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

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[Intervention Review]

Platinum-based chemotherapy for early triple-negative breast cancer

Sofia RE Mason[1,2,3,4], Melina L Willson[5], Sam J Egger[6,7], Jane Beith[3], Rachel F Dear[8,9], Annabel Goodwin[8,10]

[1]Garvan Institute of Medical Research, Darlinghurst, Australia. [2]St Vincent's Clinical School, UNSW, Sydney, Australia. [3]Chris O'Brien Lifehouse, Camperdown, Australia. [4]Concord Clinical School, The University of Sydney, Concord Repatriation General Hospital, Concord, Australia. [5]Evidence Integration, NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia. [6]Cancer Research Division, Cancer Council NSW, Sydney, Australia. [7]The Daffodil Centre, The University of Sydney, Sydney, Australia. [8]Sydney Medical School, The University of Sydney, Sydney, Australia. [9]The Kinghorn Cancer Centre, Darlinghurst, Australia. [10]Concord Clinical School, The University of Sydney, Concord Repatriation General Hospital, Concord, Australia

Contact: Sofia RE Mason, sofia.mason@unsw.edu.au.

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ABSTRACT

Background

Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer associated with shorter survival and a higher likelihood of the cancer returning. In early TNBC, platinum-based chemotherapy has been shown to improve pathological complete response (pCR); however, its effect on long-term survival outcomes has not been fully elucidated and recommendations to include platinum chemotherapy are not consistent in international guidelines.

Objectives

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

Search methods

We used standard, extensive Cochrane search methods. The latest search date was 4 April 2022.

Selection criteria

We included randomised controlled trials examining neoadjuvant or adjuvant platinum chemotherapy for early TNBC.

Data collection and analysis

We used standard Cochrane methods. Our primary outcomes were disease-free survival (DFS) and overall survival (OS). Our secondary outcomes were pCR, treatment adherence, grade III or IV toxicity related to chemotherapy, and quality of life. Prespecified subgroups included BRCA mutation status, homologous recombination deficiency (HRD) status, frequency of chemotherapy, type of platinum agent used, and the presence or absence of anthracycline chemotherapy. We assessed risk of bias using Cochrane's RoB 1 tool and certainty of evidence using the GRADE approach.

Main results

From 3972 records, we included 20 published studies involving 21 treatment comparisons, and 25 ongoing studies. For most domains, risk of bias was low across studies. There were 16 neoadjuvant chemotherapy studies (one of which combined neoadjuvant and adjuvant therapy) and four adjuvant chemotherapy trials. Most studies used carboplatin (17 studies) followed by cisplatin (two), and lobaplatin (one). Eight studies had an anthracycline-free intervention arm, five of which had a carboplatin-taxane intervention compared to an anthracycline-taxane control.

All studies reporting DFS and OS used carboplatin. Inclusion of platinum chemotherapy improved DFS in neoadjuvant and adjuvant settings (neoadjuvant: hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.53 to 0.75; 7 studies, 8 treatment comparisons, 1966 participants; high-certainty evidence; adjuvant: HR 0.69, 95% CI 0.54 to 0.88; 4 studies, 1256 participants; high-certainty evidence). Platinum chemotherapy in the regimen improved OS (neoadjuvant: HR 0.69, 95% CI 0.55 to 0.86; 7 studies, 8 treatment comparisons, 1973 participants; high-certainty evidence; adjuvant: 0.70, 95% CI 0.50 to 0.96; 4 studies, 1256 participants; high-certainty evidence). Median follow-up for survival outcomes ranged from 36 to 97.6 months.

Our analysis confirmed platinum chemotherapy increased pCR rates (risk ratio (RR) 1.44, 95% CI 1.31 to 1.59; 15 studies, 16 treatment comparisons, 3083 participants; high-certainty evidence). Subgroup analyses showed no evidence of differences in DFS according to BRCA mutation status, HRD status, lymph node status, or whether the intervention arm contained anthracycline chemotherapy or not.

Platinum chemotherapy was associated with reduced dose intensity, with participants more likely to require chemotherapy delays (RR 2.23, 95% CI 1.70 to 2.94; 4 studies, 5 treatment comparisons, 1053 participants; moderate-certainty evidence), dose reductions (RR 1.77, 95% CI 1.56 to 2.02; 7 studies, 8 treatment comparisons, 2055 participants; moderate-certainty evidence) and early cessation of treatment (RR 1.20, 95% CI 1.04 to 1.38; 16 studies, 17 treatment comparisons, 4178 participants; moderate-certainty evidence). Increased haematological toxicity occurred in the platinum group who were more likely to experience grade III/IV neutropenia (RR 1.53, 95% CI 1.43 to 1.63; 19 studies, 20 treatment comparisons, 4849 participants; moderate-certainty evidence), anaemia (RR 8.20, 95% CI 5.66 to 11.89; 18 studies, 19 treatment comparisons, 4757 participants; moderate-certainty evidence) and thrombocytopenia (RR 7.59, 95% CI 5.10 to 11.29; 18 studies, 19 treatment comparisons, 4731 participants; moderate-certainty evidence). There was no evidence of a difference between chemotherapy groups in febrile neutropenia (RR 1.16, 95% CI 0.89 to 1.49; 11 studies, 3771 participants; moderate-certainty evidence). Renal impairment was very rare (0.4%, 2 events in 463 participants; note 3 studies reported 0 events in both arms; 4 studies; high-certainty evidence). Treatment-related death was very rare (0.2%, 7 events in 3176 participants and similar across treatment groups; RR 0.58, 95% 0.14 to 2.33; 10 studies, 11 treatment comparisons; note 8 studies reported treatment-related deaths but recorded 0 events in both groups. Thus, the RR and CIs were calculated from 3 studies rather than 11; 3176 participants; high-certainty evidence). Five studies collected quality of life data but did not report them.

Authors' conclusions

Platinum-based chemotherapy using carboplatin in the adjuvant or neoadjuvant setting improves long-term outcomes of DFS and OS in early TNBC, with no evidence of differences by subgroup. This was at the cost of more frequent chemotherapy delays and dose reductions, and greater haematological toxicity, though serious adverse events including neuropathy, febrile neutropenia or treatment-related death were not increased.

These findings support the use of platinum-based chemotherapy for people with early TNBC. The optimal dose and regimen are not defined by this analysis, but there is a suggestion that similar relative benefits result from the addition of carboplatin to either anthracycline-free regimens or those containing anthracycline agents.

PLAIN LANGUAGE SUMMARY

Platinum-containing chemotherapy for women before or after surgery for early triple-negative breast cancer

Key messages

Chemotherapy including the platinum-based medicine carboplatin improves survival and reduces the chance of cancer returning for people with early triple negative breast cancer.

However, it is also associated with increased side effects.

What is triple-negative breast cancer?

Triple-negative breast cancer makes up 15% of breast cancer cases. It is a type of breast cancer that does not have any of the three receptors commonly found on breast cancer cells – the oestrogen, progesterone and HER2 receptors. Early breast cancer is defined as cancer limited to the breast and lymph nodes in the armpit, and it can usually be cured.

How is early triple-negative breast cancer treated?

Treatments for early triple-negative breast cancer include:

– surgery to remove the cancer from the breast and lymph nodes;

– radiotherapy to the breast and lymph nodes, used to prevent the cancer from coming back in these areas;

– chemotherapy, used to prevent the cancer from coming back anywhere in the body. This can be given before surgery (called 'neoadjuvant') or after surgery (called 'adjuvant').

What did we want to find out?

There are many types of chemotherapy used in triple-negative breast cancer. We wanted to find out if a specific class of chemotherapy called 'platinum-based chemotherapy' increases:

– the length of time people stayed alive without cancer recurrence after diagnosis (disease-free survival);

– the total length of life after diagnosis (overall survival);

– the likelihood that the cancer had disappeared in the removed breast and lymph node tissue when chemotherapy was given before surgery (pathological complete response).

We also wanted to find out if platinum-based chemotherapy was associated with more unwanted outcomes like chemotherapy delays, dose reductions or side effects.

What did we do?

We searched for studies looking at chemotherapy for early triple-negative breast cancer that compared regimens containing platinum chemotherapy to regimens without platinum chemotherapy.

We compared and summarised the results of the studies, and rated our confidence in the evidence based on factors such as study methods and size.

What did we find?

We found 20 studies that involved 4688 people with early triple-negative breast cancer, with average follow-up in studies ranging from three to eight years.

Platinum chemotherapy was associated with longer disease-free survival and overall survival, and reduced the chance of disease recurrence and death by about one third. These benefits were seen with chemotherapy used before surgery (neoadjuvant) or after surgery (adjuvant). When used before surgery, it also improved the likelihood of a pathological complete response.

We did not find that any particular subgroup, such as people with a high-risk gene mutation, had more benefit from platinum chemotherapy.

However, people receiving platinum chemotherapy were more likely to need the dose of their chemotherapy to be reduced, or to have a delay in their chemotherapy. They were also more likely to stop chemotherapy early.

Platinum chemotherapy also caused more serious side effects including low blood cell counts. It was not associated with an increase in having fevers associated with low white blood cell counts (febrile neutropenia), nerve damage symptoms (neuropathy) or death caused by treatment.

What are the limitations of the evidence?

The evidence was generally of high quality and included enough data to make judgements to answer our main questions.

However, there were many types of chemotherapy used across studies. Although we have shown that platinum chemotherapy improves long-term outcomes, we do not know what the best chemotherapy combination is.

None of the studies reported quality of life, which we had initially set out to measure and record.

How up-to-date is this evidence?

This evidence is up-to-date to April 2022.

SUMMARY OF FINDINGS

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

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

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

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

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DFS:** disease-free survival; **HR:** hazard ratio; **OS:** overall survival; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434916258784592377.

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

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

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

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

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

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **DFS:** disease-free survival; **HR:** hazard ratio; **OS:** overall survival; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434981690495911791.

Summary of findings 3. Platinum-containing chemotherapy compared to chemotherapy without platinum for early triple-negative breast cancer

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

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

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with chemotherapy without platinum	Risk with platinum-containing chemotherapy				
Participants requiring chemotherapy delays	154 per 1000	**344 per 1000** (263 to 454)	**RR 2.23** (1.70 to 2.94)	1053 (5 RCTs)	⊕⊕⊕⊕ **High**	—
Participants requiring dose reduction	278 per 1000	**492 per 1000** (433 to 561)	**RR 1.77** (1.56 to 2.02)	2055 (8 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
Anaemia (grade III/IV)	13 per 1000	**105 per 1000** (72 to 152)	**RR 8.20** (5.66 to 11.89)	4757 (19 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—

follow-up: range 6 weeks to 38 weeks						
Febrile neutropenia (grade III/IV) follow-up: range 12 weeks to 38 weeks	56 per 1000	**65 per 1000** (50 to 83)	**RR 1.16** (0.89 to 1.49)	3771 (12 RCTs)	⊕⊕⊕⊖ **Moderate**[a]	—
Renal impairment (grade III/IV) follow-up: range 6 weeks to 16 weeks	4 studies reported renal impairment. 1 study reported 2 events in 60 people in the platinum arm (3%) and 0 events in 57 people in the non-platinum arm. None of the other studies reported any grade III/IV events		—	463 (4 RCTs)	⊕⊕⊕⊕ **High**	—
Quality of life	4 studies collected quality of life information using validated questionnaires but none of these reported data.		—	—	—	—

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_434915765589228984.

[a] Downgraded one level for inconsistency due to marked variability between trials, demonstrated by a wide range of hazard ratios and confidence intervals with minimal overlap.

BACKGROUND

Description of the condition

Breast cancer is the most common type of cancer in women and the most common cause of cancer death (Ferlay 2018). Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer, which lacks hormone receptors and human epidermal growth factor receptor 2 (HER2) expression. It is associated with shorter survival and a higher likelihood of recurrence, and comprises about 15% of breast cancer diagnoses (Foulkes 2010; Lin 2012). Early TNBC is defined as cancer that has not spread beyond the breast or axillary lymph nodes, and is potentially curable. Surgery, radiotherapy, and chemotherapy are used to minimise the chance of relapse.

TNBC is more likely to be associated with heritable causes than other breast cancer subtypes. Over 10% of people diagnosed with TNBC under the age of 50 years, without known family history of breast or ovarian cancer, have a heritable mutation in either breast cancer gene 1 or gene 2 (*BRCA1* or *BRCA2*) (Shimelis 2018). Whilst *BRCA1* mutation is the most strongly associated, other heritable gene mutations (i.e. *BRCA2*; partner and localizer of BRCA2 (*PALB2*); RAD51 paralogue D (*RAD51D*) and BRCA1 associated RING domain 1 (*BARD1*)) have also shown associations with TNBC and higher lifetime risks of breast cancer. These mutations are implicated in DNA repair and genomic stability. A heritable mutation in either a high-risk or moderate-risk breast cancer gene was found in 12% of the study population with TNBC (compared to 5% for all breast cancer cases), highlighting the importance of referring women with TNBC for genetic counselling, even when there is no known family history of cancer (Shimelis 2018). Guidelines recommend genetic testing for women who are diagnosed at young ages (less than 50 years); if there is a family history of breast, ovarian, prostate, or pancreatic cancer; or if they are of Ashkenazi Jewish ancestry.

Description of the intervention

Standard chemotherapy used in the adjuvant or neoadjuvant setting for TNBC involves anthracycline and taxane chemotherapy, combined with cyclophosphamide. The role of adjuvant chemotherapy is to treat micrometastatic systemic disease, which is not detectable by standard blood tests and imaging. Chemotherapy is indicated for most women with TNBC who are in good health. The National Comprehensive Cancer Network (NCCN) Guidelines recommend offering chemotherapy to women with TNBC whose cancer size is larger than 1 cm, or any size with involvement of their lymph nodes. Chemotherapy may also be considered for women with smaller tumours.

The intervention being studied is platinum-based chemotherapy (cisplatin or carboplatin) alone or in addition to the standard adjuvant or neoadjuvant chemotherapy, to determine whether this improves survival from early TNBC. Our primary outcomes were overall survival (OS) and disease-free survival (DFS). Achieving a pathological complete response (pCR) has strong prognostic value, particularly in the TNBC subtype (Cortazar 2014). Because of the assumed association between survival and pCR, many trials assess pCR while either waiting for data to mature or as their primary endpoint before deciding whether larger trials are feasible. Consequently, we reported pCR, along with OS and DFS.

How the intervention might work

Platinum agents damage DNA by causing single-strand DNA breaks, resulting in apoptosis. DNA repair deficiencies are associated with germline or somatic mutations in *BRCA1*, *BRCA2*, and *PALB2*, which are frequently associated with TNBC. This is a proposed mechanism for the increased efficacy of the DNA-damaging effects of platinum chemotherapy for TNBC. With genomic profiling, women identified as having basal-type TNBC are also seen to have DNA-repair deficiency (Guo 2017). Besides breast cancer, an enhanced response to platinum-based chemotherapy is seen in women with *BRCA* mutations who have ovarian cancer (Pennington 2014), and *BRCA*-associated pancreatic cancer (O'Reilly 2020). Poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown efficacy for women with advanced BRCA breast cancer, although this treatment has not been compared to their response to platinum.

Potential adverse effects of platinum include an increase in myelosuppression, which can lead to dose omissions, interruptions or dose reduction of platinum chemotherapies, other chemotherapy drugs, or both. There are risks of additional toxicity from myelosuppression, with febrile neutropenia, anaemia or bleeding due to thrombocytopenia. Long-term toxicities from platinum chemotherapy can include peripheral neuropathy, ototoxicity and renal impairment.

Why it is important to do this review

This review will clarify the role of platinum-based chemotherapy in early TNBC to determine if there is a significant improvement in OS or other disease outcomes with comparable toxicity to non-platinum-based chemotherapy. Previous reviews on this topic suggested that the addition of platinum chemotherapy increases rates of pCR at the cost of an increase in adverse events (Pandy 2019; Poggio 2018). However, new trials have been published since these reviews.

Maximising the efficacy of treatment of early breast cancer will reduce rates of metastatic, incurable disease and premature death from this condition. However, given this is a population where the intention is long-term survival, the prevention of permanent toxicity is also a priority.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included 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 non-platinum 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

We included 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). We included trials with all study locations, and participants of all ethnicities. We excluded trials that did not assess women for HER2 status.

Types of interventions

The intervention of interest was any chemotherapy regimen that contained platinum chemotherapy compared to regimens without platinum chemotherapy. Included studies addressed either adjuvant (postsurgery) or neoadjuvant (presurgery) delivery of chemotherapy for early TNBC. We recorded and compared the dose and duration of chemotherapy.

Types of outcome measures

Primary outcomes

- **Disease-free survival (DFS)**, 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. We included similar outcomes, such as progression-free survival and time-to-progression in this section.
- **Overall survival (OS)**, time-to-event outcome defined as the time from randomisation or study entry until death from any cause.

Secondary outcomes

- **Pathological complete response (pCR)** (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** – quality of life information is typically not collected in these types of trials, we aimed to report any quality of life data as measured by the many validated tools available to trialists, and at all reported time points.

Search methods for identification of studies

Electronic searches

We performed a search the following databases up to the 4 April 2022.

- The Cochrane Breast Cancer Group's (CBCG's) Specialised Register. Details of the search strategies used by the Group for the identification of studies and the procedure used to code references are outlined in the Group's module (breastcancer.cochrane.org/sites/breastcancer.cochrane.org/files/public/uploads/specialised_register_details.pdf). We identified and considered for inclusion any trial with the keywords: 'Cisplatin', 'cisplatinum', 'carboplatin', 'carboplatinum', 'platin', 'platinum', 'platinum diamminodichloride', 'cis-diamminedichloroplatinum', 'cis-dichlorodiammineplatinum', 'biocisplatinum', 'dichlorodiammineplatinum', 'nsc-119875', 'platidiam', 'platino', 'Platinol', 'cis-diamminedichloroplatinum', 'cis-platinum', 'cis-diammine (cyclobutanedicarboxylato) platinum', 'cbdca', 'jm-8', 'nsc-241240', 'paraplatin';
- Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, latest issue); see Appendix 1
- MEDLINE OvidSP (top up search to complement CBCG's Specialised Register); see Appendix 2
- Embase OvidSP (1947 to present); see Appendix 3
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal for all prospectively registered and ongoing trials (apps.who.int/trialsearch/Default.aspx); see Appendix 4
- ClinicalTrials.gov (clinicaltrials.gov/); see Appendix 5

Searching other resources

We screened the reference lists of identified relevant trials or reviews to help identify additional studies. We obtained a full article or abstract for each reference reporting a potentially eligible trial.

We searched the abstracts of recent conference proceedings not yet included in the CBCG's Specialised Register or medical databases, including the American Society of Clinical Oncology annual meeting, European Society of Medical Oncology Congress and San Antonio Breast Cancer Symposium.

We searched systematic reviews on the topic using PubMed Clinical Queries.

We contacted the lead investigators of potentially eligible ongoing and completed trials listed in the trial registries to see if their study was complete or study results could be provided.

Data collection and analysis

Selection of studies

Two review authors (SM and AG) independently applied the selection criteria to each reference identified by the search strategy. There were no disagreements by review requiring resolution.

We included English-language studies and studies that were translated. We recorded the selection process in the PRISMA flow diagram.

We recorded a selection of excluded studies in the Characteristics of excluded studies table.

Data extraction and management

We extracted data using standard extraction forms. We collected information on study design; randomisation methods; baseline characteristics of participants; setting; chemotherapy regimens (chemotherapy agent, dose, number of cycles); deliverability of treatment, assessed by dose intensity, dose delays or interruptions; and primary and secondary outcomes. We also collected details regarding type of toxicity for grade III or IV events (according to National Cancer Institute Common Terminology Criteria for

Adverse Events (CTCAE 2017)), length of follow-up and sources of funding.

Two review authors (SM and MW) independently extracted the data, and resolved disagreements with the support of AG and SE. For studies with more than one publication, we extracted data from all publications, and considered the most recent full-text version of the study to be the primary reference. We combined records relating to the same study under the overall trial ID. For one included study, one colleague checked and conducted data extraction and risk of bias assessments for the translated material.

We entered data into RevMan Web 2022 for analysis.

Assessment of risk of bias in included studies

We assessed bias using Cochrane's RoB 1 tool (Higgins 2011). The domains assessed were sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. In oncology, an open-label approach is often used as it is difficult to obscure differing treatment schedules and potential toxicities from patients and care providers. Therefore, we grouped the blinding of outcome assessment domain with outcome measures from most unlikely to most likely to be influenced by a lack of blinding. The outcomes were segregated into DFS, OS, pCR, toxicity and treatment adherence, and quality of life.

Two review authors (SM and MW) independently assessed the risk of bias, with guidance provided by two other review authors (AG and SE). We incorporated the results of this risk of bias assessment into the interpretation of results.

Measures of treatment effect

We used the following effect measures.

- Time-to-event outcomes (DFS, OS): expressed as a hazard ratio (HR) with 95% confidence intervals (CI). For HRs and variances which were not reported in the trial publications, we calculated summary statistics indirectly using the methods outlined in Tierney 2007. In the 'Notes' section of the Characteristics of included studies table, we recorded the use of indirect methods, and whether the trial publications reported an assessment of the proportional hazards assumption. HRs less than 1.0 favour regimens with platinum chemotherapy, and HRs greater than 1.0 favour regimens without platinum chemotherapy.
- Dichotomous outcomes (pCR, completion of regimens, toxicity): expressed as risk ratio (RR) with 95% CI. We reported the ratios of treatment effects for pCR (a favourable event) so that RRs greater than 1.0 favour regimens with platinum chemotherapy, and RRs less than 1.0 favour regimens without platinum chemotherapy. For completion of regimens or toxicity outcomes (unfavourable events), RRs greater than 1.0 favour regimens without platinum chemotherapy and RRs less than 1.0 favour regimens with platinum chemotherapy. Data for toxicity were the population included in the study regardless of the proportion of participants with TNBC;
- Continuous data (quality of life): collected but not reported in any of the studies. If sufficient quality of life data becomes available in future review updates, the effect measure would likely be a mean difference (MD) if studies used the same scales or standardised mean difference (SMD) if studies used different scales, with 95% CI. We would interpret and report SMDs in a more easily interpreted scale for readers, considering the minimal important clinical difference (MICD) to put results into context (McGlothlin 2014). Each quality of life measurement scale may have a different MICD and we plan to review these estimates for each instrument. We would use an MICD of 0.2 to 0.5 as a guide for patient-reported outcomes.

Two review authors (SB and MW) extracted data from each trial and discussed any data queries with two other review authors (AG and SE).

Unit of analysis issues

The trial participants were the unit of analysis in this review. One trial was a three-arm study (Brightness: BrighTNess comparison 1 and BrighTNess comparison 2). For this study, we halved the number of women in the control group to allow for a comparison with the two different platinum-containing arms. The *Cochrane Handbook for Systematic Reviews of Interventions* suggests these methods to correct for multiple intervention or control groups (Higgins 2020).

Dealing with missing data

We attempted to contact authors of included studies in writing, to request missing data (e.g. dosing or toxicity). We contacted the following authors of included studies (Ando 2014; BrighTNess: BrighTNess comparison 1 and BrighTNess comparison 2; I-SPY2).

We also contacted studies recorded in the WHO ICTRP and ClinicalTrials.gov that have not yet published their results. We discussed the impact of any missing data.

Assessment of heterogeneity

Recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* have guided the assessment of heterogeneity (Deeks 2020). We examined diversity by visually inspecting the forest plots, Chi^2 test and I^2 statistic. We used a cut-off point of P = 0.10 for the Chi^2 test. The I^2 statistic "describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance)" (Section 10.10.2, Deeks 2020). We acknowledge that there is much uncertainty in measures such as I^2 statistic when there are few studies. Noting these limitations, we used it as a rough guide for interpretation, using these thresholds for the I^2 statistic:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity and
- 75% to 100%: considerable heterogeneity

The importance of the observed value of the I^2 statistic depends on the magnitude and direction of effects, and strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic: uncertainty in the value of the I^2 statistic is substantial when the number of studies is small; Deeks 2020).

Assessment of reporting biases

As there were fewer than 10 studies contributing to meta-analyses, we were unable to investigate publication or other bias using funnel plot asymmetry.

Where possible, we reviewed the protocols of included studies to assess outcome reporting bias.

Data synthesis

We used the following methods to synthesise the data:

- time-to-event data (DFS, OS) – we used a fixed-effect model with an inverse-variance model; as there was no evidence of substantial heterogeneity, a random-effects model (DerSimonian and Laird with inverse-variance method) was not required;
- dichotomous outcomes (pCR, completion of regimens, toxicity) – we used a fixed-effect model (Mantel-Haenszel model (Mantel 1959)); as there was no evidence of substantial heterogeneity, a random-effects model (DerSimonian and Laird method; (DerSimonian 1986)) was not required;
- continuous data (quality of life) – no data were reported. If data are reported in future review updates, we intend to use a fixed-effect model with an inverse variance method (Deeks 2011); or if there is evidence of substantial heterogeneity, a random-effects model (DerSimonian and Laird with inverse-variance method).

In the case of pCR, one study was an adaptive platform trial and reported results as an estimated rate of complete response with a 95% Bayesian probability interval. In order to include these data in the meta-analysis, we calculated the discrete number of events in each group by using the adjusted probabilities of pCR.

Though there were occasional zero event toxicity outcomes in a single arm for dichotomous outcomes, the Mantel-Haenszel methods requires zero-cell corrections only if the same cell is zero in all the included studies (Deeks 2020), which was not the case in our data. In instances where there were no events in both arms of study, we followed the standard practice of excluding that study from the meta-analysis. The rationale behind this is that these studies do not offer any insight into the direction or magnitude of the relative effect of the treatment (Deeks 2020).

Subgroup analysis and investigation of heterogeneity

We examined the following subgroups

- Germline BRCA mutations
- Somatic mutation of HRD
- Lymph node status
- Type of platinum agent used in the platinum arm
- Types of chemotherapy
  - Trials where the only difference across treatment arms was the use of platinum, that is platinum plus regimen A versus regimen A, described as same backbone chemotherapy with or without platinum
  - Anthracycline-containing regimens (may include taxane) versus non-anthracycline regimen
- Timing of platinum agent, that is weekly versus every two weeks versus every three weeks

We conducted subgroup analyses to assess the effects of the above factors on clinical outcomes and heterogeneity.

Sensitivity analysis

We conducted the following sensitivity analyses based on:

- differences in the definition of triple negative that had a hormone receptor (oestrogen receptor (ER)/progesterone receptor (PR)) expression cut-off other than less than 1% or was not defined;
- potentially confounding extra treatments (e.g. the intervention contained a platinum as well as an additional anticancer agent) on the primary outcomes;
- a high or unclear risk of bias;
- considerable heterogeneity (i.e. I^2 statistic between 75% and 100%). In this case, a random-effects approach was additionally conducted.

Summary of findings and assessment of the certainty of the evidence

Teams of two review authors (from SM, MW, AG and SE) assessed the certainty of the evidence for critical outcomes using the GRADE approach. This approach uses five considerations, bias, inconsistency, indirectness, imprecision and publication bias, to provide rationale for downgrading or upgrading the evidence (Schünemann 2013). We assessed each outcome, and presented the information in summary of findings tables, using GRADEpro GDT software (GRADEpro GDT). The key outcomes assessed were:

- DFS;
- OS;
- pCR after neoadjuvant therapy;
- completion of regimens:
  - dose intensity, number of cycles completed, treatment delays;
- any grade III/IV toxicity related to chemotherapy (stratified by haematological or non-haematological toxicity):
  - non-haematological toxicity, specifically peripheral neuropathy, renal impairment;
  - haematological toxicity, specifically febrile neutropenia, anaemia;
- quality of life.

We reported summary of findings for time-to-event outcomes (DFS and OS) at two and five years (with non-platinum group risks estimated from the mean of non-platinum group Kaplan-Meier probabilities at two and five years). For all other outcomes, we reported when the outcome was measured (e.g. pCR measured after surgical intervention shortly after completing neoadjuvant chemotherapy).

RESULTS

Description of studies

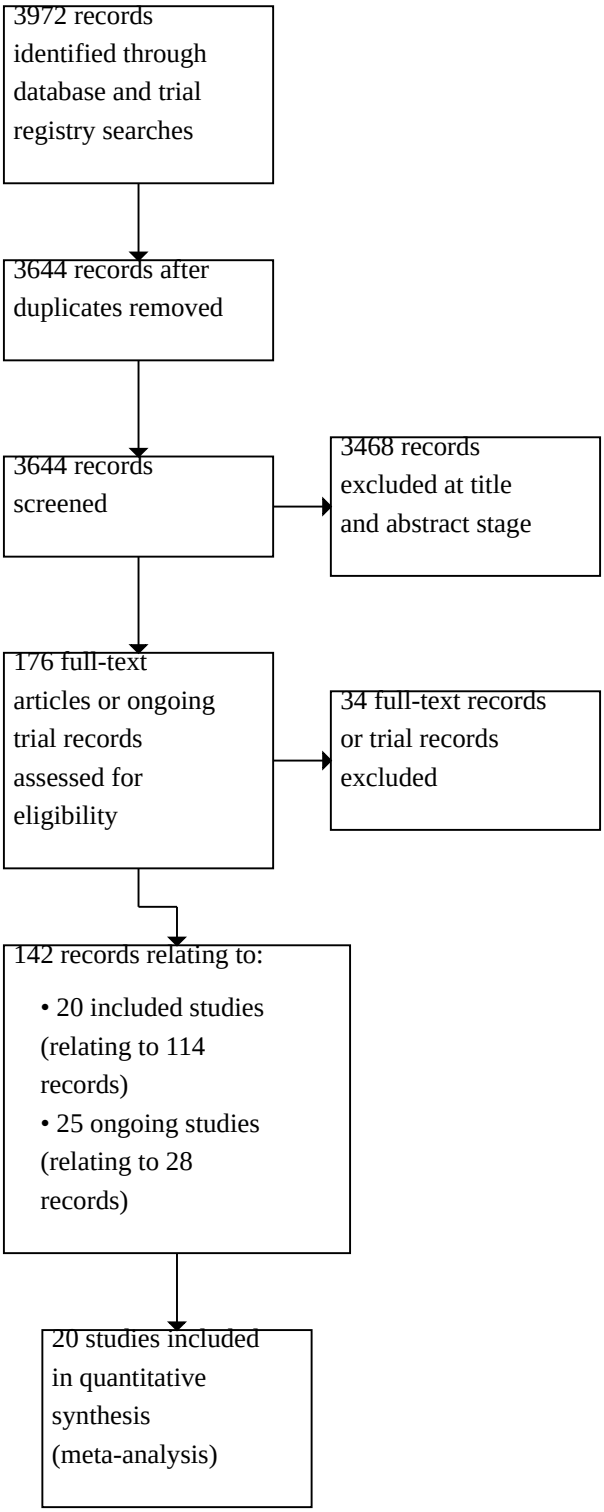
Results of the search

Database and trial registry searches yielded 3972 records, and we screened the titles and abstracts of 3644 records after removing duplicates. We excluded 3468 records at title and abstract screening stage, and screened 176 full-text articles or ongoing trial records.

Of these, 114 records related to 20 included studies involving 21 treatment comparisons, and 28 records related to 25 ongoing studies. We excluded 34 records and presented the reasons for exclusion for the five studies that one may expect to find in the review the Characteristics of excluded studies table.

See PRISMA flowchart (Figure 1).

Figure 1. Study flow diagram.



Included studies

See Characteristics of included studies table.

The 20 included studies, involving 4468 participants, contributed to 21 treatment comparisons outlined in Table 1. Notably, the BrighTNess study has more than one intervention that was split into two treatment comparisons (BrighTNess comparison 1; BrighTNess comparison 2), which is why the number of studies and treatment comparisons included in an analysis may differ.

Table 2 details the number of treatment comparisons by subgroup and efficacy outcome.

- 15 studies (16 treatment comparisons) involved neoadjuvant chemotherapy with one study combining neoadjuvant and adjuvant therapy, and four studies involved adjuvant chemotherapy
- 17 studies (18 treatment comparisons) used carboplatin, two studies used cisplatin and one study used lobaplatin
- nine studies had an anthracycline-free intervention arm
- six studies stratified results for BRCA mutations, one trial for HRD status, and three by lymph node status
- six studies (seven treatment comparisons) used the same chemotherapy backbone (i.e. platinum agent plus regimen A versus regimen A) and 14 trials used a different backbone (i.e. regimen A versus regimen B)

We included studies that examined other subtypes of breast cancer, provided the outcome of DFS, OS or pCR was described for the TNBC subgroup. For such studies, only efficacy analyses are reported for the TNBC group (Ando 2014; GEICAM 2006-03; GeparOcto; GeparOLA; GeparSixto; I-SPY2; TBCRC 030). Other outcomes including toxicity and the completion of chemotherapy regimens may be reported for the whole cohort if subgroup data were not published. This is not considered a significant change from the protocol because participants with TNBC are unlikely to have substantially different chemotherapy adverse effects compared to participants with other subtypes of breast cancer.

