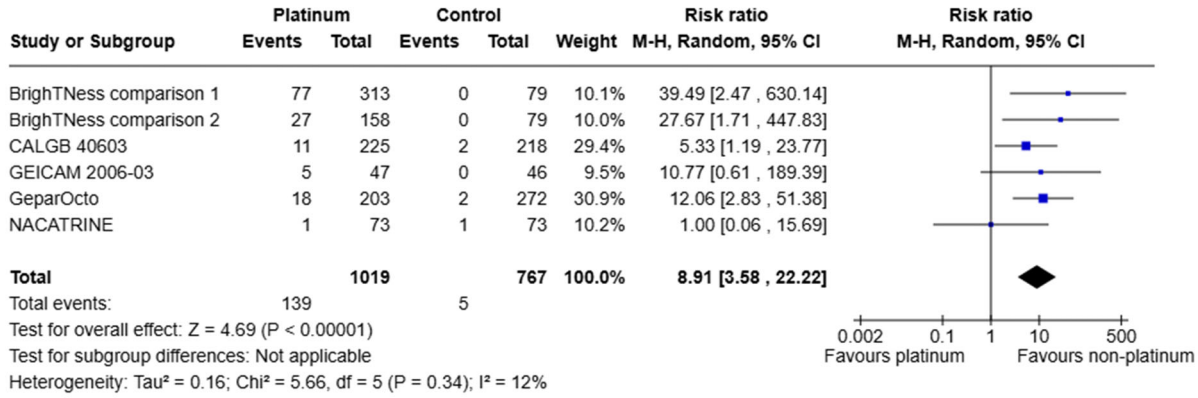


Figure 73 Febrile neutropenia: sensitivity analysis

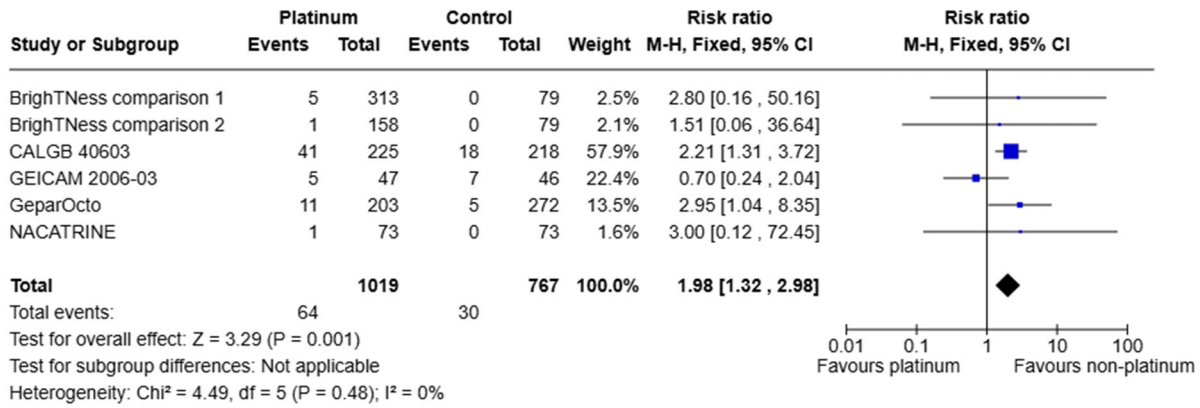


Figure 74 Leukopenia: sensitivity analysis

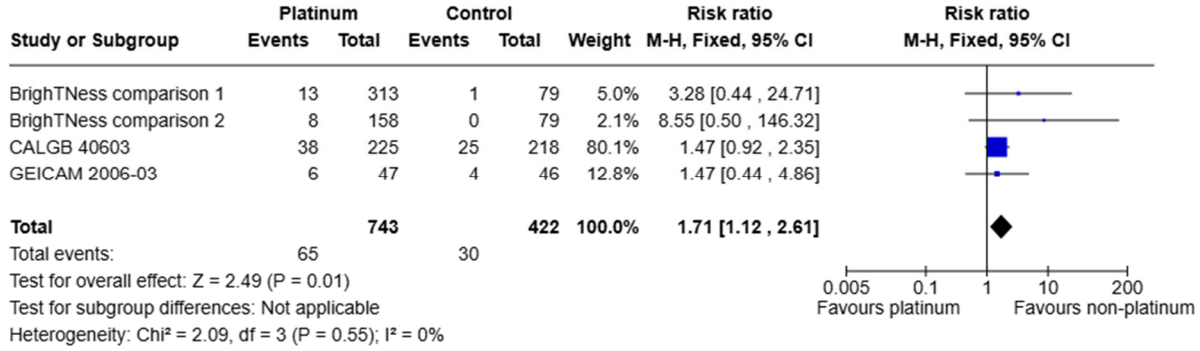


Figure 75 Neutropenia: sensitivity analysis

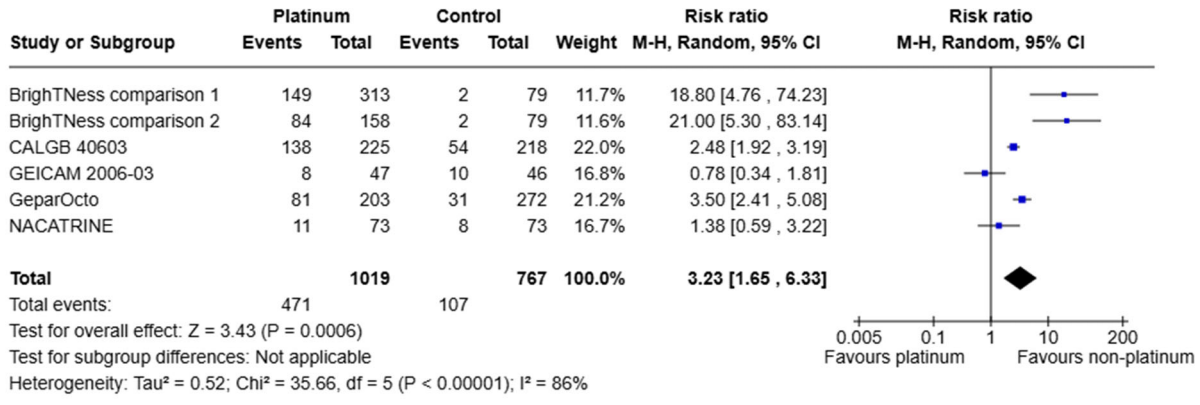


Figure 76 Thrombocytopenia: sensitivity analysis

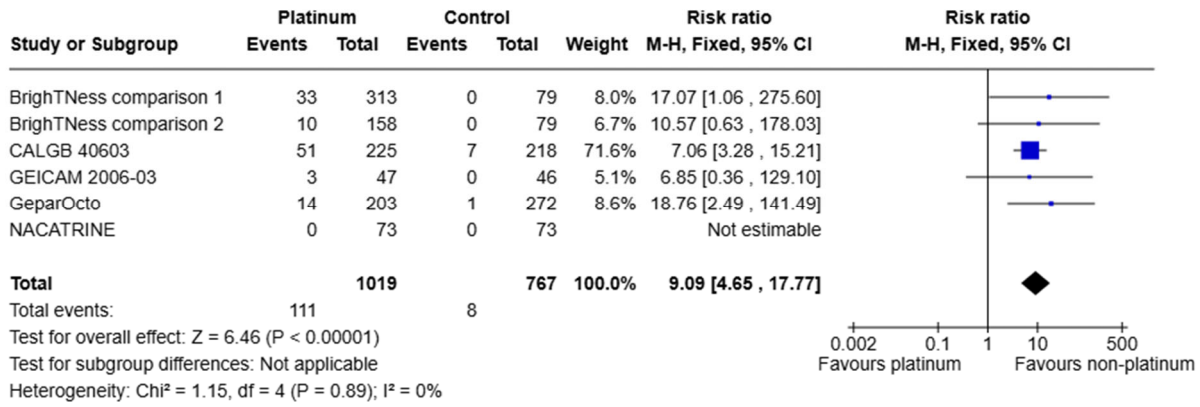


Figure 77 Alanine aminotransferase increased: sensitivity analysis

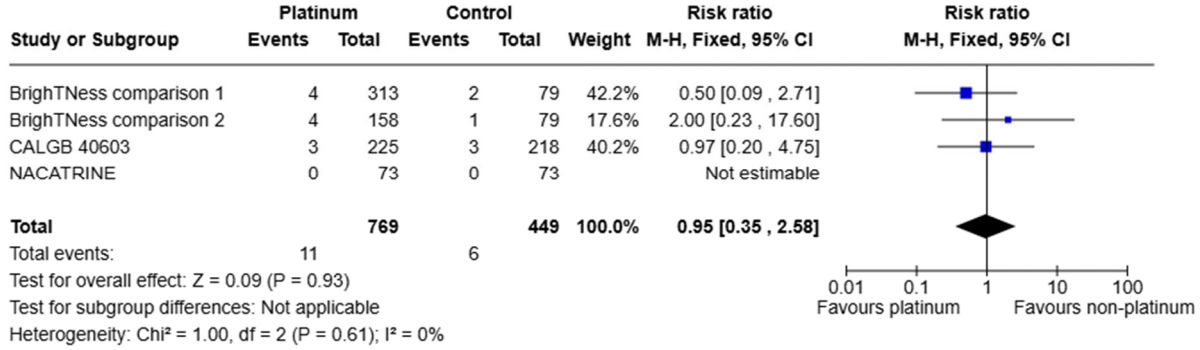


Figure 78 Aspartate aminotransferase increased: sensitivity analysis

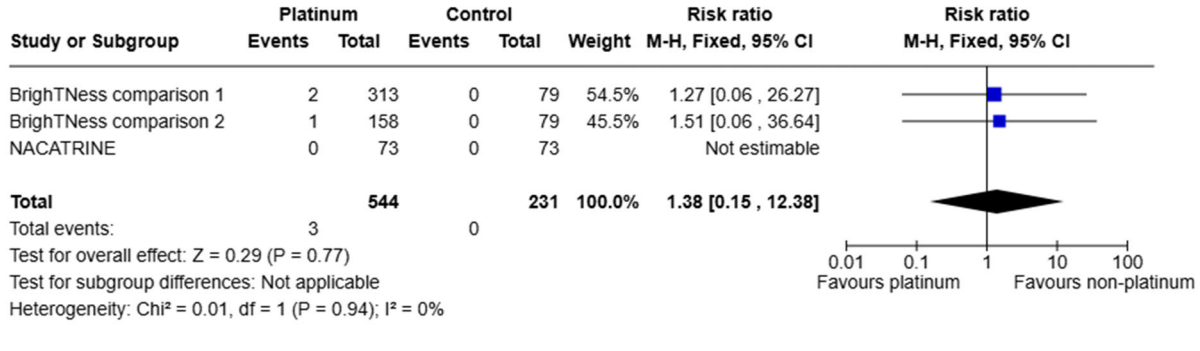


Figure 79 Constipation: sensitivity analysis

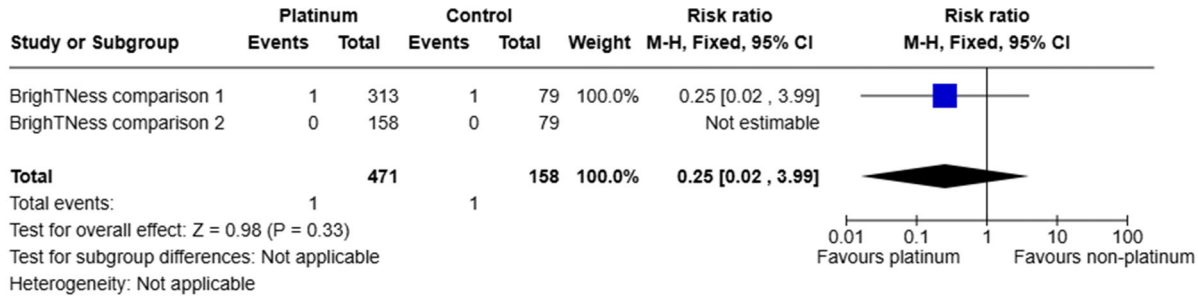


Figure 80 Diarrhoea: sensitivity analysis

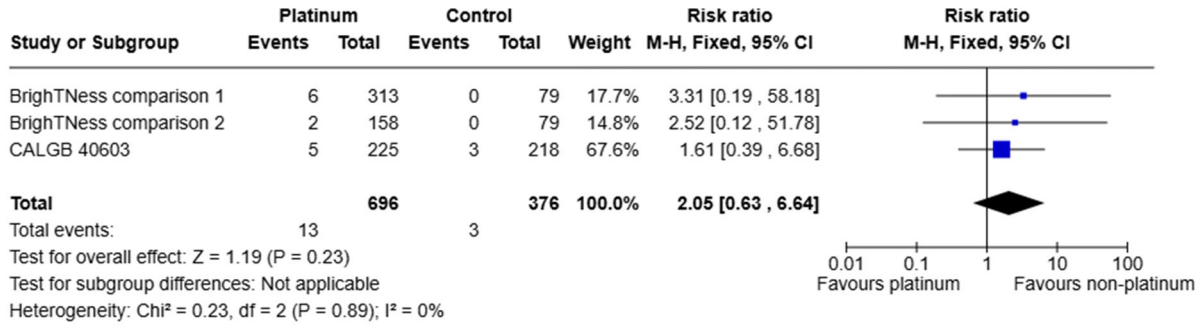