Notably, there were studies where participants in the intervention group received platinum agents as well as other experimental interventions. In Nasr 2015, participants randomised to the intervention received platinum chemotherapy as well as a further year of metronomic oral chemotherapy. Trialists in BrighTNess examined the effects of both carboplatin and veliparib. To compare all participants in this trial receiving platinum chemotherapy, we split this study into two analysis groups, or 'treatment comparisons' (BrighTNess comparison 1 intervention: paclitaxel, veliparib and carboplatin followed by doxorubicin and cyclophosphamide (AC), and BrighTNess comparison 2 intervention: paclitaxel and carboplatin followed by AC). Both were compared to the control group of paclitaxel alone followed by AC.

Excluded studies

We excluded 34 records on full-text review owing to:

- incorrect study population (12 records). We excluded studies where the population included people with TNBC with residual disease after chemotherapy and surgery; studies on unresectable or metastatic TNBC; studies which included hormone receptor-positive or HER2-positive subtypes of breast cancer, and did not separately report outcomes for TNBC; and studies where HER-2 status was not determined or reported;
- incorrect intervention (12 records). We excluded studies employing high-dose chemotherapy requiring autologous stem cell transplant;
- incorrect study design (three records). We excluded retrospective or non-randomised study designs;
- studies not reporting critical outcomes (one study). We excluded one study that did not measure DFS, OS or pCR; such studies often reported other outcomes including breast-conserving surgery rate.
- meta-analyses (six papers). We checked meta-analyses for eligible references, and whether our results were concordant.

The reasons for excluding five studies that may be expected in this review are provided in the Characteristics of excluded studies table.

Ongoing studies

We identified 25 eligible ongoing studies from trial records and abstract publications based on the available information (see Characteristics of ongoing studies table).

- 15 studies examined neoadjuvant chemotherapy, eight studies examined adjuvant therapy and two studies included both neoadjuvant and adjuvant therapy
- 18 studies used carboplatin, six studies used cisplatin, and one study used lobaplatin
- Nine studies reported DFS or OS as a primary outcome and 18 reported DFS or OS as a secondary outcome

The results of the more recent studies are pending; however, it is considered that the inactive older trial records are unlikely to produce results despite emails requesting outcome data from the trialists (NCT03168880; NCT00919880; NCT01752686).

Risk of bias in included studies

See Figure 2 for a summary of risk of bias judgements of the included studies.

Figure 2.

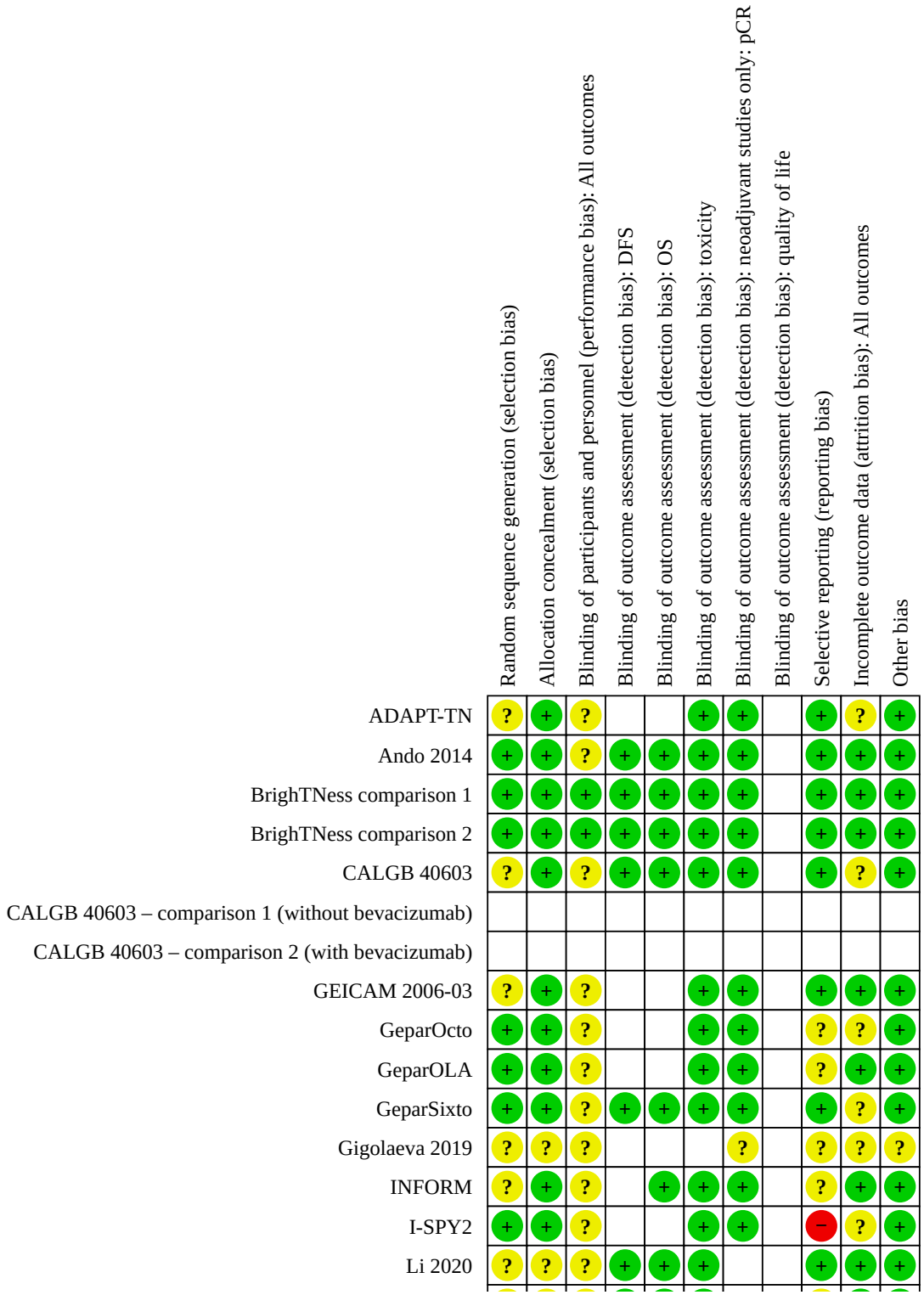
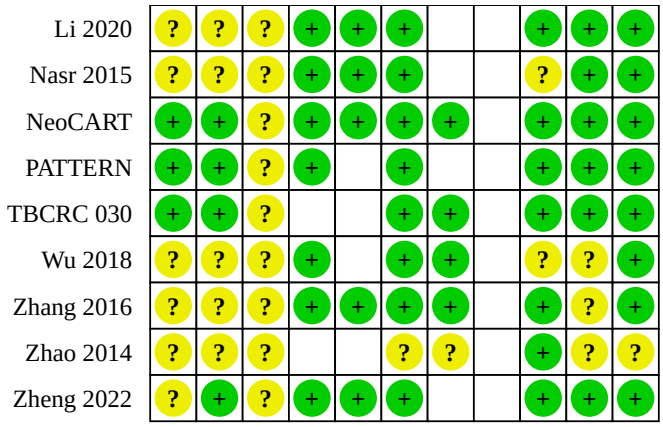


Figure 2. (Continued)



Allocation

Nine studies (10 treatment comparisons) were at low risk of bias for random sequence generation and 14 studies (15 treatment comparisons) for allocation concealment. Those deemed at unclear risk did not detail procedures for randomisation (ADAPT-TN; CALGB 40603; INFORM; GEICAM 2006-03; Gigolaeva 2019; Li 2020; Nasr 2015; Wu 2018; Zhang 2016; Zhao 2014; Zheng 2022), or whether allocation was performed centrally (Gigolaeva 2019; Li 2020; Nasr 2015; Wu 2018; Zhao 2014; Zhang 2016).

Blinding

Nineteen studies were described as open-label. Performance bias due to lack of blinding of participants and personnel was not considered to be a serious concern given the objective nature of the efficacy outcomes and most toxicity outcomes. As such, these studies were deemed at unclear risk of bias. One study was double blinded throughout the course of the trial (BrighTNess), and judged at low risk of bias for all outcomes.

We assessed detection bias by outcome. For DFS, OS, pCR and toxicity, lack of blinding was perceived as unlikely to have an impact given the nature or method in which each outcome is assessed (i.e. through imaging, biochemical tests, reviewed by independent panels, or a combination of these). All studies reporting DFS or OS were perceived to be at low risk of bias. All studies reporting pCR were deemed to be at low risk of bias except for two studies at unclear risk because the papers did not provide any information on tests used or process to evaluate tumour response (Gigolaeva 2019; Zhao 2014). Similarly, studies reporting toxicities were at low risk of bias except for one study as no information was provided on how toxicity was assessed (Zhao 2014). None of the studies that collected quality of life measures reported data and no risk of bias assessment was possible.

Incomplete outcome data

Most studies did not complete a true intention-to-treat analysis, in that participants who were randomised but did not receive treatment were excluded from the efficacy and safety analysis. Notably, only a very small number of participants were excluded in each study after randomisation. Nine studies were at unclear risk of bias. We judged six studies at unclear risk of bias because the reasons for excluding participants were not detailed (CALGB 40603; GeparOcto; GeparSixto; Wu 2018; Zhang 2016; Zhao 2014). One study was at unclear risk of attrition bias as there were several randomised people with missing pCR data that could not be accounted for (ADAPT-TN). Two studies did not provide a CONSORT diagram or associated information and were classified at unclear risk of bias (Gigolaeva 2019; I-SPY2).

Selective reporting

One study was at high risk of bias as it did not report DFS or OS, despite these outcomes being listed in the trial registry records (I-SPY2). As pCR data were reported in 2016, these important long-term efficacy outcomes would have been expected to be reported by 2022. Four studies with more recent publications which have not yet published results on critical outcomes were at unclear risk (GeparOLA; GeparOcto; INFORM; Wu 2018). Two additional studies did not provide sufficient information for an assessment and were judged at unclear risk of bias (e.g. abstract only; Gigolaeva 2019; Nasr 2015).

Four studies identified quality of life as an outcome in their trial registry records or publications (BrighTNess; GeparOcto; I-SPY2; Zheng 2022); however, there were no published reports of quality of life measures from these studies.

Other potential sources of bias

One study was published in abstract form only and did not have an identifiable trial registration record (Gigolaeva 2019). As such, the risk of bias assessment was limited and assessed as unclear. Another study required translation (Zhao 2014). While outcome measures were provided in the translation, we did not have sufficient translated information to make risk of bias assessments for this domain and most others.

Effects of interventions

See: **Summary of findings 1** Platinum-containing chemotherapy compared to chemotherapy without platinum in neoadjuvant therapy for early triple-negative breast cancer; **Summary of findings 2** Platinum-containing chemotherapy compared to chemotherapy without platinum in adjuvant therapy for early triple-negative breast cancer; **Summary of findings 3** Platinum-containing chemotherapy compared to chemotherapy without platinum for early triple-negative breast cancer

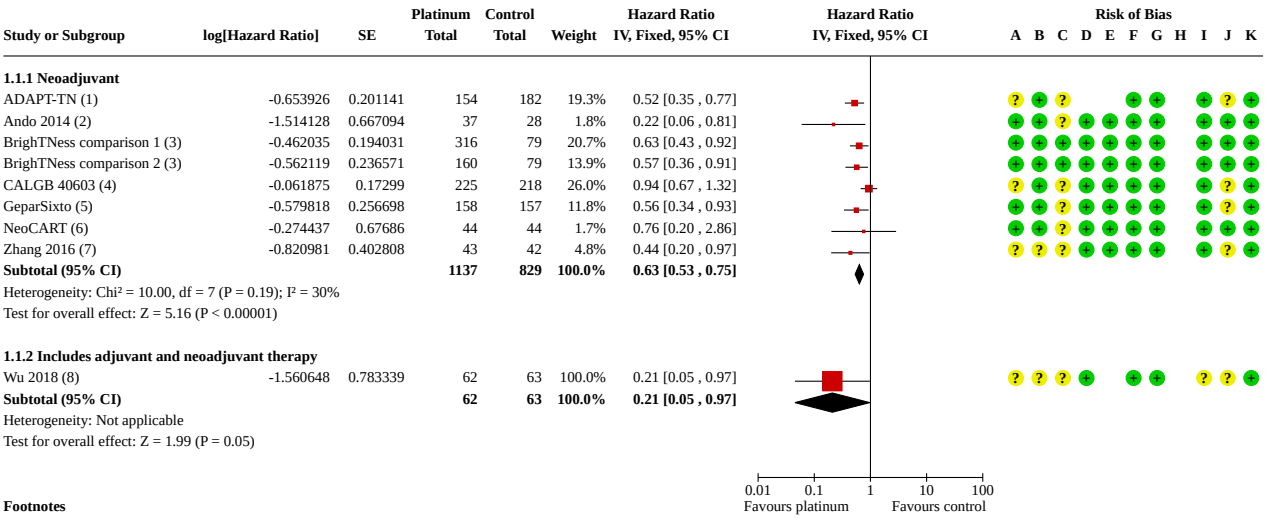
Neoadjuvant therapy

See Summary of findings 1.

Disease-free survival

Ten of the 16 neoadjuvant studies collected data on DFS; however, two studies did not report data (GeparOcto; I-SPY2). Median follow-up ranged from 36 to 94.8 months. Platinum-based chemotherapy improved DFS compared to non-platinum-containing chemotherapy (HR 0.63, 95% CI 0.53 to 0.75; P < 0.001, I^2 = 30%; 7 studies, 8 treatment comparisons; high-certainty evidence; Analysis 1.1; Figure 3). A total of 1966 people were included in the analysis with an estimated 500 DFS events.

Figure 3.



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

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): DFS
(E) Blinding of outcome assessment (detection bias): OS
(F) Blinding of outcome assessment (detection bias): toxicity
(G) Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR
(H) Blinding of outcome assessment (detection bias): quality of life
(I) Selective reporting (reporting bias)
(J) Incomplete outcome data (attrition bias)
(K) Other bias

One other study reported on DFS following neoadjuvant and adjuvant treatment, but results could not be separated for neoadjuvant therapy alone (Wu 2018). Based on this one study, the results suggested an improvement in DFS in the platinum-based chemotherapy group (HR 0.21, 95% CI 0.05 to 0.97; 1 study, 125 participants).

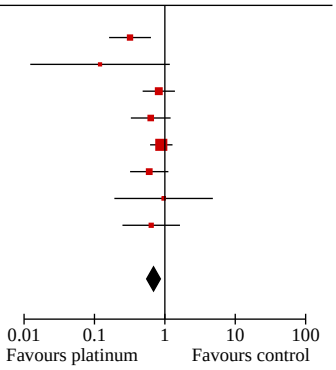
Overall survival

Ten of the 16 neoadjuvant studies collected data on OS; however, two studies collected data but did not report them (GeparOcto; I-SPY2). Median follow-up ranged from 36 to 94.8 months. Platinum chemotherapy reduced mortality (HR 0.69, 95% CI 0.55 to 0.86; P = 0.001, I^2 = 29%; 7 studies, 8 treatment comparisons; high-certainty evidence; Analysis 1.2; Figure 4). A total of 1973 participants were involved in these studies, with an estimated 307 deaths.

Figure 4.

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

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



Footnotes

(1) Median follow-up 36 months
(2) Median follow-up 6.6 years
(3) Median follow-up 4.5 years
(4) Median follow-up 7.9 years
(5) Median follow-up 47.3 months
(6) Median follow-up 37 months
(7) Median follow-up 55 months

One other study collected "all-cause mortality" and reported no deaths in either group and an HR was not provided or estimable (INFORM). Follow-up time statistics for these data are unknown.

Pathological complete response

Fifteen trials (16 treatment comparisons) involving only neoadjuvant treatment reported pCR outcome data. Platinum chemotherapy was associated with a large improvement in the rate of pCR (RR 1.44, 95% CI 1.31 to 1.59, P = 0.009, I^2 = 52%; 15 studies, 16 treatment comparisons, 3083 participants; high-certainty evidence; Analysis 1.3.1; Figure 5). One study reported adjusted probabilities of pCR rather than discrete numbers and a sensitivity analysis (removing the adjusted values) gave a very similar result for pCR (RR 1.43, 95% CI 1.30 to 1.58; 3023 participants) (I-SPY2).

Figure 5.

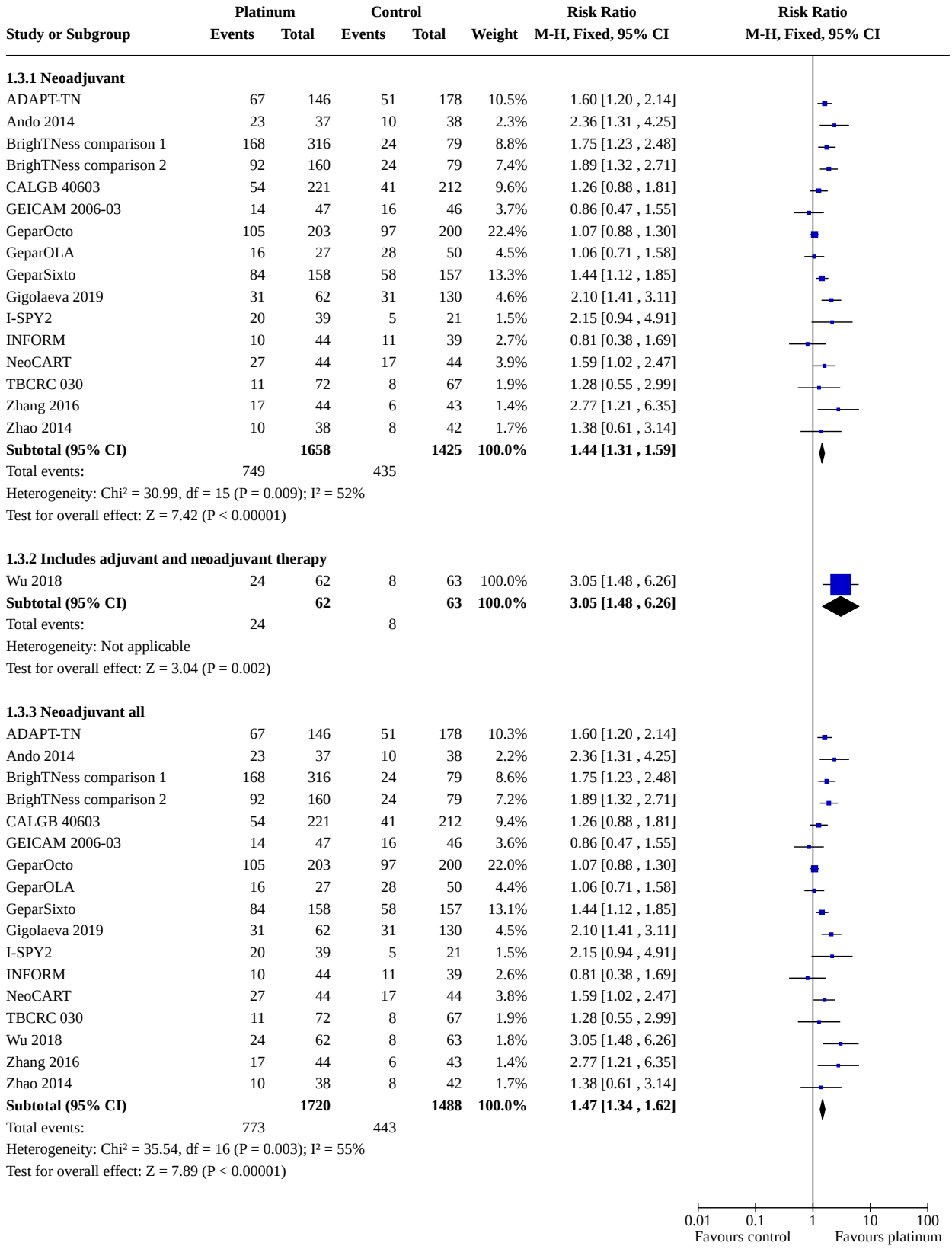
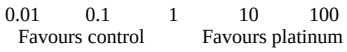


Figure 5. (Continued)



One other study that combined neoadjuvant and adjuvant therapy also showed an improvement in tumour response (RR 3.05, 95% CI 1.48 to 6.26; 125 participants) (Wu 2018).

Adjuvant therapy

See Summary of findings 2.

Disease-free survival

All four studies of adjuvant chemotherapy collected and reported DFS with median follow-up ranging from 52 to 97.6 months. Platinum chemotherapy improved DFS (HR 0.69, 95% CI 0.54 to 0.88; P = 0.003, I^2 = 38%; high-certainty evidence; Analysis 2.1; Figure 3). These studies included 1256 participants, with an estimated 262 DFS events.

Overall survival

All four studies collected and reported OS with follow-up ranging from 52 to 97.6 months. Adjuvant platinum chemotherapy extended OS (HR 0.70, 95% CI 0.50 to 0.96; P = 0.03, I^2 = 53%; high-certainty evidence; Analysis 2.2; Figure 4). A total of 1256 participants were included in this analysis, with an estimated 153 deaths.

All studies

To assess the effect of platinum agents on treatment adherence and toxicity overall, we combined data from neoadjuvant and adjuvant studies. See Summary of findings 3.

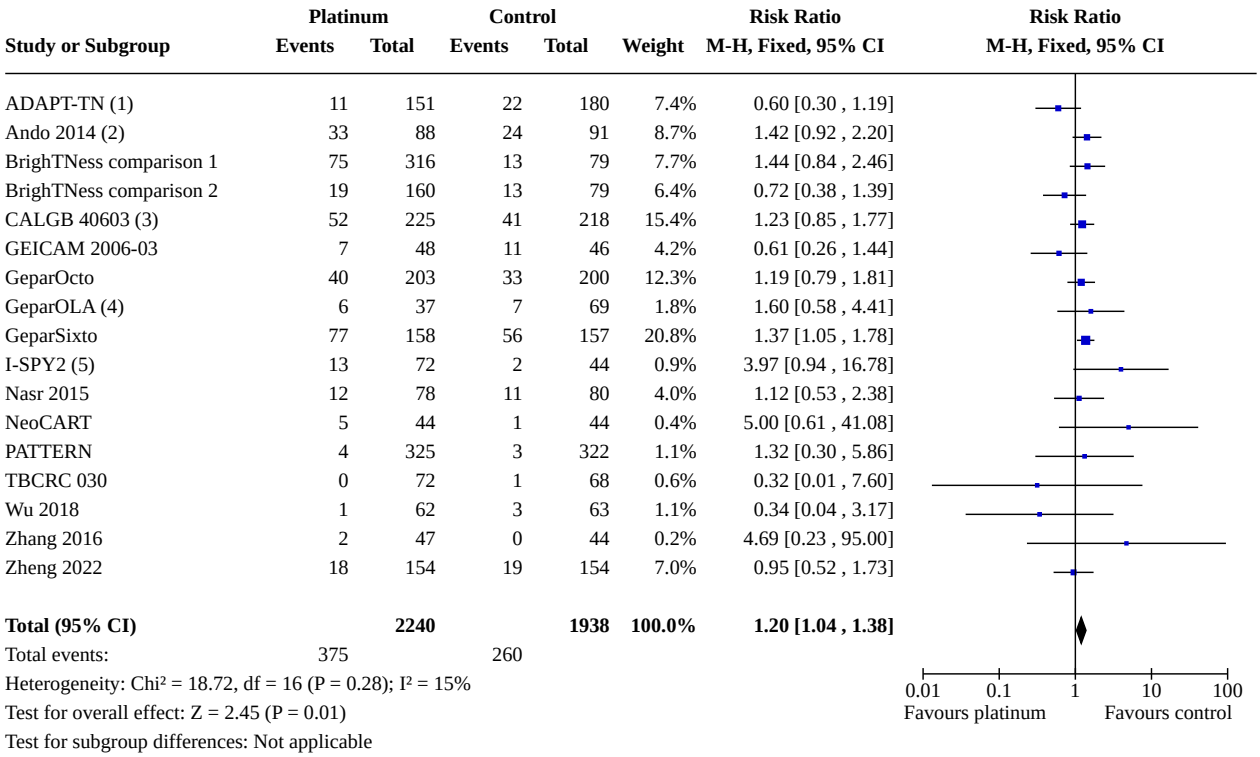
Completion of regimens

Participants receiving platinum chemotherapy were more than twice as likely to have delay in starting the next cycle of chemotherapy (RR 2.23, 95% CI 1.70 to 2.94; P < 0.001, I^2 = 70%; 4 studies, 5 treatment comparisons; moderate-certainty evidence; Analysis 3.1).

Participants receiving platinum chemotherapy were also more likely to require dose reductions (RR 1.77, 95% CI 1.56 to 2.02; P < 0.001; I^2 = 91%; 7 studies, 8 treatment comparisons; moderate-certainty evidence; Analysis 3.2).

Participants receiving platinum chemotherapy were 20% more likely to require early cessation of treatment (RR 1.20, 95% CI 1.04 to 1.38; P = 0.01; I^2 = 15%; 16 studies, 17 treatment comparisons; high-certainty evidence; Analysis 3.3; Figure 6). This was not always due to toxicity, as indicated by some studies that provided reasons for early cessation (early cessation due to toxicity: ADAPT-TN: 45% in intervention group versus 45% in control group; CALGB 40603: 40% in intervention group versus 32% in control group; I-SPY2: 77% in intervention group versus 50% in control group). Other reasons included progression of disease, withdrawal of consent/refusal of treatment or other/unknown.

Figure 6.



Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN (1)	11	151	22	180	7.4%	0.60 [0.30 , 1.19]
Ando 2014 (2)	33	88	24	91	8.7%	1.42 [0.92 , 2.20]
BrighTNess comparison 1	75	316	13	79	7.7%	1.44 [0.84 , 2.46]
BrighTNess comparison 2	19	160	13	79	6.4%	0.72 [0.38 , 1.39]
CALGB 40603 (3)	52	225	41	218	15.4%	1.23 [0.85 , 1.77]
GEICAM 2006-03	7	48	11	46	4.2%	0.61 [0.26 , 1.44]
GeparOcto	40	203	33	200	12.3%	1.19 [0.79 , 1.81]
GeparOLA (4)	6	37	7	69	1.8%	1.60 [0.58 , 4.41]
GeparSixto	77	158	56	157	20.8%	1.37 [1.05 , 1.78]
I-SPY2 (5)	13	72	2	44	0.9%	3.97 [0.94 , 16.78]
Nasr 2015	12	78	11	80	4.0%	1.12 [0.53 , 2.38]
NeoCART	5	44	1	44	0.4%	5.00 [0.61 , 41.08]
PATTERN	4	325	3	322	1.1%	1.32 [0.30 , 5.86]
TBCRC 030	0	72	1	68	0.6%	0.32 [0.01 , 7.60]
Wu 2018	1	62	3	63	1.1%	0.34 [0.04 , 3.17]
Zhang 2016	2	47	0	44	0.2%	4.69 [0.23 , 95.00]
Zheng 2022	18	154	19	154	7.0%	0.95 [0.52 , 1.73]
Total (95% CI)		**2240**		**1938**	**100.0%**	**1.20 [1.04 , 1.38]**
Total events:	375		260			

Heterogeneity: Chi² = 18.72, df = 16 (P = 0.28); I² = 15%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable

Footnotes

(1) 6/11 in intervention and 10/22 in control groups discontinued treatment early due to toxicity.
(2) Data reported for entire cohort; 40% of entire cohort had TNBC.
(3) 21/52 in intervention and 13/41 in control groups discontinued treatment early due to toxicity.
(4) Data reported for entire cohort; 73% of cohort had TNBC.
(5) Data reported for the entire cohort; 52% of cohort had TNBC. 10/13 in intervention and 1/2 in control groups discontinued due to toxicity.

Any grade III/IV toxicity

We collected data for grade III/IV haematological toxicity, neuropathy, nausea, renal impairment and treatment-related death.

Haematological toxicity

Participants receiving platinum-based chemotherapy were more likely to have grade III/IV neutropenia (RR 1.53, 95% CI 1.43 to 1.63; P < 0.001; I^2 = 97%; 19 studies, 20 treatment comparisons; moderate-certainty evidence; Analysis 3.4). Participants receiving platinum-based chemotherapy were unlikely to have higher rates of grade III/IV febrile neutropenia (RR 1.16, 95% CI 0.89 to 1.49; P = 0.27, I^2 = 69%; 11 studies, 12 treatment comparisons; moderate-certainty evidence; Analysis 3.5).

For platinum recipients, there were considerably higher risks of anaemia (RR 8.20, 95% CI 5.66 to 11.89; P < 0.001; I^2 = 42%; 18 studies, 19 treatment comparisons; moderate-certainty evidence; Analysis 3.6). There is likely to be a much higher risk of thrombocytopenia in participants receiving platinum chemotherapy (RR 7.59, 95% CI 5.10 to 11.29; P < 0.001, I^2 = 44%; 18 studies, 19 treatment comparisons; moderate-certainty evidence; Analysis 3.7).

Non-haematological toxicity

There is likely little to no difference in rates of grade III/IV neuropathy associated with platinum chemotherapy (RR 1.22, 95% CI 0.95 to 1.57; P = 0.12, I^2 = 0; 14 studies, 15 treatment comparisons; moderate-certainty evidence; Analysis 3.8).

Participants receiving platinum chemotherapy had a higher rate of grade III/IV nausea (RR 1.89, 95% CI 1.30 to 2.74; P < 0.001; I^2 = 0; 16 studies, 17 treatment comparisons; high-certainty evidence; Analysis 3.9).

Four studies reported data on renal impairment (INFORM; Li 2020; Wu 2018; Zhao 2014). One study reported two events in 60 people in the platinum arm (3%) and no events in 57 people in the non-platinum arm. None of the other studies reported any grade III/IV renal impairment (Analysis 3.10).

Treatment-related death

Treatment-related death was a very rare event, with seven events in 3094 participants. This outcome was not different between platinum and non-platinum intervention arms (RR 0.58, 95% CI 0.14 to 2.33; P = 0.44, I^2 = 0; 10 studies, 11 treatment comparisons; note 8 studies reported treatment-related deaths but recorded 0 events

in both groups. Thus, the RR and CIs were calculated from 3 studies rather than 11; high-certainty evidence; Analysis 3.11).

Quality of life

Although a prespecified outcome of four studies (1198 participants), there were no published quality of life data in the eligible studies available for this review.

Subgroup analysis

Disease-free survival

BRCA mutation status

Four studies, with 1452 participants, reported DFS outcomes stratified by *BRCA* mutation status (BrighTNess; GeparSixto; PATTERN; Zheng 2022). There was no evidence of a difference in DFS outcomes based on *BRCA* mutation status (*BRCA* wild-type: HR 0.65, 95% CI 0.50 to 0.85; *BRCA* mutation: HR 0.72, 95% CI 0.41 to 1.25; P = 0.76; Analysis 4.1). The number of participants in these trials with a known *BRCA* mutation was small, with 222 pathogenic variant carriers, of whom 118 received platinum.

Homologous recombination deficiency status

One study, with 521 participants, reported DFS according to HRD status, based on a multigene panel including 12 breast cancer homologous recombination repair (HRR) associated susceptibility genes (*ATM*, *ATR*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *FANCM*, *PALB2*, *RAD51C*, *RAD51D* and *RECQL*) (PATTERN). There was no evidence of a difference in outcomes between HRD-positive and HRD-negative participants (HRD-positive: HR 0.39, 95% CI 0.15 to 1.00; HRD negative: HR 0.70, 95% CI 0.42 to 1.15; Analysis 5.1) with no subgroup difference (P = 0.28). As there was a small number of participants with HRD-positive tumours (120 participants), this analysis may be underpowered.

Lymph node status

Three studies, with 1097 participants, reported DFS according to lymph node status (Li 2020; PATTERN; Zheng 2022). Participants were 29% lymph node-positive and 71% lymph node negative in this analysis. There was a trend towards benefit for the addition of platinum in both subgroups (lymph node-positive: HR 0.86, 95% CI 0.54 to 1.37; lymph node-negative: HR 0.82, 95% CI 0.55 to 1.22; Analysis 6.1); there was no subgroup difference (P = 0.85).

Type of platinum agent used

Eleven of 12 studies reporting DFS used carboplatin, demonstrating a benefit (HR 0.65, 95% CI 0.57 to 0.75; Analysis 7.1). The remaining study reporting DFS assessed a novel platinum compound, lobaplatin, given both before and after surgery. This study also demonstrated DFS benefit albeit with wide CIs (HR 0.21, 95% CI 0.05 to 0.98).

Same chemotherapy backbone for intervention and control arm

There was a benefit from the addition of platinum whether this was added to an anthracycline/taxane backbone, or as another combination. There was no subgroup difference in DFS benefit between the seven studies with a different backbone (HR 0.62, 95% CI 0.51 to 0.76) and in the five studies with the same backbone (HR 0.67, 95% CI 0.55 to 0.81) with a P value for subgroup difference of 0.63 (Analysis 8.1).

Anthracycline-free platinum arm

In the 12 studies (13 treatment comparisons) reporting DFS, seven had intervention arms combining platinum chemotherapy with anthracycline chemotherapy (including doxorubicin, epirubicin and non-pegylated liposomal doxorubicin). Six treatment comparisons had anthracycline-free platinum intervention arms. Both subgroups had a similar impact on DFS (anthracycline-free intervention: HR 0.59, 95% CI 0.47 to 0.73; anthracycline-containing intervention: HR 0.69, 95% CI 0.57 to 0.83; Analysis 9.1); there was little evidence of a subgroup difference (P = 0.27).

Schedule of platinum agent

There was benefit across all schedules: three-weekly (HR 0.71, 95% CI 0.59 to 0.85; 9 treatment comparisons), two-weekly (HR 0.31, 95% CI 0.14 to 0.70; 1 study) and weekly groups (HR 0.58, 95% CI 0.45 to 0.74; 3 studies).

Overall survival

BRCA mutation, homologous recombination deficiency, lymph node status

No studies reported OS outcomes stratified for BRCA, HRD or lymph node status.

Type of platinum agent used

All studies reporting OS used carboplatin. Therefore, there were insufficient data to assess OS benefit in agents other than carboplatin.

Same backbone

There was improved OS in the seven studies with a different chemotherapy backbone in the platinum compared to the control arm (HR 0.62, 95% CI 0.47 to 0.81) and in the four studies with the same chemotherapy backbone (HR 0.75, 95% CI 0.57 to 0.99); there was little to no difference between groups (P = 0.85; Analysis 8.2).

Anthracycline-free platinum arm

Eleven studies reported OS, and of these five had intervention arms adding platinum chemotherapy to anthracycline chemotherapy, and six had anthracycline-free intervention arms with a platinum-taxane combination. There was a survival benefit in both subgroups (anthracycline-free studies: HR 0.57, 95% CI 0.41 to 0.78; 1607 participants; anthracycline-containing studies: HR 0.77, 95% CI 0.61 to 0.96; 1622 participants); there was no difference between groups (P = 0.14; Analysis 9.2).

Schedule of platinum agent

There was benefit for OS across all treatment schedules: three-weekly (HR 0.79, 95% CI 0.64 to 0.99; 8 treatment comparisons), two-weekly (HR 0.14, 95% CI 0.04 to 0.52; 1 study) and weekly groups (HR 0.55, 95% CI 0.39 to 0.78; 3 studies) (Analysis 10.2).

Pathological complete response

BRCA mutation status

Five studies, with 1478 participants, were included in this analysis, including four studies (five treatment comparisons) that reported pCR stratified by BRCA mutation status (BrighTNess; GeparOcto; GeparOLA; GeparSixto), and one study that contained only participants with a BRCA mutation (INFORM). There was no evidence of a difference between groups (BRCA wild-type: RR 1.40,

95% CI 1.21 to 1.63; BRCA mutation: RR 1.11, 95% CI 0.91 to 1.36; P = 0.07; Analysis 4.2).

Homologous recombination deficiency status

One study with 104 participants reported rates of pCR according to HRD status (TBCRC 030). There was no evidence of a difference between subgroups (HRD-positive: RR 0.90, 95% CI 0.28 to 2.84; HRD-negative: RR 0.25, 95% CI 0.03 to 2.18; Analysis 5.2; P = 0.31).

Lymph node status

Two studies, with 721 participants, reported pCR rates according to lymph node status. There was a similar pCR benefit from addition of platinum in both subgroups (lymph node-positive: RR 1.89, 95% CI 1.31 to 2.73; lymph node-negative: HR 1.83, 95% CI 1.35 to 2.50; Analysis 6.2) (P = 0.91 for subgroup differences).

Type of platinum agent used

In the pCR analysis, there was a clear benefit in the studies using carboplatin (HR 1.45, 95% CI 1.32 to 1.60; 12 studies, 2801 participants) and lobaplatin (RR 3.05, 95% CI 1.48 to 6.26; 1 study, 125 participants), but not in the studies using cisplatin (RR 1.00, 95% CI 0.58 to 1.75; 2 studies, 222 participants; Analysis 7.3; INFORM; TBCRC 030); there was weak evidence of a subgroup difference (P = 0.07). This supports the DFS and OS findings in that the clearest evidence for benefit in this meta-analysis is for carboplatin, with a single study supporting the use of lobaplatin.

Same backbone

There was weak evidence of a difference in pCR benefit between the subgroup of nine studies with a different backbone (RR 1.35, 95% CI 1.18 to 1.53; 1473 people) and in the subgroup of six studies with the same backbone (RR 1.59, 95% CI 1.38 to 1.84; 1675 people) with a P value for subgroup differences of 0.09 (Analysis 8.3).

Anthracycline-free platinum arm

Outcomes for pCR were similar amongst the 10 treatment comparisons with an anthracycline-containing intervention (RR 1.44, 95% CI 1.29 to 1.61), and the six studies with anthracycline-free intervention (RR 1.53, 95% CI 1.24 to 1.89) with a P value for subgroup differences of 0.61 (Analysis 9.3).

Schedule of platinum agent

There was an increased likelihood of pCR across the three-weekly (11 treatment comparisons, RR 1.61, 95% CI 1.38 to 1.87) and weekly groups (5 studies, RR 1.34, 95% CI 1.19 to 1.52) in Analysis 10.3, with minimal evidence of subgroup differences (P = 0.07).

Sensitivity analyses

Hormone receptor immunohistochemistry cut-off other than less than 1%

The ideal hormone receptor IHC cut-off varied between studies on this topic. Although less than 1% was the most commonly used definition, other cut-offs included less than 5% and less than 10%.

- When stratified by hormone receptor IHC cut-off, improved DFS was similar in studies that defined TNBC by less than 1% hormone receptor staining (HR 0.60, 95% CI 0.50 to 0.71; ADAPT-TN; BrighTNess; GeparSixto; Li 2020; NeoCART; PATTERN; Zheng 2022) compared to studies in this review where the cut-off was less than 10% or not stated (HR 0.76, 95% CI 0.59 to 0.98; less than 10%: Ando 2014; CALGB 40603; Wu 2018; Zhang 2016; not stated: Nasr 2015). There was no difference between subgroups (P = 0.11).
- There was improvement in OS in studies that defined TNBC by less than 1% hormone receptor staining (HR 0.62, 95% CI 0.49 to 0.79; 2468 participants; ADAPT-TN; BrighTNess; GeparSixto; Li 2020; NeoCART; PATTERN; Zheng 2022), and in the group of studies where the cut-off was less than 10% or not stated (HR 0.81, 95% CI 0.60 to 1.07; 761 participants; less than 10%: Ando 2014; CALGB 40603; Zhang 2016; not stated: Nasr 2015). There was no difference between subgroups (P = 0.18).
- An association between platinum chemotherapy and likelihood of pCR was similar in the less than 1% cut-off subgroup (RR 1.42, 95% CI 1.26 to 1.58; ADAPT-TN; BrighTNess; GeparOcto; GeparOLA; GeparSixto; NeoCART), and the subgroup of studies with a cut-off of less than 5%, 10% or not stated (RR of 1.57, 95% CI 1.30 to 1.90; less than 5%: TBCRC 030, less than 10%: Ando 2014; CALGB 40603; Wu 2018; Zhang 2016; not stated: GEICAM 2006-03; Gigolaeva 2019; Zhao 2014). There was no difference between subgroups (P = 0.35).

Potentially confounding treatments in intervention arm

Multiple studies tested interventions combined with platinum chemotherapy. These treatments were viewed as potentially confounding in this sensitivity analysis. However, notably, all of these extra treatments have subsequently been found to be ineffective (Banys-Paluchowski 2017; BrighTNess; Shepherd 2022). The studies of note included Nasr 2015, which provided the intervention group with a further 12 months of metronomic chemotherapy; BrighTNess comparison 1, which included veliparib; and CALGB 40603, which provided one group with bevacizumab.

The sensitivity analysis for outcome measures revealed the following.

- The DFS effect was similar when studies with potentially confounding extra treatments were removed (HR 0.60, 95% CI 0.50 to 0.71). This was done by removing Nasr 2015 and BrighTNess comparison 1, and using only the bevacizumab-free arm of CALGB-40603.
- This OS effect was similar when two studies with potentially confounding extra treatments (Nasr 2015; BrighTNess comparison 1) were removed (HR 0.64, 95% CI 0.52 to 0.79).
- The likelihood of pCR was similar when one study with potentially confounding extra treatment (BrighTNess comparison 1) was removed (HR 1.49, 95% CI 1.35 to 1.63).

High or unclear risk of bias

- All studies reporting DFS or OS had an overall low risk of bias so a sensitivity analysis was not performed for these outcomes.
- For pCR, the effect of removing two studies with most or all domains at unclear risk (Zhao 2014; Gigolaeva 2019) was minimal on the likelihood of pCR (RR 1.44, 95% CI 1.30 to 1.59).

Outcomes with considerably heterogeneity

We applied a random-effects model to the two outcomes with considerable heterogeneity (i.e. an I^2 value of 75% to 100%). Both of these analyses resulted in a similar magnitude RR, but with wider CIs.

- Participants requiring a dose reduction: RR 2.18, 95% CI 1.08 to 4.41 compared to RR 1.77, 95% CI 1.56 to 2.02 with a fixed-effect model.
- Neutropenia: RR 1.68, 95% CI 1.12 to 2.52 compared to RR 1.53, 95% CI 1.43 to 1.63 with a fixed-effect model.

DISCUSSION

Summary of main results

Platinum-based chemotherapy using carboplatin in the adjuvant or neoadjuvant setting improved long-term outcomes of DFS and OS in early TNBC, regardless of the examined subgroups. This was at the cost of more frequent chemotherapy delays and dose reductions, and greater haematological toxicity as presented in Summary of findings 3. There was benefit from platinum when platinum agents were added to both anthracycline-containing regimens and in anthracycline-free regimens.

Though there are certainly increased haematological toxicities associated with platinum chemotherapy, permanent toxicity such as grade III/IV neuropathy and treatment-related death were not different between groups. These trials did not report important quality-of-life measures.

Attempts in this review to refine subgroups of triple-negative biology, such as those with BRCA mutations or altered HRD status, have higher benefit from platinum therapy found no predictive role. The certainty of this evidence was low since numbers were low. Only one study assessed the role of HRD status on efficacy outcomes in our analysis. It remains unclear if more modern and focused HRD testing may offer better biomarkers for participants who will benefit from platinum chemotherapy. We were also unable to identify if there may be a subgroup of participants who might not benefit, and for whom de-escalation therapy might be appropriate.

Overall completeness and applicability of evidence

These results were generally applicable to people with early TNBC, allowing for the trial to define hormone receptor cut-offs which ranged from 1% to 10%. The range of ages captured in these trials was from 19 to 82 years. Outcomes based on age were not available. Information on participant gender was not collected.

While racial background of participants was not captured in our analysis, these trials took place in several countries in Europe, Asia and the US. Black and African participants are likely to be a notable ethnic gap in this meta-analysis given the dearth of trials occurring on the African continent and the low participation rates of Black Americans in cancer clinical trials (Awidi 2021).

Recruitment of the included trials started between six and 16 years ago, and as such the standard therapy arms may not reflect current international standards. This is a shifting target, and the advent of new treatments used in early TNBC such as immunotherapy and PARP inhibitors, as well as the clinical heterogeneity of chemotherapy used in these studies, means the best regimen and timing of platinum chemotherapy remains unclear. This review also does not provide insight into the use of post-neoadjuvant capecitabine, which is currently part of standard care for people with residual disease after neoadjuvant chemotherapy for TNBC. ECOG-ACRIN EA1131 assessed whether platinum chemotherapy can replace capecitabine, but this study was excluded from this review given the study population included only those with residual disease. Further research into this area is warranted, particularly given the increasing number of drugs used in TNBC and increasing interest in biomarker-directed treatment rationalisation.

Many of the studies examining neoadjuvant chemotherapy only report pCR, which is a surrogate marker for long-term benefit. Several studies did not report on certain important toxicity outcomes such as febrile neutropenia, renal impairment and treatment-related death. The number of participants in subgroups of BRCA mutation status, HRD status and lymph node status were relatively small and may not have provided sufficient power to sufficiently address whether there are different outcomes for these groups. Recent data suggest that a DFS and OS benefit only exists for people aged less than 50 years (Gupta 2022); however, we did not include age as a subgroup analysis, neither were there outcome data reported stratified based on age in the studies analysed.

No quality of life outcomes were reported. This is an important measure particularly when assessing outcomes which are more accurately reported by participants, such as fatigue and effects on cognition. As such, we may be missing important impacts of the addition of platinum chemotherapy on participants of these clinical trials both acutely and in the longer term.

Use of platinum chemotherapy is variable, and at the time of writing is still not routinely recommended in NCCN or European Society for Medical Oncology guidelines. A lack of DFS and OS benefit is often cited as a reservation to the routine use of platinum chemotherapy. This review presents relevant, adequately powered outcome data to support the use of platinum chemotherapy in early TNBC, acknowledging the increased rate of haematological toxicity.

Quality of the evidence

This systematic review provides evidence from 20 studies, with 4468 participants, and provides high-certainty evidence supporting the addition of platinum chemotherapy in the neoadjuvant and adjuvant settings with an increase in DFS and OS.

An important methodological limitation in this meta-analysis is that all but one of the included trials adopted an open-label design. It is considered that the efficacy outcomes of DFS, OS and pCR are unlikely to be affected by a lack of blinding. However, the risk of bias may be increased for more subjective toxicity assessments such as nausea and neuropathy.

Clinical heterogeneity was present in the chemotherapy regimens, and in the type, timing and duration of the platinum agent. Some trials used platinum in addition to an existing regimen (e.g. adding carboplatin to doxorubicin-cyclophosphamide followed by paclitaxel), while others used platinum in place of other agents (e.g. comparing carboplatin-docetaxel to doxorubicin-cyclophosphamide followed by paclitaxel) or used as a single agent. In other trials, extra treatments such as veliparib, bevacizumab and metronomic chemotherapy were also added.

Despite the clinical heterogeneity, this meta-analysis demonstrated generally high-certainty, consistent evidence for the primary outcome measures of DFS and OS. However, there was a significant degree of heterogeneity in many of the treatment delivery and toxicity outcome categories, including chemotherapy delays, dose reductions, neutropenia and febrile neutropenia. This resulted in downgrading of the certainty of evidence, as demonstrated in Summary of findings 3.

Potential biases in the review process

Using standard Cochrane search methods, we identified numerous trial records. Our final 20 trials were consistent with previous reviews and studies cited in local and international guidelines. There is a high likelihood that all relevant trials were identified.

Unfortunately, not all relevant data could be obtained. Notably, multiple studies listed outcomes including DFS, OS and quality of life which were never published. The lack of DFS and OS data reported in particular for cisplatin could indicate publication bias, given its failure to produce a benefit in pCR.

In this review, we included studies with intervention treatments in addition to carboplatin, such as veliparib, bevacizumab and metronomic chemotherapy. While these trials were potentially confounding, a sensitivity analysis showed that removing these trials had a minimal impact on the pooled outcome analysis.

Several studies recruited subgroups other than TNBC. These trials were only included if outcome measures were reported separately or only included less than 20% of participants with non-TNBC. However, treatment completion and toxicity information were not always reported for each breast cancer subtype. As such, we presented these measures for the whole group who were receiving the same treatment, which may be a potential source of bias.

Agreements and disagreements with other studies or reviews

Early meta-analyses of randomised, retrospective and prospective studies by Petrelli 2014, Poggio 2018, Wang 2017, and Pandy 2019 showed an improvement in pCR associated with the use of platinum chemotherapy. None of the listed studies that examined DFS or OS were able to demonstrate a difference from the addition of platinum, likely due to a lack of reporting of these outcome measures and immature follow-up.

More recently, Saleh 2021 performed a meta-analysis of 14 randomised or retrospective trials of platinum-based perioperative chemotherapy. They found platinum chemotherapy was associated with an improvement in DFS but not OS. The inclusion of retrospective trials may have been a confounder in this analysis.

Our findings have aligned with those of Bian 2021, who found in seven randomised controlled trials that platinum-based perioperative chemotherapy improved both DFS and OS for people with early TNBC. They explored subgroups including the setting of chemotherapy (adjuvant versus neoadjuvant) and lymph node status. This was the first meta-analysis to demonstrate an OS benefit. Our review builds on the findings of this study, including more trials and adding additional subgroup analyses including BRCA, HRD, hormone receptor IHC % positive thresholds, chemotherapy content and timing.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides high-certainty evidence that platinum-based chemotherapy with carboplatin is associated with improved disease-free survival (DFS), overall survival (OS) and pathological complete response in early triple-negative breast cancer (TNBC). This is at the cost of increased grade III/IV haematological toxicity, though serious adverse events including febrile neutropenia or treatment-related death were not increased.

These findings support the use of carboplatin, but not cisplatin, for people with early TNBC. The optimal dose and regimen are not defined by this analysis, but there is a suggestion that similar relative benefits result from the addition of carboplatin to either anthracycline-free regimens or those containing anthracycline agents. Additionally, our analysis supports a broad rather than focused use of carboplatin based on the benefit seen across the examined subgroups.

Implications for research

We examined a single trial using lobaplatin, a novel platinum agent which is reported to have a favourable toxicity profile in other cancers (Perabo 2007). Further testing of other platinum compounds is justified if it may alleviate some of the additive toxicity associated with combination chemotherapy, such as the haematological toxicity reported in this review.

In this review, we did not identify a subgroup of TNBC which may derive greater benefit from platinum chemotherapy. Refining groups who may benefit most would be helpful to guide treatment selection. It is currently unclear if emerging biomarkers including enhanced homologous recombination deficiency testing might be helpful in future for participant selection.

Incremental improvements in DFS and OS are being provided by new anticancer agents in the setting of early disease, including immunotherapy (Schmid 2020) and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors (Tutt 2021). As we add new agents, we must also consider rationalising and de-escalating treatment for certain participants at lower risk of recurrence or who have a favourable treatment response. The use of anthracycline-free regimens is of increasing interest (Nitz 2019; Yu 2021) given these agents are implicated in long-term cardiotoxicity and secondary leukaemia. Further research into the optimal regimen is warranted.

Finally, this review has highlighted the need for ensuring reporting of the quality of life data collected in trials involving early breast cancer. The value of patient-reported outcome measures is being increasingly recognised, and whilst trials are collecting data, they are not always published in a timely manner. Consideration of these outcomes from clinical trials is essential for ensuring person-centred clinical interventions to assess objective disease control as well as more subjective health and well-being.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

ADAPT-TN

Study characteristics	
Methods	Accrual: May 2013 to January 2015
	Multicentre, 48 sites
	Phase of trial: 2
	Study design: RCT
	Country or countries where the trial was conducted: Germany
	Median follow-up: not reported

ADAPT-TN *(Continued)*

Participants	Age: median 50, range 26–75 years Nodal status of breast cancer: node positive 26%, node negative 74% Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	Arm 1: Nab-paclitaxel 125 mg/m^2 + carboplatin AUC2 days 1 and 8, every 3 weeks for 4 cycles Arm 2: Nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 days 1 and 8, every 3 weeks for 4 cycles
Outcomes	Primary • pCR, defined as absence of invasive tumour cells in breast and lymph nodes (ypT0/is ypN0) Secondary • Toxicity, according to NCI CTCAE version 4.0 • EFS, defined as time from registration to any invasive relapse, secondary malignancy or death from any cause • OS – early response • Ki67 decrease > 30% or < 500 invasive cells in the 3-week serial biopsy
Notes	Trial registration record: NCT01815242 Not all randomised participants were included in the analysis; 5 excluded prior to receiving treatment (3 in intervention arm, 2 in comparator arm). Safety analysis involved people receiving ≥ 1 dose of trial medication. For DFS and OS, we estimated the hazard ratio using Tierney's method. Study did not report assessing the proportional hazards assumption. Funding considerations: funded by Celgene and Teva.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in a 1:1 ratio, method to generate random sequence was not described.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed centrally at West German Study group."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias):	Low risk	pCR was assessed by a local pathologist only. It is not reported whether this pathologist was blinded to the treatment allocation; however, pCR is viewed

ADAPT-TN *(Continued)*

neoadjuvant studies only: pCR		to be an objective outcome and unlikely to be influenced by knowledge of treatment allocation.
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary endpoints from the trial record were reported in the manuscript and subsequent abstract publications.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	CONSORT diagram showed that 5/336 randomised participants did not 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.
Other bias	Low risk	None identified.

Ando 2014

Study characteristics	
Methods	Accrual: March 2010 and September 2011 Multicentre, 10 centres Phase of trial: 2 Trial design: open-label RCT Countries: Japan Median follow-up: 12 months
Participants	Demographics and clinical characteristics were not reported separately for the participants of interest for this Cochrane Review topic. People with TNBC made up approximately 40% of the entire cohort. *For entire cohort* Age: median 47, range 30–70 years Nodal status of breast cancer: 65% node positive, 35% node negative BRCA mutation: not reported Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	Arm 1: intervention: carboplatin AUC5 every 3 weeks for 4 cycles + paclitaxel 80 mg/m^2 days 1, 8, 15 for 4 cycles, followed by 4 cycles of cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2 and fluorouracil 500 mg/m^2 every 3 weeks Arm 2: comparator: paclitaxel 80 mg/m^2 days 1, 8, 15 for 4 cycles, followed by 4 cycles of cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2 and fluorouracil 500 mg/m^2 every 3 weeks Surgery within 8 weeks after completing neoadjuvant therapy. People who had breast-conserving therapy received whole breast irradiation
Outcomes	Primary • pCR rate, defined as the 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

Ando 2014 *(Continued)*

	Secondary • DFS, defined as time from randomisation to the first appearance of any recurrence of breast cancer (local, regional or distant), or any cause of death • Clinical response rate, assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 • Breast conservation rate • Safety, assessed using the CTCAE version 4.03 • OS (not prespecified endpoint), defined as time from randomisation to death by any cause
Notes	Trial registration record: UMIN000003355. Where reported separately, we extracted data for the TNBC cohort only (42% of entire cohort) for efficacy outcomes. As data were not presented separately for toxicity, we extracted data for the entire cohort. Authors were not contacted. All randomised patients who received ≥ 1 dose of study chemotherapy were included in the analysis. Study did not report assessing the proportional hazards assumption. Funding considerations: carboplatin provided by Bristol-Myers Squibb. Study supported by Health and Labour Sciences Research Grants, Ministry of Health, Labour and Welfare, Cancer Research & Development and National Cancer Centre grants, Japan.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned to receive either … by the minimization method, with balancing of the treatment arms according to disease status, hormone receptor status and institution." (p. 402)
Allocation concealment (selection bias)	Low risk	"Central registration" listed in trial registration record.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Evaluated centrally by 3 breast pathologists.

Ando 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes listed in trial registration record were reported in trial publications. OS was not prespecified but collected later on and is a critical outcome for this review topic.
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram (p.404) showed that 2 participants randomised were excluded from analyses due to both participants refusing treatment.
Other bias	Low risk	None identified.

BrighTNess comparison 1

Study characteristics	
Methods	Accrual: April 2014 to March 2016 Multicentre, 145 sites Phase of trial: 3 Study design: quadruple-blind (participant, care provider, investigator, outcomes assessor) RCT Country or countries where the trial was conducted: Germany, Spain, USA, Korean, France, Czech Republic, Russia, Belgium, Australia, Hungary, Italy, UK, Canada, Taiwan, Netherlands Median follow-up: 4.5 years
Participants	Age: median 50, range 40–59 years Nodal status of breast cancer: 42% node positive, 58% node negative Proportion of people with BRCA mutations: 15% Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	A 3-arm study that has been split in this Cochrane Review into 2 separate pairwise comparisons. Arm 1 (arm named 'paclitaxel + carboplatin + veliparib' in trial publication): paclitaxel 80 mg/m^2 intravenously weekly plus carboplatin AUC6 every 3 weeks for 12 weeks plus veliparib 50 mg twice a day, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles Arm 2 (named 'paclitaxel + carboplatin placebo + veliparib placebo' group in trial publication): paclitaxel 80 mg/m^2 intravenously weekly for 12 weeks, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles
Outcomes	Primary • pCR, defined as the absence of residual invasive disease on evaluation of the resected breast specimen and resected lymph nodes following completion of neoadjuvant systemic therapy Secondary • EFS, defined as the 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 malignancy; or death from any cause • OS, defined as the number of days from the day of randomisation to the date of death • Suitability of breast-conservation surgery

BrighTNess comparison 1 *(Continued)*

- Toxicity, graded according to NCI CTCAE v4.0-quality of life, using EORTC QLQ-C30, EORTC QLQ-BR23 and EQ-5D 5L

Notes	Trial registration record: NCT02032277 All randomised participants included in intention-to-treat analysis. Study did not report assessing the proportional hazards assumption. Funding considerations: funded by AbbVie, who participated in the design of the study, collection, analysis and interpretation of the data, as well as the writing, review and approval of the manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned (2:1:1) to one of three treatment groups by an interactive response technology system using permuted blocks (block size of four) within strata. The randomisation schedule was created by the statistics department of the study funder (AbbVie, North Chicago, IL, USA)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation schedule … was forwarded to a third-party vendor (Endpoint Clinical) to be implemented via the interactive response technology system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded. Quote: "The study funder, members of the academic steering committee, investigators, study site personnel, and patients remained masked to each patient's treatment throughout the course of the study."
Blinding of outcome assessment (detection bias): DFS	Low risk	Blinding of outcome assessment occurred.
Blinding of outcome assessment (detection bias): OS	Low risk	Blinding of outcome assessment occurred.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using CTCAE, and double-blind study.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Double-blind, local assessment with central review. Quote: "Pathological complete response was assessed by local pathology review of the resected breast specimen and lymph node tissue on haematoxylin and eosin-stained samples. The local pathology reports were centrally reviewed by members of the steering committee to confirm the accuracy of data entry for the endpoint."
Selective reporting (reporting bias)	Low risk	Quality of life was a prespecified tertiary endpoint but not reported. All primary and secondary outcomes, including DFS and OS, were reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis performed – all participants who were randomised were included in the analysis, including those who withdrew consent or did not proceed to surgery.
Other bias	Low risk	None identified.

BrighTNess comparison 2

Study characteristics	
Methods	See BrighTNess comparison 1
Participants	See BrighTNess comparison 1
Interventions	A 3-arm study that has been split in this Cochrane Review into 2 pair-wise comparisons. Arm 1 (arm named 'paclitaxel + carboplatin + veliparib placebo' group in trial publication): paclitaxel 80 mg/m^2 intravenously weekly plus carboplatin AUC6 every 3 weeks for 12 weeks, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles Arm 2 (named 'paclitaxel + carboplatin placebo + veliparib placebo' group in trial publication): paclitaxel 80 mg/m^2 intravenously weekly for 12 weeks, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles
Outcomes	See BrighTNess comparison 1
Notes	See BrighTNess comparison 1

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned (2:1:1) to one of three treatment groups by an interactive response technology system using permuted blocks (block size of four) within strata. The randomisation schedule was created by the statistics department of the study funder (AbbVie, North Chicago, IL, USA)."
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation schedule … was forwarded to a third-party vendor (Endpoint Clinical) to be implemented via the interactive response technology system."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "The study funder, members of the academic steering committee, investigators, study site personnel, and patients remained masked to each patient's treatment throughout the course of the study."
Blinding of outcome assessment (detection bias): DFS	Low risk	Blinding of outcome assessment occurred.
Blinding of outcome assessment (detection bias): OS	Low risk	Blinding of outcome assessment occurred.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using CTCAE, and double-blind study.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Double-blind, local assessment with central review. Quote: "Pathological complete response was assessed by local pathology review of the resected breast specimen and lymph node tissue on haematoxylin and eosin-stained samples. The local pathology reports were centrally re-

BrighTNess comparison 2 *(Continued)*

		viewed by members of the steering committee to confirm the accuracy of data entry for the endpoint."
Selective reporting (reporting bias)	Low risk	Quality of life was a prespecified tertiary endpoint but not reported. All primary and secondary outcomes, including DFS and OS, were reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis performed – all participants who were randomised were included in the analysis, including those who withdrew consent or did not proceed to surgery.
Other bias	Low risk	None identified.

CALGB 40603

Study characteristics	
Methods	Accrual: May 2009 to August 2012 Multicentre Phase of trial: 2–3 Study design: open-label RCT Country or countries where the trial was conducted: USA Median follow-up: 7.9 years for EFS and OS data
Participants	Age: mean and range not reported. 60% aged 40–59 years Nodal status of breast cancer: 52% node positive, 42% node negative, 7% missing Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	4-arm study that has been grouped here into 2 categories according to carboplatin use. Arm 1 (listed as arms 3 and 4 in the trial publication): paclitaxel 80 mg/m^2 weekly + carboplatin AUC6, 3 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles ± bevacizumab 10 mg/kg every 2 weeks for 9 cycles Arm 2 (listed as arms 1 and 2 in the trial publication): paclitaxel 80 mg/m^2 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles ± bevacizumab 10 mg/kg every 2 weeks for 9 cycles Where possible, we reported pair-wise comparisons of arm 1 vs arm 3 (see CALGB 40603 – comparison 1 (without bevacizumab)), and arm 2 vs arm 4 (see CALGB 40603 – comparison 2 (with bevacizumab)).
Outcomes	Primary • pCR breast – absence of residual invasive disease with or without ductal carcinoma in situ (ypT0/is) Secondary • pCR breast/axilla – pCR breast and the absence of any tumour deposit > 0.2 mm in sampled axillary nodes (ypT0/isN0) • Treatment delivery • Treatment-related toxicity, graded according to NCI CTCAE v4.0

CALGB 40603 *(Continued)*

- RCB-conversion from clinically node positive to pathologically node negative
- Conversion from breast-conserving surgery ineligible to breast-conserving surgery eligible
- RFS/EFS for up to 10 years, defined as time from random assignment to local, regional or distant recurrence, any second invasive cancer, or death from any cause
- Time to first failure for up to 10 years
- OS for up to 10 years, defined as time from random assignment to death from any cause
- Distant RFS, defined as time from random assignment to detection of metastatic disease or death attributed to disease progression

Notes	Trial registration record: NCT00861705 Not all randomised participants were included in intention-to-treat analysis – participants who withdrew consent before completing neoadjuvant chemotherapy were excluded from pCR analyses. Study authors appeared to have assessed proportional hazards assumption. Funding considerations: funded in part by NCI grants, Genentech, the Breast Cancer Research Foundation, and the American Recovery and Research Act. These sources were not involved in data analysis or preparation of manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in 2 × 2 format, method not described.
Allocation concealment (selection bias)	Low risk	Study protocol stated participant registration and randomisation occurs through CALGB web-based system. It is most likely that randomisation was centralised.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Pathological response was determined locally, without central pathological review. It was not reported whether this pathologist was blinded to the treatment allocation, however pCR is viewed to be an objective outcome and unlikely to be influenced by knowledge of treatment allocation.
Selective reporting (reporting bias)	Low risk	All prespecified primary endpoints from the trial record were reported in the manuscript. Some secondary outcome measures, including radiographic response, clinical response, and incidence and severity of postoperative complications were not reported; however, these were not considered to be critical

CALGB 40603 *(Continued)*

		outcomes for this review topic. OS, a secondary outcome, was reported in a subsequent publication.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.
Other bias	Low risk	None identified.

CALGB 40603 – comparison 1 (without bevacizumab)

Study characteristics	
Methods	See details in CALGB 40603
Participants	See details in CALGB 40603
Interventions	4-arm study that has been split into 2 treatment comparisons where possible. Treatment comparison 1 includes: Arm 1 (listed as arm 3 in the trial publication): paclitaxel 80 mg/m^2 weekly + carboplatin AUC6, 3 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles Arm 2 (listed as arm 1 in the trial publication): paclitaxel 80 mg/m^2 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles
Outcomes	See details in CALGB 40603
Notes	See details in CALGB 40603

CALGB 40603 – comparison 2 (with bevacizumab)

Study characteristics	
Methods	See details in CALGB 40603
Participants	See details in CALGB 40603
Interventions	4-arm study that has been split into 2 treatment comparisons where possible. Treatment comparison 2 includes: Arm 1 (listed as arm 4 in the trial publication): paclitaxel 80 mg/m^2 weekly + carboplatin AUC6, 3 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles and bevacizumab 10 mg/kg every 2 weeks for 9 cycles Arm 2 (listed as arm 2 in the trial publication): paclitaxel 80 mg/m^2 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles and bevacizumab 10 mg/kg every 2 weeks for 9 cycles
Outcomes	See details in CALGB 40603

CALGB 40603 – comparison 2 (with bevacizumab) *(Continued)*

Notes	See details in CALGB 40603

GEICAM 2006-03

Study characteristics	
Methods	Accrual: April 2007 to January 2010 Multicentre Phase of trial: 2 Study design: open-label RCT Country or countries where the trial was conducted: Spain Median follow-up: not reported
Participants	Age: median 47, range 27–75 years Nodal status of breast cancer: 52% node positive, 48% node negative Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	4-arm study (luminal A standard treatment, luminal A selective treatment, basal standard treatment, basal selective treatment). For this Cochrane Review, 2/4 treatment arms were relevant, i.e. data on the basal phenotype. Arm 1 ("Group 2 standard treatment" in trial registry record): epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by docetaxel 75 mg/m^2 + carboplatin AUC6 every 3 weeks for 4 cycles Arm 2 ("Group 2 selective treatment" in trial registry record): epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 for 4 cycles followed by docetaxel 75 mg/m^2 every 3 weeks for 4 cycles After neoadjuvant therapy, participants had mastectomy or conservative surgery Postoperative radiotherapy was given at physician's discretion.
Outcomes	Primary • pCR in the breast, as per Miller and Payne criteria Secondary • Safety, graded using the NCI CTCAE version 3.0. The worst grade for each participant was reported • Clinical response, according to RECIST criteria before surgery • Mastectomy rate and breast-conservative surgery rate • Axillary node status at time of surgery
Notes	Trial registration record: NCT00432172 All randomised participants who received a dose of study treatment were included in the analysis; 1 participant never received treatment and was excluded.