Figure 81 Hypertension: sensitivity analysis

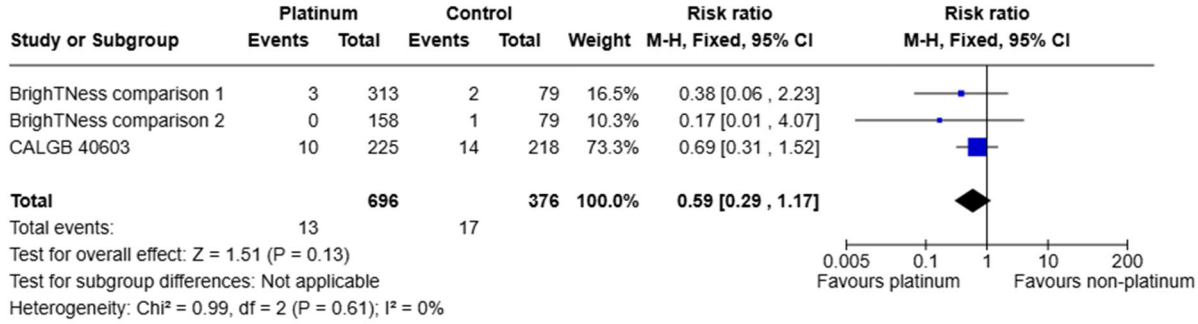


Figure 82 Pneumonia: sensitivity analysis

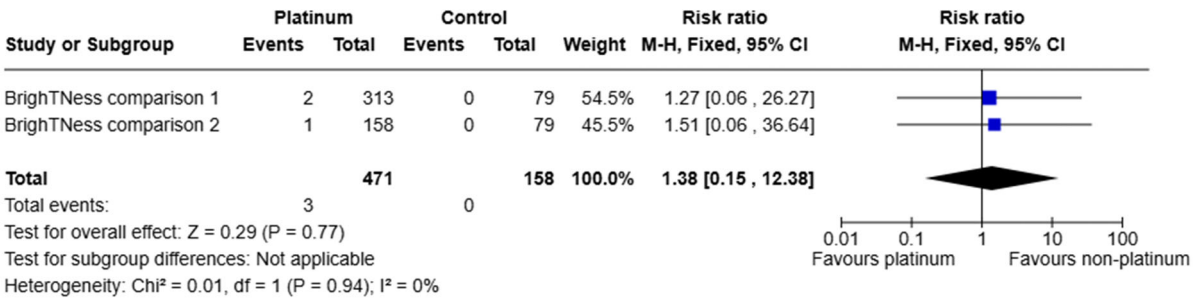


Figure 83 Nausea: sensitivity analysis

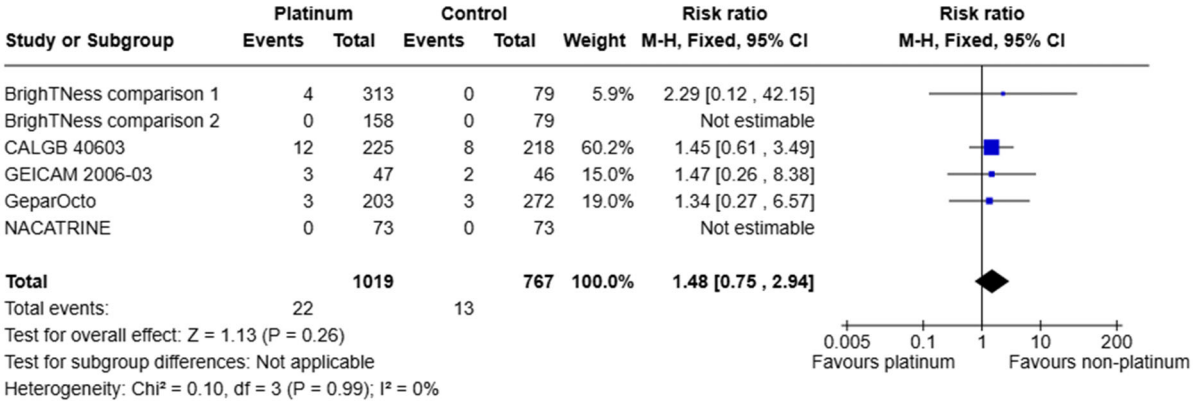


Figure 84 Oral mucositis: sensitivity analysis

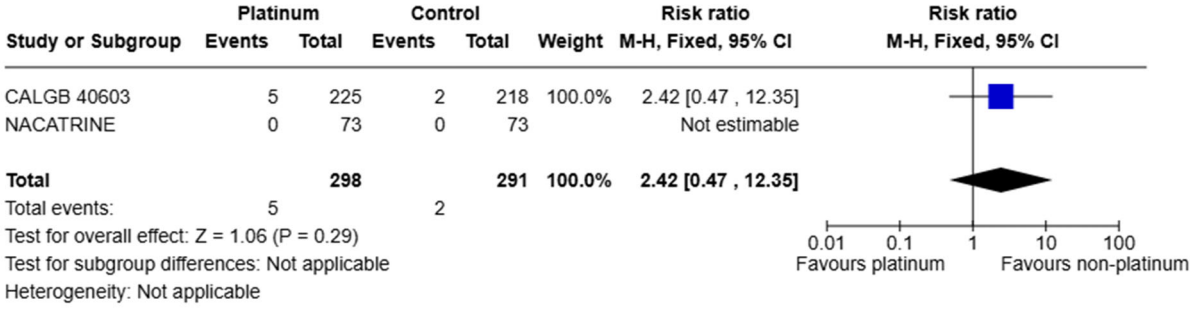


Figure 85 Vomiting: sensitivity analysis

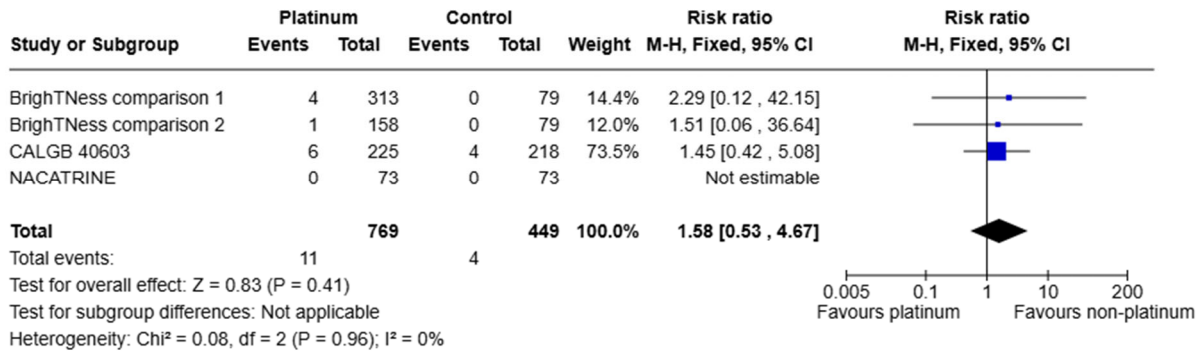
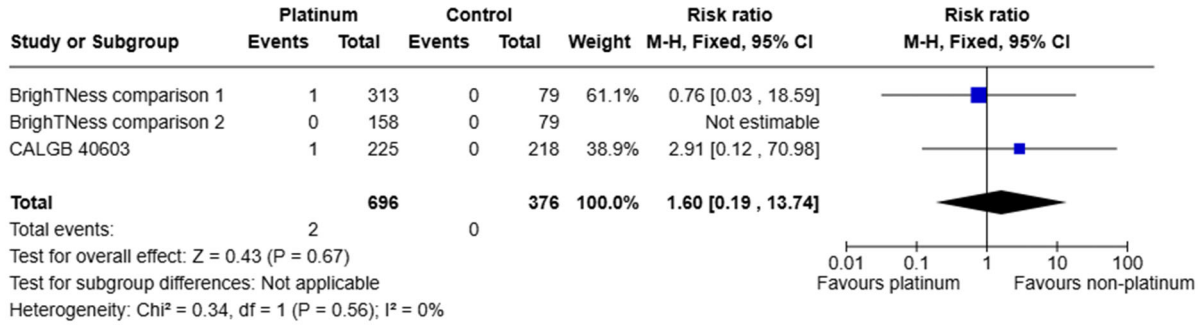


Figure 86 Treatment related death: sensitivity analysis



Long term adverse events: sensitivity analysis

Figure 87 Fatigue: sensitivity analysis

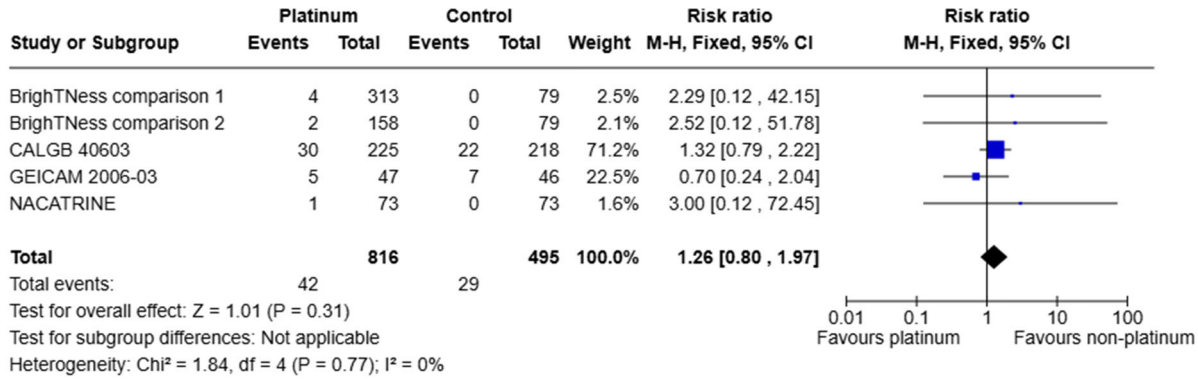


Figure 88 Neuropathy: sensitivity analysis

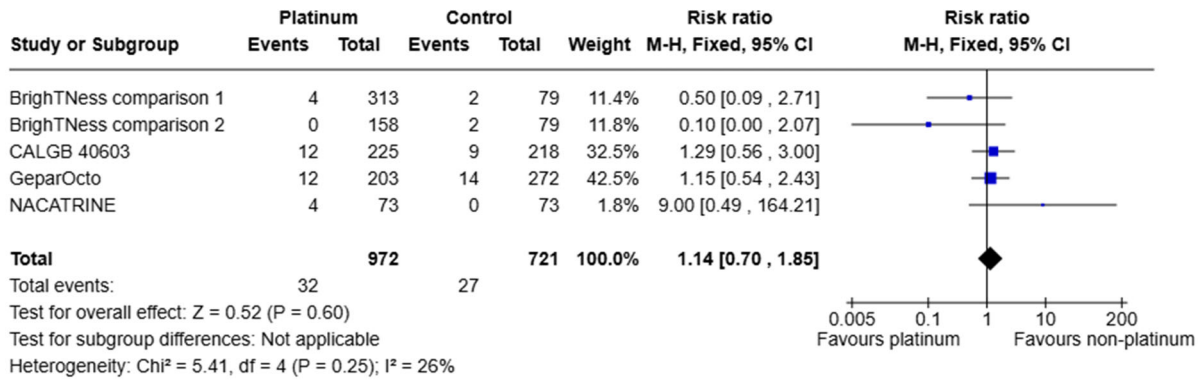
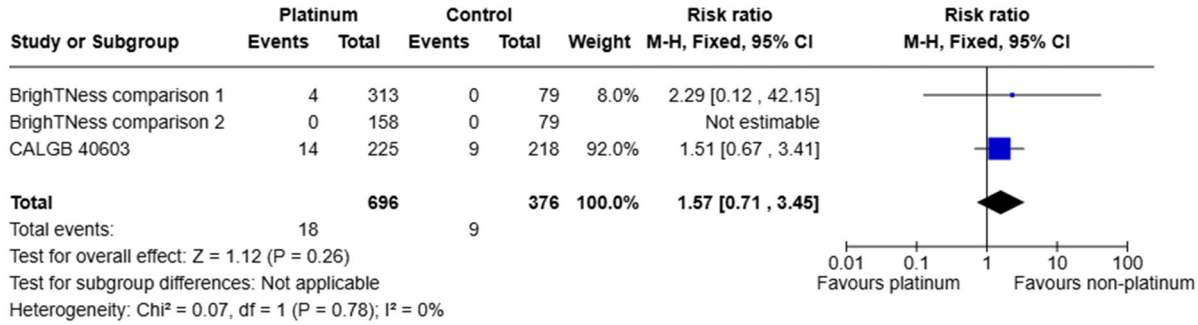