GEICAM 2006-03 *(Continued)*

	Funding considerations: partially supported by Pfizer and sponsored by the Spanish Breast Cancer Research Group.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients randomly assigned, in a 1:1 ratio." (p.488) No details provided on method to generate random sequence. Some imbalances in baseline characteristics (i.e. ECOG, menopausal status, grade).
Allocation concealment (selection bias)	Low risk	Quote: "randomization was centralized at the GEICAM headquarters." (p.488)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes were graded as per CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	pCR was viewed as an objective outcome with the study using Miller and Payne criteria.
Selective reporting (reporting bias)	Low risk	All outcomes listed in trial registration record reported either in trial publication or results reporting page in trial registry. All-cause mortality added as a new outcome collected and reported on.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants who were randomised and received treatment were included in analysis. 1/94 participants did not receive treatment and were excluded from analysis.
Other bias	Low risk	None identified.

GeparOcto

Study characteristics

Methods	Accrual: December 2014 to June 2016 Multicentre, 57 centres Phase of trial: 3 Study design: open-label RCT Country or countries where the trial was conducted: Germany Median follow-up: not reported
Participants	*For the triple-negative cohort* (43% of entire cohort of the trial)

GeparOcto *(Continued)*

	Age: median 48, range 21–76 years Nodal status of breast cancer: 34% node positive, 66% node negative Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	Arm 1: paclitaxel 80 mg/m^2 weekly + non-pegylated liposomal doxorubicin 20 mg/m^2 weekly + carboplatin AUC1.5 weekly for 18 weeks Arm 2: epirubicin 150 mg/m^2 + paclitaxel 225 mg/m^2 + cyclophosphamide 2000 mg/m^2 every 2 weeks for 3 cycles Note: carboplatin only added for TNBC subgroup in this trial
Outcomes	Outcomes as listed in trial publication and trial registry record. Primary • pCR, defined as no microscopic evidence of residual invasive viable tumour cells in all resected specimens of the breast and axilla Secondary • Breast-conserving surgery rate • Clinical response • Toxicity, graded according to NCI-CTCAE v4.0 • Treatment adherence (including relative total dose intensity) • Locoregional invasive recurrence survival • Invasive DFS • OS • Regional RFS • Quality of life, using FACT-An (Anaemia and Fatigue questionnaire) • Ovarian function • Axilla-conserving surgery rate
Notes	Trial registration record: NCT02125344 All randomised participants who started treatment were included analysis, 16 were excluded who did not receive any protocol treatment and it was unclear if they were part of the TNBC cohort or not. Time-to-event outcomes collected but not yet reported. Funding considerations: funded by Roche, Amgen, Teva and Vifor.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by dynamic allocation using the Pocock and Simon minimisation method." (p.1, supplementary material)
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised centrally at the German Breast Group headquarters."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.

GeparOcto *(Continued)*

Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and involved regular laboratory tests, etc. at the end of each cycle. Therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Local pathologists were blinded to treatment assignment. Further, all local histopathological reports were centrally evaluated by an independent pathologist blinded to treatment and not otherwise involved in the trial.
Selective reporting (reporting bias)	Unclear risk	The primary outcome was reported. Efficacy outcomes (including OS, distant DFS, etc.) were briefly reported in a 2020 abstract but subgroup data were not provided. Study was completed in 2017 with pCR data reported in 2019.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.
Other bias	Low risk	None identified.

GeparOLA

Study characteristics	
Methods	Accrual: September 2016 to July 2018 Multicentre, 27 recruiting sites Phase of trial: 2 State study design: open-label non-comparative RCT Country or countries where the trial was conducted: Germany Median follow-up: not reported
Participants	*For the entire cohort* (people with TNBC made up 72.6%) Age: median 47.0 years, range 25.0 to 71.0 years Nodal status of breast cancer: 32% node positive, 68% node negative. Note imbalance: carboplatin group 54% node negative, olaparib group 75% node negative Proportion of participants with BRCA mutations: 56% on central testing, 86% on local testing Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: study included only people with HRD (HRD score high, germline or somatic BRCA1/2 mutation), or both HRD score high and germline or somatic BRCA1/2 mutation
Interventions	Arm 1: paclitaxel 80 mg/m^2 + carboplatin AUC2 weekly for 12 weeks followed by epirubucin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles Arm 2: paclitaxel 80 mg/m^2 weekly + olaparib 100 mg twice a day for 12 weeks followed by epirubucin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles
Outcomes	Primary • pCR – defined as no residual invasive tumour in breast and in axillary lymph nodes (ypT0/is ypN0)

GeparOLA *(Continued)*

	Secondary • Response by other pCR definitions • Rate of breast-conserving surgery • Compliance end points (i.e. dose reductions, treatment delays, treatment interruptions and premature treatment discontinuations) • Toxicity, according to NCI-CTC v4.0 • Efficacy in predefined subgroups
Notes	Trial registration record: NCT0278933 All randomised participants who received a dose of study therapy were included in the modified intention-to-treat analysis. Funding considerations: funded by AstraZeneca, Germany. Role in writing and statistical analysis was not reported. Study developed by German Breast Group and Arbeitsgemeinschaft Gynakologische Onkologie Breast.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was carried out at a 1.757: 1 rate using the Pocock minimisation method." (p.51)
Allocation concealment (selection bias)	Low risk	No description whether randomisation was centralised, although probably done as involved randomisation across multiple sites.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Evaluated by local pathologists and centrally reviewed by an independent pathologist blinded to treatment group.
Selective reporting (reporting bias)	Unclear risk	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.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1/107 participants were withdrawn and study authors conducted a modified intention-to-treat analysis.
Other bias	Low risk	None identified.

GeparSixto

Study characteristics

GeparSixto *(Continued)*

Methods	Accrual: August 2011 and December 2012 Multicentre, 54 centres Phase of trial: 2 State study design: RCT Country or countries where the trial was conducted: Germany Median follow-up: 47.3 months
Participants	Demographic and clinical characteristics were not reported separately for the TNBC cohort (53.6% of entire cohort). *For the entire cohort* (i.e. people diagnosed with TNBC and HER2-positive breast cancer). Age: median 48 (21–78) years Nodal status of breast cancer: 47% node positive, 53% node negative Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none *For TNBC cohort only* BRCA mutation: 18% in carboplatin arm (26/146); 17% in comparator arm (24/145); 93% of participants had samples tested for germline mutations
Interventions	Arm 1: carboplatin AUC2 or 1.5 weekly + paclitaxel 80 mg/m^2 weekly + non-pegylated liposomal doxorubicin 20 mg/m^2 weekly + bevacizumab 15 mg/kg every 3 weeks for 18 weeks Arm 2: paclitaxel 80 mg/m^2 + non-pegylated liposomal doxorubicin 20 mg/m^2 weekly + bevacizumab 15 mg/kg every 3 weeks for 18 weeks
Outcomes	Primary (as listed in the trial publication and trial registry record) • pCR rate (ypT0 ypN0), defined as no invasive and no non-invasive residuals in breast and lymph nodes Secondary • Tolerability/safety, graded as per NCI CTCAE version 4.0 • Locoregional invasive RFS • Regional RFS • Distant DFS • Invasive DFS, defined as time in months from randomisation until any invasive locoregional (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 • OS, defined as time in months from randomisation until death due to any cause, and participants alive were censored at the date of the last contact • Treatment adherence • Clinical and imaging response • Regression grade • Breast and axilla conservation rate • Molecular markers, circulating tumour cells, pharmacogenetic and ovarian function substudies
Notes	Trial registration record: NCT01426880

GeparSixto *(Continued)*

Study included people with triple-negative or HER-2-positive breast cancer. Data for efficacy outcomes were reported separately for TNBC cohort. However, for toxicity, we extracted data for the entire cohort.

7 randomised patients did not start treatment and were not included in the analysis.

Study did not report assessing the proportional hazards assumption.

For DFS BRCA1 and 2 mutation, we estimated the hazard ratio using Tierney's method.

Funding considerations: funded by GlaxoSmithKline, Roche, and Teva. The authors state that the funders had no role in the collection, analysis or interpretation of the data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done … in a 1:1 ratio … and was stratified according to biological subtype and Ki67 level. The minimisation method of Pockock and Simon was used for randomisation." (p.749)
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was done centrally at the German Breast Group headquarters."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open label study. Although study investigators and participants were aware of treatment allocation and may have been associated with some performance bias, bias was not considered to be of serious concern given types of outcomes collected.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes were graded as per CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Quote: "Pathological response of the breast tumour and axillary lymph nodes were assessed by local pathologists. Pathological reports were reviewed by one independent board certified pathologist (KE) from whom treatment assignments were masked, and response was staged in accordance with the Union for International Cancer Control TNM system." (p.750)
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported. Important outcomes including DFS and OS are included and updated in subsequent publications.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.

GeparSixto *(Continued)*

Other bias	Low risk	None identified.

Gigolaeva 2019

Study characteristics

Methods	Accrual: not reported Single centre Phase of trial: not reported Study design: RCT Country or countries where the trial was conducted: Russia Median follow-up: not reported
Participants	Age: median 47, range 32–62 years Nodal status of breast cancer: not reported Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: not reported
Interventions	Arm 1: doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by carboplatin AUC2 weekly + eribulin 1.4 mg/m^2 OR paclitaxel 175 mg/m^2 every 3 weeks for 12 weeks Arm 2: doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 for 12 weeks
Outcomes	Primary • pCR, 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) Secondary: none reported
Notes	Trial registration record could not be found. Abstract only available. Full article has not yet been published. Contact details for the authors could not be found to request an update on results or published works. Funding considerations: "no significant conflicts of interest" (p.S70) declared in the abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A randomized prospective study" … "randomization (2:1)." No additional details were provided in the abstract.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in the abstract.

Gigolaeva 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided in the abstract.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Unclear risk	No information provided on tests used or process to evaluate response.
Selective reporting (reporting bias)	Unclear risk	Unable to assess from the abstract. A trial registration record could not be found.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reporting of attrition or exclusions in the available abstract.
Other bias	Unclear risk	Unable to assess from the abstract.

I-SPY2

Study characteristics	
Methods	Accrual: May 2010 to July 2012 Multicentre, 30 sites Phase of trial: 2 Study design: open-label adaptive/platform RCT Country or countries where the trial was conducted: USA Median follow-up: not reported
Participants	Demographic and clinical characteristics presented below were not described separately for the hormone receptor-negative cohort (i.e. 52% of the entire cohort). *For the entire cohort* Age: median 49, range 24–71 years Nodal status of breast cancer: 46% node positive, 54% node negative Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none BRCA status collected: BRCA1/2 mutation – 17% in intervention arm, 7% in comparator arm
Interventions	Arm 1: paclitaxel 80 mg/m^2 + veliparib 50 mg orally twice daily + carboplatin AUC6 every 3 weeks for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles Arm 2: paclitaxel 80 mg/m^2 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles
Outcomes	Primary

I-SPY2 *(Continued)*

- Probability of pCR, defined as the absence of residual cancer in the breast or lymph nodes at the time of surgery

Secondary listed in trial publication and trial registry record (none reported in this paper)

- Predictive and prognostic indices to predict pCR and RCB
- 3- and 5-year RFS
- 3- and 5-year OS
- Adverse events (presurgery, postsurgery up to 1-year follow-up)
- MRI functional tumour volume
- RCB

Notes	Trial registration record: NCT01042379 Contacted for results for pCR in the triple negative subgroup. Only participants who received treatment were included in the analysis. Of those participants who did not receive treatment, it was unclear whether they were part of the TNBC cohort. Time-to-event outcomes collected but not yet reported. Funding considerations: funded by charitable donations and pharmaceutical companies including Johnson & Johnson, Genentech.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "… biomarker profiles are used for randomizing each participant to a treatment arm … for every participant that is randomized, there is a 20% chance the participant will be randomized to the control arm" as part of this adaptive trial design. Trial uses web-based randomisation system.
Allocation concealment (selection bias)	Low risk	Randomisation was adaptive design with drug regimens being added or dropped depending on their efficacy. The registration and randomisation process was web-based therefore it was unlikely that those involved in the trial were aware of intended treatment allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and involved regular laboratory tests, etc. at the end of each cycle. Therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	A study-trained pathologist evaluated pCR. The Study Lead Pathologist made the final assessment on any indeterminate or contested results. It was unclear whether the pathologists were blinded; however, pCR is generally viewed as an objective outcome and there was a minimal risk of treatment allocation affecting pCR assessment.
Selective reporting (reporting bias)	High risk	The primary outcome was reported; however, RFS and OS are yet to be reported. As pCR data were reported in 2016, other important long-term efficacy outcomes would be expected to have been reported by 2022.
Incomplete outcome data (attrition bias)	Unclear risk	CONSORT diagram was not provided for the cohort of interest in this review (i.e. TNBC); therefore, a judgement could not be made.

I-SPY2 *(Continued)*
All outcomes

Other bias	Low risk	None identified.

INFORM

Study characteristics	
Methods	Accrual: January 2012 to January 2019 Multicentre, 13 centres Phase of trial: 2 Study design: open-label RCT Country or countries where the trial was conducted: USA Median follow-up: not reported
Participants	Demographic and clinical characteristics presented below were not described separately for the hormone receptor-negative cohort (i.e. 64–70% of the entire cohort). *For the entire cohort* Age: mean 42, range 24–73 years Nodal status of breast cancer: 45% node positive, 55% node negative Adjuvant or neoadjuvant: neoadjuvant All participants were germline BRCA carriers (69% BRCA1 mutation; 30% BRCA2 mutation, 2% both) Notable exclusion criteria: none Study population included HER2 negative, hormone receptor-positive cancers
Interventions	Arm 1: cisplatin 75 mg/m^2 every 3 weeks for 4 cycles Arm 2: doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2–3 weeks for 4 cycles (every 2 weeks for TNBC cohort) Radiotherapy mandated for all participants not having a mastectomy
Outcomes	Primary (as per trial publication and trial registry record) • pCR (ypT0/is, N0), defined as absence of residual invasive disease with or without DCS and negative pre-treatment SLNB Secondary • RCB 0/1 rate, using MD Anderson Cancer Centre calculator • Clinical response rate, as per RECIST v1.1; number of partial and complete responses after preoperative therapy • Toxicity, specifically grade III and IV adverse events • Prechemotherapy biopsies • Miller Payne 4 and 5 (near pCR) • RFS • RFS with pCR or without pCR

INFORM *(Continued)*

	• All-cause mortality, a measure of all deaths, due to any cause
Notes	Trial registration record: NCT01670500 Trial stopped early due to slow accrual. All randomised participants who started treatment were included in the analysis, 1 was excluded who did not receive any protocol treatment. Funding considerations: funded by the Breast Cancer Research Foundation, Susan G Komen, and Myriad Genetics.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was stratified by tumor ER status (…) and by treatment site." (p. 1541) Baseline characteristics were generally well-balanced (except for age and tumour stage). No details about how random sequence was generated.
Allocation concealment (selection bias)	Low risk	No description whether randomisation was centralised, although probably done as involved randomisation across multiple sites.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and involved regular laboratory tests, etc. at the end of each cycle. Therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Pathological responses were centrally determined by the study pathologist. Central pathology review consisted of clear definitions of how to assess residual cancer following chemotherapy. It is unclear whether the central pathologist was blinded but given that pCR is an objective outcome, there was a minimal risk of treatment allocation affecting pCR assessment.
Selective reporting (reporting bias)	Unclear risk	Most outcomes prespecified in trial registry record have been reported in trial publication, except for RFS.
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram indicated reasons for 1 exclusion in the comparator arm. Analysis of randomised and those that were allocated to treatment.
Other bias	Low risk	None identified.

Li 2020

Study characteristics

Li 2020 *(Continued)*

Methods	Accrual: June 2011 to December 2015 Single centre Phase of trial: 3 Study design: open-label RCT Country or countries where the trial was conducted: China Median follow-up: 57.3 months
Participants	Age: median 49, range 22–64 years Nodal status of breast cancer: 37% node positive, 63% node negative Adjuvant or neoadjuvant: adjuvant Notable exclusion criteria: none
Interventions	Arm 1: paclitaxel 150 mg/m^2 + carboplatin AUC3 every 2 weeks for 8 cycles Arm 2: epirubicin 80 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles followed by paclitaxel 175 mg/m^2 every 2 weeks for 4 cycles
Outcomes	Primary • 3-year DFS rate, defined as the date of randomisation to the date of the first local/distant recurrence (in the absence of other primary malignancies) Secondary • OS, defined as the time from randomisation to death due to any cause • Toxicity, according to NCI-CTCAE, version 3.0
Notes	Trial registration record: NCT01378533 All randomised participants were included in analysis. Study did not report assessing the proportional hazards assumption. Funding considerations: funded by the National Key Research and Development Program of China and the Chinese Academy of Medical Science Initiative for Innovative Medicine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Simple randomization was conducted … using random allocation sequence" (p.487) but no details provided as to how random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No information provided at single site.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.

Li 2020 *(Continued)*

Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and involved regular laboratory tests, etc. at the end of each cycle. Therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Selective reporting (reporting bias)	Low risk	All outcomes listed in trial registration record were reported in trial publication. OS was not prespecified but collected later and was a primary outcome for this review.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants randomised were included in the analysis irrespective of outcome being measured or treatment actually received.
Other bias	Low risk	None identified.

Nasr 2015

Study characteristics	
Methods	Accrual: November 2008 to December 2014 Multicentre, 4 centres Phase of trial: 3 Study design: RCT Country or countries where the trial was conducted: Egypt Median follow-up: 52 months
Participants	Age: mean 46, 95% confidence interval 32 to 62 years Nodal status of breast cancer: 94% node positive, 6% node negative Adjuvant or neoadjuvant: adjuvant Notable exclusion criteria: none
Interventions	Arm 1: 5-fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 every 3 weeks for 3 cycles then docetaxel 80 mg/m^2 + carboplatin AUC5 every 3 weeks for 3 cycles, followed by postoperative radiotherapy, followed by oral cyclophosphamide 50 mg daily, and methotrexate 2.5 mg orally twice daily on days 1, 2 of each week every 28 days for 1 year Arm 2: 5-fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 every 3 weeks for 3 cycles then docetaxel 100 mg/m^2 every 3 weeks for 3 cycles Note: intervention is addition of carboplatin AND 12 months of metronomic chemotherapy
Outcomes	Primary

Nasr 2015 *(Continued)*

- DFS, defined as the time of randomisation until relapse, recurrence or the last follow-up visit
- OS, defined as the time of randomisation until death or the last follow-up visit

Secondary

- Toxicity, assessed according to NCI CTC version 2.0. Early toxicity includes toxicities during treatment and up until 8 weeks after treatment; late toxicity includes toxicities following 8 weeks after treatment
- Treatment discontinuation, delays and dose reductions reported

Notes	No trial registration record identified in the World Health Organization International Clinical Trials Registry Platform. All randomised participants were included as intention-to-treat analysis for all outcomes. Note: none of the efficacy or safety outcome data (in tables or figures) presented the denominators. Study did not report assessing the proportional hazards assumption. For DFS and OS, we estimated the hazard ratio using Tierney's method. Funding considerations: not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to one of [two] groups." (p.3) No further details were provided.
Allocation concealment (selection bias)	Unclear risk	No description whether randomisation was centralised, although probably done as involved randomisation across multiple sites.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Selective reporting (reporting bias)	Unclear risk	Prespecified outcome measures including DFS and OS were reported. However, limited data were provided and the OS Kaplan-Meier curve was difficult to interpret.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Paper indicated that all randomised participants were included in analysis. Number of participants who did not receive treatment were equal across treatment arms (i.e. 3 participants in each).
Other bias	Low risk	None identified.

NeoCART

Study characteristics

Methods	Accrual: September 2016 to December 2019 Multicentre, 6 centres Phase of trial: 2 Study design: open-label RCT Country or countries where the trial was conducted: China Median follow-up: 37 months
Participants	Age: median 50, range 19–69 years Nodal status of breast cancer: 58% node positive, 42% node negative Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	Arm 1: docetaxel 75 mg/m^2 + carboplatin AUC6, 3 weekly for 6 cycles Arm 2: epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by docetaxel 100 mg/m^2 every 3 weeks for 4 cycles
Outcomes	Primary • pCR, defined as the absence of invasive tumour cells in the breast and axilla (ypT0/is ypN0) Secondary • OS, defined as time from randomisation until death with any cause • EFS, defined as time from randomisation to disease progression, disease recurrence (local, regional, distant or contralateral (invasive or non-invasive)) or death from any cause • Breast-conserving surgery rate • Toxicity, graded according to NCI CTCAE v4.0
Notes	Trial registration record: NCT03154749 Only participants who received treatment were included in the analysis. 5 randomised participants who did not receive treatment were excluded. Study did not report assessing the proportional hazards assumption. Funding considerations: this work was supported by local public and private grants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized by means of a permuted block randomization scheme using an interactive response system (IxRS)."
Allocation concealment (selection bias)	Low risk	Quote: "The treatment allocation list was created, and randomization was performed centrally at the leading research center of Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences."

NeoCART *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes were graded as per CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Although there was no information regarding blinding of the local pathologist who assessed this outcome, pCR was viewed to be an objective outcome. A review by the pathologist on whether pCR had been achieved or not was unlikely to be influenced by unblinding.
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the trial registry record were reported in trial publication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram outlined 5 participants who were randomised (3 in intervention group, 2 in control group) were excluded due to patient preference. The trial publication stated that it was an intention-to-treat analysis but this was not the case. Survival outcomes included the number of participants who received treatment.
Other bias	Low risk	None identified.

PATTERN

Study characteristics	
Methods	Accrual: July 2011 to April 2016 Multicentre, 9 centres Phase of trial: 3 Study design: open-label RCT Country or countries where the trial was conducted: China Median follow-up: 62 months
Participants	Age: mean 51, range 44–57 years Nodal status of breast cancer: 26% node positive, 74% node negative Adjuvant or neoadjuvant: adjuvant Notable exclusion criteria: none

PATTERN *(Continued)*

Interventions	Arm 1: paclitaxel 80 mg/m^2 + carboplatin AUC2 days 1, 8 and 15 every 28 days for 6 cycles Arm 2: cyclophosphamide 500 mg/m^2 + epirubicin 100 mg/m^2 + fluorouracil 500 mg/m^2 every 3 weeks for 3 cycles followed by docetaxel 100 mg/m^2 every 3 weeks for 3 cycles
Outcomes	Primary • DFS, defined as the time from randomisation until breast cancer recurrence (local, regional or distant), second primary cancer or death from any cause Secondary • OS, defined as time from randomisation until death with any cause • Distant DFS, defined as the time from random assignment to distant recurrence or death • Relapse-free survival, defined as time from random assignment to local, regional, distant relapse or death • DFS in BRCA carriers • Toxicity, graded according to NCI CTCAE v4.0
Notes	Trial registration record: NCT01216111 All randomised participants were included in intention-to-treat analysis. Study did not report assessing the proportional hazards assumption. Funding considerations: work supported by grants from the National Natural Science Foundation of China, and by local public and private grants. The manuscript stated the funders had no role in the design or conduct of the trial or the writing of the manuscript.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomisation was performed via an interactive web-response system … randomization was stratified according to pathological node status, age …, and tumor size." (p.1392) Baseline characteristics across groups were well-balanced.
Allocation concealment (selection bias)	Low risk	Randomisation was centralised and involved randomisation across multiple sites.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and involved regular laboratory tests, etc. at the end of each cycle. Therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the trial registry record were reported in trial publication.

PATTERN *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram outlines reasons for exclusions and similar number of participants discontinued to similar reasons (adverse events, lost to follow-up, etc.). Efficacy outcomes included the number of participants randomised.
Other bias	Low risk	None identified.

TBCRC 030

Study characteristics	
Methods	Accrual: April 2014 to January 2018 Multicentre Phase of trial: 2 Study design: open-label RCT Country or countries where the trial was conducted: USA Median follow-up: not reported
Participants	Age: median 53, range 28–82 years Nodal status of breast cancer: 37% node positive, 63% node negative Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: people with a known BRCA mutation were excluded
Interventions	Arm 1: cisplatin 75 mg/m^2 every 3 weeks for 4 cycles Arm 2: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles Both arms proceeded to surgery and further provider-choice adjuvant chemotherapy
Outcomes	Primary outcomes recorded in trial publication and trial registry record • pCR, assessed using RCB score (RCB0 = pCR) and RCB0/1 and by HRD status. Outcome evaluated after definitive breast surgery, up to 4–5 months from enrolment Secondary • Toxicity, graded using NCI CTCAE version 4.0 • Positive predictive value of HRD score • Treatment completion
Notes	Trial registration record: NCT01982448 Study stopped early due to withdrawal of sponsor support. Randomised participants who received study treatment were included in the analysis, 7 participants who were randomised did not receive the study intervention and were excluded. Funding considerations: funded by Myriad Genetics.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

TBCRC 030 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly allocated to the study in a 1:1 ratio stratified by initial lymph node assessment as well as tumour size." (p.1519)
Allocation concealment (selection bias)	Low risk	No description whether randomisation was centralised, although probably done as involved randomisation across multiple sites.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and involved regular laboratory tests, etc. at the end of each cycle. Therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Although there was no information regarding blinding of the pathologist who assessed this outcome, pCR was viewed to be an objective outcome. A review by the pathologist on whether pCR had been achieved or not was unlikely to be influenced by unblinding.
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the trial registry record were reported in the trial publication.
Incomplete outcome data (attrition bias) All outcomes	Low risk	CONSORT diagram showed that 7/147 participants (3 in the intervention arm and 4 in the comparator arm) did not proceed with treatment due to patient and investigator decisions. For pCR analysis, only those who received treatment were included in the analysis. Justifications as to why this was the case were provided.
Other bias	Low risk	None identified.

Wu 2018

Study characteristics	
Methods	Accrual: January 2014 and February 2017 Single centre Phase of trial: 2 State study design: open-label RCT Country: China Median follow-up: not reported
Participants	Age: median 47, range 33–70 years Nodal status of breast cancer: 60% node positive, 40% node negative BRCA mutation: not reported Adjuvant or neoadjuvant: both (perioperative chemotherapy) Notable exclusion criteria: none

Wu 2018 *(Continued)*

Interventions	Arm 1: before surgery: lobaplatin 30 mg/m^2 + epirubicin 80 mg/m^2 + docetaxel 75 mg/m^2 every 3 weeks for 4 cycles; after surgery: 2 cycles Arm 2: before surgery: epirubicin 80 mg/m^2 + docetaxel 75 mg/m^2 every 3 weeks for 4 cycles; after surgery: 2 cycles
Outcomes	Primary • pCR, defined as pCR in the breast with the absence of any tumour deposit ≥ 0.2 mm in sampled axillary nodes or with negative pretreated sentinel lymph nodes Secondary • Overall response rate (complete and partial response), assessed according to the World Health Organization Response Evaluation Criteria for Solid tumours • Toxicity, defined according to NCI CTCAE version 3.0 • Recurrence, defined as reappearance of carcinoma at site of surgical intervention • Metastasis, defined as any recurrence in lymph nodes or distant organs Note: trial registration record lists additional outcomes as part of main objectives, i.e. OS and DFS
Notes	Trial registration record: ChiCTR-TRC-14005019 Study authors analysed participants who received chemotherapy rather than those participants who were randomised. Study did not report assessing the proportional hazards assumption. Funding considerations: funded by the Clinical Research Fund of Southwest Hospital, China and the Natural Science Fund of China (81302315).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation generated using a website (research randomizer). Baseline clinical characteristics were generally well-balanced across treatment groups with exceptions being for participants aged ≥ 60 years, and stage II and III breast cancers.
Allocation concealment (selection bias)	Unclear risk	No information provided at single-centre study.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes graded using the CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias):	Low risk	Although there was no information regarding blinding of the pathologist who assessed this outcome, pCR was viewed to be an objective outcome. A review

Wu 2018 *(Continued)*

neoadjuvant studies only: pCR		by the pathologist on whether pCR had been achieved or not was unlikely to be influenced by unblinding.
Selective reporting (reporting bias)	Unclear risk	Trial registry record indicates OS and DFS were the main objectives of this study; the trial publication stated that survival analyses were not yet possible due to short follow-up times. No further publications have been presented with results for these important outcomes.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	CONSORT diagram (p.3) showed that a very small proportion of participants who were randomised (1 in intervention; 2 in comparator arms) were not included as part of an intention-to-treat analyses. Reasons for the exclusion were not provided.
Other bias	Low risk	None identified.

Zhang 2016

Study characteristics	
Methods	Accrual: May 2006 to December 2012 Single centre Phase of trial: 2 Study design: open-label RCT Country where the trial was conducted: China Median follow-up: 55 months
Participants	Age: median 47, range 24–73 years Nodal status of breast cancer: 77% node positive, 23% node negative Adjuvant or neoadjuvant: neoadjuvant Notable exclusion criteria: none
Interventions	Arm 1: paclitaxel 175 mg/m^2, day 1 + carboplatin AUC5, day 2, every 3 weeks for 4–6 cycles Arm 2: epirubicin 75 mg/m^2, day 1 + paclitaxel 175 mg/m^2, day 2, every 3 weeks for 4–6 cycles
Outcomes	Primary • pCR, defined as no residual invasive cancer in both excised breast tissue and axillary lymph nodes, or only carcinoma in situ Secondary • Relapse-free survival, defined as from the date of randomisation to the date of the first local or distant recurrence • OS, defined as the date of randomisation to the date of death or last follow-up • Objective response rate, assessed using the RECIST version 1.0 • Safety, according to the NCI CTCAE v3.0
Notes	Trial registration record: NCT01276769

Zhang 2016 *(Continued)*

Participants who underwent surgery and were not lost to follow-up after surgery were included in analysis for efficacy outcomes. However, all randomised participants were included in toxicity assessment.

Study did not report assessing the proportional hazards assumption.

For relapse-free survival and OS, we estimated the hazard ratio using Tierney's method.

Funding considerations: funded by the Cancer Hospital, Chinese Academy of Medical Sciences.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "TNBC were stratified according to clinical stage, and then randomized to receive PC … or EP regimen." (p.60654) Baseline characteristics were generally well-balanced across groups except for node involvement. No details about how random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	No information provided about what occurred at single site.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes were graded as per CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and, therefore, knowing treatment allocation may have had minimal effect on the grading of outcomes.
Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Low risk	Although there was no information regarding blinding of the pathologist who assessed this outcome, pCR was viewed to be an objective outcome. A review by the pathologist on whether pCR had been achieved or not was unlikely to be influenced by unbinding.
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the trial registry record were reported in trial publication.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	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.
Other bias	Low risk	None identified.

Zhao 2014

Study characteristics	
Methods	Accrual: April 2006 to February 2014 Single centre Phase of trial: not reported Trial design: RCT, no further details provided Country where the trial was conducted: China Follow-up: not reported
Participants	Age: median 52 years Nodal status of breast cancer: 83% node positive, 17% node negative Adjuvant or neoadjuvant: neoadjuvant BRCA mutation: not reported Notable exclusion criteria: none
Interventions	Arm 1: paclitaxel 175 mg/m^2 day 1, carboplatin AUC5 day 2, every 3 weeks for 2 cycles Arm 2: epirubicin 75 mg/m^2 day 1, paclitaxel 175 mg/m^2 day 2, every 3 weeks for 2 cycles
Outcomes	Outcomes listed in trial publication (not split by primary or secondary outcomes) • pCR • Clinical complete remission • Adverse events (graded) but name of scale was not provided
Notes	Trial registration record could not be identified. Study authors did not appear to have analysed results based on the number of participants randomised (i.e. 2 participants were excluded from analysis with reasons not provided). Funding considerations: not collected.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients … were randomly assigned to …" Method to generate random sequence was not described.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not reported in the journal publication.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information relating to blinding of participants or personnel was provided in the journal publication.
Blinding of outcome assessment (detection bias): toxicity	Unclear risk	No details were provided relating to blinding of outcome assessment for toxicities.

Zhao 2014 *(Continued)*

Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR	Unclear risk	No details were provided relating to blinding of outcome assessment for pCR.
Selective reporting (reporting bias)	Low risk	Outcomes described in the methods section in the trial publication were reported. We did not identify a trial record to cross-check outcome reporting.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants in the 1 treatment arm dropped out with no details provided. They were not included in the analysis. No CONSORT diagram was provided.
Other bias	Unclear risk	Some translated material but insufficient detail to rule out any other bias.

Zheng 2022

Study characteristics	
Methods	Accrual: June 2009 and October 2015 Multicentre, 3 centres Phase of trial: 2 State study design: open-label RCT Country or countries where the trial was conducted: China Median follow-up: 97.6 months
Participants	Age: median 48.4, range 42–56 years Nodal status of breast cancer: 34% node positive, 66% node negative Adjuvant or neoadjuvant: adjuvant Notable exclusion criteria: none
Interventions	Arm 1: docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 + carboplatin AUC5, every 3 weeks for 6 cycles Arm 2: epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2, every 3 weeks for 4 cycles, followed by docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 every 3 weeks for 4 cycles
Outcomes	Primary • DFS, defined as period from the date of pathological diagnosis to the date of first relapse (included local, regional or metastatic) or death from any cause Secondary • OS, defined as period from date of pathological diagnosis to the date of death from any cause • Toxicity • Quality of life (listed in abstract in *Journal of Clinical Oncology* supplement) • Exploratory analyses of germline BRCA status and PD-L1 expression
Notes	Trial registration record: NCT01150513 All randomised participants were included in intention-to-treat analysis.