Figure 89 Pain: sensitivity analysis

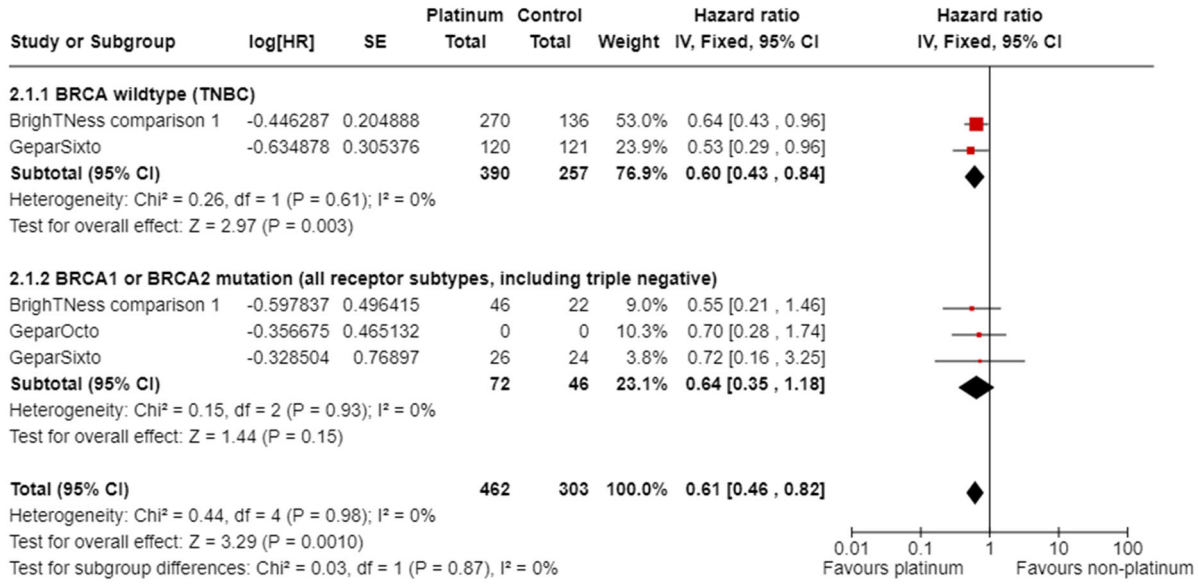


Germline BRCA mutation analyses

The following meta-analyses were carried out taking data from the BRCA germline mutations subgroups of the TNBC population and from 2 of these trials which also reported data for all receptor subtypes (GeparOcto and GeparOLA). See section 1.1.3 Methods and process for more details on studies included for the germline BRCA mutation analyses.

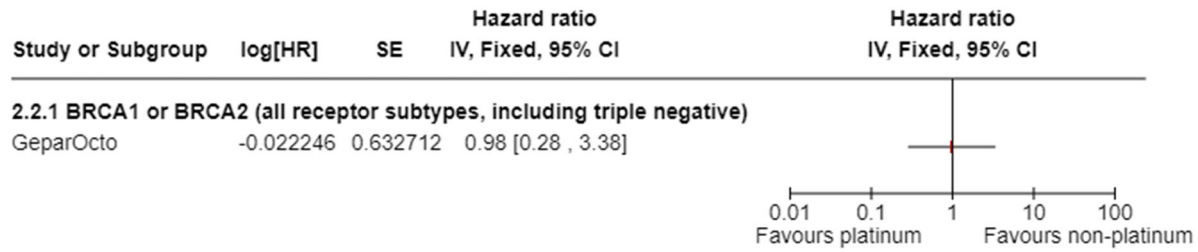
Disease free survival

Figure 90 Disease free survival



Overall survival

Figure 91 Overall survival



Pathological complete response

Figure 92 Pathological complete response (random effects model)

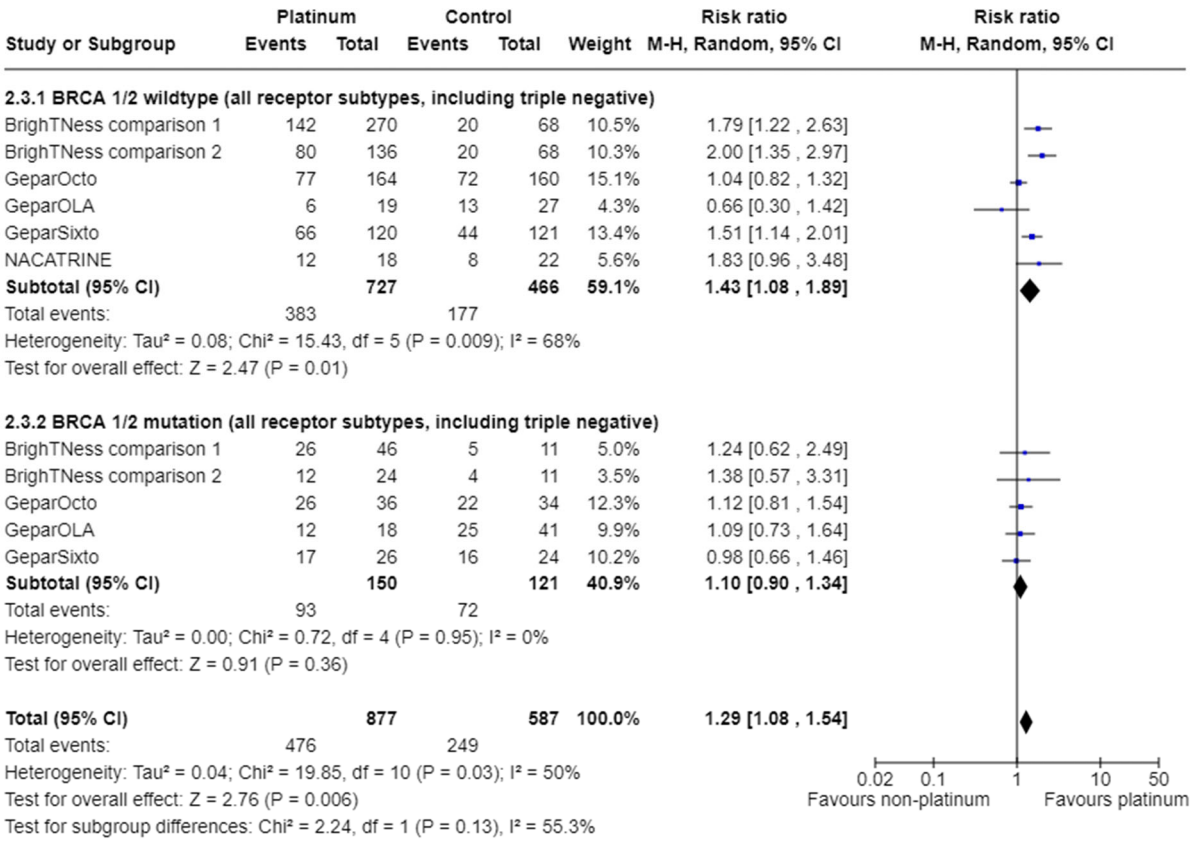
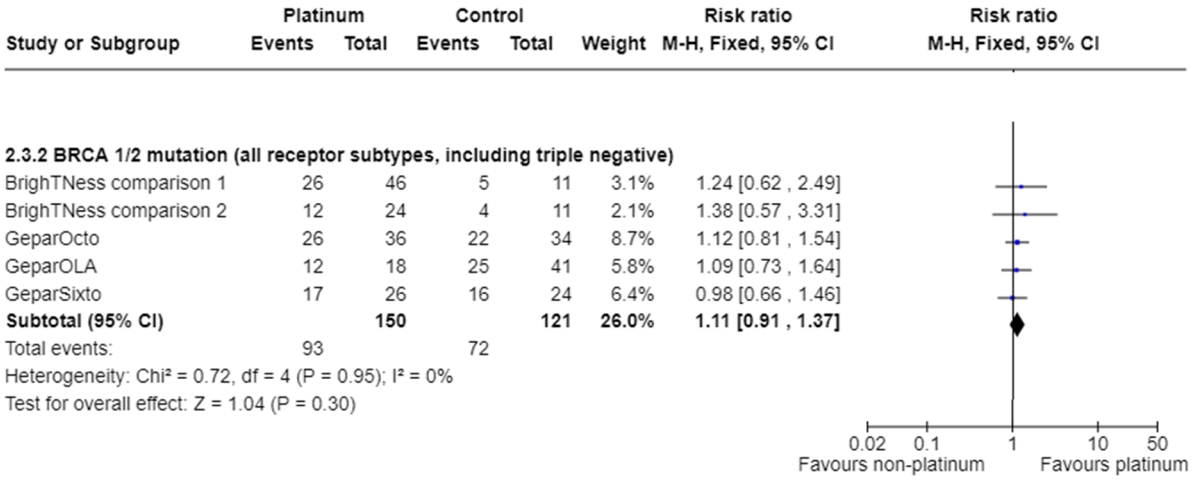


Figure 93 Pathological complete response (fixed effects model)



Appendix F – GRADE

Triple negative breast cancer analyses

Disease-free survival

Table 18 Disease-free survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival: main analysis (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
9 (ADAPT-TN, Ando 2014, BrighTNess, CALGB 40603, GeparOcto, GeparSixto, NACATRINE, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	1413	1102	HR 0.67 (0.58 to 0.79)	Not estimable	Moderate	CRITICAL
Outcome: Disease-free survival; subgroup: BRCA mutation status - BRCA wildtype (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
2 (BrighTNess, GeparSixto)	randomised trials	not serious	not serious	not serious	not serious	none	390	257	HR 0.60 (0.43 to 0.84)	Not estimable	High	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Outcome: Disease-free survival; subgroup: BRCA mutation status - BRCA mutation (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
2 (BrighTNess, GeparSixto)	randomised trials	not serious	not serious	not serious	very serious[b]	none	72	46	HR 0.60 (0.26 to 1.36)	Not estimable	Low	CRITICAL
Outcome: Disease-free survival; subgroup: Same backbone chemotherapy with or without platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 53%)												
5 (Ando 2014, BrighTNess, CALGB 40603, GeparSixto, NACATRINE)	randomised trials	serious[a]	serious[c]	not serious	not serious	none	969	644	HR 0.69 (0.52 to 0.93)	Not estimable	Low	CRITICAL
Outcome: Disease-free survival; subgroup: Different backbone chemotherapy with or without platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy) – Fixed effects model												
4 (ADAPT-TN, GeparOcto, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	444	468	HR 0.59 (0.45 to 0.77)	Not estimable	Moderate	CRITICAL
Outcome: Disease-free survival; subgroup: Lymph node status - N stage: 0 (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.77 (0.41 to 1.43)	Not estimable	Very low	CRITICAL
Outcome: Disease-free survival; subgroup: Lymph node status - N stage: 1 (HR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
1 (CALGB 40603)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	Not reported	Not reported	HR 1.12 (0.68 to 1.84)	Not estimable	Very low	CRITICAL
Outcome: Disease-free survival; subgroup: Lymph node status - N stage: 2 or 3 (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.63 (0.27 to 1.47)	Not estimable	Very low	CRITICAL
Outcome: Disease-free survival; subgroup: Anthracycline content of chemotherapy - Anthracycline-free platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
3 (ADAPT-TN, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	241	268	HR 0.52 (0.37 to 0.73)	Not estimable	Moderate	CRITICAL
Outcome: Disease-free survival; subgroup: Anthracycline content of chemotherapy - Anthracycline-containing platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
6 (Ando 2014, BrighTNess, CALGB 40603, GeparOcto, GeparSixto, NACATRINE)	randomised trials	serious[a]	serious[c]	not serious	not serious	none	1172	834	HR 0.72 (0.61 to 0.86)	Not estimable	Low	CRITICAL
Outcome: Disease-free survival; subgroup: Age - Age <40 years (HR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
1 (CALGB 40603)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.73 (0.32 to 1.65)	Not estimable	Very low	CRITICAL
Outcome: Disease-free survival; subgroup: Age - Age 40 to 59 years (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	Not reported	Not reported	HR 1.13 (0.74 to 1.72)	Not estimable	Very low	CRITICAL
Outcome: Disease-free survival; subgroup: Age - Age ≥60 years (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.59 (0.26 to 1.35)	Not estimable	Very low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

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 and the number of participants was less than 500, outcome was downgraded two levels

c. I^2 was between 41% and 60%, outcome was downgraded one level

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

Overall survival

Table 19 Overall survival

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
Overall survival: main analysis (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
9 (ADAPT-TN, Ando 2014, BrighTNess, CALGB 40603, GeparOcto, GeparSixto, NACATRINE, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	1413	1109	HR 0.72 (0.59 to 0.88)	Not estimable	Moderate	CRITICAL
Outcome: Overall survival; subgroup: Same backbone chemotherapy with or without platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
5 (Ando 2014, BrighTNess, CALGB 40603, GeparSixto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	serious[d]	none	969	644	HR 0.80 (0.63 to 1.01)	Not estimable	Low	CRITICAL
Outcome: Overall survival; subgroup: Different backbone chemotherapy with or without platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
4 (ADAPT-TN, GeparOcto, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	444	468	HR 0.54 (0.37 to 0.78)	Not estimable	Moderate	CRITICAL
Outcome: Overall survival; subgroup: Lymph node status - N stage: 0 (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[c]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.94 (0.46 to 1.94)	Not estimable	Very low	CRITICAL
Outcome: Overall survival; subgroup: Lymph node status - N stage: 1 (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[c]	not serious	very serious[b]	none	Not reported	Not reported	HR 1.22 (0.73 to 2.04)	Not estimable	Very low	CRITICAL
Outcome: Overall survival; subgroup: Lymph node status - N stage: 2 or 3 (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[c]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.98 (0.38 to 2.54)	Not estimable	Very low	CRITICAL
Outcome: Overall survival; subgroup: Anthracycline content of chemotherapy - Anthracycline-free platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
3 (ADAPT-TN, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	241	268	HR 0.45 (0.26 to 0.75)	Not estimable	Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
Outcome: Overall survival; subgroup: Anthracycline content of chemotherapy - Anthracycline-containing platinum (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
6 (Ando 2014, BrighTNess, CALGB 40603, GeparOcto, GeparSixto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	not serious	none	1172	841	HR 0.78 (0.63 to 0.96)	Not estimable	Moderate	CRITICAL
Outcome: Overall survival; subgroup: Age - Age <40 years (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[c]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.67 (0.26 to 1.72)	Not estimable	Very low	CRITICAL
Outcome: Overall survival; subgroup: Age - Age 40 to 59 years (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[c]	not serious	very serious[b]	none	Not reported	Not reported	HR 1.50 (0.95 to 2.38)	Not estimable	Very low	CRITICAL
Outcome: Overall survival; subgroup: Age - Age ≥60 years (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (CALGB 40603)	randomised trials	serious[a]	serious[c]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.59 (0.24 to 1.43)	Not estimable	Very low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

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 and the number of participants was less than 500, outcome was downgraded two levels

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

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

Pathological complete response

Table 20 Pathological complete response

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Pathological complete response: main analysis (RR greater than 1 favours platinum based neoadjuvant chemotherapy)												
13 (ADAPT-TN, Ando 2014, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, GeparOLA, GeparSixto, Gigolaeva 2019, NACATRINE, NeoCART, Zhang 2016, Zhao 2014)	randomised trials	serious[a]	serious[c]	not serious	not serious	none	740/1576 (47.0%)	433/1371 (31.6%)	RR 1.48 (1.27 to 1.73)	152 more per 1,000 (from 85 more to 231 more)	Low	CRITICAL
Outcome: Pathological complete response; subgroup: BRCA mutation status - BRCA wildtype (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 67%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
5 (BrighTNess, GeparOcto, GeparOLA, GeparSixto, NACATRINE)	randomised trials	serious[a]	very serious[e]	not serious	not serious	none	383/723 (53.0%)	177/462 (38.3%)	RR 1.43 (1.08 to 1.89)	165 more per 1,000 (from 31 more to 341 more)	Very low	CRITICAL
Outcome: Pathological complete response; subgroup: BRCA mutation status - BRCA mutation (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Fixed effects model												
4 (BrighTNess, GeparOcto, GeparOLA, GeparSixto)	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	91/144 (63.2%)	62/106 (58.5%)	RR 1.17 (0.95 to 1.44)	99 more per 1,000 (from 29 fewer to 257 more)	Very low	CRITICAL
Outcome: Pathological complete response; subgroup: BRCA mutation status - BRCA wildtype (OR greater than 1 favours platinum based neoadjuvant chemotherapy)												
1 (NACATRINE)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	58	59	OR 1.67 (0.75 to 3.70)	Not estimable	Very low	CRITICAL
Outcome: Pathological complete response; subgroup: BRCA mutation status - BRCA mutation (OR greater than 1 favours platinum based neoadjuvant chemotherapy)												
1 (NACATRINE)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	15	14	OR 2.75 (0.58 to 13.01)	Not estimable	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Outcome: Pathological complete response; subgroup: Same backbone chemotherapy with or without platinum (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Fixed effects model												
6 (Ando 2014, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparSixto, NACATRINE)	randomised trials	not serious	not serious	not serious	not serious	none	467/1012 (46.1%)	195/684 (28.5%)	RR 1.53 (1.33 to 1.76)	151 more per 1,000 (from 94 more to 217 more)	High	CRITICAL
Outcome: Pathological complete response; subgroup: Different backbone chemotherapy with or without platinum (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 64%)												
7 (ADAPT-TN, GeparOcto, GeparOLA, Gigolaeva 2019, NeoCART, Zhang 2016, Zhao 2014)	randomised trials	serious[a]	very serious[e]	not serious	not serious	none	273/564 (48.4%)	238/687 (34.6%)	RR 1.47 (1.14 to 1.89)	163 more per 1,000 (from 49 more to 308 more)	Very low	CRITICAL
Outcome: Pathological complete response; subgroup: Lymph node status - Lymph node positive (RR greater than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (BrighTNess, Zhang 2016)	randomised trials	not serious	not serious	not serious	not serious	none	113/246 (45.9%)	24/105 (22.9%)	RR 1.89 (1.31 to 2.73)	203 more per 1,000 (from 71 more to 395 more)	High	CRITICAL
Outcome: Pathological complete response; subgroup: Lymph node status - Lymph node negative (RR greater than 1 favours platinum based neoadjuvant chemotherapy)												
2 (BrighTNess, Zhang 2016)	randomised trials	not serious	not serious	not serious	not serious	none	164/274 (59.9%)	31/96 (32.3%)	RR 1.83 (1.35 to 2.50)	268 more per 1,000 (from 113 more to 484 more)	High	CRITICAL
Outcome: Pathological complete response; subgroup: Anthracycline content of chemotherapy - Anthracycline-free platinum (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Fixed effects model												
4 (ADAPT-TN, NeoCART, Zhang 2016, Zhao 2014)	randomised trials	serious[a]	not serious	not serious	not serious	none	121/272 (44.5%)	82/307 (26.7%)	RR 1.67 (1.33 to 2.09)	179 more per 1,000 (from 88 more to 291 more)	Moderate	CRITICAL
Outcome: Pathological complete response; subgroup: Anthracycline content of chemotherapy - Anthracycline-containing platinum (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 62%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
9 (Ando 2014, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, GeparOLA, GeparSixto, Gigolaeva 2019, NACATRINE)	randomised trials	serious[a]	very serious[e]	not serious	not serious	none	619/1304 (47.5%)	351/1064 (33.0%)	RR 1.44 (1.20 to 1.73)	145 more per 1,000 (from 66 more to 241 more)	Very low	CRITICAL
Outcome: Pathological complete response; subgroup: Age - Age 40 years or less (OR greater than 1 favours platinum based neoadjuvant chemotherapy)												
2 (NeoCART, Zhang 2016)	randomised trials	not serious	not serious	not serious	very serious[b]	none	Not reported	Not reported	OR 3.02 (0.74 to 12.30)	Not estimable	Low	CRITICAL
Outcome: Pathological complete response; subgroup: Age - Age more than 40 years (OR greater than 1 favours platinum based neoadjuvant chemotherapy)												
2 (NeoCART, Zhang 2016)	randomised trials	not serious	not serious	not serious	serious[g]	none	Not reported	Not reported	OR 2.93 (1.37 to 6.26)	Not estimable	Moderate	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

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 and the number of participants was less than 500, outcome was downgraded two levels

c. I2 was between 41% and 60%, outcome was downgraded one level

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

e. I2 was greater than >60%, outcome was downgraded two levels

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

g. Number of participants was less than 500, outcome was downgraded one level

Breast cancer mortality

Table 21 Breast cancer mortality

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
Breast cancer mortality (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (Zhang 2016)	randomised trials	very serious[b]	serious[a]	not serious	serious[c]	none	0/47 (0.0%)	11/44 (25.0%)	RR 0.04 (0.00 to 0.67)	240 fewer per 1,000 (from 82 to 0 fewer)	Very low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. Data was only available from one study, 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. Number of participants was less than 500, outcome was downgraded one level

Local and/or locoregional recurrence

Table 22 Local and/or locoregional recurrence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Local and/or locoregional recurrence (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
5 (Ando 2014, BrighTNess, CALGB 40603, GeparSixto, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	69/938 (7.4%)	74/612 (12.1%)	RR 0.62 (0.45 to 0.85)	46 fewer per 1,000 (from 67 fewer to 18 fewer)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk 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

Breast conservation rate

Table 23 Breast conservation rate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
Breast conservation rate (RR greater than 1 favours platinum based neoadjuvant chemotherapy)												
4 (BrighTNess, GEICAM 2006-03, NACATRINE, NeoCART)	randomised trials	not serious	not serious	not serious	serious[a]	none	344/625 (55.0%)	146/306 (47.7%)	RR 1.08 (0.93 to 1.24)	38 more per 1,000 (from 33 fewer to 115 more)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

Explanations

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

Treatment adherence

Table 24 Treatment adherence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Treatment adherence: early cessation of treatment (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
9 (ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, GeparSixto, NACATRINE, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	301/1425 (21.1%)	199/1120 (17.8%)	RR 1.18 (1.01 to 1.39)	32 more per 1,000 (from 2 more to 69 more)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk 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