Zheng 2022 *(Continued)*

The proportional hazards assumption was assessed and not met.

For DFS and OS, we estimated the hazard ratio using Tierney's method.

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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in a 1:1 ratio, method not described.
Allocation concealment (selection bias)	Low risk	Randomisation was performed 'centrally' and enroled participants at 3 institutions. It is likely that central allocation was done.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	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.
Blinding of outcome assessment (detection bias): DFS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): OS	Low risk	Lack of blinding unlikely to influence this outcome.
Blinding of outcome assessment (detection bias): toxicity	Low risk	Toxicity outcomes were graded as per CTCAE. Although the study was open-label, grading symptoms using the CTCAE is standardised and therefore knowing treatment allocation may have had minimal effect on the grading of outcomes.
Selective reporting (reporting bias)	Low risk	All prespecified primary and secondary outcomes were reported. Important outcomes including DFS and OS are included at updated in subsequent publications. Quality of life was collected (as per conference abstract) but not yet reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis performed – all participants who were randomised were included in the analysis.
Other bias	Low risk	None identified.

AUC: area under the curve; BRCA: breast cancer gene; CALGB: Cancer and Leukemia Group B; CTCAE: Common Terminology Criteria for Adverse Events; DFS: disease-free survival; ECOG: Eastern Cooperative Oncology Group; EFS: event-free survival; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Breast Cancer; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patient; EQ-5D 5L: 5-level Euroqol EQ-5D; FACT-An: Functional Assessment of Cancer Therapy – Anaemia; HRD: homologous recombination deficiency; MRI: magnetic resonance imaging; NCI CTC: National Cancer Institute Common Toxicity Criteria; NCI: National Cancer Institute; OS: overall survival; pCR: pathological complete response; RCB: residual cancer burden; RCT: randomised controlled trial; RECIST: Response Evaluation Criteria in Solid Tumors Criteria; RFS: recurrence-free survival; TNBC: triple-negative breast cancer.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
ECOG-ACRIN EA1131	Study population included only people with TNBC with residual disease.
Jiang 2019	Paper was translated and we were advised that this study was not an RCT.
NCT00004092	It was not possible to decipher whether the cohort included people with TNBC. HER2 status was not checked.
SICOG 9908	Data were not reported separately for people with TNBC. Study investigators were contacted but did not respond.
UMIN000030780 – jRCTs051180210	Study population included only people with TNBC with residual disease.

HER2: human epidermal receptor 2; RCT: randomised controlled trial; TNBC: triple-negative breast cancer.

Characteristics of ongoing studies *[ordered by study ID]*

ChiCTR1800019501

Study name	A randomized controlled phase II clinical trial comparing neoadjuvant TP (docetaxel + cisplatin) with TAC (docetaxel + adriamycin + cyclophosphamide) regimen in the treatment of operable triple negative breast cancer
Methods	Accrual: recruiting Accrual target: 212 participants Single-centre, phase 2 RCT Trial is being conducted in China Blinding: not specified
Participants	Clinical T2-T4c or T1C with axillary lymph node-positive Neoadjuvant setting
Interventions	Arm 1: intervention: docetaxel and cisplatin for 6 cycles Arm 2: comparator: docetaxel, doxorubicin and cyclophosphamide for 6 cycles
Outcomes	Primary • Pathological complete response rate Secondary • Safety • Disease-free survival • Rate of breast-conserving surgery • Clinical response rate • ypT0ypN0, ypT0/is ypN+, ypT1mic ypN0/+
Starting date	Planned start date: 1 December 2018

ChiCTR1800019501 *(Continued)*	
	Estimated completion date: 31 May 2025
Contact information	Contact: Liu Zhenzhen (liuzhenzhen73@163.com)
Notes	Trial registration link: www.chictr.org.cn/showprojEN.html?proj=31567 Trial sponsor: He'nan Cancer Hospital Funding considerations: self-funded

ChiCTR1900023776	
Study name	A randomized, controlled, single-center clinical study for the efficacy and safety of docetaxel plus lobaplatin versus docetaxel plus epirubicin for neoadjuvant therapy in triple-negative breast cancer
Methods	Accrual: recruiting Accrual target: 120 Single-centre, phase 2 or 3 (unspecified) RCT Trial is being conducted in China Blinding: not specified
Participants	People with T2 and above Adjuvant or neoadjuvant: neoadjuvant
Interventions	ARM 1: intervention: docetaxel and lobaplatin (no further details provided) ARM 2: comparator: docetaxel and epirubicin (no further details provided)
Outcomes	Primary • Pathological complete response Secondary • Disease-free survival • Overall survival • Safety (bone marrow suppression, nausea and vomiting, and neurotoxicity)
Starting date	Planned start date: 13 June 2019 Estimated completion date: 31 December 2026
Contact information	Contact: Xiaowei Qi (qxw9908@foxmail.com)
Notes	Trial registration link: www.chictr.org.cn/showprojEN.html?proj=39908 Trial sponsor: Southwest Hospital, Army Medical University Funding considerations: self-funded

ChiCTR1900026499

Study name	Albumin-bound paclitaxel combined with carboplatin versus epirubicin combined with docetaxel as neoadjuvant therapy for triple-negative breast cancer: a multicenter randomized controlled phase IV clinical trial
Methods	Accrual: not yet recruiting Accrual target: 110 Multicentre, phase 4 RCT Trial is being conducted in China Blinding: participants, investigators, outcome assessors
Participants	People with stage II–III breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: paclitaxel and carboplatin (no further details provided) Arm 2: comparator: epirubicin and docetaxel (no further details provided)
Outcomes	Primary • Pathological complete remission rate Secondary • Breast-conserving rate • Incidence of osteoporosis • Incidence of bone-related events • Incidence of other distant organ metastasis related events • Disease-free survival • Overall survival • Adverse events
Starting date	Planned start date: 1 December 2019 Estimated completion date: 31 May 2026
Contact information	Contact: Caigang Liu (liucg@sj-hospital.org)
Notes	Trial registration link: www.chictr.org.cn/showprojEN.html?proj=44204 Trial sponsor: Shengjing Hospital of China Medical University Funding considerations: self-financed

ChiCTR2000039578

Study name	A prospective, open, multicenter, randomized controlled trial for the effect of albumin-bound paclitaxel combined with cisplatin versus epirubicin combined with cyclophosphamide sequential docetaxel neoadjuvant therapy for triple negative breast cancer
Methods	Accrual: not yet recruiting Accrual target: 240

ChiCTR2000039578 *(Continued)*

	Multicentre, phase 4 RCT Trial is being conducted in China Blinding: not specified
Participants	People with early (T2-3, N0-1, M0) or locally advanced (T2-3, N2-N3, M0) breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: paclitaxel and cisplatin (no further details provided) Arm 2: comparator: epirubicin, cyclophosphamide and docetaxel (no further details provided)
Outcomes	Primary • Pathological complete response Secondary • Breast-conserving rate • Event-free survival • Overall survival • Safety
Starting date	Planned start date: 23 October 2020 Estimated completion date: 22 October 2025
Contact information	Contact: Zhengkui Sun (403810956@qq.com)
Notes	Trial registration link: www.chictr.org.cn/showprojEN.html?proj=63610 Trial sponsor: Jiangxi Cancer Hospital Funding considerations: Jiangsu Hengrui Pharmaceutical Co, Ltd

CTRI/2017/10/010272

Study name	Comparing two types of chemotherapy in breast cancer
Methods	Accrual: not yet recruiting Accrual target: 268 Single-centre, phase 2 RCT Trial is being conducted in India Blinding: not specified
Participants	People with stage 2 and 3 breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: docetaxel 75 mg/m^2 day 1 and carboplatin AUC6 day 1 every 21 days for 6 cycles Arm 2: comparator: 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2 and cyclophosphamide 500 mg/m^2 day 1 every 21 days for 3 cycles followed by docetaxel 75 mg/m^2 day 1 for 4 cycles

CTRI/2017/10/010272 *(Continued)*

Outcomes	Primary • Pathological complete response Secondary • Objective tumour response • Disease-free survival • Overall survival • Adverse events
Starting date	Planned start date: 1 January 2017 Estimated completion date: not specified
Contact information	Contact: Biswajit Dubashi (drbiswajitdm@gmail.com)
Notes	Trial registration link: ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=20743 Trial sponsor: Jawaharlal Institute of Post Graduate Medical Education and Research Funding considerations: Jawaharlal Institute of Post Graduate Medical Education and Research, Puducherry

CTRI/2019/05/019176

Study name	A trial comparing effect of addition of carboplatin to standard neoadjuvant chemotherapy for triple negative breast cancer patients
Methods	Accrual: not yet recruiting Accrual target: 50 Single-centre, phase 3 RCT Trial is being conducted in India Blinding: not done, open-label study
Participants	People with triple-negative breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 (12 doses) plus carboplatin (AUC6) every 3 weeks for 4 cycles Arm 2: comparator: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 (12 doses) and placebo every 3 weeks for 4 cycles
Outcomes	Primary • Pathological complete response Secondary • Toxicity • Chemotherapy completion rates

CTRI/2019/05/019176 *(Continued)*

Starting date	Planned start date: 20 May 2019 Estimated completion date: May 2020
Contact information	Contact: Bhargab Jyoti Saikia (bhargabjyotisaikia@gmail.com)
Notes	Trial registration link: ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=32946 Trial sponsor: Dr B Borooah Cancer Institute, Guwahati Funding considerations: Dr B Borooah Cancer Institute, Gopinath Nagar, Assam

EUCTR2009-015238-31

Study name	Neo adjuvant chemotherapy in triple negative breast cancer (neo-TN)
Methods	Accrual: active, not recruiting Accrual target: 310 Multicentre, phase 2 and 3 RCT Trial is being conducted in the Netherlands Blinding: open-label study
Participants	Adjuvant or neoadjuvant: neoadjuvant
Interventions	ARM 1: intervention: doxorubicin, cyclophosphamide, carboplatin and thiotepa ARM 2: comparator: doxorubicin and cyclophosphamide for non-HRD tumours Other comparator arms existed but contained carboplatin
Outcomes	Primary • Mean neoadjuvant response index Secondary outcomes • Recurrence-free survival • Overall survival
Starting date	Planned start date: January 2010 Estimated completion date: December 2029
Contact information	Contact: S Linn (s.linn@nki.nl)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT01057069 Trial sponsor: The Netherlands Cancer Institute Funding considerations: KWF Netherlands

EudraCT2016-004384-39

Study name	A clinical trial that examines whether the treatment with the medication olaparib in combination with the chemotherapy carboplatin is more effective than treatment with a standard chemotherapy (anthracycline/ taxane-based) against a specific type of breast cancer
Methods	Accrual: active Accrual target: – Multicentre, phase 2 RCT Trial is being conducted in Australia Blinding: open-label study
Participants	Early invasive triple-negative breast cancer with positive homologous recombination deficiency (HRD) status Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: olioparib and carboplatin for 6 cycles Arm 2: comparator: docetaxel, doxorubicin and cyclophosphamide for 6 cycles
Outcomes	Primary • Histopathological response to preoperative chemotherapy Secondary • Occurrence of pathological complete response • Quality of life and sexual health scores
Starting date	Planned start date: not specified Estimated completion date: not specified
Contact information	Contact: ABCSG (info@abcsg.at)
Notes	Trial registration link: clinicaltrialsregister.eu/ctr-search/trial/2016-004384-39/AT Trial sponsor: Austrian Breast & Colorectal Cancer Study Group (ABCSG) Funding considerations: Astra Zeneca

NCT00919880

Study name	Comparison of neo-adjuvant weekly paclitaxel with or without carboplatin in early breast cancer
Methods	Accrual: completed, no results posted in ClinicalTrials.gov Accrual target: 148 Single-centre, phase 2 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with medium- and high-risk primary breast cancer

NCT00919880 *(Continued)*

	Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: carboplatin AUC2 mg/mL every 3 weeks for 4 cycles and paclitaxel 80 mg/m^2 every 3 weeks for 4 cycles Arm 2: comparator: paclitaxel 80 mg/m^2 every 3 weeks for 4 cycles
Outcomes	Primary • Significant effect rate (proportion of G4 and G5 as per Miller & Payne method) Secondary: none listed
Starting date	Planned start date: July 2009 Actual completion date: December 2010
Contact information	Contact: Tanfeng Wang (no contact details listed)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT00919880 Trial sponsor: Tao Ouyang Funding considerations: not provided in trial record

NCT01752686

Study name	A phase III trial of carboplatin as adjuvant chemotherapy in triple negative breast cancer
Methods	Accrual: unknown Accrual target: 587 Phase 3 RCT Trial is being conducted in South Korea Blinding: open-label study
Participants	Histologically confirmed invasive breast cancer (tumour > 2 cm, any nodal involvement) Adjuvant or neoadjuvant: adjuvant
Interventions	Arm 1: intervention: carboplatin (AUC6) on day 1, every 3 weeks for 6 cycles Arm 2: comparator: observation
Outcomes	Primary • Disease-free survival Secondary • Overall survival • Pathological complete response within total TNBC participants • Breast-conserving rate • Adverse events
Starting date	Estimated start date: March 2013

NCT01752686 *(Continued)*

	Estimated completion date: March 2018
Contact information	Contact: Byeong Woo Park (nobellg@yuhs.ac)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT01752686 Trial sponsor: Severance Hospital Funding considerations: not specified

NCT02041338

Study name	Study of optimizing neoadjuvant regimens in subtypes of breast cancer
Methods	Accrual: unknown Accrual target: 200 Single-centre, phase 2 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with stage IIa–IIIc breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: paclitaxel 175 mg/m^2 and carboplatin AUC4 every 2 weeks for 4–6 cycles Arm 2: comparator: epirubicin 75 mg/m^2 and paclitaxel 175 mg/m^2 every 3 weeks for 4–6 cycles
Outcomes	Primary • Pathological complete response rate of breast and axilla after surgery Secondary • Disease-free survival • Overall survival • Adverse events
Starting date	Planned start date: January 2014 Estimated completion date: December 2017
Contact information	Contact: Ying Fan (fanyingfy@medmail.com.cn)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT02041338 Trial sponsor: Chinese Academy of Medical Sciences Funding considerations: not specified in trial record

NCT02455141

Study name	Adjuvant treatment of EC followed by taxane ± carboplatin in triple-negative breast cancer
Methods	Accrual: recruiting Accrual target: 970 Multicentre, phase 3 RCT Trial is being conducted in China Blinding: open-label study
Participants	Histologically confirmed triple-negative breast cancer, with tumour removal by either modified radical mastectomy or local excision plus axillary lymph node dissection Adjuvant or neoadjuvant: adjuvant
Interventions	Arm 1: intervention: epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 day 1, every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 days 1, 8, 15 every 4 weeks for 4 cycles and carboplatin AUC2 for 4 cycles or, docetaxel 75 mg/m^2 day 1 every 3 weeks for 4 cycles and carboplatin AUC5–6 day 1 every 3 weeks for 4 cycles Arm 2: comparator: epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 day 1, every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 days 1 every 12 weeks or docetaxel 80–100 mg/m^2 every 3 weeks for 4 cycles
Outcomes	Primary • Disease-free survival Secondary • Overall survival • Incidence of neutropenia fever • Incidence of grade III/IV adverse effects
Starting date	Actual start date: July 2015 Estimated completion date: December 2023
Contact information	Contact: Xiaosong Chen (chenxiaosong0156@hotmail.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT02455141 Trial sponsor: Shanghai Jiao Tong University School of Medicine Funding considerations: not specified in trial record

NCT02488967

Study name	Doxorubicin hydrochloride and cyclophosphamide followed by paclitaxel with or without carboplatin in treating patients with triple-negative breast cancer
Methods	Accrual: recruiting Accrual target: 782 Multicentre, phase 3 RCT Trial is being conducted in USA

NCT02488967 *(Continued)*

	Blinding: open-label study
Participants	People with node positive or high-risk node negative triple negative breast cancer Adjuvant or neoadjuvant: adjuvant
Interventions	Arm 1: intervention: doxorubicin then paclitaxel on days 1, 8 and 15 and carboplatin on day 1 every 3 weeks for 4 cycles Arm 2: comparator: doxorubicin and cyclophosphamide on day 3 every 2 weeks for 4 cycles, followed by paclitaxel day 1 weekly for 12 weeks
Outcomes	Primary • Disease-free survival Secondary • Breast cancer-free survival • Distant recurrence-free interval • Adverse events • Overall survival • Recurrence-free interval
Starting date	Planned start date: July 2015 Estimated completion date: November 2023
Contact information	Contact: Vicente Valero (askmdanderson@mdanderson.org)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT02488967 Trial sponsor: NRG Oncology Funding considerations: not provided in trial record

NCT02641847

Study name	TA(E)C-GP versus A(E)C-T for the high risk TNBC patients and validation of the mRNA-lncRNA signature
Methods	Accrual: unknown Accrual target: 503 Single-centre, phase 2/3 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with triple-negative breast cancer confirmed by pathology Adjuvant or neoadjuvant: adjuvant
Interventions	Arm 1: intervention ('high risk group A' in trial record): docetaxel 75 mg/m^2 and doxorubicin 50 mg/m^2 or epirubicin 75 mg/m^2 on day 1 for 4 cycles and cyclophosphamide 500 mg/m^2 on day 1, gemcitabine 1250 mg/m^2 on days 1 and 8, and cisplatin 75 mg/m^2 on day 1 every 21 days for 4 cycles

NCT02641847 *(Continued)*

	Arm 2: comparator 1 and 2 ('high risk group B' and 'low risk group C' in trial record): doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 on day 1 and cyclophosphamide 600 mg/m^2 on day 1 for 4 cycles and docetaxel 100 mg/m^2 on day 1 for 4 cycles
Outcomes	Primary • Recurrence-free survival Secondary • Treatment-related adverse events • Disease-free survival • Overall survival
Starting date	Planned start date: July 2015 Estimated completion date: June 2021
Contact information	Contact: Zhi-min Shao (zhimingshao@yahoo.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT02641847 Trial sponsor: Fudan University Funding considerations: not specified in trial record

NCT02879513

Study name	Trial of adjuvant chemotherapy in breast cancer patients with pathological partial response and complete response to neoadjuvant chemotherapy
Methods	Accrual: recruiting Accrual target: 290 Single or multicentre, phase 3 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with locally advanced breast cancer and had weekly paclitaxel and cisplatin as neoadjuvant chemotherapy Adjuvant or neoadjuvant: adjuvant
Interventions	Arm 1: intervention 1 and 2 ('continue neoadjuvant regimen' and 'pathological complete response group with chemotherapy in trial record): paclitaxel 80 mg/m^2 on days 1 and 8 for 16 weeks, followed by cisplatin 25 mg/m^2 weekly on days 1, 8 and 15, every 4 weeks for 4 cycles Arm 2: comparator: epirubicin 75 mg/m^2 on day 1 every 3 weeks for 4 cycles, cyclophosphamide 500 mg/m^2 on day 1 every 3 weeks and 5-fluorouracil 500 mg/m^2 on day 1 every 3 weeks
Outcomes	Primary • Disease-free survival Second

NCT02879513 *(Continued)*

	• Overall survival • Treatment-related adverse events • Regional recurrence-free survival • Local recurrence-free survival • Distant disease-free survival
Starting date	Planned start date: January 2014 Estimated completion date: December 2022
Contact information	Contact: Jinsong Lu (lujjss@163.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT02879513 Trial sponsor: RenJi Hospital Funding considerations: not specified in trial record

NCT02978495

Study name	Neoadjuvant carboplatin in triple negative breast cancer
Methods	Accrual: recruiting Accrual target: 120 Single or multicentre, phase 2 RCT Trial is being conducted in Brazil Blinding: open-label study
Participants	People with stage II or III triple-negative breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention ('A-BRCA mutation' and 'C-BRCA wild-type' in trial record): doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 every week for 12 weeks and carboplatin AUC1.5 once a week for 12 weeks Arm 2: comparator ('B-BRCA mutation' and 'D-BRCA wild-type' in trial record): doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 once a week for 12 weeks
Outcomes	Primary • Pathological complete response Secondary • Disease-free survival • Overall survival
Starting date	Planned start date: 17 May 2017 Estimated completion date: December 2022
Contact information	Contact: Cristiano Souza (crispadua10@gmail.com)

NCT02978495 *(Continued)*

Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT02978495 Trial sponsor: Barretos Cancer Hospital Funding considerations: not specified in trial record

NCT03168880

Study name	A randomized controlled trial of neoadjuvant weekly paclitaxel versus weekly paclitaxel plus weekly carboplatin in women with large operable or locally advanced, triple negative breast cancer (TNBC)
Methods	Accrual: active, not recruiting Accrual target: 720 Single-centre, phase 3 RCT Trial is being conducted in India Blinding: open-label study
Participants	People with clinical staging T4, N0-3, M0 or T1-4, N2-3, M0 and T3, N1, M0 with triple negative hormone status Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: paclitaxel 100 mg/m^2 weekly for 8 weeks followed by carboplatin AUC2 weekly and doxorubicin 60 mg/mg^2 or epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks Arm 2: comparator: paclitaxel 100 mg/m^2 weekly for 8 weeks followed by doxorubicin 60 mg/mg^2 or epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks
Outcomes	Primary • Disease-free survival • Overall survival Secondary • Response rate
Starting date	Planned start date: April 2010 Estimated completion date: 30 November 2024
Contact information	Contact: Rajendra A Badwe (no contact details provided)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT03168880 Trial sponsor: Tata Memorial Hospital Funding considerations: not specified in trial record

NCT03201861

Study name	Addition of cisplatin to adjuvant chemotherapy for early stage breast cancer in high-risk women
Methods	Accrual: recruiting Accrual target: 762 Single-centre, phase 3 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with triple-negative breast cancer confirmed by pathology Adjuvant or neoadjuvant: adjuvant
Interventions	Arm 1: intervention: paclitaxel 80 mg/m^2 on days 1 and 8 for 12 weeks and cisplatin 25 mg/m^2 on days 1, 8 and 15 every 4 weeks for 3 cycles followed by epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 day 1 for 4 cycles Arm 2: comparator: epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 on day 1 every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 for 12 weeks or docetaxel 75 mg/m^2 on day 1 every 21 days for 4 cycles
Outcomes	Primary • Disease-free survival Secondary • Overall survival • Treatment-related adverse events
Starting date	Planned start date: 27 July 2017 Estimated completion date: 31 December 2022
Contact information	Contact: Yueyao Du (jessicayy8629@126.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT03201861 Trial sponsor: RenJi Hospital Funding considerations: not specified in trial record

NCT03876886

Study name	The trial comparing dose-dense AC-T with TP as adjuvant therapy for TNBC with homologous recombination repair deficiency
Methods	Accrual: recruiting Accrual target: 200 Single-centre, phase 3 RCT Trial is being conducted in China

NCT03876886 *(Continued)*

	Blinding: open-label study
Participants	People with histologically confirmed triple-negative breast cancer, complete tumour removal by either modified radical mastectomy or local excision plus axillary lymph node dissection Adjuvant or neoadjuvant: adjuvant
Interventions	Arm 1: intervention: paclitaxel 175 mg/m^2 on day 1 every 2 weeks for 8 cycles and carboplatin AUC3 day 2 every 2 weeks for 8 cycles Arm 2: comparator: epirubicin 90 mg/m^2 on day 1, cyclophosphamide 600 mg/m^2 on day 1 every 2 weeks for 4 cycles and paclitaxel 175 mg/m^2 on day 1 every 2 weeks for 4 cycles
Outcomes	Primary • 3-year disease-free survival Secondary • Incidence of treatment-emergent adverse events
Starting date	Planned start date: 22 February 2019 Estimated completion date: December 2024
Contact information	Contact: Binghe Xu (xubinghe@medmail.com.cn)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT03876886 Trial sponsor: Chinese Academy of Medical Sciences Funding considerations: not specified in trial record

NCT04136782

Study name	Albumin-bound paclitaxel and carboplatin versus epirubicin and docetaxel for triple-negative breast cancer
Methods	Accrual: recruiting Accrual target: 110 Multicentre, phase 4 RCT Trial is being conducted in China Blinding: participant, investigator and outcome assessor
Participants	People with stage II–III triple-negative breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: paclitaxel 125 mg/m^2 on days 1 and 8 every 21 days for 6 cycles and carboplatin AUC2 on days 1 and 8 every 21 days Arm 2: comparator: epirubicin 90 mg/m^2 on day 1 every 21 days and docetaxel 75 mg/m^2 every 3 weeks for 4 cycles
Outcomes	Primary

NCT04136782 *(Continued)*

	• Pathological complete remission rate Secondary • Breast-conserving rate • Incidence of osteoporosis • Incidence of bone-related events • Incidence of other distant organ metastatic related events • Disease-free survival • Overall survival • Adverse events
Starting date	Planned start date: 19 July 2021 Estimated completion date: 30 November 2026
Contact information	Contact: Xi Gu (jadegx@163.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT04136782 Trial sponsor: Shengjing Hospital Funding considerations: not specified in trial record

NCT04138719

Study name	Nab-paclitaxel plus carboplatin versus nab-paclitaxel plus epirubicin in the neoadjuvant therapy for breast cancer
Methods	Accrual: unknown Accrual target: 520 Multicentre, phase 2 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with histologically confirmed primary invasive triple-negative breast cancer Adjuvant or neoadjuvant: neoadjuvant
Interventions	Arm 1: intervention: paclitaxel 125 mg/m^2 on days 1 and 8 and carboplatin AUC5 on day 1 every 3 weeks for 6 cycles Arm 2: comparator: paclitaxel 125 mg/m^2 on days 1 and 8 and epirubicin 75 mg/m^2 on day 1 every 3 weeks for 6 cycles
Outcomes	Primary • Pathological complete response Secondary • Objective response rate • Disease-free survival • Adverse events

NCT04138719 *(Continued)*

Starting date	Planned start date: 20 November 2019 Estimated completion date: 20 June 2021
Contact information	Contact: Cuizhi Geng (gengcuizhi@hotmail.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT04138719 Trial sponsor: Hebei Medical University Fourth Hospital Funding considerations: not specified in trial record

NCT04296175

Study name	Carboplatin intensified chemotherapy for triple negative breast cancer (CITRINE)
Methods	Accrual: recruiting Accrual target: 808 Single-centre, phase 3 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with high-risk, triple-negative breast cancer. High risk defined as positive lymph nodes or negative lymph nodes but ki-67 is not less than 50%
Interventions	Arm 1: intervention: epirubicin 90 mg/m^2 on day 1 and cyclophosphamide 600 mg/m^2 on day 1 every 2 weeks followed by paclitaxel 80 mg/m^2 and carboplatin AUC2 on days 1, 8 and 15 every 4 weeks Arm 2: comparator: epirubicin 90 mg/m^2 on day 1 and cyclophosphamide 600 mg/m^2 on day 1 every 2 or 3 weeks followed by paclitaxel 80 mg/m^2 on days 1, 8 and 15 every 3 weeks
Outcomes	Primary • Disease-free survival Secondary • Overall survival at 3 and 5 years • Distant disease-free survival at 3 or 5 years • Recurrence-free survival at 3 and 5 years
Starting date	Planned start date: 18 September 2018 Estimated completion date: June 2025
Contact information	Contact: Zhimin Shao (zhimingshao@yahoo.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT04296175 Trial sponsor: Fudan University Funding considerations: not specified in trial record

NCT04664972

Study name	The TP regimen in the treatment of early triple negative breast cancer
Methods	Accrual: recruiting Accrual target: 166 Single or multicentre, phase 2 RCT Trial is being conducted in China Blinding: open-label study
Participants	People with clinical T2-T4c, or T1c with axillary lymph node-positive, triple-negative breast cancer
Interventions	Arm 1: intervention: docetaxel 75 mg/m^2 on day 1 and cisplatin 25 mg/m^2 on days 1, 2 and 3 every 3 weeks for 6 cycles Arm 2: comparator: docetaxel 75 mg/m^2, adriamycin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles
Outcomes	Primary • Pathological complete remission rate Secondary • Clinical response rate • Difference of pathological complete remission rate between BRCA mutation and wildtype
Starting date	Planned start date: 23 November 2018 Estimated completion date: 23 November 2022
Contact information	Contact: Dechuang Jiao (jiaodechuang@163.com)
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT04664972 Trial sponsor: Henan Cancer Hospital Funding considerations: not specified in trial record

Nordic Trip

Study name	Nordic trip, a randomized phase 3 study in early triple negative breast cancer
Methods	Accrual: recruiting Accrual target: 1800 Multicentre, phase 3 RCT Trial is being conducted in Sweden, Denmark, Finland and Iceland Blinding: open-label study
Participants	People with early triple-negative breast cancer stage I (> 10 mm) to III

Nordic Trip *(Continued)*

	Adjuvant or neoadjuvant: both
Interventions	Arm 1: intervention: carboplatin followed by epirubicin and cyclophosphamide (further details not provided) Arm 2: comparator(s): paclitaxel followed epirubicin and cyclophosphamide or capecitabine followed by epirubicin and cyclophosphamide
Outcomes	Primary • Invasive disease-free survival Secondary • Invasive disease-free survival in subsets of triple-negative breast cancer and BRCA-mutation status
Starting date	Planned start date: not specified Estimated completion date: not specified
Contact information	Contact: Niklas Loman (niklas.loman@med.lu.se)
Notes	Trial registration link: not specified Trial sponsor: not specified Funding considerations: not specified

PEARLY

Study name	Carboplatin in EARLY triple negative breast cancer trial (PEARLY Trial)
Methods	Accrual: recruiting Accrual target: 840 Multicentre, phase 3 RCT Trial is being conducted in South Korea Blinding: open-label study
Participants	People with stage II/III operable triple-negative breast cancer Adjuvant or neoadjuvant: both
Interventions	Arm 1: intervention: doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by taxane (docetaxel 75 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly for 12 doses) plus carboplatin AUC5 every 3 weeks for 4 cycles
Outcomes	Primary • 5-year event-free survival Secondary • Overall survival • Distant recurrence-free survival • Locoregional recurrence-free survival

PEARLY *(Continued)*	• Pathological complete rate
Starting date	Planned start date: December 2015 Estimated completion date: March 2023
Contact information	Contact: Joo Hyuk Sohn, Yonsei University
Notes	Trial registration link: clinicaltrials.gov/ct2/show/NCT02441933 Trial sponsor: Yonsei University Funding considerations: not specified in trial record

AUC: area under the curve; RCT: randomised controlled trial.