Shorter term adverse events

Table 25 Shorter term adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Anaemia (RR less than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 56%)												
7 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NACATRINE, NeoCART, Zhao 2014)	randomised trials	serious[a]	serious[c]	not serious	not serious	none	156/1101 (14.2%)	13/853 (1.5%)	RR 6.21 (2.24 to 17.23)	79 more per 1,000 (from 19 more to 247 more)	Low	IMPORTANT
Febrile neutropenia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
5 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	not serious	none	64/1019 (6.3%)	30/767 (3.9%)	RR 1.98 (1.32 to 2.98)	38 more per 1,000 (from 13 more to 77 more)	Moderate	IMPORTANT
Leukopenia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
4 (ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03)	randomised trials	serious[a]	not serious	not serious	not serious	none	68/894 (7.6%)	33/603 (5.5%)	RR 1.67 (1.11 to 2.51)	37 more per 1,000 (from 6 more to 83 more)	Moderate	IMPORTANT
Neutropenia (RR less than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 90%)												
9 (ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NACATRINE, NeoCART, Zhang 2016, Zhao 2014)	randomised trials	serious[a]	very serious[f]	not serious	not serious	none	545/1299 (42.0%)	189/1077 (17.5%)	RR 1.88 (1.09 to 3.23)	154 more per 1,000 (from 16 more to 391 more)	Very low	IMPORTANT
Thrombocytopenia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
7 (ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	not serious	none	116/1188 (9.8%)	11/962 (1.1%)	RR 7.01 (3.93 to 12.48)	69 more per 1,000 (from 34 more to 131 more)	Moderate	IMPORTANT
Alanine aminotransferase increased (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
3 (ADAPT-TN, BrighTNess, CALGB 40603)	randomised trials	serious[a]	not serious	not serious	not serious	none	16/847 (1.9%)	27/556 (4.9%)	RR 0.47 (0.24 to 0.92)	26 fewer per 1,000 (from 37 fewer to 4 fewer)	Moderate	IMPORTANT
Aspartate aminotransferase increased (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
2 (ADAPT-TN, BrighTNess)	randomised trials	serious[a]	not serious	not serious	serious[e]	none	6/622 (1.0%)	2/338 (0.6%)	RR 1.61 (0.40 to 6.38)	4 more per 1,000 (from 4 fewer to 32 more)	Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Constipation (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
2 (ADAPT-TN, BrighTNess)	randomised trials	not serious	not serious	not serious	serious[e]	none	1/464 (0.2%)	2/259 (0.8%)	RR 0.32 (0.04 to 2.63)	5 fewer per 1,000 (from 7 fewer to 13 more)	Moderate	IMPORTANT
Dehydration (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (BrighTNess)	randomised trials	not serious	serious[d]	not serious	serious[e]	none	1/158 (0.6%)	0/79 (0.0%)	RR 1.51 (0.06 to 36.64)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT
Diarrhoea (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
4 (ADAPT-TN, BrighTNess, CALGB 40603, NeoCART)	randomised trials	serious[a]	not serious	not serious	serious[e]	none	16/891 (1.8%)	7/600 (1.2%)	RR 1.48 (0.61 to 3.60)	6 more per 1,000 (from 5 fewer to 30 more)	Low	IMPORTANT
Dizziness (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (BrighTNess)	randomised trials	not serious	not serious	not serious	serious[e]	none	1/158 (0.6%)	0/79 (0.0%)	RR 1.51 (0.06 to 36.64)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Moderate	IMPORTANT
Dyspnoea (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (BrighTNess)	randomised trials	not serious	not serious	not serious	serious[e]	none	0/313 (0.0%)	1/79 (1.3%)	RR 0.08 (0.00 to 2.07)	12 fewer per 1,000 (from 0 fewer to 14 more)	Moderate	IMPORTANT
Gamma-glutamyltransferase increased (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (ADAPT-TN)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	3/151 (2.0%)	2/180 (1.1%)	RR 1.79 (0.30 to 10.56)	9 more per 1,000 (from 8 fewer to 106 more)	Very low	IMPORTANT
Hyperglycaemia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (BrighTNess)	randomised trials	not serious	not serious	not serious	serious[e]	none	6/471 (1.3%)	2/158 (1.3%)	RR 1.10 (0.23 to 5.27)	1 more per 1,000 (from 10 fewer to 54 more)	Moderate	IMPORTANT
Hypersensitivity (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (GEICAM 2006-03)	randomised trials	not serious	seriousd	serious[g]	very serious[b]	none	1/47 (2.1%)	2/46 (4.3%)	RR 0.49 (0.05 to 5.21)	22 fewer per 1,000 (from 41 fewer to 183 more)	Very low	IMPORTANT
Hypertension (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
3 (ADAPT-TN, BrighTNess, CALGB 40603)	randomised trials	serious[a]	not serious	not serious	serious[e]	none	14/847 (1.7%)	18/556 (3.2%)	RR 0.61 (0.31 to 1.20)	13 fewer per 1,000 (from 22 fewer to 6 more)	Low	IMPORTANT
Hypokalaemia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (BrighTNess, CALGB 40603)	randomised trials	serious[a]	not serious	not serious	serious[e]	none	11/696 (1.6%)	5/376 (1.3%)	RR 1.57 (0.59 to 4.18)	8 more per 1,000 (from 5 fewer to 42 more)	Low	IMPORTANT
Hyponatraemia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (BrighTNess)	randomised trials	not serious	serious[d]	not serious	serious[e]	none	3/313 (1.0%)	0/79 (0.0%)	RR 1.78 (0.09 to 34.18)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT
Increased ALT/AST ratio (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (NeoCART)	randomised trials	not serious	not serious	not serious	very serious[b]	none	1/44 (2.3%)	0/44 (0.0%)	RR 3.00 (0.13 to 71.70)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT
Infection (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
1 (GEICAM 2006-03)	randomised trials	not serious	serious[d]	serious[g]	very serious[b]	none	4/47 (8.5%)	4/46 (8.7%)	RR 0.98 (0.26 to 3.68)	2 fewer per 1,000 (from 64 fewer to 233 more)	Very low	IMPORTANT
Liver function test increased (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (ADAPT-TN)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	0/151 (0.0%)	8/180 (4.4%)	RR 0.11 (0.01 to 1.94)	40 fewer per 1,000 (from 44 fewer to 42 more)	Very low	IMPORTANT
Lymphopenia (RR less than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 59%)												
2 (BrighTNess, GEICAM 2006-03)	randomised trials	not serious	serious[c]	not serious	serious[e]	none	4/518 (0.8%)	3/204 (1.5%)	RR 0.48 (0.04 to 6.21)	8 fewer per 1,000 (from 14 fewer to 77 more)	Low	IMPORTANT
Nausea (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
6 (ADAPT-TN, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, Zhao 2014)	randomised trials	seriousa	not serious	not serious	serious[e]	none	28/977 (2.9%)	18/837 (2.2%)	RR 1.45 (0.81 to 2.60)	10 more per 1,000 (from 4 fewer to 34 more)	Low	IMPORTANT
Oral mucositis (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
2 (ADAPT-TN, CALGB 40603)	randomised trials	serious[a]	not serious	not serious	serious[e]	none	5/376 (1.3%)	3/398 (0.8%)	RR 1.61 (0.41 to 6.23)	5 more per 1,000 (from 4 fewer to 39 more)	Low	IMPORTANT
Pneumonia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
2 (ADAPT-TN, BrighTNess)	randomised trials	serious[a]	not serious	not serious	serious[e]	none	5/622 (0.8%)	2/338 (0.6%)	RR 1.28 (0.30 to 5.48)	2 more per 1,000 (from 4 fewer to 27 more)	Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Pruritus (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (NACATRINE)	randomised trials	serious[a]	serious[d]	not serious	very serious[b]	none	1/73 (1.4%)	0/73 (0.0%)	RR 3.00 (0.12 to 72.45)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Very low	IMPORTANT
Pyrexia (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (BrighTNess)	randomised trials	not serious	serious[d]	not serious	serious[e]	none	1/471 (0.2%)	1/158 (0.6%)	RR 0.40 (0.07 to 2.35)	4 fewer per 1,000 (from 6 fewer to 9 more)	Low	IMPORTANT
Sinusitis (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (BrighTNess)	randomised trials	not serious	serious[d]	not serious	serious[e]	none	2/313 (0.6%)	0/79 (0.0%)	RR 1.27 (0.06 to 26.27)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT
Stomatitis (RR less than 1 favours platinum based neoadjuvant chemotherapy) Random effects model (I2 57%)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
1 (BrighTNess)	randomised trials	not serious	serious[d]	not serious	serious[e]	none	2/471 (0.4%)	1/158 (0.6%)	RR 0.48 (0.02 to 13.59)	3 fewer per 1,000 (from 6 fewer to 80 more)	Low	IMPORTANT
Syncope (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (BrighTNess)	randomised trials	not serious	serious[d]	not serious	serious[e]	none	5/471 (1.1%)	1/158 (0.6%)	RR 1.16 (0.19 to 6.94)	1 more per 1,000 (from 5 fewer to 38 more)	Low	IMPORTANT
Vomiting (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
4 (BrighTNess, CALGB 40603, NeoCART, Zhang 2016)	randomised trials	serious[a]	not serious	not serious	serious[e]	none	14/787 (1.8%)	11/464 (2.4%)	RR 0.92 (0.42 to 2.05)	2 fewer per 1,000 (from 14 fewer to 25 more)	Low	IMPORTANT
Treatment-related death (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
2 (BrighTNess, CALGB 40603)	randomised trials	not serious	not serious	not serious	serious[e]	none	2/538 (0.4%)	0/297 (0.0%)	RR 1.60 (0.19 to 13.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Moderate	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

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 and the number of participants was less than 500, outcome was downgraded two levels

c. I2 was between 41% and 60%, outcome was downgraded one level

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

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

f. I2 was greater than >60%, outcome was downgraded two levels

g. Greater than >50% of the weight in a meta-analysis came from partially indirect or indirect studies, outcome was downgraded one level

Longer term adverse events

Table 26 Longer term adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Fatigue (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
4 (BrighTNess, CALGB 40603, GEICAM 2006-03, NACATRINE)	randomised trials	serious[a]	not serious	not serious	serious[c]	none	42/816 (5.1%)	29/495 (5.9%)	RR 1.26 (0.80 to 1.97)	15 more per 1,000 (from 12 fewer to 57 more)	Low	IMPORTANT
Neuropathy (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
6 (ADAPT-TN, BrighTNess, CALGB 40603, GeparOcto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	serious[c]	none	34/1123 (3.0%)	28/901 (3.1%)	RR 1.18 (0.73 to 1.89)	6 more per 1,000 (from 8 fewer to 28 more)	Low	IMPORTANT
Pain (RR less than 1 favours platinum based neoadjuvant chemotherapy)												

4 (ADAPT-TN, BrighTNess, CALGB 40603, NeoCART)	randomised trials	serious[a]	not serious	not serious	serious[c]	none	22/733 (3.0%)	12/521 (2.3%)	RR 1.54 (0.78 to 3.05)	12 more per 1,000 (from 5 fewer to 47 more)	Low	IMPORTANT
Pulmonary embolism (RR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (BrighTNess)	randomised trials	not serious	serious[b]	not serious	serious[c]	none	3/471 (0.6%)	1/158 (0.6%)	RR 0.92 (0.15 to 5.51)	1 fewer per 1,000 (from 5 fewer to 29 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **OR:** odds ratio; **RR:** risk ratio

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

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

Triple negative breast cancer sensitivity analyses removing studies where an anthracycline is not included in one or both arms

Table 27 Triple negative breast cancer: sensitivity analyses

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Outcome: Disease-free survival; sensitivity analysis: Anthracycline content of chemotherapy												
6 (Ando 2014, BrighTNess, CALGB 40603, GeparOcto, GeparSixto, NACATRINE)	randomised trials	serious[a]	serious[b]	not serious	not serious	none	1172	834	HR 0.72 (0.61 to 0.86)	Not estimable	Low	CRITICAL
Outcome: Overall survival; sensitivity analysis: Anthracycline content of chemotherapy												
6 (Ando 2014, BrighTNess, CALGB 40603, GeparOcto, GeparSixto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	not serious	none	1172	831	HR 0.78 (0.63 to 0.96)	Not estimable	Moderate	CRITICAL
Outcome: Pathological complete response; sensitivity analysis: Anthracycline content of chemotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
9 (Ando 2014, BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, GeparOLA, GeparSixto, Gigolaeva 2019, NACATRINE)	randomised trials	serious[a]	very serious[c]	not serious	not serious	none	619/1304 (47.5%)	351/1064 (33.0%)	RR 1.44 (1.20 to 1.73)	145 more per 1,000 (from 66 more to 241 more)	Very low	CRITICAL
Local and/or locoregional recurrence; sensitivity analysis: Anthracycline content of chemotherapy												
4 (Ando 2014, BrighTNess, CALGB 40603, GeparSixto)	randomised trials	serious[a]	not serious	not serious	not serious	none	64/891 (7.2%)	67/568 (11.8%)	RR 0.61 (0.44 to 0.85)	46 fewer per 1,000 (from 66 fewer to 18 fewer)	Moderate	IMPORTANT
Breast conservation rate; sensitivity analysis: Anthracycline content of chemotherapy												
3 (BrighTNess, GEICAM 2006-03, NACATRINE)	randomised trials	not serious	not serious	not serious	serious[d]	none	328/581 (56.5%)	129/262 (49.2%)	RR 1.09 (0.94 to 1.26)	44 more per 1,000 (from 30 fewer to 128 more)	Moderate	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Treatment adherence: early cessation of treatment; sensitivity analysis: Anthracycline content of chemotherapy												
6 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, GeparSixto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	not serious	none	283/1183 (23.9%)	176/852 (20.7%)	RR 1.21 (1.03 to 1.43)	43 more per 1,000 (from 6 more to 89 more)	Moderate	IMPORTANT
Anaemia; sensitivity analysis: Anthracycline content of chemotherapy												
5 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	not serious	none	139/1019 (13.6%)	5/767 (0.7%)	RR 8.91 (3.58 to 22.22)	52 more per 1,000 (from 17 more to 138 more)	Moderate	IMPORTANT
Febrile neutropenia; sensitivity analysis: Anthracycline content of chemotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
5 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	not serious	none	64/1019 (6.3%)	30/767 (3.9%)	RR 1.98 (1.32 to 2.98)	38 more per 1,000 (from 13 more to 77 more)	Moderate	IMPORTANT
Leukopenia; sensitivity analysis: Anthracycline content of chemotherapy												
3 (BrighTNess, CALGB 40603, GEICAM 2006-03)	randomised trials	serious[a]	not serious	not serious	not serious	none	65/743 (8.7%)	30/422 (7.1%)	RR 1.71 (1.12 to 2.61)	50 more per 1,000 (from 9 more to 114 more)	Moderate	IMPORTANT
Neutropenia; sensitivity analysis: Anthracycline content of chemotherapy												
5 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NACATRINE)	randomised trials	serious[a]	very serious[c]	not serious	not serious	none	471/1019 (46.2%)	107/767 (14.0%)	RR 3.23 (1.65 to 6.33)	311 more per 1,000 (from 91 more to 744 more)	Very low	IMPORTANT
Thrombocytopenia; sensitivity analysis: Anthracycline content of chemotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
4 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	not serious	none	111/946 (11.7%)	8/694 (1.2%)	RR 9.09 (4.65 to 17.77)	93 more per 1,000 (from 42 more to 193 more)	Moderate	IMPORTANT
Alanine aminotransferase increased; sensitivity analysis: Anthracycline content of chemotherapy												
2 (BrighTNess, CALGB 40603)	randomised trials	not serious	not serious	not serious	serious[d]	none	11/696 (1.6%)	6/376 (1.6%)	RR 0.95 (0.35 to 2.58)	1 fewer per 1,000 (from 10 fewer to 25 more)	Moderate	IMPORTANT
Aspartate aminotransferase increased; sensitivity analysis: Anthracycline content of chemotherapy												
1 (BrighTNess)	randomised trials	not serious	serious[e]	not serious	serious[d]	none	3/471 (0.6%)	0/158 (0.0%)	RR 1.38 (0.15 to 12.38)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT
Constipation; sensitivity analysis: Anthracycline content of chemotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (BrighTNess)	randomised trials	not serious	serious[e]	not serious	very serious[f]	none	1/313 (0.3%)	1/79 (1.3%)	RR 0.25 (0.02 to 3.99)	9 fewer per 1,000 (from 12 fewer to 38 more)	Very low	IMPORTANT
Diarrhoea; sensitivity analysis: Anthracycline content of chemotherapy												
2 (BrighTNess, CALGB 40603)	randomised trials	serious[a]	not serious	not serious	serious[d]	none	13/696 (1.9%)	3/376 (0.8%)	RR 2.05 (0.63 to 6.64)	8 more per 1,000 (from 3 fewer to 45 more)	Low	IMPORTANT
Hypertension; sensitivity analysis: Anthracycline content of chemotherapy												
2 (BrighTNess, CALGB 40603)	randomised trials	seriousa	not serious	not serious	serious[d]	none	13/696 (1.9%)	17/376 (4.5%)	RR 0.59 (0.29 to 1.17)	19 fewer per 1,000 (from 32 fewer to 8 more)	Low	IMPORTANT
Pneumonia; sensitivity analysis: Anthracycline content of chemotherapy												
1 (BrighTNess)	randomised trials	not serious	serious[e]	not serious	serious[d]	none	3/471 (0.6%)	0/158 (0.0%)	RR 1.38 (0.15 to 12.38)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Nausea; sensitivity analysis: Anthracycline content of chemotherapy												
4 (BrighTNess, CALGB 40603, GEICAM 2006-03, GeparOcto)	randomised trials	serious[a]	not serious	not serious	serious[d]	none	22/788 (2.8%)	13/615 (2.1%)	RR 1.48 (0.75 to 2.94)	10 more per 1,000 (from 5 fewer to 41 more)	Low	IMPORTANT
Oral mucositis; sensitivity analysis: Anthracycline content of chemotherapy												
1 (CALGB 40603)	randomised trials	serious[a]	serious[e]	not serious	very serious[f]	none	5/225 (2.2%)	2/218 (0.9%)	RR 2.42 (0.47 to 12.35)	13 more per 1,000 (from 5 fewer to 104 more)	Very low	IMPORTANT
Vomiting; sensitivity analysis: Anthracycline content of chemotherapy												
2 (BrighTNess, CALGB 40603)	randomised trials	serious[a]	not serious	not serious	serious[d]	none	11/696 (1.6%)	4/376 (1.1%)	RR 1.58 (0.53 to 4.67)	6 more per 1,000 (from 5 fewer to 39 more)	Low	IMPORTANT
Treatment-related death; sensitivity analysis: Anthracycline content of chemotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
2 (BrighTNess, CALGB 40603)	randomised trials	not serious	not serious	not serious	serious[d]	none	2/538 (0.4%)	0/297 (0.0%)	RR 1.60 (0.19 to 13.74)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Moderate	IMPORTANT
Fatigue; sensitivity analysis: Anthracycline content of chemotherapy												
4 (BrighTNess, CALGB 40603, GEICAM 2006-03, NACATRINE)	randomised trials	serious[a]	not serious	not serious	serious[d]	none	42/816 (5.1%)	29/495 (5.9%)	RR 1.26 (0.80 to 1.97)	15 more per 1,000 (from 12 fewer to 57 more)	Low	IMPORTANT
Neuropathy; sensitivity analysis: Anthracycline content of chemotherapy												
4 (BrighTNess, CALGB 40603, GeparOcto, NACATRINE)	randomised trials	serious[a]	not serious	not serious	serious[d]	none	32/972 (3.3%)	27/721 (3.7%)	RR 1.14 (0.70 to 1.85)	5 more per 1,000 (from 11 fewer to 32 more)	Low	IMPORTANT
Pain; sensitivity analysis: Anthracycline content of chemotherapy												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum based**	**Non-platinum based**	**Relative (95% CI)**	**Absolute (95% CI)**		
2 (BrighTNess, CALGB 40603)	randomised trials	serious[a]	not serious	not serious	serious[d]	none	18/538 (3.3%)	9/297 (3.0%)	RR 1.57 (0.71 to 3.45)	17 more per 1,000 (from 9 fewer to 74 more)	Low	IMPORTANT