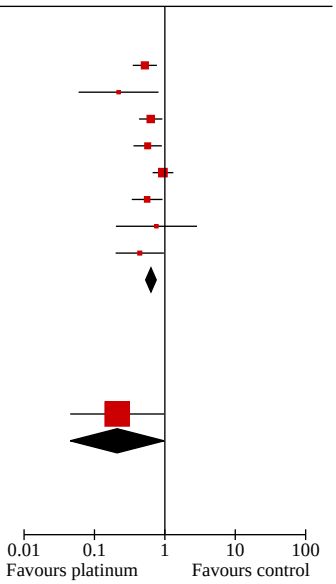
DATA AND ANALYSES

Comparison 1. Neoadjuvant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Disease-free survival	9		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Neoadjuvant	8	1966	Hazard Ratio (IV, Fixed, 95% CI)	0.63 [0.53, 0.75]
1.1.2 Includes adjuvant and neoadjuvant therapy	1	125	Hazard Ratio (IV, Fixed, 95% CI)	0.21 [0.05, 0.97]
1.2 Overall survival	8	1973	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.55, 0.86]
1.3 Pathological complete response	17		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.3.1 Neoadjuvant	16	3083	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.31, 1.59]
1.3.2 Includes adjuvant and neoadjuvant therapy	1	125	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [1.48, 6.26]
1.3.3 Neoadjuvant all	17	3208	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.34, 1.62]

Analysis 1.1. Comparison 1: Neoadjuvant, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
1.1.1 Neoadjuvant						
ADAPT-TN (1)	-0.653926	0.201141	154	182	19.3%	0.52 [0.35 , 0.77]
Ando 2014 (2)	-1.514128	0.667094	37	28	1.8%	0.22 [0.06 , 0.81]
BrighTNess comparison 1 (3)	-0.462035	0.194031	316	79	20.7%	0.63 [0.43 , 0.92]
BrighTNess comparison 2 (3)	-0.562119	0.236571	160	79	13.9%	0.57 [0.36 , 0.91]
CALGB 40603 (4)	-0.061875	0.17299	225	218	26.0%	0.94 [0.67 , 1.32]
GeparSixto (5)	-0.579818	0.256698	158	157	11.8%	0.56 [0.34 , 0.93]
NeoCART (6)	-0.274437	0.67686	44	44	1.7%	0.76 [0.20 , 2.86]
Zhang 2016 (7)	-0.820981	0.402808	43	42	4.8%	0.44 [0.20 , 0.97]
Subtotal (95% CI)			**1137**	**829**	**100.0%**	**0.63 [0.53 , 0.75]**
Heterogeneity: Chi² = 10.00, df = 7 (P = 0.19); I² = 30%						
Test for overall effect: Z = 5.16 (P < 0.00001)						
1.1.2 Includes adjuvant and neoadjuvant therapy						
Wu 2018 (8)	-1.560648	0.783339	62	63	100.0%	0.21 [0.05 , 0.97]
Subtotal (95% CI)			**62**	**63**	**100.0%**	**0.21 [0.05 , 0.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						

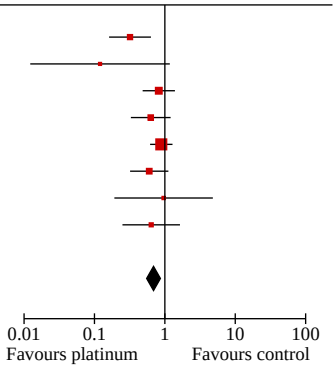


Footnotes

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

Analysis 1.2. Comparison 1: Neoadjuvant, Outcome 2: Overall survival

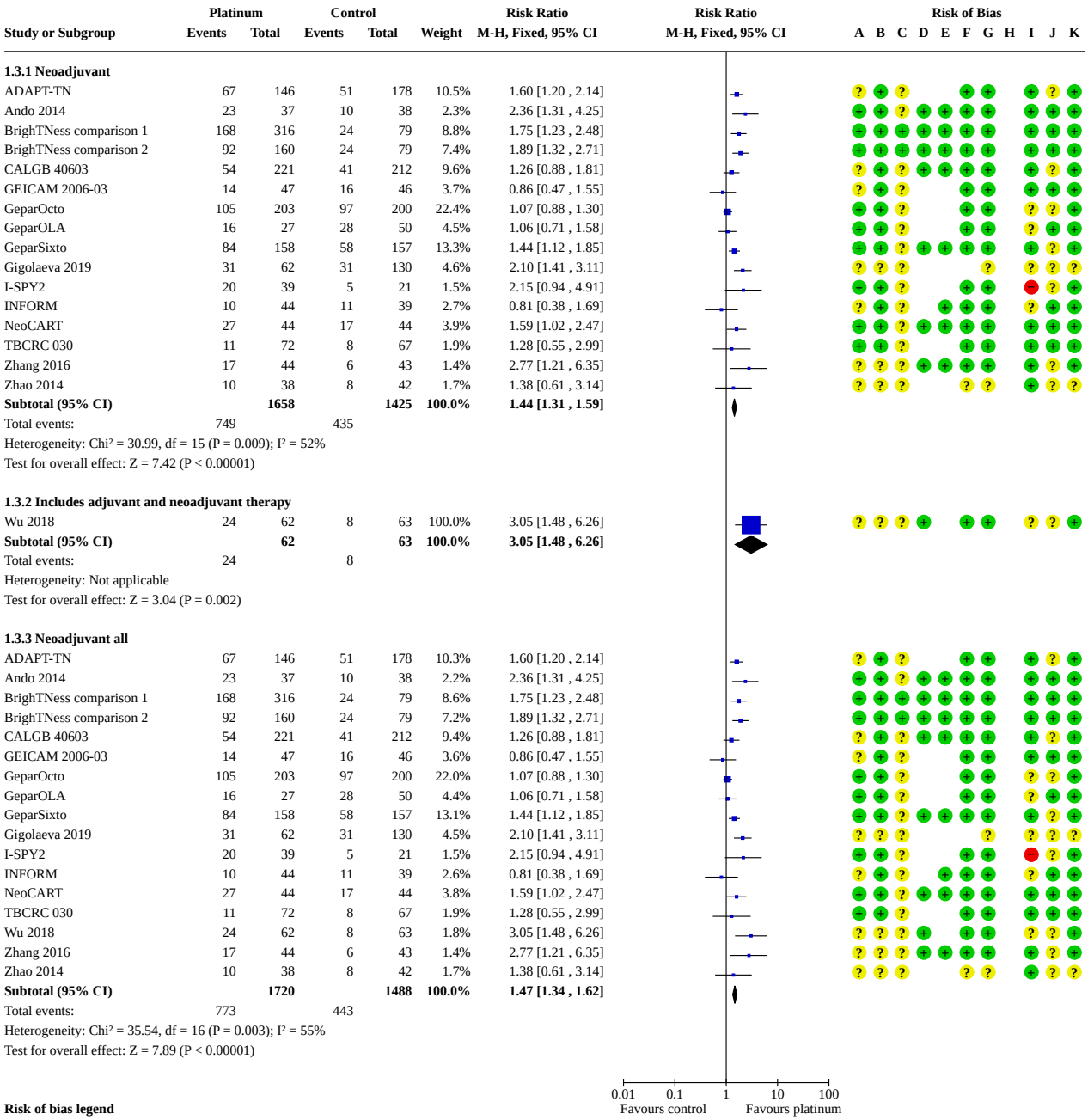
Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
ADAPT-TN (1)	-1.139434	0.349056	154	182	10.8%	0.32 [0.16 , 0.63]
Ando 2014 (2)	-2.120264	1.164396	37	38	1.0%	0.12 [0.01 , 1.18]
BrighTNess comparison 1 (3)	-0.198451	0.269406	316	79	18.1%	0.82 [0.48 , 1.39]
BrighTNess comparison 2 (3)	-0.462035	0.331456	160	79	12.0%	0.63 [0.33 , 1.21]
CALGB 40603 (4)	-0.116534	0.186911	225	218	37.6%	0.89 [0.62 , 1.28]
GeparSixto (5)	-0.510826	0.319588	158	154	12.9%	0.60 [0.32 , 1.12]
NeoCART (6)	-0.040822	0.821693	44	44	1.9%	0.96 [0.19 , 4.81]
Zhang 2016 (7)	-0.446287	0.479853	43	42	5.7%	0.64 [0.25 , 1.64]
Total (95% CI)			**1137**	**836**	**100.0%**	**0.69 [0.55 , 0.86]**
Heterogeneity: Chi² = 9.82, df = 7 (P = 0.20); I² = 29%						
Test for overall effect: Z = 3.23 (P = 0.001)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Median follow-up 36 months
(2) Median follow-up 6.6 years
(3) Median follow-up 4.5 years
(4) Median follow-up 7.9 years
(5) Median follow-up 47.3 months
(6) Median follow-up 37 months
(7) Median follow-up 55 months

Analysis 1.3. Comparison 1: Neoadjuvant, Outcome 3: Pathological complete response



Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Neoadjuvant						
ADAPT-TN	67	146	51	178	10.5%	1.60 [1.20 , 2.14]
Ando 2014	23	37	10	38	2.3%	2.36 [1.31 , 4.25]
BrighTNess comparison 1	168	316	24	79	8.8%	1.75 [1.23 , 2.48]
BrighTNess comparison 2	92	160	24	79	7.4%	1.89 [1.32 , 2.71]
CALGB 40603	54	221	41	212	9.6%	1.26 [0.88 , 1.81]
GEICAM 2006-03	14	47	16	46	3.7%	0.86 [0.47 , 1.55]
GeparOcto	105	203	97	200	22.4%	1.07 [0.88 , 1.30]
GeparOLA	16	27	28	50	4.5%	1.06 [0.71 , 1.58]
GeparSixto	84	158	58	157	13.3%	1.44 [1.12 , 1.85]
Gigolaeva 2019	31	62	31	130	4.6%	2.10 [1.41 , 3.11]
I-SPY2	20	39	5	21	1.5%	2.15 [0.94 , 4.91]
INFORM	10	44	11	39	2.7%	0.81 [0.38 , 1.69]
NeoCART	27	44	17	44	3.9%	1.59 [1.02 , 2.47]
TBCRC 030	11	72	8	67	1.9%	1.28 [0.55 , 2.99]
Zhang 2016	17	44	6	43	1.4%	2.77 [1.21 , 6.35]
Zhao 2014	10	38	8	42	1.7%	1.38 [0.61 , 3.14]
Subtotal (95% CI)		**1658**		**1425**	**100.0%**	**1.44 [1.31 , 1.59]**
Total events:	749		435			
Heterogeneity: Chi² = 30.99, df = 15 (P = 0.009); I² = 52%						
Test for overall effect: Z = 7.42 (P < 0.00001)						
1.3.2 Includes adjuvant and neoadjuvant therapy						
Wu 2018	24	62	8	63	100.0%	3.05 [1.48 , 6.26]
Subtotal (95% CI)		**62**		**63**	**100.0%**	**3.05 [1.48 , 6.26]**
Total events:	24		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.04 (P = 0.002)						
1.3.3 Neoadjuvant all						
ADAPT-TN	67	146	51	178	10.3%	1.60 [1.20 , 2.14]
Ando 2014	23	37	10	38	2.2%	2.36 [1.31 , 4.25]
BrighTNess comparison 1	168	316	24	79	8.6%	1.75 [1.23 , 2.48]
BrighTNess comparison 2	92	160	24	79	7.2%	1.89 [1.32 , 2.71]
CALGB 40603	54	221	41	212	9.4%	1.26 [0.88 , 1.81]
GEICAM 2006-03	14	47	16	46	3.6%	0.86 [0.47 , 1.55]
GeparOcto	105	203	97	200	22.0%	1.07 [0.88 , 1.30]
GeparOLA	16	27	28	50	4.4%	1.06 [0.71 , 1.58]
GeparSixto	84	158	58	157	13.1%	1.44 [1.12 , 1.85]
Gigolaeva 2019	31	62	31	130	4.5%	2.10 [1.41 , 3.11]
I-SPY2	20	39	5	21	1.5%	2.15 [0.94 , 4.91]
INFORM	10	44	11	39	2.6%	0.81 [0.38 , 1.69]
NeoCART	27	44	17	44	3.8%	1.59 [1.02 , 2.47]
TBCRC 030	11	72	8	67	1.9%	1.28 [0.55 , 2.99]
Wu 2018	24	62	8	63	1.8%	3.05 [1.48 , 6.26]
Zhang 2016	17	44	6	43	1.4%	2.77 [1.21 , 6.35]
Zhao 2014	10	38	8	42	1.7%	1.38 [0.61 , 3.14]
Subtotal (95% CI)		**1720**		**1488**	**100.0%**	**1.47 [1.34 , 1.62]**
Total events:	773		443			
Heterogeneity: Chi² = 35.54, df = 16 (P = 0.003); I² = 55%						
Test for overall effect: Z = 7.89 (P < 0.00001)						

Risk of bias legend

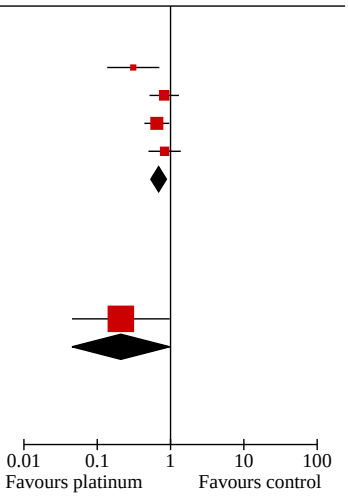
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias): DFS
(E) Blinding of outcome assessment (detection bias): OS
(F) Blinding of outcome assessment (detection bias): toxicity
(G) Blinding of outcome assessment (detection bias): neoadjuvant studies only: pCR
(H) Blinding of outcome assessment (detection bias): quality of life
(I) Selective reporting (reporting bias)
(J) Incomplete outcome data (attrition bias)
(K) Other bias

Comparison 2. Adjuvant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Disease-free survival	5		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1.1 Adjuvant	4	1256	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.54, 0.88]
2.1.2 Includes adjuvant and neoadjuvant therapy	1	125	Hazard Ratio (IV, Fixed, 95% CI)	0.21 [0.05, 0.97]
2.2 Overall survival	4	1256	Hazard Ratio (IV, Fixed, 95% CI)	0.70 [0.50, 0.96]
2.3 Disease-free survival without Wu 2018	4		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Adjuvant	4	1256	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.54, 0.88]

Analysis 2.1. Comparison 2: Adjuvant, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
2.1.1 Adjuvant						
Li 2020 (1)	-1.171183	0.417558	70	73	9.0%	0.31 [0.14 , 0.70]
Nasr 2015 (2)	-0.198451	0.235707	78	80	28.2%	0.82 [0.52 , 1.30]
PATTERN (3)	-0.430783	0.199024	325	322	39.5%	0.65 [0.44 , 0.96]
Zheng 2022 (4)	-0.18633	0.258992	154	154	23.3%	0.83 [0.50 , 1.38]
Subtotal (95% CI)			**627**	**629**	**100.0%**	**0.69 [0.54 , 0.88]**
Heterogeneity: Chi² = 4.81, df = 3 (P = 0.19); I² = 38%						
Test for overall effect: Z = 3.00 (P = 0.003)						
2.1.2 Includes adjuvant and neoadjuvant therapy						
Wu 2018 (5)	-1.560648	0.783339	62	63	100.0%	0.21 [0.05 , 0.97]
Subtotal (95% CI)			**62**	**63**	**100.0%**	**0.21 [0.05 , 0.97]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



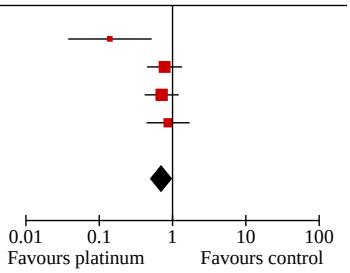
Footnotes

(1) Median follow-up 57.3 months
(2) Median follow-up 52 months
(3) Median follow-up 62 months
(4) Median follow-up 97.6 months
(5) Median follow-up not reported

Analysis 2.2. Comparison 2: Adjuvant, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
Li 2020 (1)	-1.966113	0.668645	70	73	6.1%	0.14 [0.04 , 0.52]
Nasr 2015 (2)	-0.248461	0.280263	78	80	34.5%	0.78 [0.45 , 1.35]
PATTERN (3)	-0.34249	0.272033	325	322	36.6%	0.71 [0.42 , 1.21]
Zheng 2022 (4)	-0.139262	0.344804	154	154	22.8%	0.87 [0.44 , 1.71]
Total (95% CI)			**627**	**629**	**100.0%**	**0.70 [0.50 , 0.96]**

Heterogeneity: Chi² = 6.34, df = 3 (P = 0.10); I² = 53%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable



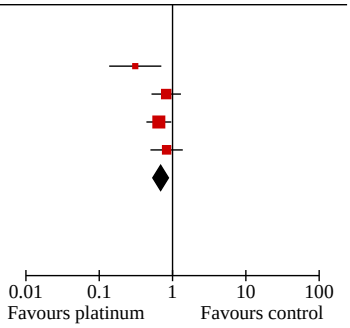
Footnotes
(1) Median follow-up 57.3 months
(2) Median follow-up 52 months
(3) Median follow-up 62 months
(4) Median follow-up 97.6 months

Analysis 2.3. Comparison 2: Adjuvant, Outcome 3: Disease-free survival without Wu 2018

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
2.3.1 Adjuvant						
Li 2020 (1)	-1.171183	0.417558	70	73	9.0%	0.31 [0.14 , 0.70]
Nasr 2015 (2)	-0.198451	0.235707	78	80	28.2%	0.82 [0.52 , 1.30]
PATTERN (3)	-0.430783	0.199024	325	322	39.5%	0.65 [0.44 , 0.96]
Zheng 2022 (4)	-0.18633	0.258992	154	154	23.3%	0.83 [0.50 , 1.38]
Subtotal (95% CI)			**627**	**629**	**100.0%**	**0.69 [0.54 , 0.88]**

Heterogeneity: Chi² = 4.81, df = 3 (P = 0.19); I² = 38%
Test for overall effect: Z = 3.00 (P = 0.003)

Test for subgroup differences: Not applicable



Footnotes
(1) Median follow-up 57.3 months
(2) Median follow-up 52 months
(3) Median follow-up 62 months
(4) Median follow-up 97.6 months

Comparison 3. All studies: treatment adherence and toxicities

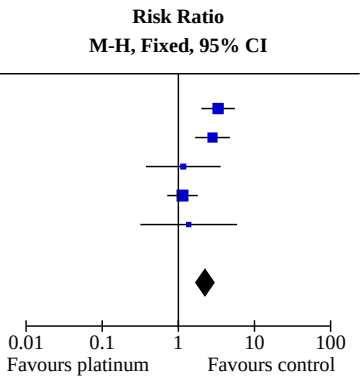
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Participants requiring chemotherapy delays	5	1053	Risk Ratio (M-H, Fixed, 95% CI)	2.23 [1.70, 2.94]
3.2 Participants requiring dose reduction	8	2055	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.56, 2.02]
3.3 Early cessation of treatment	17	4178	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.04, 1.38]
3.4 Neutropenia	20	4849	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.43, 1.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5 Febrile neutropenia	12	3771	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.89, 1.49]
3.6 Anaemia	19	4757	Risk Ratio (M-H, Fixed, 95% CI)	8.20 [5.66, 11.89]
3.7 Thrombocytopenia	19	4731	Risk Ratio (M-H, Fixed, 95% CI)	7.59 [5.10, 11.29]
3.8 Neuropathy	15	4312	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.95, 1.57]
3.9 Nausea	17	4228	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.30, 2.74]
3.10 Renal impairment	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.11 Treatment-related death	11	3176	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.14, 2.33]
3.12 Participants requiring dose reduction – random effects	8	2055	Risk Ratio (M-H, Random, 95% CI)	2.18 [1.08, 4.41]
3.13 Neutropenia – random effects	20	4849	Risk Ratio (M-H, Random, 95% CI)	1.68 [1.12, 2.52]

Analysis 3.1. Comparison 3: All studies: treatment adherence and toxicities, Outcome 1: Participants requiring chemotherapy delays

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
BrighTNess comparison 1	173	316	13	79	30.2%	3.33 [2.00 , 5.52]
BrighTNess comparison 2	74	160	13	79	25.3%	2.81 [1.66 , 4.75]
INFORM (1)	6	60	5	58	7.4%	1.16 [0.37 , 3.59]
Li 2020	25	70	23	73	32.7%	1.13 [0.71 , 1.80]
Nasr 2015	4	78	3	80	4.3%	1.37 [0.32 , 5.91]
Total (95% CI)		**684**		**369**	**100.0%**	**2.23 [1.70 , 2.94]**
Total events:	282		57			

Heterogeneity: Chi² = 13.12, df = 4 (P = 0.01); I² = 70%
Test for overall effect: Z = 5.76 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

(1) Data reported for entire cohort where TNBC made up 64–70% of cohort

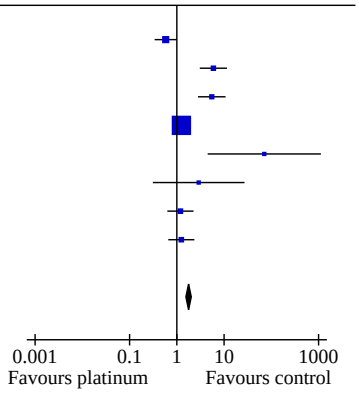
Analysis 3.2. Comparison 3: All studies: treatment adherence and toxicities, Outcome 2: Participants requiring dose reduction

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	17	140	33	158	12.6%	0.58 [0.34 , 1.00]
BrighTNess comparison 1	190	316	8	79	5.2%	5.94 [3.06 , 11.52]
BrighTNess comparison 2	89	160	8	79	4.4%	5.49 [2.81 , 10.75]
GeparSixto (1)	204	295	162	293	66.0%	1.25 [1.10 , 1.42]
I-SPY2 (2)	57	72	0	44	0.3%	70.89 [4.49 , 1118.87]
INFORM	3	60	1	58	0.4%	2.90 [0.31 , 27.08]
Li 2020	16	70	14	73	5.6%	1.19 [0.63 , 2.26]
Nasr 2015	17	78	14	80	5.6%	1.25 [0.66 , 2.35]
Total (95% CI)		**1191**		**864**	**100.0%**	**1.77 [1.56 , 2.02]**
Total events:	593		240			

Heterogeneity: Chi² = 78.31, df = 7 (P < 0.00001); I² = 91%

Test for overall effect: Z = 8.61 (P < 0.00001)

Test for subgroup differences: Not applicable



Footnotes

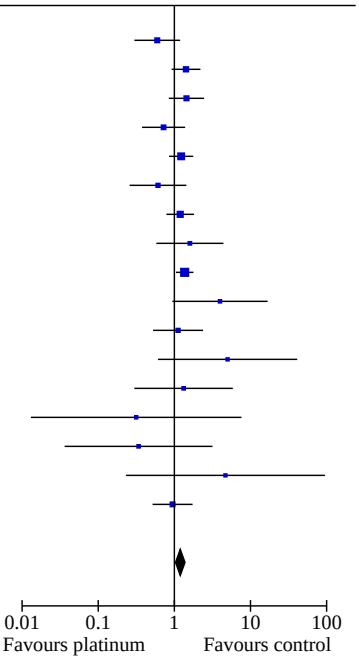
(1) Data reported for entire cohort. TNBCs made up 54% of cohort

(2) Data reported for entire cohort. Participants with TNBC made up 52% of entire cohort

Analysis 3.3. Comparison 3: All studies: treatment adherence and toxicities, Outcome 3: Early cessation of treatment

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN (1)	11	151	22	180	7.4%	0.60 [0.30 , 1.19]
Ando 2014 (2)	33	88	24	91	8.7%	1.42 [0.92 , 2.20]
BrighTNess comparison 1	75	316	13	79	7.7%	1.44 [0.84 , 2.46]
BrighTNess comparison 2	19	160	13	79	6.4%	0.72 [0.38 , 1.39]
CALGB 40603 (3)	52	225	41	218	15.4%	1.23 [0.85 , 1.77]
GEICAM 2006-03	7	48	11	46	4.2%	0.61 [0.26 , 1.44]
GeparOcto	40	203	33	200	12.3%	1.19 [0.79 , 1.81]
GeparOLA (4)	6	37	7	69	1.8%	1.60 [0.58 , 4.41]
GeparSixto	77	158	56	157	20.8%	1.37 [1.05 , 1.78]
I-SPY2 (5)	13	72	2	44	0.9%	3.97 [0.94 , 16.78]
Nasr 2015	12	78	11	80	4.0%	1.12 [0.53 , 2.38]
NeoCART	5	44	1	44	0.4%	5.00 [0.61 , 41.08]
PATTERN	4	325	3	322	1.1%	1.32 [0.30 , 5.86]
TBCRC 030	0	72	1	68	0.6%	0.32 [0.01 , 7.60]
Wu 2018	1	62	3	63	1.1%	0.34 [0.04 , 3.17]
Zhang 2016	2	47	0	44	0.2%	4.69 [0.23 , 95.00]
Zheng 2022	18	154	19	154	7.0%	0.95 [0.52 , 1.73]
Total (95% CI)		**2240**		**1938**	**100.0%**	**1.20 [1.04 , 1.38]**
Total events:	375		260			

Heterogeneity: Chi² = 18.72, df = 16 (P = 0.28); I² = 15%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable



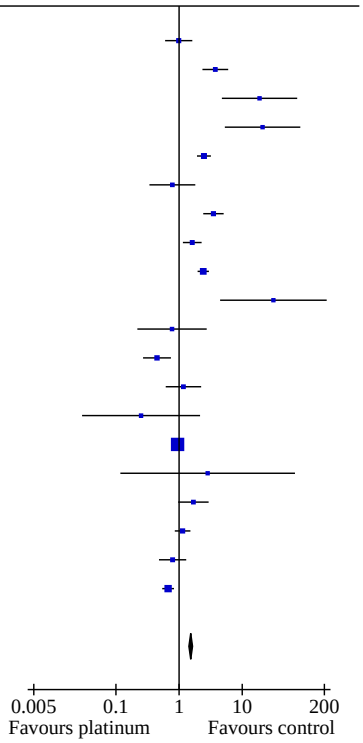
Footnotes

(1) 6/11 in intervention and 10/22 in control groups discontinued treatment early due to toxicity.
(2) Data reported for entire cohort; 40% of entire cohort had TNBC.
(3) 21/52 in intervention and 13/41 in control groups discontinued treatment early due to toxicity.
(4) Data reported for entire cohort; 73% of cohort had TNBC.
(5) Data reported for the entire cohort; 52% of cohort had TNBC. 10/13 in intervention and 1/2 in control groups discontinued due to toxicity.

Analysis 3.4. Comparison 3: All studies: treatment adherence and toxicities, Outcome 4: Neutropenia

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	24	151	29	180	3.5%	0.99 [0.60 , 1.62]
Ando 2014	58	88	16	91	2.1%	3.75 [2.34 , 5.99]
BrighTNess comparison 1	149	313	2	79	0.4%	18.80 [4.76 , 74.23]
BrighTNess comparison 2	84	158	2	79	0.4%	21.00 [5.30 , 83.14]
CALGB 40603	138	225	54	218	7.2%	2.48 [1.92 , 3.19]
GEICAM 2006-03	8	47	10	46	1.3%	0.78 [0.34 , 1.81]
GeparOcto	81	203	31	272	3.5%	3.50 [2.41 , 5.08]
GeparOLA	26	37	30	69	2.8%	1.62 [1.15 , 2.27]
GeparSixto	192	295	79	293	10.4%	2.41 [1.96 , 2.97]
I-SPY2	51	72	1	44	0.2%	31.17 [4.46 , 217.58]
INFORM	4	60	5	58	0.7%	0.77 [0.22 , 2.74]
Li 2020	15	70	35	73	4.5%	0.45 [0.27 , 0.74]
Nasr 2015	16	78	14	80	1.8%	1.17 [0.61 , 2.24]
NeoCART	1	44	4	44	0.5%	0.25 [0.03 , 2.15]
PATTERN	283	322	297	320	39.2%	0.95 [0.90 , 1.00]
TBCRC 030	1	72	0	68	0.1%	2.84 [0.12 , 68.44]
Wu 2018	24	61	14	60	1.9%	1.69 [0.97 , 2.94]
Zhang 2016	34	47	28	44	3.8%	1.14 [0.86 , 1.51]
Zhao 2014	15	38	21	42	2.6%	0.79 [0.48 , 1.30]
Zheng 2022	67	154	100	154	13.2%	0.67 [0.54 , 0.83]
Total (95% CI)		**2535**		**2314**	**100.0%**	**1.53 [1.43 , 1.63]**
Total events:	1271		772			

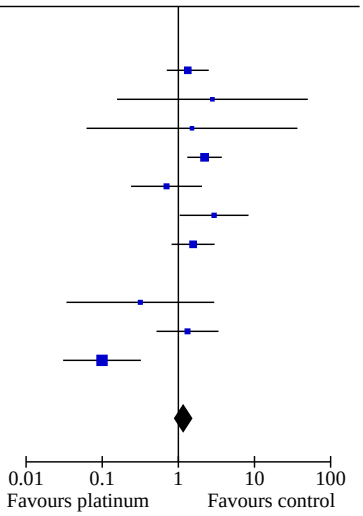
Heterogeneity: Chi² = 544.76, df = 19 (P < 0.00001); I² = 97%
Test for overall effect: Z = 12.55 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: All studies: treatment adherence and toxicities, Outcome 5: Febrile neutropenia

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	0	151	0	180		Not estimable
Ando 2014	18	88	14	91	13.9%	1.33 [0.71 , 2.51]
BrighTNess comparison 1	5	313	0	79	0.8%	2.80 [0.16 , 50.16]
BrighTNess comparison 2	1	158	0	79	0.7%	1.51 [0.06 , 36.64]
CALGB 40603	41	225	18	218	18.5%	2.21 [1.31 , 3.72]
GEICAM 2006-03	5	47	7	46	7.1%	0.70 [0.24 , 2.04]
GeparOcto (1)	11	203	5	272	4.3%	2.95 [1.04 , 8.35]
GeparSixto (2)	22	295	14	293	14.2%	1.56 [0.81 , 2.99]
I-SPY2 (3)	0	72	0	44		Not estimable
INFORM	1	60	3	57	3.1%	0.32 [0.03 , 2.96]
Nasr 2015	9	78	7	80	7.0%	1.32 [0.52 , 3.37]
PATTERN	3	322	30	320	30.4%	0.10 [0.03 , 0.32]
Total (95% CI)		**2012**		**1759**	**100.0%**	**1.16 [0.89 , 1.49]**
Total events:	116		98			

Heterogeneity: Chi² = 29.31, df = 9 (P = 0.0006); I² = 69%
Test for overall effect: Z = 1.11 (P = 0.27)
Test for subgroup differences: Not applicable



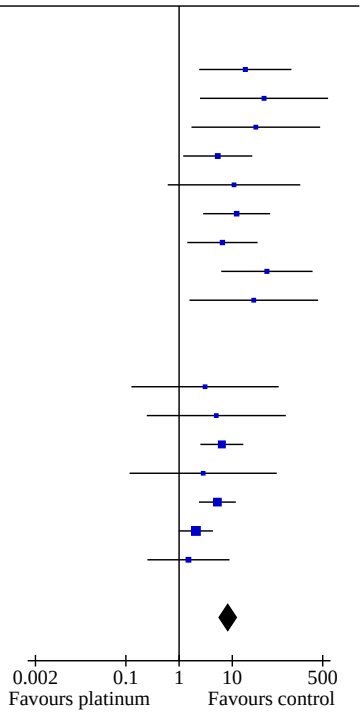
Footnotes

(1) Toxicity data reported for whole cohort
(2) Toxicity data reported for whole cohort. TNBS made up 54% of cohort
(3) Toxicity data reported for whole cohort. TNBC made up 52% of cohort

Analysis 3.6. Comparison 3: All studies: treatment adherence and toxicities, Outcome 6: Anaemia

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	0	151	0	180		Not estimable
Ando 2014	17	88	1	91	3.1%	17.58 [2.39 , 129.30]
BrighTNess comparison 1	77	313	0	79	2.5%	39.49 [2.47 , 630.14]
BrighTNess comparison 2	27	158	0	79	2.1%	27.67 [1.71 , 447.83]
CALGB 40603	11	225	2	218	6.4%	5.33 [1.19 , 23.77]
GEICAM 2006-03	5	47	0	46	1.6%	10.77 [0.61 , 189.39]
GeparOcto	18	203	2	272	5.4%	12.06 [2.83 , 51.38]
GeparOLA	7	37	2	69	4.4%	6.53 [1.43 , 29.84]
GeparSixto	45	295	1	293	3.1%	44.69 [6.20 , 322.10]
I-SPY2	20	72	0	44	1.9%	25.27 [1.57 , 407.68]
INFORM	0	60	0	57		Not estimable
Li 2020	0	70	0	73		Not estimable
Nasr 2015	1	78	0	80	1.5%	3.08 [0.13 , 74.38]
NeoCART	2	44	0	44	1.6%	5.00 [0.25 , 101.25]
PATTERN	32	322	5	320	15.7%	6.36 [2.51 , 16.12]
TBCRC 030	1	72	0	68	1.6%	2.84 [0.12 , 68.44]
Wu 2018	32	61	6	60	19.0%	5.25 [2.37 , 11.63]
Zhao 2014	15	38	8	42	23.8%	2.07 [0.99 , 4.33]
Zheng 2022	3	154	2	154	6.3%	1.50 [0.25 , 8.85]
Total (95% CI)		**2488**		**2269**	**100.0%**	**8.20 [5.66 , 11.89]**
Total events:	313		29			

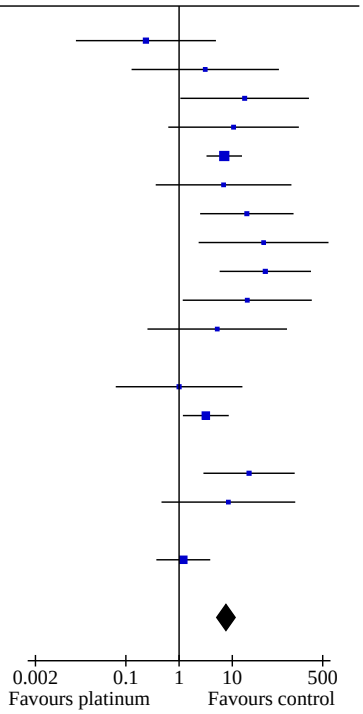
Heterogeneity: Chi² = 25.99, df = 15 (P = 0.04); I² = 42%
Test for overall effect: Z = 11.10 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: All studies: treatment adherence and toxicities, Outcome 7: Thrombocytopenia

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	0	151	2	180	8.2%	0.24 [0.01 , 4.92]
Ando 2014	1	88	0	91	1.8%	3.10 [0.13 , 75.12]
BrighTNess comparison 1	33	313	0	79	2.9%	17.07 [1.06 , 275.60]
BrighTNess comparison 2	10	158	0	79	2.4%	10.57 [0.63 , 178.03]
CALGB 40603	51	225	7	218	25.7%	7.06 [3.28 , 15.21]
GEICAM 2006-03	3	47	0	46	1.8%	6.85 [0.36 , 129.10]
GeparOcto	14	203	1	272	3.1%	18.76 [2.49 , 141.49]
GeparOLA	10	37	0	69	1.3%	38.68 [2.33 , 642.16]
GeparSixto	42	295	1	293	3.6%	41.72 [5.78 , 301.10]
I-SPY2	15	72	0	44	2.2%	19.11 [1.17 , 311.61]
Li 2020	2	70	0	73	1.8%	5.21 [0.25 , 106.66]
Nasr 2015	0	78	0	80		Not estimable
NeoCART	1	44	1	44	3.6%	1.00 [0.06 , 15.49]
PATTERN	16	322	5	320	18.1%	3.18 [1.18 , 8.58]
TBCRC 030	0	72	0	68		Not estimable
Wu 2018	21	61	1	60	3.6%	20.66 [2.87 , 148.74]
Zhang 2016	4	47	0	44	1.9%	8.44 [0.47 , 152.32]
Zhao 2014	0	38	0	42		Not estimable
Zheng 2022	6	154	5	154	18.0%	1.20 [0.37 , 3.85]
Total (95% CI)		**2475**		**2256**	**100.0%**	**7.59 [5.10 , 11.29]**
Total events:	229		23			