CI: confidence interval; **HR:** hazard ratio; **RR:** risk 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. I2 was between 41% and 60%, outcome was downgraded one level

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

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

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

f. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

Germline BRCA mutation analyses

Critical outcomes

Table 28 Critical outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum based	Non-platinum based	Relative (95% CI)	Absolute (95% CI)		
Disease-free survival - BRCA wildtype (TNBC) (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
2 (BrighTNess, GeparSixto)	randomised trials	not serious	not serious	not serious	not serious	none	390	257	HR 0.60 (0.43 to 0.84)	Not estimable	High	CRITICAL
Disease-free survival - BRCA1 or BRCA2 mutation (all receptor subtypes, including triple negative) (GeparOcto trial reported BRCA1 or BRCA2 mutation for all receptor subtypes; total sample size: n=96) (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
3 (BrighTNess, GeparOcto, GeparSixto)	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	72	46	HR 0.64 (0.35 to 1.18)	Not estimable	Very low	CRITICAL
Disease-free survival - total (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
3 (BrighTNess, GeparOcto, GeparSixto)	randomised trials	not serious	not serious	not serious	not serious	none	462	303	HR 0.61 (0.46 to 0.82)	Not estimable	High	CRITICAL

Overall survival - BRCA1 or BRCA2 mutation (all receptor subtypes, including triple negative; total sample size: n=96) (HR less than 1 favours platinum based neoadjuvant chemotherapy)												
1 (GeparOcto)	randomised trials	serious[a]	serious[c]	not serious	very serious[b]	none	Not reported	Not reported	HR 0.98 (0.28 to 3.38)	Not estimable	Very low	CRITICAL
Pathological complete response - BRCA 1/2 wildtype (all receptor subtypes, including triple negative) (GeparOLA trial reported BRCA1 or BRCA2 mutation for all receptor subtypes) (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 68%)												
5 (BrighTNess, GeparOcto, GeparOLA, GeparSixto, NACATRINE)	randomised trials	serious[a]	very serious[d]	not serious	not serious	none	383/727 (52.7 %)	177/466 (38.0%)	RR 1.43 (1.08 to 1.89)	163 more per 1,000 (from 30 more to 338 more)	Very low	CRITICAL
Pathological complete response - BRCA 1/2 mutation (all receptor subtypes, including triple negative) (GeparOLA trial reported BRCA1 or BRCA2 mutation for all receptor subtypes) (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Fixed effects model												
4 (BrighTNess, GeparOcto, GeparOLA, GeparSixto)	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	93/150 (62.0%) Previously 93/152	72/121 (59.5%) Previously 68/115	RR 1.11 (0.91 to 1.37)	65 more per 1,000 (from 54 fewer to 220 more)	Very low	CRITICAL
Pathological complete response - total (RR greater than 1 favours platinum based neoadjuvant chemotherapy) – Random effects model (I2 50%)												
5 (BrighTNess, GeparOcto, GeparOLA, GeparSixto, NACATRINE)	randomised trials	serious[a]	serious[e]	not serious	not serious	none	476/877 (54.3%) Previously 476/876	249/587 (42.4%) Previously 247/584	RR 1.29 (1.08 to 1.54)	123 more per 1,000 (from 34 more to 229 more)	Low	CRITICAL

CI: confidence interval; **HR:** hazard ratio; **RR:** risk 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

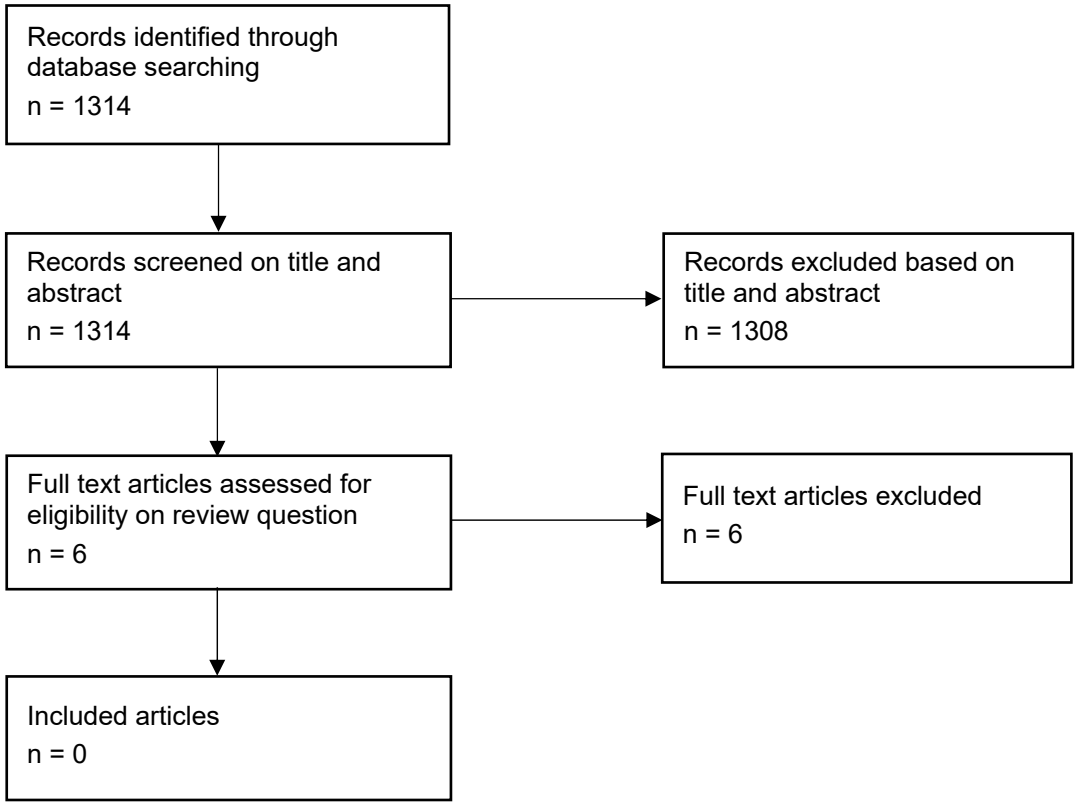
b. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

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

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

e. I2 was between 41% and 60%, outcome was downgraded one level

Appendix G – Economic evidence study selection



Appendix I – Health economic model

No original economic modelling was undertaken.

Appendix J – Excluded studies

The systematic review by Mason et al. 2023 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 Mason et al. 2023.

Effectiveness studies

Study	Reason for exclusion
Blohmer, Jens-Uwe, Link, Theresa, Reinisch, Mattea et al. (2022) Effect of Denosumab Added to 2 Different nab-Paclitaxel Regimens as Neoadjuvant Therapy in Patients With Primary Breast Cancer: The GeparX 2 x 2 Randomized Clinical Trial. JAMA oncology 8(7): 1010-1018	- Study does not contain a relevant intervention *Carboplatin was an additional treatment. Peripheral sensory neuropathy frequency was reported on people receiving additional carboplatin but total number of people taking carboplatin was not reported*
Caramelo, Olga, Silva, Cristina, Caramelo, Francisco et al. (2019) The effect of neoadjuvant platinum-based chemotherapy in BRCA mutated triple negative breast cancers -systematic review and meta-analysis. Hereditary cancer in clinical practice 17: 11	- Systematic review used as source of primary studies
Caramelo, Olga, Silva, Cristina, Caramelo, Francisco et al. (2022) Efficacy of different neoadjuvant treatment regimens in BRCA-mutated triple negative breast cancer: a systematic review and meta-analysis. Hereditary cancer in clinical practice 20(1): 34	- Systematic review used as source of primary studies
Chai, Yue, Chen, Yujie, Zhang, Di et al. (2022) Homologous Recombination Deficiency (HRD) and BRCA 1/2 Gene Mutation for Predicting the Effect of Platinum-Based Neoadjuvant Chemotherapy of Early-Stage Triple-Negative Breast Cancer (TNBC): A Systematic Review and Meta-Analysis. Journal of personalized medicine 12(2)	- Systematic review used as source of primary studies
Feng, W., He, Y., Zhang, H. et al. (2022) A meta-analysis of the effect and safety of platinum-based neoadjuvant chemotherapy in treatment of resectable triple-negative	- Systematic review used as source of primary studies