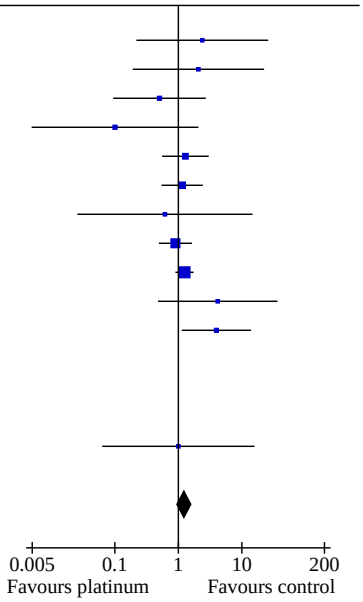
Heterogeneity: Chi² = 26.81, df = 15 (P = 0.03); I² = 44%
Test for overall effect: Z = 10.00 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: All studies: treatment adherence and toxicities, Outcome 8: Neuropathy

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	2	151	1	180	1.1%	2.38 [0.22 , 26.04]
Ando 2014	2	88	1	91	1.2%	2.07 [0.19 , 22.40]
BrighTNess comparison 1	4	313	2	79	3.7%	0.50 [0.09 , 2.71]
BrighTNess comparison 2	0	158	2	79	3.9%	0.10 [0.00 , 2.07]
CALGB 40603	12	225	9	218	10.7%	1.29 [0.56 , 3.00]
GeparOcto	12	203	14	272	14.0%	1.15 [0.54 , 2.43]
GeparOLA	0	37	1	69	1.2%	0.61 [0.03 , 14.71]
GeparSixto	19	295	21	293	24.7%	0.90 [0.49 , 1.64]
I-SPY2	47	72	23	44	33.5%	1.25 [0.90 , 1.73]
Li 2020	4	70	1	73	1.1%	4.17 [0.48 , 36.41]
PATTERN	12	322	3	320	3.5%	3.98 [1.13 , 13.95]
TBCRC 030	0	72	0	68		Not estimable
Wu 2018	0	61	0	60		Not estimable
Zhang 2016	0	47	0	44		Not estimable
Zheng 2022	1	154	1	154	1.2%	1.00 [0.06 , 15.84]
Total (95% CI)		**2268**		**2044**	**100.0%**	**1.22 [0.95 , 1.57]**
Total events:	115		79			

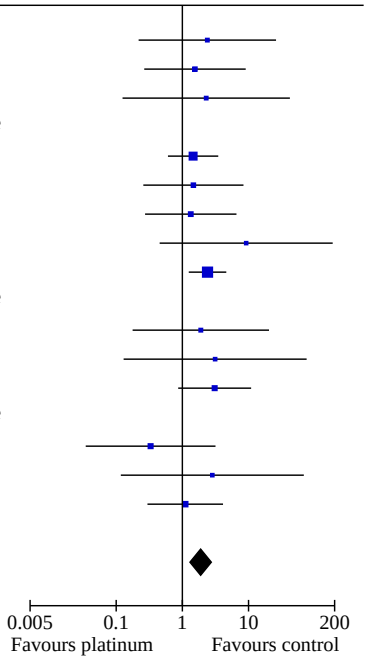
Heterogeneity: Chi² = 10.06, df = 11 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: All studies: treatment adherence and toxicities, Outcome 9: Nausea

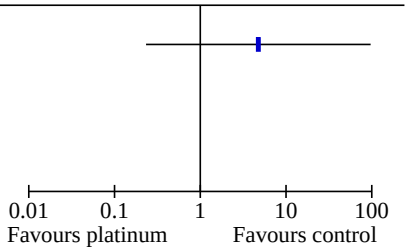
Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	2	151	1	180	2.2%	2.38 [0.22 , 26.04]
Ando 2014	3	88	2	91	4.8%	1.55 [0.27 , 9.06]
BrighTNess comparison 1	4	313	0	79	2.0%	2.29 [0.12 , 42.15]
BrighTNess comparison 2	0	58	0	79		Not estimable
CALGB 40603	12	225	8	218	20.0%	1.45 [0.61 , 3.49]
GEICAM 2006-03	3	47	2	46	5.0%	1.47 [0.26 , 8.38]
GeparOcto	3	203	3	272	6.3%	1.34 [0.27 , 6.57]
GeparOLA	2	37	0	69	0.9%	9.21 [0.45 , 186.96]
GeparSixto	29	295	12	293	29.7%	2.40 [1.25 , 4.61]
I-SPY2	0	72	0	44		Not estimable
INFORM	2	60	1	57	2.5%	1.90 [0.18 , 20.38]
Li 2020	1	70	0	73	1.2%	3.13 [0.13 , 75.49]
Nasr 2015	9	78	3	80	7.3%	3.08 [0.87 , 10.94]
NeoCART	0	44	0	44		Not estimable
PATTERN	1	322	3	320	7.4%	0.33 [0.03 , 3.17]
TBCRC 030	1	72	0	68	1.3%	2.84 [0.12 , 68.44]
Zhao 2014	4	38	4	42	9.4%	1.11 [0.30 , 4.12]
Total (95% CI)		**2173**		**2055**	**100.0%**	**1.89 [1.30 , 2.74]**
Total events:	76		39			

Heterogeneity: Chi² = 5.94, df = 13 (P = 0.95); I² = 0%
Test for overall effect: Z = 3.36 (P = 0.0008)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: All studies: treatment adherence and toxicities, Outcome 10: Renal impairment

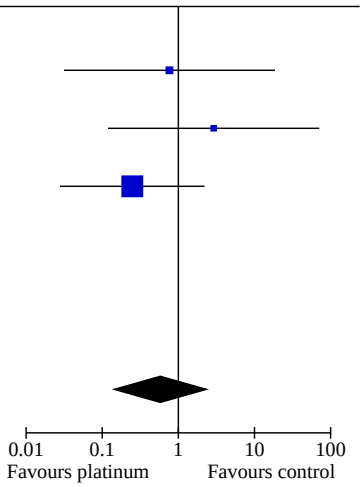
Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
INFORM	2	60	0	57	4.75 [0.23 , 96.93]
Li 2020	0	70	0	73	Not estimable
Wu 2018	0	61	0	60	Not estimable
Zhao 2014	0	38	0	44	Not estimable



Analysis 3.11. Comparison 3: All studies: treatment adherence and toxicities, Outcome 11: Treatment-related death

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	0	151	0	180		Not estimable
BrighTNess comparison 1 (1)	1	313	0	79	15.0%	0.76 [0.03 , 18.59]
BrighTNess comparison 2	0	158	0	79		Not estimable
CALGB 40603 (2)	1	225	0	218	9.5%	2.91 [0.12 , 70.98]
GeparOLA	0	37	0	69		Not estimable
GeparSixto (3)	1	295	4	293	75.5%	0.25 [0.03 , 2.21]
Li 2020	0	70	0	73		Not estimable
PATTERN	0	322	0	320		Not estimable
Wu 2018	0	61	0	60		Not estimable
Zhang 2016	0	47	0	44		Not estimable
Zhao 2014	0	38	0	44		Not estimable
Total (95% CI)		**1717**		**1459**	**100.0%**	**0.58 [0.14 , 2.33]**
Total events:	3		4			

Heterogeneity: Chi² = 1.59, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)
Test for subgroup differences: Not applicable



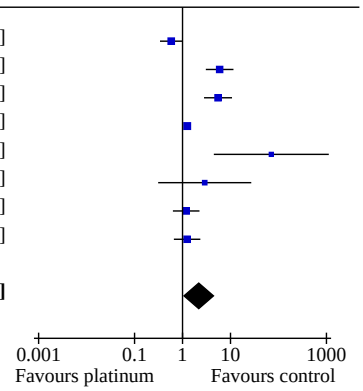
Footnotes

(1) Death occurred in AC segment of chemotherapy (not during platinum component)
(2) Cause of death not specified
(3) Death in platinum arm due to port infection. Deaths in control arm due to: 2 cardiac, 2 neutropenic events

Analysis 3.12. Comparison 3: All studies: treatment adherence and toxicities, Outcome 12: Participants requiring dose reduction – random effects

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ADAPT-TN	17	140	33	158	15.0%	0.58 [0.34 , 1.00]
BrighTNess comparison 1	190	316	8	79	14.4%	5.94 [3.06 , 11.52]
BrighTNess comparison 2	89	160	8	79	14.3%	5.49 [2.81 , 10.75]
GeparSixto (1)	204	295	162	293	16.4%	1.25 [1.10 , 1.42]
I-SPY2 (2)	57	72	0	44	4.7%	70.89 [4.49 , 1118.87]
INFORM	3	60	1	58	6.2%	2.90 [0.31 , 27.08]
Li 2020	16	70	14	73	14.5%	1.19 [0.63 , 2.26]
Nasr 2015	17	78	14	80	14.5%	1.25 [0.66 , 2.35]
Total (95% CI)		**1191**		**864**	**100.0%**	**2.18 [1.08 , 4.41]**
Total events:	593		240			

Heterogeneity: Tau² = 0.79; Chi² = 78.31, df = 7 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.16 (P = 0.03)
Test for subgroup differences: Not applicable



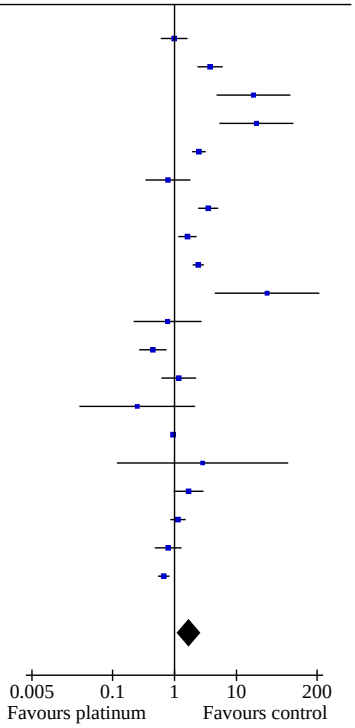
Footnotes

(1) Data reported for entire cohort. TNBCs made up 54% of cohort
(2) Data reported for the entire cohort. Participants with TNBC made up 52% of entire cohort

Analysis 3.13. Comparison 3: All studies: treatment adherence and toxicities, Outcome 13: Neutropenia – random effects

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
ADAPT-TN	24	151	29	180	5.8%	0.99 [0.60 , 1.62]
Ando 2014	58	88	16	91	5.8%	3.75 [2.34 , 5.99]
BrighTNess comparison 1	149	313	2	79	3.7%	18.80 [4.76 , 74.23]
BrighTNess comparison 2	84	158	2	79	3.7%	21.00 [5.30 , 83.14]
CALGB 40603	138	225	54	218	6.2%	2.48 [1.92 , 3.19]
GEICAM 2006-03	8	47	10	46	5.0%	0.78 [0.34 , 1.81]
GeparOcto	81	203	31	272	6.0%	3.50 [2.41 , 5.08]
GeparOLA	26	37	30	69	6.1%	1.62 [1.15 , 2.27]
GeparSixto	192	295	79	293	6.2%	2.41 [1.96 , 2.97]
I-SPY2	51	72	1	44	2.6%	31.17 [4.46 , 217.58]
INFORM	4	60	5	58	3.9%	0.77 [0.22 , 2.74]
Li 2020	15	70	35	73	5.8%	0.45 [0.27 , 0.74]
Nasr 2015	16	78	14	80	5.5%	1.17 [0.61 , 2.24]
NeoCART	1	44	4	44	2.3%	0.25 [0.03 , 2.15]
PATTERN	283	322	297	320	6.3%	0.95 [0.90 , 1.00]
TBCRC 030	1	72	0	68	1.3%	2.84 [0.12 , 68.44]
Wu 2018	24	61	14	60	5.7%	1.69 [0.97 , 2.94]
Zhang 2016	34	47	28	44	6.1%	1.14 [0.86 , 1.51]
Zhao 2014	15	38	21	42	5.8%	0.79 [0.48 , 1.30]
Zheng 2022	67	154	100	154	6.2%	0.67 [0.54 , 0.83]
Total (95% CI)		**2535**		**2314**	**100.0%**	**1.68 [1.12 , 2.52]**
Total events:	1271		772			

Heterogeneity: Tau² = 0.68; Chi² = 544.76, df = 19 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable

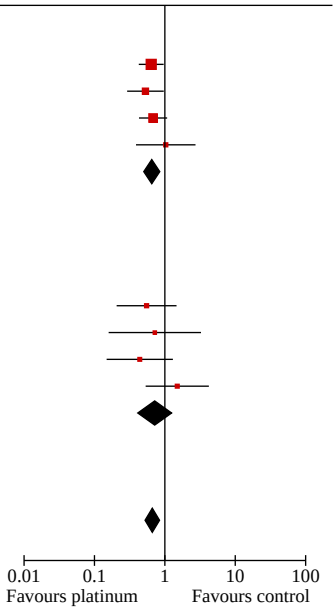


Comparison 4. BRCA mutation status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Disease-free survival	4	1452	Hazard Ratio (IV, Fixed, 95% CI)	0.66 [0.52, 0.84]
4.1.1 BRCA wildtype	4	1230	Hazard Ratio (IV, Fixed, 95% CI)	0.65 [0.50, 0.85]
4.1.2 BRCA mutation	4	222	Hazard Ratio (IV, Fixed, 95% CI)	0.72 [0.41, 1.25]
4.2 Pathological complete response	6	1478	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.17, 1.49]
4.2.1 BRCA wildtype	5	1145	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.21, 1.63]
4.2.2 BRCA mutation	6	333	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.91, 1.36]

Analysis 4.1. Comparison 4: BRCA mutation status, Outcome 1: Disease-free survival

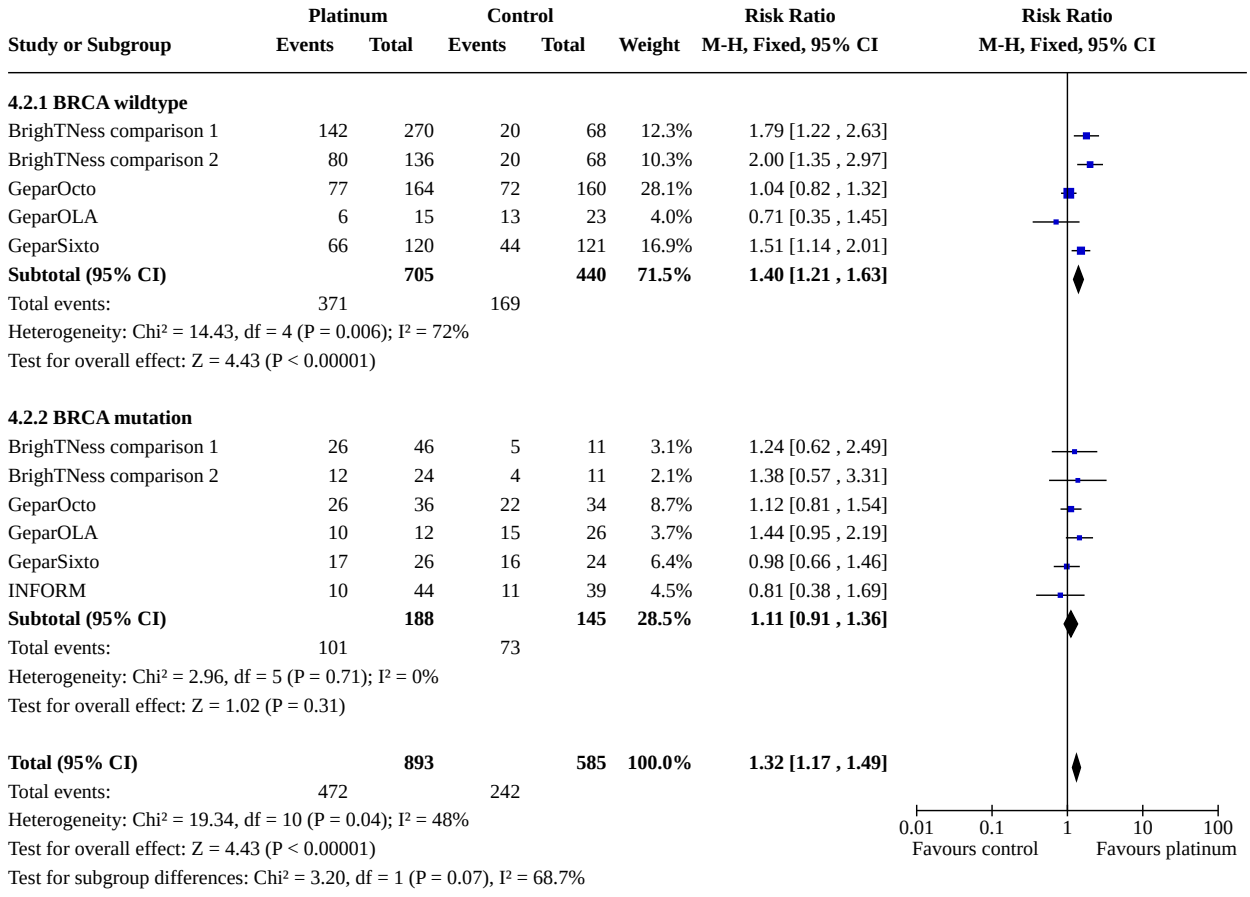
Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
4.1.1 BRCA wildtype						
BrighTNess comparison 1 (1)	-0.446287	0.207532	270	136	33.8%	0.64 [0.43 , 0.96]
GeparSixto	-0.634878	0.305376	120	121	15.6%	0.53 [0.29 , 0.96]
PATTERN	-0.385662	0.234936	235	237	26.4%	0.68 [0.43 , 1.08]
Zheng 2022	0.029559	0.496415	62	49	5.9%	1.03 [0.39 , 2.73]
Subtotal (95% CI)			**687**	**543**	**81.7%**	**0.65 [0.50 , 0.85]**
Heterogeneity: Chi² = 1.35, df = 3 (P = 0.72); I² = 0%						
Test for overall effect: Z = 3.21 (P = 0.001)						
4.1.2 BRCA mutation						
BrighTNess comparison 1 (1)	-0.597837	0.499862	46	22	5.8%	0.55 [0.21 , 1.47]
GeparSixto	-0.328504	0.770531	26	24	2.5%	0.72 [0.16 , 3.26]
PATTERN	-0.820981	0.552854	34	32	4.8%	0.44 [0.15 , 1.30]
Zheng 2022	0.405465	0.527453	12	26	5.2%	1.50 [0.53 , 4.22]
Subtotal (95% CI)			**118**	**104**	**18.3%**	**0.72 [0.41 , 1.25]**
Heterogeneity: Chi² = 3.02, df = 3 (P = 0.39); I² = 1%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)			**805**	**647**	**100.0%**	**0.66 [0.52 , 0.84]**
Heterogeneity: Chi² = 4.46, df = 7 (P = 0.73); I² = 0%						
Test for overall effect: Z = 3.40 (P = 0.0007)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.76), I² = 0%						



Footnotes

(1) For BrigTNess comparison 2, the hazard ratio for the BRCA subgroups was unable to be calculated and therefore not presented in this table

Analysis 4.2. Comparison 4: BRCA mutation status, Outcome 2: Pathological complete response



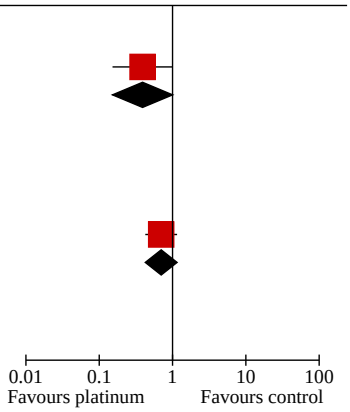
Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 BRCA wildtype						
BrighTNess comparison 1	142	270	20	68	12.3%	1.79 [1.22 , 2.63]
BrighTNess comparison 2	80	136	20	68	10.3%	2.00 [1.35 , 2.97]
GeparOcto	77	164	72	160	28.1%	1.04 [0.82 , 1.32]
GeparOLA	6	15	13	23	4.0%	0.71 [0.35 , 1.45]
GeparSixto	66	120	44	121	16.9%	1.51 [1.14 , 2.01]
Subtotal (95% CI)		**705**		**440**	**71.5%**	**1.40 [1.21 , 1.63]**
Total events:	371		169			
Heterogeneity: Chi² = 14.43, df = 4 (P = 0.006); I² = 72%						
Test for overall effect: Z = 4.43 (P < 0.00001)						
4.2.2 BRCA mutation						
BrighTNess comparison 1	26	46	5	11	3.1%	1.24 [0.62 , 2.49]
BrighTNess comparison 2	12	24	4	11	2.1%	1.38 [0.57 , 3.31]
GeparOcto	26	36	22	34	8.7%	1.12 [0.81 , 1.54]
GeparOLA	10	12	15	26	3.7%	1.44 [0.95 , 2.19]
GeparSixto	17	26	16	24	6.4%	0.98 [0.66 , 1.46]
INFORM	10	44	11	39	4.5%	0.81 [0.38 , 1.69]
Subtotal (95% CI)		**188**		**145**	**28.5%**	**1.11 [0.91 , 1.36]**
Total events:	101		73			
Heterogeneity: Chi² = 2.96, df = 5 (P = 0.71); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
Total (95% CI)		**893**		**585**	**100.0%**	**1.32 [1.17 , 1.49]**
Total events:	472		242			
Heterogeneity: Chi² = 19.34, df = 10 (P = 0.04); I² = 48%						
Test for overall effect: Z = 4.43 (P < 0.00001)						
Test for subgroup differences: Chi² = 3.20, df = 1 (P = 0.07), I² = 68.7%						

Comparison 5. Homologous recombination deficiency (HRD) status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Disease-free survival	1		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
5.1.1 HRD positive	1	120	Hazard Ratio (IV, Fixed, 95% CI)	0.39 [0.15, 1.00]
5.1.2 HRD negative	1	401	Hazard Ratio (IV, Fixed, 95% CI)	0.70 [0.42, 1.15]
5.2 Pathological complete response	1	104	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.24, 1.72]
5.2.1 Homologous recombination deficiency (HRD)+	1	74	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.28, 2.84]
5.2.2 HRD−	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.18]

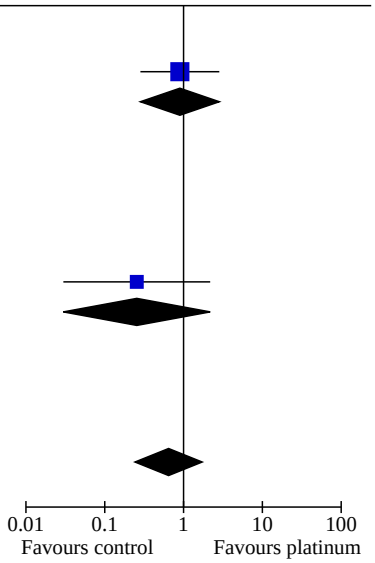
Analysis 5.1. Comparison 5: Homologous recombination deficiency (HRD) status, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
5.1.1 HRD positive						
PATTERN	-0.941609	0.481404	59	61	100.0%	0.39 [0.15 , 1.00]
Subtotal (95% CI)			**59**	**61**	**100.0%**	**0.39 [0.15 , 1.00]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
5.1.2 HRD negative						
PATTERN	-0.356675	0.254731	202	199	100.0%	0.70 [0.42 , 1.15]
Subtotal (95% CI)			**202**	**199**	**100.0%**	**0.70 [0.42 , 1.15]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%						



Analysis 5.2. Comparison 5: Homologous recombination deficiency (HRD) status, Outcome 2: Pathological complete response

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.2.1 Homologous recombination deficiency (HRD)+						
TBCRC 030	5	39	5	35	60.8%	0.90 [0.28 , 2.84]
Subtotal (95% CI)		**39**		**35**	**60.8%**	**0.90 [0.28 , 2.84]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.85)						
5.2.2 HRD−						
TBCRC 030	1	17	3	13	39.2%	0.25 [0.03 , 2.18]
Subtotal (95% CI)		**17**		**13**	**39.2%**	**0.25 [0.03 , 2.18]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
Total (95% CI)		**56**		**48**	**100.0%**	**0.65 [0.24 , 1.72]**
Total events:	6		8			
Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² = 3%						
Test for overall effect: Z = 0.87 (P = 0.38)						
Test for subgroup differences: Chi² = 1.03, df = 1 (P = 0.31), I² = 2.6%						



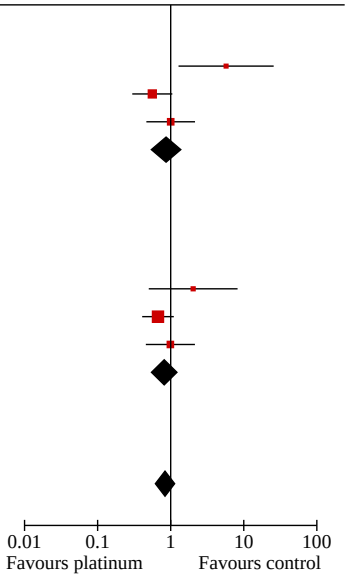
Comparison 6. Lymph node status

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Disease-free survival	3	1097	Hazard Ratio (IV, Fixed, 95% CI)	0.84 [0.62, 1.13]
6.1.1 Lymph node positive	3	323	Hazard Ratio (IV, Fixed, 95% CI)	0.86 [0.54, 1.37]
6.1.2 Lymph node negative	3	774	Hazard Ratio (IV, Fixed, 95% CI)	0.82 [0.55, 1.22]

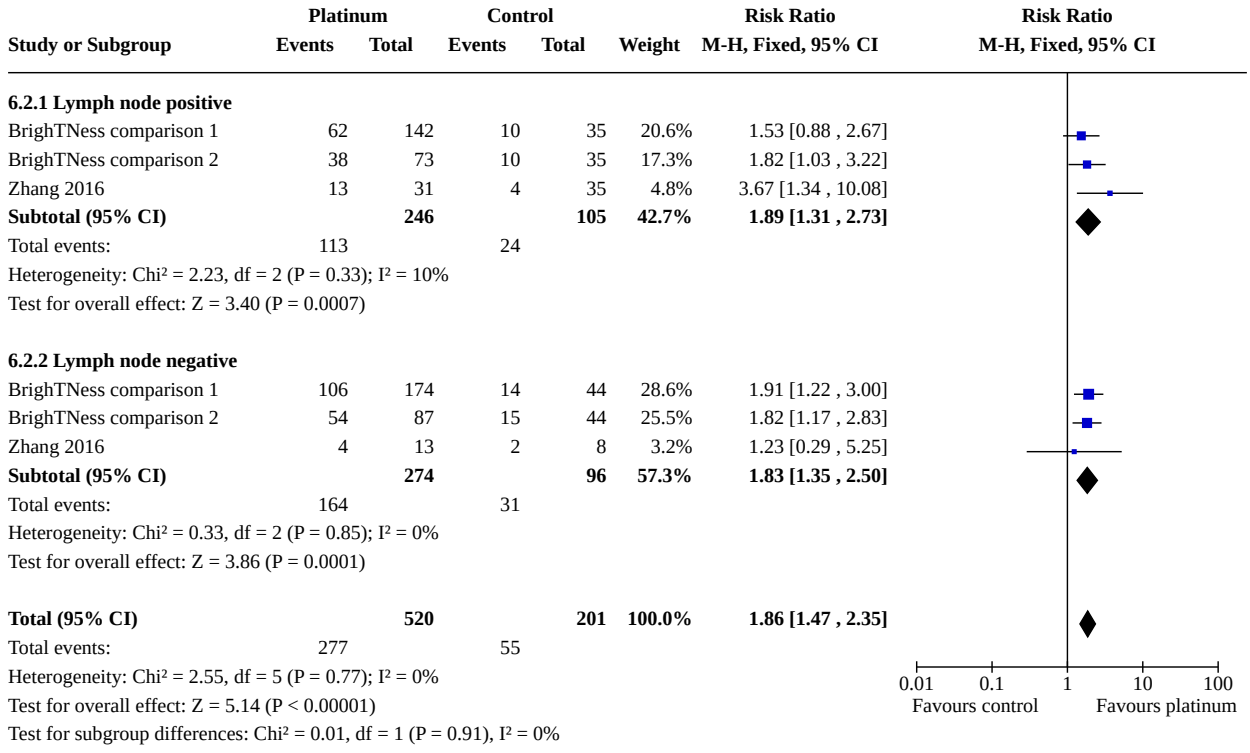
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Pathological complete response	3	721	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [1.47, 2.35]
6.2.1 Lymph node positive	3	351	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.31, 2.73]
6.2.2 Lymph node negative	3	370	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.35, 2.50]

Analysis 6.1. Comparison 6: Lymph node status, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
6.1.1 Lymph node positive						
Li 2020	1.745716	0.764729	23	29	4.1%	5.73 [1.28 , 25.65]
PATTERN	-0.579818	0.322006	88	77	23.1%	0.56 [0.30 , 1.05]
Zheng 2022	0	0.39099	45	61	15.7%	1.00 [0.46 , 2.15]
Subtotal (95% CI)			**156**	**167**	**42.8%**	**0.86 [0.54 , 1.37]**
Heterogeneity: Chi² = 8.07, df = 2 (P = 0.02); I² = 75%						
Test for overall effect: Z = 0.62 (P = 0.54)						
6.1.2 Lymph node negative						
Li 2020	0.708036	0.713916	47	44	4.7%	2.03 [0.50 , 8.23]
PATTERN	-0.400478	0.254076	237	244	37.1%	0.67 [0.41 , 1.10]
Zheng 2022	-0.01005	0.394558	109	93	15.4%	0.99 [0.46 , 2.15]
Subtotal (95% CI)			**393**	**381**	**57.2%**	**0.82 [0.55 , 1.22]**
Heterogeneity: Chi² = 2.47, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)			**549**	**548**	**100.0%**	**0.84 [0.62 , 1.13]**
Heterogeneity: Chi² = 10.58, df = 5 (P = 0.06); I² = 53%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%						



Analysis 6.2. Comparison 6: Lymph node status, Outcome 2: Pathological complete response

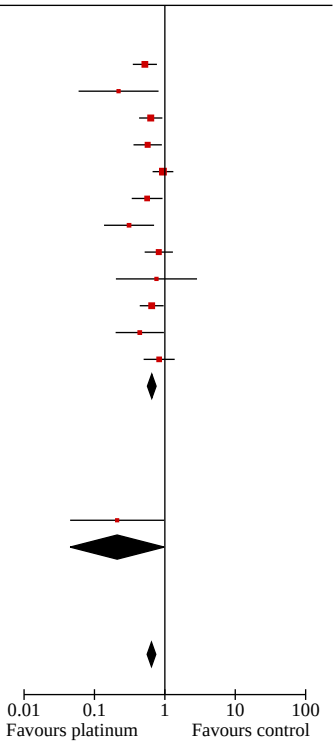


Comparison 7. Type of platinum agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Disease-free survival	13	3347	Hazard Ratio (IV, Fixed, 95% CI)	0.65 [0.56, 0.74]
7.1.1 Carboplatin	12	3222	Hazard Ratio (IV, Fixed, 95% CI)	0.65 [0.57, 0.75]
7.1.2 Lobaplatin	1	125	Hazard Ratio (IV, Fixed, 95% CI)	0.21 [0.05, 0.98]
7.2 Overall survival	12		Hazard Ratio (IV, Fixed, 95% CI)	Subtotals only
7.2.1 Carboplatin	12	3229	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.58, 0.83]
7.3 Pathological complete response	16	3148	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.33, 1.61]
7.3.1 Carboplatin	13	2801	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.32, 1.60]
7.3.2 Cisplatin	2	222	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.58, 1.75]
7.3.3 Lobaplatin	1	125	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [1.48, 6.26]