Study	Reason for exclusion
breast cancer. Anti-Cancer Drugs 33(1): e52-e60	
Freitas, Ana Julia Aguiar, Nunes, Caroline Rocha, Mano, Max Senna et al. (2023) Gene expression alterations predict the pathological complete response in triple-negative breast cancer exploratory analysis of the NACATRINE trial. Scientific reports 13(1): 21411	- Secondary publication of an included study that does not provide any additional relevant information *NACATRINE trial; this publication aimed to identify the biomarkers of pathological complete response*
Gerber, B., Schneeweiss, A., Mobus, V. et al. (2022) Pathological Response in the Breast and Axillary Lymph Nodes after Neoadjuvant Systemic Treatment in Patients with Initially Node-Positive Breast Cancer Correlates with Disease Free Survival: An Exploratory Analysis of the GeparOcto Trial. Cancers 14(3): 521	- Secondary publication of an included study that does not provide any additional relevant information *GeparOcto trial; data not reported by treatment arms*
Gluz, Oleg, Nitz, Ulrike, Kolberg-Liedtke, Cornelia et al. (2022) De-escalated Neoadjuvant Chemotherapy in Early Triple-Negative Breast Cancer (TNBC): Impact of Molecular Markers and Final Survival Analysis of the WSG-ADAPT-TN Trial. Clinical cancer research : an official journal of the American Association for Cancer Research 28(22): 4995-5003	- Secondary publication of an included study that does not provide any additional relevant information *ADAPT-TN trial; outcomes reported by pathological complete response*
Golshan, M, Loibl, S, Wong, SM et al. (2020) Breast Conservation After Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer: surgical Results From the BrighTNess Randomized Clinical Trial. JAMA surgery 155(3): e195410	- Secondary publication of an included study that does not provide any additional relevant information *BrighTNess trial; breast conservation rate was not reported by treatment arm*
Golshan, M, Wong, SM, Loibl, S et al. (2020) Early assessment with magnetic resonance imaging for prediction of pathologic response to neoadjuvant chemotherapy in triple-negative breast cancer: results from the phase III BrighTNess trial. European journal of surgical oncology 46(2): 223-228	- Secondary publication of an included study that does not provide any additional relevant information *BrighTNess trial; outcome data was diagnostic accuracy*

Study	Reason for exclusion
Hahnen, Eric, Lederer, Bianca, Hauke, Jan et al. (2017) Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA oncology 3(10): 1378-1385	- Secondary publication of an included study that does not provide any additional relevant information *GeparSixto trial; data already reported by Mason 2023*
Jia, Xiaomeng, Wang, Kainan, Xu, Lingzhi 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
Kolberg-Liedtke, Cornelia, Feuerhake, Friedrich, Garke, Madlen et al. (2022) Impact of stromal tumor-infiltrating lymphocytes (sTILs) on response to neoadjuvant chemotherapy in triple-negative early breast cancer in the WSG-ADAPT TN trial. Breast cancer research : BCR 24(1): 58	- Secondary publication of an included study that does not provide any additional relevant information *ADAPT TN trial; outcomes reported by stromal tumour-infiltrating lymphocytes levels*
Li ZY, Zhang Z, Cao XZ et al. (2020) Platinum-based neoadjuvant chemotherapy for triple-negative breast cancer: a systematic review and meta-analysis. The Journal of international medical research 48(10): 300060520964340	- Systematic review used as source of primary studies
Lin, Canling, Cui, Jiajun, Peng, Zhen et al. (2022) Efficacy of platinum-based and non-platinum-based drugs on triple-negative breast cancer: meta-analysis. European journal of medical research 27(1): 201	- Systematic review used as source of primary studies
Mason, Sofia Re, Willson, Melina L, Egger, Sam J et al. (2024) Platinum chemotherapy for early triple-negative breast cancer. Breast (Edinburgh, Scotland) 75: 103712	- Secondary publication of an included study that does not provide any additional relevant information *Same data reported by Mason et al. 2023 as a Cochrane systematic review*
Mayer, E.L., Abramson, V., Jankowitz, R. et al. (2020) TBCRC 030: a phase II study of preoperative cisplatin versus paclitaxel in triple-negative breast cancer: evaluating the homologous	- Taxane was not included in the neoadjuvant regimen

Study	Reason for exclusion
recombination deficiency (HRD) biomarker. Annals of Oncology 31(11): 1518-1525	
Mukhtar, Rita A, Chau, Harrison, Woriax, Hannah et al. (2023) Breast Conservation Surgery and Mastectomy Have Similar Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From 1462 Patients on the Prospective, Randomized I-SPY2 Trial. Annals of surgery 278(3): 320-327	- Secondary publication of an included study that does not provide any additional relevant information *I-SPY2 trial; outcomes were reported by type of surgery without data on neoadjuvant chemotherapy*
Osdoit, Marie, Yau, Christina, Symmans, W Fraser et al. (2022) Association of Residual Ductal Carcinoma In Situ With Breast Cancer Recurrence in the Neoadjuvant I-SPY2 Trial. JAMA surgery 157(11): 1034-1041	- Secondary publication of an included study that does not provide any additional relevant information *I-SPY2 trial; outcomes reported by Residual Ductal Carcinoma In Situ rather than by treatment arm*
Pathak, Neha, Sharma, Aparna, Elavarasi, Arunmozhimaran et al. (2022) Moment of truth-adding carboplatin to neoadjuvant/adjuvant chemotherapy in triple negative breast cancer improves overall survival: An individual participant data and trial-level Meta-analysis. Breast (Edinburgh, Scotland) 64: 7-18	- Systematic review used as source of primary studies
Petrelli, Fausto, Ghidini, Antonio, Rea, Carmen et al. (2024) Platinum dose in neoadjuvant therapy for triple-negative breast cancer: A systematic review and network meta-analysis. Current problems in cancer 50: 101096	- Systematic review used as source of primary studies
Pohl-Rescigno, Esther, Hauke, Jan, Loibl, Sibylle et al. (2020) Association of Germline Variant Status With Therapy Response in High-risk Early-Stage Breast Cancer: A Secondary Analysis of the GeparOcto Randomized Clinical Trial. JAMA oncology 6(5): 744-748	- Secondary publication of an included study that does not provide any additional relevant information *GeparOcto trial; data already reported by Mason 2023*
Rugo HS, Olopade OI, DeMichele A et al. (2016) Adaptive Randomization of Veliparib-Carboplatin Treatment in	- Taxane was not included in the neoadjuvant regimen

Study	Reason for exclusion
Breast Cancer. The New England journal of medicine 375(1): 23-34	
Saleh, R.R., Nadler, M.B., Desnoyers, A. et al. (2021) Platinum-based chemotherapy in early-stage triple negative breast cancer: A meta-analysis. Cancer Treatment Reviews 100: 102283	- Systematic review used as source of primary studies
Severson, Tesa M, Wolf, Denise M, Yau, Christina et al. (2017) The BRCA1ness signature is associated significantly with response to PARP inhibitor treatment versus control in the I-SPY 2 randomized neoadjuvant setting. Breast cancer research : BCR 19(1): 99	- Taxane was not included in the neoadjuvant regimen
Sharma, Priyanka, Kimler, Bruce F., O'Dea, Anne et al. (2021) Randomized Phase II Trial of Anthracycline-free and Anthracycline-containing Neoadjuvant Carboplatin Chemotherapy Regimens in Stage I–III Triple-negative Breast Cancer (NeoSTOP). Clin Cancer Res 27(4): 975-982	- Comparator in study does not match that specified in protocol *Both arms with carboplatin*
Sun, Wanyi, Wu, Yun, Ma, Fei 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
Tung, Nadine, Arun, Banu, Hacker, Michele R et al. (2020) TBCRC 031: Randomized Phase II Study of Neoadjuvant Cisplatin Versus Doxorubicin-Cyclophosphamide in Germline BRCA Carriers With HER2-Negative Breast Cancer (the INFORM trial). Journal of clinical oncology : official journal of the American Society of Clinical Oncology 38(14): 1539-1548	- Taxane was not included in the neoadjuvant regimen
Ueno, T., Kitano, S., Masuda, N. et al. (2022) Immune microenvironment, homologous recombination deficiency, and therapeutic response to	- Comparator in study does not match that specified in protocol

Study	Reason for exclusion
neoadjuvant chemotherapy in triple-negative breast cancer: Japan Breast Cancer Research Group (JBCRG)22 TR. BMC Medicine 20(1): 136	*Taxanes or anthracyclines were not included in the non-platinum arms*
Vliek, Sonja, Hilbers, Florentine S, van Werkhoven, Erik et al. (2023) High-dose alkylating chemotherapy in BRCA-altered triple-negative breast cancer: the randomized phase III NeoTN trial. NPJ breast cancer 9(1): 75	- Comparator in study does not match that specified in protocol *All participants received carboplatin*
Wang, Chang-Jun, Xu, Ying, Lin, Yan et al. (2020) Platinum-Based Neoadjuvant Chemotherapy for Breast Cancer With BRCA Mutations: A Meta-Analysis. Frontiers in oncology 10: 592998	- Systematic review used as source of primary studies
Wu X, Tang P, Li S et al. (2018) A randomized and open-label phase II trial reports the efficacy of neoadjuvant lobaplatin in breast cancer. Nature communications 9(1): 832	- Data not reported in an extractable format *Data on neoadjuvant and adjuvant platinum-based chemotherapy are not reported separately*
Yang, Ciqiu, Li, Peiyong, Chen, Yitian et al. (2024) Pooled analysis of NeoCARH and NeoCART trials: patient-reported outcomes in patients with early-stage breast cancer receiving platinum-based or anthracycline-based neoadjuvant chemotherapy. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 32(6): 401	- Data not reported in an extractable format *Pooled analysis of 2 trials; approximately 40% with triple negative breast cancer and 60% with HER2 positive breast cancer; data not reported separately*
Zhao, Fuxing, Shen, Guoshuang, Dong, Qiuxia et al. (2023) Impact of platinum-based chemotherapy on the prognosis of early triple-negative breast cancer: a systematic review and meta-analysis. Clinical and experimental medicine 23(6): 2025-2040	- Systematic review used as source of primary studies

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Economic studies

None.

Appendix K– Research recommendations – full details

K1.1 Research recommendation 1

What is the clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen in people with invasive breast cancer who have a germline BRCA mutation, but who do not have triple-negative breast cancer?

K1.1.1 Why this is important

The committee highlighted that there was limited evidence on neoadjuvant chemotherapy for people with germline BRCA mutations in general, and in particular for those people who did not also have TNBC, and it was insufficient to make any specific recommendations for these groups of people. This evidence came from subgroup data from 2 studies and with small sample sizes on people with germline BRCA mutation of all receptor subtypes (GeparOcto [Schneeweiss et al. 2019]: n=96; and GeparOLA [Fasching et al. 2021]: n=59). Therefore, a research recommendation was developed to cover this gap in the evidence.

K1.1.2 Rationale for research recommendation

Table title (caption style)

Importance to 'patients' or the population	Little is known about the clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen in people with invasive breast cancer who have a germline BRCA mutation but who do not have triple-negative breast cancer. A greater understanding on the clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen will help to provide the best intervention to people with invasive breast cancer who have a germline BRCA mutation but who do not have triple-negative breast cancer.
Relevance to NICE guidance	Most of the evidence about the clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen considered in this review was in people with invasive breast cancer who had triple-negative breast cancer. Limited evidence was available in people with invasive breast cancer who had a germline BRCA mutation but who did not have triple-negative breast cancer.
Relevance to the NHS	More evidence could help clinicians to offer the best type of neoadjuvant chemotherapy to people with invasive breast cancer who have a germline BRCA mutation but who do not have triple-negative breast cancer.
National priorities	No specific national priorities.
Current evidence base	Subgroup data from 2 studies and with small sample sizes on people with germline BRCA mutation of all receptor subtypes.
Equality considerations	A list of health inequalities issues were identified during the development of recommendations on neoadjuvant chemotherapy and listed in the equality and health inequalities assessment.

K1.1.3 Modified PICO table

Population	**Inclusion:** • Adults (18 and over) who have invasive breast cancer that is of any receptor subtype (apart from TNBC) and who have BRCA germline mutations. **Exclusion:** • Adults (18 and over) who have invasive breast cancer that is triple negative. • Adults (18 and over) who have invasive breast cancer who do not have BRCA germline mutations. • Adults (18 and over) with newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Adults (18 and over) with Paget's disease of the breast with no invasive component.
Intervention	A neoadjuvant regimen containing a platinum
Comparator	A neoadjuvant regimen (same as the intervention) without platinum

Outcome	**Primary outcomes:**
	• Pathological complete response
	• Overall survival
	• Disease-free survival
	
	Secondary outcomes:
	• Breast cancer mortality
	• Quality of life
	• Adverse events
	  ○ treatment-related mortality
	  ○ treatment-related morbidity including short -term adverse events and long-term consequences of treatment
	• Adherence to or completion of treatment regimens (early cessation of treatment)
	• Local and/or locoregional recurrence
	• Breast conservation rate
	• Number of people who actively choose mastectomy but could have had breast conserving surgery

Study design	Randomised controlled trial, real world evidence: cohort study
Timeframe	Long term
Additional information	None

K2.1 Research recommendation 2

What is the real-world evidence on clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen in people with invasive breast cancer that is triple negative and/or with a germline BRCA mutation who are often excluded from clinical trials, such as:

- people 65 years and older, or
- people who are pregnant, or
- people with male reproductive organs?

K2.1.1 Why this is important

The committee noted that current evidence was mainly from studies including younger people (the median age of participants being from 45 to 52 years old), with older people being underrepresented given their incidence of TNBC. There was no evidence available on the effects of these treatments on pregnant people or on people with male reproductive organs (men, trans women and non-binary people who currently have testes). The committee acknowledged that these people are usually excluded from clinical trials even though they are also at risk of having TNBC and could be candidates for neoadjuvant chemotherapy. The committee also highlighted that real world evidence (RWE) is available that could fill in these gaps for groups of people not recruited to participate in RCTs. For example, the SAIL databank in Wales and the Systemic Anti-Cancer Therapy Dataset (SACT) could be used as sources of real world evidence for outcomes following platinum based neoadjuvant chemotherapy use. Therefore, a research recommendation was developed to cover this gap in the evidence.

K2.1.2 Rationale for research recommendation

Table title (caption style)

Importance to 'patients' or the population	Little is known about the clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen in people with TNBC or with a germline BRCA mutation who are either over 60 years old, pregnant, or who have male reproductive organs. A greater understanding on the clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen will help to provide the best intervention to people with TNBC or with a germline BRCA mutation who are either over 60 years old, pregnant, or who have male reproductive organs.
Relevance to NICE guidance	Most of the evidence about the clinical and cost effectiveness of adding a platinum to a neoadjuvant chemotherapy regimen considered in this review was in people with female reproductive organs aged 40 to 60 years who had TNBC. No evidence was available in people with TNBC who were pregnant, or who had male reproductive organs.
Relevance to the NHS	More evidence could help clinicians to offer the best type of neoadjuvant chemotherapy to people with TNBC who are older than 60 years, who are pregnant, or who have male reproductive organs.

National priorities	No specific national priorities
Current evidence base	Limited evidence was available for people who were older than 60. No evidence was available for people who were pregnant or who had male reproductive organs.
Equality considerations	A list of health inequalities issues were identified during the development of recommendations on neoadjuvant chemotherapy and listed in the equality and health inequalities assessment.

K2.1.3 Modified PICO table

Population	**Inclusion:** • Adults (18 and over) who have invasive breast cancer that is triple negative and/or who have BRCA germline mutations and who: • are 65 years or older or • are pregnant or • have male reproductive organs **Exclusion:** • Adults who are younger than 65 years old. • Adults (18 and over) who are not pregnant. • Adults (18 and over) who do not have male reproductive organs (men, trans women and non-binary people who currently have testes). • Adults (18 and over) with newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Adults (18 and over) with Paget's disease of the breast with no invasive component.
Intervention	A neoadjuvant regimen containing a platinum
Comparator	A neoadjuvant regimen without platinum

Outcome	**Primary outcomes:**
	• Pathological complete response
	• Overall survival
	• Disease-free survival
	
	Secondary outcomes:
	• Breast cancer mortality
	• Quality of life
	• Adverse events
	  ○ treatment-related mortality
	  ○ treatment-related morbidity including short -term adverse events and long-term consequences of treatment
	• Adherence to or completion of treatment regimens (early cessation of treatment)
	• Local and/or locoregional recurrence
	• Breast conservation rate
	• Number of people who actively choose mastectomy but could have had breast conserving surgery

Study design	Real world evidence: cohort study
Timeframe	Long term
Additional information	None

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2

Appendix L – Methods

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2024 NICE guidelines manual and described in Appendix B and section 1.1.3.1.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies. Study investigators were contacted for missing data when time and resources allowed (when this occurred, this was noted in the evidence review and relevant data was included).

Incorporating published evidence syntheses

If published evidence syntheses were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were considered for use as the primary source of data, rather than extracting information from primary studies. Syntheses considered for inclusion in this way were quality assessed to assess their suitability using the appropriate checklist, as outlined in Table 29. Note that this quality assessment was solely used to assess the quality of the synthesis in order to decide whether it could be used as a source of data, as outlined in Table 30, not the quality of evidence contained within it, which was assessed in the usual way as outlined in the section on 'Appraising the quality of evidence'.

Table 29 Checklists for published evidence syntheses

Type of synthesis	Checklist for quality appraisal
Systematic review of quantitative evidence	ROBIS

Each published evidence synthesis was classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each published evidence synthesis was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

The way that a published evidence synthesis was used in the evidence review depended on its quality and applicability, as defined in Table 30. When published evidence syntheses were used as a source of primary data, data from these evidence syntheses were quality assessed and presented in GRADE tables in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were checked to ensure none of the data had been double counted through this process.

Table 30 Criteria for using published evidence syntheses as a source of data

Quality	Applicability	Use of published evidence synthesis
High	Fully applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted.
High	Partially applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Quality	Applicability	Use of published evidence synthesis
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. When there were 2 treatment alternatives, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager (web version). A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Random effects models were fitted when significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken. For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I^2 < 50\%$) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs were quality assessed using the Cochrane Risk of Bias Tool 2. Risk of bias for single studies were conducted once for objective outcomes, once for subjective outcomes, and once for adverse events. Where there is a published approach to overall risk of bias judgement this should be used. Where there is no published approach developers should use their judgement and include a statement of the rationale for the overall judgement included in EPPI and evidence table. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Where systematic reviews were used as a source of evidence for RCTs but they do not use the Cochrane Risk of Bias Tool 1 for risk of bias, the judgements were taken from that review and converted to Cochrane risk of bias Tool 2 judgements so that all RCTs were assessed in the same way. Descriptions of the approach taken are written in the methods specific to the review.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. Clinical decision threshold that were used in the guideline are given in Table 31 and also reported in the relevant evidence reviews.

Table 31 Identified Clinical decision thresholds

Outcome	Clinical decision threshold	Source
Quality of life FACT-G total	3 to 7 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life FACT-B total	7 to 8 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life TOI (trial outcome index) of FACT-B	5 to 6 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life BCS of FACT-B	2 to 3 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life WHOQOL-100	1 point	Den Oudsten, B.L., Zijlstra, W.P. & De Vries, J. The minimal clinical important difference in the World Health Organization Quality of Life instrument—100. Support Care Cancer 21, 1295–1301 (2013). https://doi.org/10.1007/s00520-012-1664-8

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 32. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 32 Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than <50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 50% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than <50% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than >50% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. Not serious: If the I^2 was less than <40%, the outcome was not downgraded. Serious: If the I^2 was between 41% and 60%, the outcome was downgraded one level or if data on the outcome was only available from one study. Very serious: If the I^2 was greater than >60%, the outcome was downgraded two levels.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of

GRADE criteria	Reasons for downgrading quality
	publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

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Appendix M – Additional tables

Table 33 Outcome definitions from primary studies

Study details	Pathological complete response	Disease-free survival	Overall survival	Adverse events - morbidity	Lymph node status
ADAPT-TN Gluz (2018)	Absence of invasive tumour cells in the breast and lymph nodes (ypT0/is ypN0)	Time from registration to any invasive relapse, secondary malignancy or death from any cause	Death from any cause	Toxicity criteria were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0	Study did not report data for this subgroup
Ando (2014)	Absence of viable invasive tumour in both the breast and axillary nodes. Residual DCIS in the breast and no invasive tumour in the axillary nodes was also classified as having a pCR	Time from randomisation to the first appearance of any recurrence of breast cancer (local, regional or distant), or any cause of death	Time from randomisation to death by any cause	Grade 3–4 adverse events (NCI-CTCAE version 4.03)	Study did not report data for this subgroup
BrighTNess Loibl (2018)	Absence of residual invasive disease on evaluation of the resected breast specimen and resected lymph nodes following completion of neoadjuvant systemic therapy	Time from randomisation to documentation of the first of the following events: failure to reach potential curative surgery; local, regional, or distant invasive recurrence of breast cancer following curative surgery; a new breast cancer or secondary	Number of days from the day of randomisation to the date of death	Adverse events were graded according to National Cancer Institute Common Terminology Criteria version 4.0. Safety data were analysed by the study funder and the academic steering committee. Adverse event monitoring was done from the time of	Axillary nodal status (positive or negative) was confirmed by biopsy

		malignancy; or death from any cause		administration of study drugs until 30 days following discontinuation of protocol treatment. Serious adverse events were collected from the time the patient signed the informed consent form. Laboratory monitoring (haematology, clinical chemistry, urinalysis, and coagulation) was done from baseline (28 days or less before first dose of study drug) to a final visit up to 30 days after the last dose of study drug. Laboratory assessments were done every 3 weeks during segment 1 and every 2 or 3 weeks during segment 2	
CALGB 40603 Shepherd (2022)	Absence of residual invasive disease with or without ductal carcinoma in situ (ypT0/is)	Time from random assignment to local, regional, or distant recurrence, any second invasive cancer, or death from any cause; patients not undergoing surgery were considered to have had an EFS event when	Time from random assignment to death from any cause	Treatment-related toxicities (as defined by Common Toxicity Criteria for Adverse Events, version 4.0)	Study did not report data for this subgroup

		they were removed from study treatment			
GEICAM 2006-03 Alba (2012)	pCR in the breast, as per Miller and Payne criteria	Study did not report data for this outcome	Study did not report data for this outcome	Adverse events were graded following the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [21]; the worst grade for each patient was reported	Study did not report data for this subgroup
GeparOcto Schneeweiss (2019)	No microscopic evidence of residual invasive viable tumour cells in all resected specimens of the breast and axilla	Invasive DFS: any invasive locoregional (ipsilateral breast, locoregional lymph nodes) recurrence of disease, any invasive contralateral BC, any distant recurrence of disease, any secondary malignancy, or death as a result of any cause, whichever occurred first	Death due to any cause	Toxicity reported as adverse events (AEs) was based on NCI-CTCAE v4.0	Histologically confirmed axillary lymph node involvement: lymphocyte-predominant breast cancer (no: stromal tumour infiltrating lymphocytes [sTIL]<60%; yes: sTIL>=60%)
GeparOLA Fasching (2021)	No residual invasive tumour in breast and in axillary lymph nodes (ypT0/is ypN0)	Study did not report data for this outcome	Study did not report data for this outcome	Toxicity was reported as adverse events (AEs) irrespective of relatedness to study treatment based on NCI-CTC criteria v4.0.	Clinical nodal status
GeparSixto von Minckwitz (2014)	Rate (ypT0 ypN0), defined as no invasive and no non-invasive residuals in breast and lymph nodes	Invasive DFS, defined as time in months from randomisation until any invasive locoregional	Time in months from randomisation until death due to any cause, and participants alive	Toxic effects were graded in accordance with the National Cancer Institute's Common	Clinical nodal status

		(ipsilateral breast, local/regional lymph nodes) recurrence of disease, any invasive contralateral breast cancer, any distant recurrence of disease, any secondary malignancy, or death due to any cause, whichever occurred first	were censored at the date of the last contact	Terminology Criteria for Adverse Events, version 4.0. A standard definition was used for serious adverse events, except that uncomplicated neutropenia grade IV was not regarded as such an event	
Gigolaeva (2019)	According to Miller-Payne grading system (i.e. grade 5 where no malignant cells were identified at the site of the tumour, DCIS may be present)	Study did not report data for this outcome	Study did not report data for this outcome	Not reported	Study did not report data for this subgroup
NACATRINE de Padua Souza (2023)	No invasive tumour in the breast and lymph nodes (ypT0ypN0)	Invasive DFS defined as the time from random assignment to invasive disease recurrence or death from any cause	Interval from random assignment to death from any reason	Adverse events (AEs) were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03	Study did not report data for this subgroup
NeoCART Zhang (2022)	Absence of invasive tumour cells in the breast and axilla (ypT0/is ypN0)	Time from randomisation to disease progression, disease recurrence (local, regional, distant or contralateral (invasive or non-invasive)) or death from any cause	Time from randomisation until death with any cause	The National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) was employed to assess the level of toxicity.	Study did not report data for this subgroup
Zhang (2016)	No residual invasive cancer in both excised breast tissue	Relapse-free survival, defined as from the date of randomisation to the	Date of randomisation to date of death or last follow-up	Adverse effects were defined in accordance with the National Cancer	Clinical nodal status

	and axillary lymph nodes, or only carcinoma in situ	date of the first local or distant recurrence		Institute Common Toxicity Criteria for Adverse Events (CTCAE version 3.0)	
Zhao (2014)	Study in Chinese	Study in Chinese	Study did not report data for this outcome	Study in Chinese	Study in Chinese

1 **Table 34 Long-term adverse events identified by the committee**

Neuropathy
Renal impairment
Fatigue
Tinnitus
Increased creatine
Thromboembolic event (e.g., VTE and Arterial thrombosis)
Pain
Weight loss

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