Analysis 7.1. Comparison 7: Type of platinum agent, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
7.1.1 Carboplatin						
ADAPT-TN (1)	-0.653926	0.201141	154	182	12.8%	0.52 [0.35 , 0.77]
Ando 2014 (2)	-1.514128	0.667094	37	28	1.2%	0.22 [0.06 , 0.81]
BrighTNess comparison 1 (3)	-0.462035	0.194031	316	79	13.7%	0.63 [0.43 , 0.92]
BrighTNess comparison 2 (3)	-0.562119	0.236571	160	79	9.2%	0.57 [0.36 , 0.91]
CALGB 40603 (4)	-0.061875	0.17299	225	218	17.2%	0.94 [0.67 , 1.32]
GeparSixto (5)	-0.579818	0.256698	158	157	7.8%	0.56 [0.34 , 0.93]
Li 2020 (6)	-1.171183	0.417558	70	73	3.0%	0.31 [0.14 , 0.70]
Nasr 2015 (7)	-0.198451	0.235707	78	80	9.3%	0.82 [0.52 , 1.30]
NeoCART (8)	-0.274437	0.67686	44	44	1.1%	0.76 [0.20 , 2.86]
PATTERN (9)	-0.430783	0.199024	325	322	13.0%	0.65 [0.44 , 0.96]
Zhang 2016 (10)	-0.820981	0.402808	43	42	3.2%	0.44 [0.20 , 0.97]
Zheng 2022 (11)	-0.18633	0.258992	154	154	7.7%	0.83 [0.50 , 1.38]
Subtotal (95% CI)			**1764**	**1458**	**99.2%**	**0.65 [0.57 , 0.75]**
Heterogeneity: Chi² = 15.08, df = 11 (P = 0.18); I² = 27%						
Test for overall effect: Z = 5.94 (P < 0.00001)						
7.1.2 Lobaplatin						
Wu 2018	-1.560648	0.784546	62	63	0.8%	0.21 [0.05 , 0.98]
Subtotal (95% CI)			**62**	**63**	**0.8%**	**0.21 [0.05 , 0.98]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
Total (95% CI)			**1826**	**1521**	**100.0%**	**0.65 [0.56 , 0.74]**
Heterogeneity: Chi² = 17.15, df = 12 (P = 0.14); I² = 30%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.07, df = 1 (P = 0.15), I² = 51.6%						



Footnotes

(1) Median follow-up 36 months
(2) Median follow-up 6.6 years
(3) Median follow-up 4.5 years
(4) Median follow-up 7.9 years
(5) Median follow-up 47.3 months
(6) Median follow-up 57.3 months
(7) Median follow-up 52 months
(8) Median follow-up 37 months
(9) Median follow-up 62 months
(10) Median follow-up 55 months. Included relapse events only.
(11) Median follow-up 97.6 months

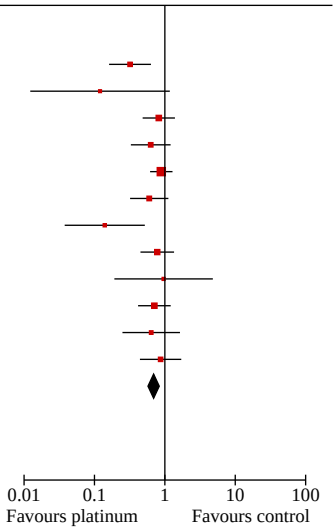
Analysis 7.2. Comparison 7: Type of platinum agent, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
7.2.1 Carboplatin						
ADAPT-TN (1)	-1.139434	0.349056	154	182	7.3%	0.32 [0.16 , 0.63]
Ando 2014 (2)	-2.120264	1.164396	37	38	0.7%	0.12 [0.01 , 1.18]
BrighTNess comparison 1 (3)	-0.198451	0.269406	316	79	12.2%	0.82 [0.48 , 1.39]
BrighTNess comparison 2 (3)	-0.462035	0.331456	160	79	8.1%	0.63 [0.33 , 1.21]
CALGB 40603 (4)	-0.116534	0.186911	225	218	25.3%	0.89 [0.62 , 1.28]
GeparSixto (5)	-0.510826	0.319588	158	154	8.7%	0.60 [0.32 , 1.12]
Li 2020 (6)	-1.966113	0.668645	70	73	2.0%	0.14 [0.04 , 0.52]
Nasr 2015 (7)	-0.248461	0.280263	78	80	11.3%	0.78 [0.45 , 1.35]
NeoCART (8)	-0.040822	0.821693	44	44	1.3%	0.96 [0.19 , 4.81]
PATTERN (9)	-0.34249	0.272033	325	322	12.0%	0.71 [0.42 , 1.21]
Zhang 2016 (10)	-0.446287	0.479853	43	42	3.8%	0.64 [0.25 , 1.64]
Zheng 2022 (11)	-0.139262	0.344804	154	154	7.4%	0.87 [0.44 , 1.71]
Subtotal (95% CI)			**1764**	**1465**	**100.0%**	**0.69 [0.58 , 0.83]**

Heterogeneity: $Chi^2 = 16.16$, df = 11 (P = 0.14); $I^2 = 32\%$

Test for overall effect: Z = 3.91 (P < 0.0001)

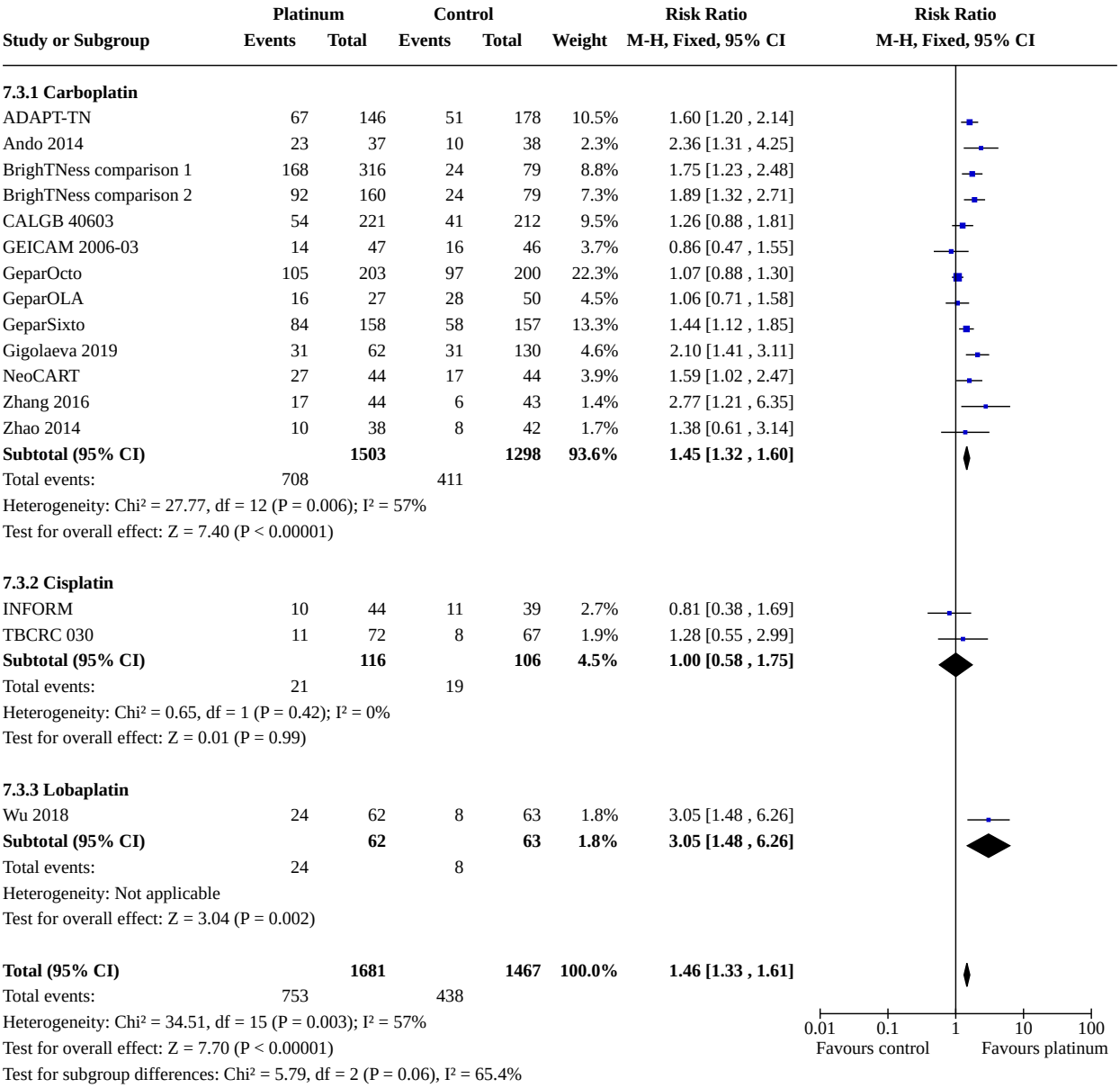
Test for subgroup differences: Not applicable



Footnotes

(1) Median follow-up 36 months
(2) Median follow-up 6.6 years
(3) Median follow-up 4.5 years
(4) Median follow-up 7.9 years
(5) Median follow-up 47.3 months
(6) Median follow-up 57.3 months
(7) Median follow-up 52 months
(8) Median follow-up 37 months
(9) Median follow-up 62 months
(10) Median follow-up 55 months
(11) Median follow-up 97.6 months

Analysis 7.3. Comparison 7: Type of platinum agent, Outcome 3: Pathological complete response



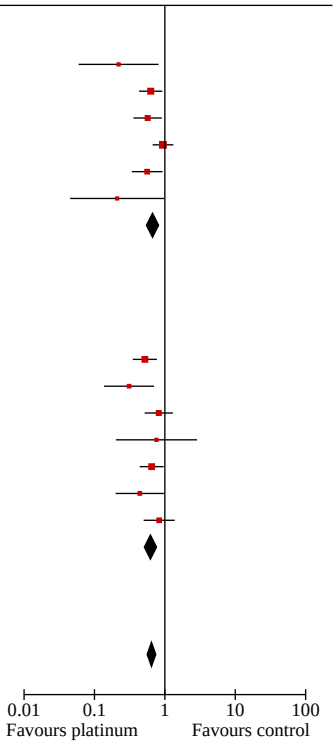
Comparison 8. Same backbone chemotherapy with or without platinum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Disease-free survival	13	3357	Hazard Ratio (IV, Fixed, 95% CI)	0.65 [0.56, 0.74]
8.1.1 Same backbone	6	1592	Hazard Ratio (IV, Fixed, 95% CI)	0.67 [0.55, 0.81]
8.1.2 Different backbone	7	1765	Hazard Ratio (IV, Fixed, 95% CI)	0.62 [0.51, 0.76]
8.2 Overall survival	12	3232	Hazard Ratio (IV, Fixed, 95% CI)	0.68 [0.56, 0.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2.1 Same backbone	5	1467	Hazard Ratio (IV, Fixed, 95% CI)	0.75 [0.57, 0.99]
8.2.2 Different backbone	7	1765	Hazard Ratio (IV, Fixed, 95% CI)	0.62 [0.47, 0.81]
8.3 Pathological complete response	16	3148	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.33, 1.61]
8.3.1 Same backbone	7	1675	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.38, 1.84]
8.3.2 Different backbone	9	1473	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.18, 1.53]

Analysis 8.1. Comparison 8: Same backbone chemotherapy with or without platinum, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
8.1.1 Same backbone						
Ando 2014 (1)	-1.514128	0.667094	37	38	1.2%	0.22 [0.06 , 0.81]
BrighTNess comparison 1 (2)	-0.462035	0.194031	316	79	13.7%	0.63 [0.43 , 0.92]
BrighTNess comparison 2 (2)	-0.562119	0.236571	160	79	9.2%	0.57 [0.36 , 0.91]
CALGB 40603 (3)	-0.061875	0.17299	225	218	17.2%	0.94 [0.67 , 1.32]
GeparSixto (4)	-0.579818	0.256698	158	157	7.8%	0.56 [0.34 , 0.93]
Wu 2018 (5)	-1.560648	0.784546	62	63	0.8%	0.21 [0.05 , 0.98]
Subtotal (95% CI)			**958**	**634**	**50.0%**	**0.67 [0.55 , 0.81]**
Heterogeneity: Chi² = 9.86, df = 5 (P = 0.08); I² = 49%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
8.1.2 Different backbone						
ADAPT-TN (6)	-0.653926	0.201141	154	182	12.8%	0.52 [0.35 , 0.77]
Li 2020 (7)	-1.171183	0.417558	70	73	3.0%	0.31 [0.14 , 0.70]
Nasr 2015 (8)	-0.198451	0.235707	78	80	9.3%	0.82 [0.52 , 1.30]
NeoCART (9)	-0.274437	0.67686	44	44	1.1%	0.76 [0.20 , 2.86]
PATTERN (10)	-0.430783	0.199024	325	322	13.0%	0.65 [0.44 , 0.96]
Zhang 2016 (11)	-0.820981	0.402808	43	42	3.2%	0.44 [0.20 , 0.97]
Zheng 2022 (12)	-0.18633	0.258992	154	154	7.7%	0.83 [0.50 , 1.38]
Subtotal (95% CI)			**868**	**897**	**50.0%**	**0.62 [0.51 , 0.76]**
Heterogeneity: Chi² = 7.06, df = 6 (P = 0.31); I² = 15%						
Test for overall effect: Z = 4.65 (P < 0.00001)						
Total (95% CI)			**1826**	**1531**	**100.0%**	**0.65 [0.56 , 0.74]**
Heterogeneity: Chi² = 17.15, df = 12 (P = 0.14); I² = 30%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

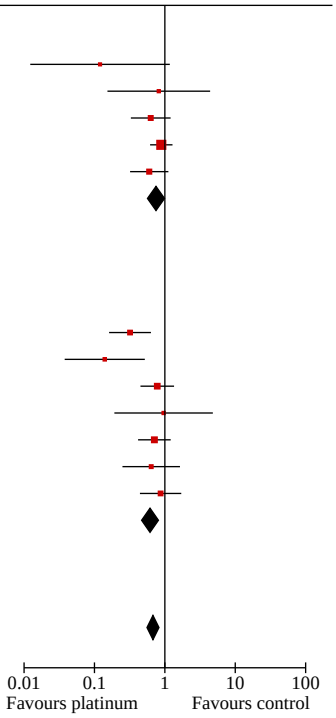


Footnotes

(1) Median follow-up 6.6 years
(2) Median follow-up 4.5 years
(3) Median follow-up 7.9 years
(4) Median follow-up 47.3 months
(5) Median follow-up not reported
(6) Median follow-up 36 months
(7) Median follow-up 57.3 months
(8) Median follow-up 52 months
(9) Median follow-up 37 months
(10) Median follow-up 62 months
(11) Median follow-up 55 months. Included relapse events only
(12) Median follow-up 97.6 months

Analysis 8.2. Comparison 8: Same backbone chemotherapy with or without platinum, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
8.2.1 Same backbone						
Ando 2014 (1)	-2.120264	1.164396	37	38	0.7%	0.12 [0.01 , 1.18]
BrighTNess comparison 1 (2)	-0.198451	0.856811	316	79	1.4%	0.82 [0.15 , 4.40]
BrighTNess comparison 2 (2)	-0.462035	0.331456	160	79	9.1%	0.63 [0.33 , 1.21]
CALGB 40603 (3)	-0.116534	0.186911	225	218	28.5%	0.89 [0.62 , 1.28]
GeparSixto (4)	-0.510826	0.319588	158	157	9.7%	0.60 [0.32 , 1.12]
Subtotal (95% CI)			**896**	**571**	**49.4%**	**0.75 [0.57 , 0.99]**
Heterogeneity: Chi² = 4.09, df = 4 (P = 0.39); I² = 2%						
Test for overall effect: Z = 2.04 (P = 0.04)						
8.2.2 Different backbone						
ADAPT-TN (5)	-1.139434	0.349056	154	182	8.2%	0.32 [0.16 , 0.63]
Li 2020 (6)	-1.966113	0.668645	70	73	2.2%	0.14 [0.04 , 0.52]
Nasr 2015 (7)	-0.248461	0.280263	78	80	12.7%	0.78 [0.45 , 1.35]
NeoCART (8)	-0.040822	0.821693	44	44	1.5%	0.96 [0.19 , 4.81]
PATTERN (9)	-0.34249	0.272033	325	322	13.4%	0.71 [0.42 , 1.21]
Zhang 2016 (10)	-0.446287	0.479853	43	42	4.3%	0.64 [0.25 , 1.64]
Zheng 2022 (11)	-0.139262	0.344804	154	154	8.4%	0.87 [0.44 , 1.71]
Subtotal (95% CI)			**868**	**897**	**50.6%**	**0.62 [0.47 , 0.81]**
Heterogeneity: Chi² = 10.71, df = 6 (P = 0.10); I² = 44%						
Test for overall effect: Z = 3.46 (P = 0.0005)						
Total (95% CI)			**1764**	**1468**	**100.0%**	**0.68 [0.56 , 0.82]**
Heterogeneity: Chi² = 15.76, df = 11 (P = 0.15); I² = 30%						
Test for overall effect: Z = 3.90 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%						



Footnotes

(1) Median follow-up 6.6 years
(2) Median follow-up 4.5 years
(3) Median follow-up 7.9 years
(4) Median follow-up 47.3 months
(5) Median follow-up 36 months
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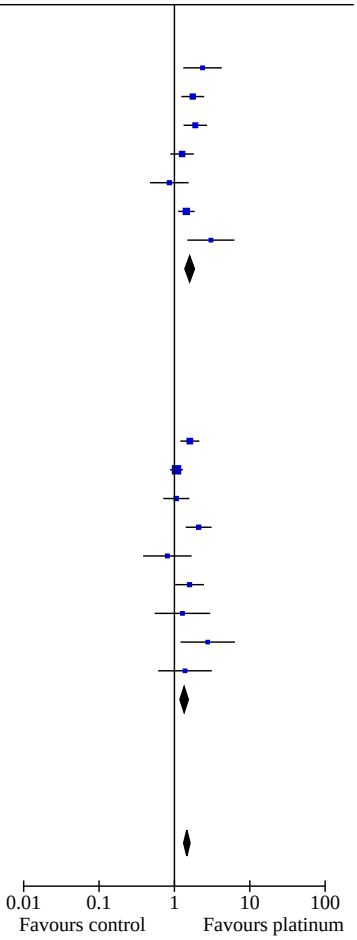
(7) Median follow-up 52 months
(8) Median follow-up 37 months
(9) Median follow-up 62 months
(10) Median follow-up 55 months
(11) Median follow-up 97.6 months

Analysis 8.3. Comparison 8: Same backbone chemotherapy with or without platinum, Outcome 3: Pathological complete response

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 Same backbone						
Ando 2014	23	37	10	38	2.3%	2.36 [1.31 , 4.25]
BrighTNess comparison 1	168	316	24	79	8.8%	1.75 [1.23 , 2.48]
BrighTNess comparison 2	92	160	24	79	7.3%	1.89 [1.32 , 2.71]
CALGB 40603	54	221	41	212	9.5%	1.26 [0.88 , 1.81]
GEICAM 2006-03	14	47	16	46	3.7%	0.86 [0.47 , 1.55]
GeparSixto	84	158	58	157	13.3%	1.44 [1.12 , 1.85]
Wu 2018	24	62	8	63	1.8%	3.05 [1.48 , 6.26]
Subtotal (95% CI)		**1001**		**674**	**46.6%**	**1.59 [1.38 , 1.84]**
Total events:	459		181			
Heterogeneity: Chi² = 12.47, df = 6 (P = 0.05); I² = 52%						
Test for overall effect: Z = 6.26 (P < 0.00001)						
8.3.2 Different backbone						
ADAPT-TN	67	146	51	178	10.5%	1.60 [1.20 , 2.14]
GeparOcto	105	203	97	200	22.3%	1.07 [0.88 , 1.30]
GeparOLA	16	27	28	50	4.5%	1.06 [0.71 , 1.58]
Gigolaeva 2019	31	62	31	130	4.6%	2.10 [1.41 , 3.11]
INFORM	10	44	11	39	2.7%	0.81 [0.38 , 1.69]
NeoCART	27	44	17	44	3.9%	1.59 [1.02 , 2.47]
TBCRC 030	11	72	8	67	1.9%	1.28 [0.55 , 2.99]
Zhang 2016	17	44	6	43	1.4%	2.77 [1.21 , 6.35]
Zhao 2014	10	38	8	42	1.7%	1.38 [0.61 , 3.14]
Subtotal (95% CI)		**680**		**793**	**53.4%**	**1.35 [1.18 , 1.53]**
Total events:	294		257			
Heterogeneity: Chi² = 18.38, df = 8 (P = 0.02); I² = 56%						
Test for overall effect: Z = 4.55 (P < 0.00001)						
Total (95% CI)		**1681**		**1467**	**100.0%**	**1.46 [1.33 , 1.61]**
Total events:	753		438			
Heterogeneity: Chi² = 34.51, df = 15 (P = 0.003); I² = 57%						
Test for overall effect: Z = 7.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.91, df = 1 (P = 0.09), I² = 65.7%						



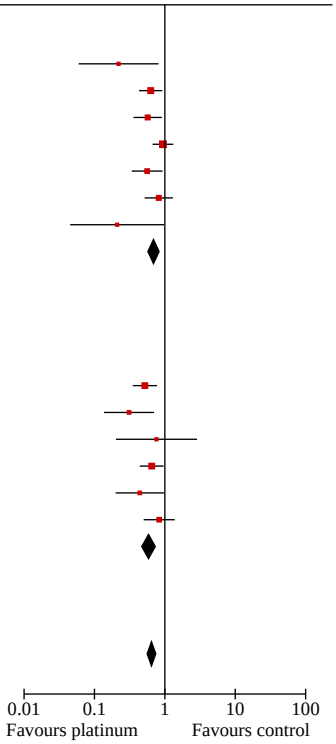
Comparison 9. Anthracycline content of chemotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Disease-free survival	13	3347	Hazard Ratio (IV, Fixed, 95% CI)	0.65 [0.56, 0.74]
9.1.1 Anthracycline-containing platinum	7	1740	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.57, 0.83]
9.1.2 Anthracycline-free platinum	6	1607	Hazard Ratio (IV, Fixed, 95% CI)	0.59 [0.47, 0.73]
9.2 Overall survival	12	3229	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.58, 0.83]
9.2.1 Anthracycline-containing platinum	6	1622	Hazard Ratio (IV, Fixed, 95% CI)	0.77 [0.61, 0.96]
9.2.2 Anthracycline-free platinum	6	1607	Hazard Ratio (IV, Fixed, 95% CI)	0.57 [0.41, 0.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Pathological complete response	16	3148	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.33, 1.61]
9.3.1 Anthracycline-containing platinum	10	2347	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.29, 1.61]
9.3.2 Anthracycline-free platinum	6	801	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.24, 1.89]

Analysis 9.1. Comparison 9: Anthracycline content of chemotherapy, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
9.1.1 Anthracycline-containing platinum						
Ando 2014 (1)	-1.514128	0.667094	37	28	1.2%	0.22 [0.06 , 0.81]
BrighTNess comparison 1 (2)	-0.462035	0.194031	316	79	13.7%	0.63 [0.43 , 0.92]
BrighTNess comparison 2 (2)	-0.562119	0.236571	160	79	9.2%	0.57 [0.36 , 0.91]
CALGB 40603 (3)	-0.061875	0.17299	225	218	17.2%	0.94 [0.67 , 1.32]
GeparSixto (4)	-0.579818	0.256698	158	157	7.8%	0.56 [0.34 , 0.93]
Nasr 2015 (5)	-0.198451	0.235707	78	80	9.3%	0.82 [0.52 , 1.30]
Wu 2018 (6)	-1.560648	0.783339	62	63	0.8%	0.21 [0.05 , 0.97]
Subtotal (95% CI)			**1036**	**704**	**59.3%**	**0.69 [0.57 , 0.83]**
Heterogeneity: Chi² = 10.51, df = 6 (P = 0.10); I² = 43%						
Test for overall effect: Z = 3.98 (P < 0.0001)						
9.1.2 Anthracycline-free platinum						
ADAPT-TN (7)	-0.653926	0.201141	154	182	12.8%	0.52 [0.35 , 0.77]
Li 2020 (8)	-1.171183	0.417558	70	73	3.0%	0.31 [0.14 , 0.70]
NeoCART (9)	-0.274437	0.67686	44	44	1.1%	0.76 [0.20 , 2.86]
PATTERN (10)	-0.430783	0.199024	325	322	13.0%	0.65 [0.44 , 0.96]
Zhang 2016 (11)	-0.820981	0.402808	43	42	3.2%	0.44 [0.20 , 0.97]
Zheng 2022 (12)	-0.18633	0.258992	154	154	7.7%	0.83 [0.50 , 1.38]
Subtotal (95% CI)			**790**	**817**	**40.7%**	**0.59 [0.47 , 0.73]**
Heterogeneity: Chi² = 5.41, df = 5 (P = 0.37); I² = 8%						
Test for overall effect: Z = 4.75 (P < 0.00001)						
Total (95% CI)			**1826**	**1521**	**100.0%**	**0.65 [0.56 , 0.74]**
Heterogeneity: Chi² = 17.16, df = 12 (P = 0.14); I² = 30%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.24, df = 1 (P = 0.27), I² = 19.3%						

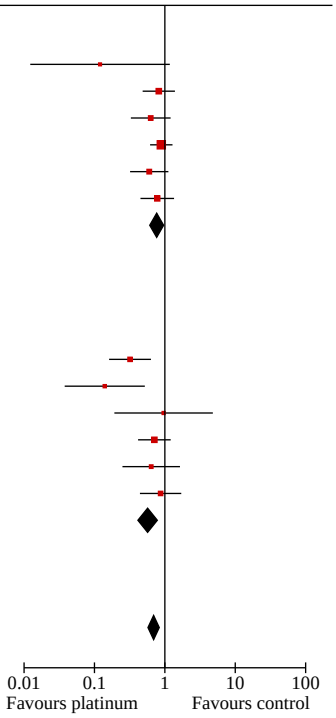


Footnotes

(1) Median follow-up 6.6 years
(2) Median follow-up 4.5 years
(3) Median follow-up 7.9 years
(4) Median follow-up 47.3 months
(5) Median follow-up 52 months
(6) Median follow-up not reported
(7) Median follow-up 36 months
(8) Median follow-up 57.3 months
(9) Median follow-up 37 months
(10) Median follow-up 62 months
(11) Median follow-up 55 months. Included relapse events only
(12) Median follow-up 97.6 months

Analysis 9.2. Comparison 9: Anthracycline content of chemotherapy, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
9.2.1 Anthracycline-containing platinum						
Ando 2014 (1)	-2.120264	1.164396	37	38	0.7%	0.12 [0.01 , 1.18]
BrighTNess comparison 1 (2)	-0.198451	0.269406	316	79	12.2%	0.82 [0.48 , 1.39]
BrighTNess comparison 2 (2)	-0.462035	0.331456	160	79	8.1%	0.63 [0.33 , 1.21]
CALGB 40603 (3)	-0.116534	0.186911	225	218	25.3%	0.89 [0.62 , 1.28]
GeparSixto (4)	-0.510826	0.319588	158	154	8.7%	0.60 [0.32 , 1.12]
Nasr 2015 (5)	-0.248461	0.280263	78	80	11.3%	0.78 [0.45 , 1.35]
Subtotal (95% CI)			**974**	**648**	**66.2%**	**0.77 [0.61 , 0.96]**
Heterogeneity: Chi² = 4.18, df = 5 (P = 0.52); I² = 0%						
Test for overall effect: Z = 2.31 (P = 0.02)						
9.2.2 Anthracycline-free platinum						
ADAPT-TN (6)	-1.139434	0.349056	154	182	7.3%	0.32 [0.16 , 0.63]
Li 2020 (7)	-1.966113	0.668645	70	73	2.0%	0.14 [0.04 , 0.52]
NeoCART (8)	-0.040822	0.821693	44	44	1.3%	0.96 [0.19 , 4.81]
PATTERN (9)	-0.34249	0.272033	325	322	12.0%	0.71 [0.42 , 1.21]
Zhang 2016 (10)	-0.446287	0.479853	43	42	3.8%	0.64 [0.25 , 1.64]
Zheng 2022 (11)	-0.139262	0.344804	154	154	7.4%	0.87 [0.44 , 1.71]
Subtotal (95% CI)			**790**	**817**	**33.8%**	**0.57 [0.41 , 0.78]**
Heterogeneity: Chi² = 9.76, df = 5 (P = 0.08); I² = 49%						
Test for overall effect: Z = 3.49 (P = 0.0005)						
Total (95% CI)			**1764**	**1465**	**100.0%**	**0.69 [0.58 , 0.83]**
Heterogeneity: Chi² = 16.16, df = 11 (P = 0.14); I² = 32%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
Test for subgroup differences: Chi² = 2.22, df = 1 (P = 0.14), I² = 55.0%						



Footnotes

(1) Median follow-up 6.6 years
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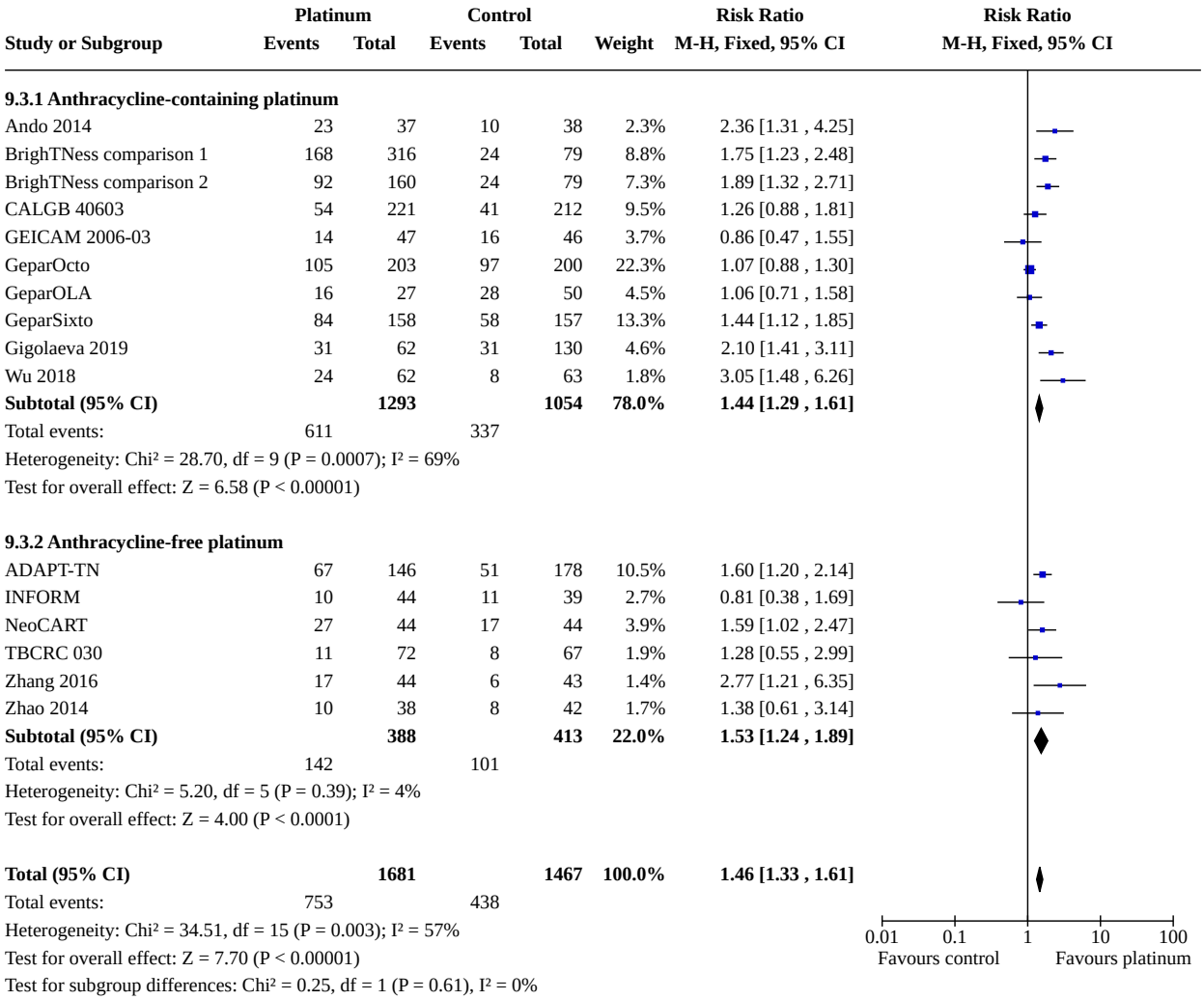
(3) Median follow-up 7.9 years
(4) Median follow-up 47.3 months
(5) Median follow-up 52 months
(6) Median follow-up 36 months
(7) Median follow-up 57.3 months
(8) Median follow-up 37 months
(9) Median follow-up 62 months
(10) Median follow-up 55 months
(11) Median follow-up 97.6 months

Analysis 9.3. Comparison 9: Anthracycline content of chemotherapy, Outcome 3: Pathological complete response



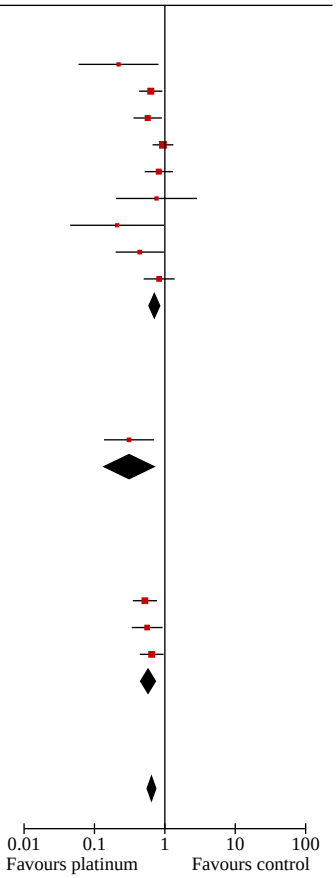
Comparison 10. Schedule of platinum agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Disease-free survival	13	3347	Hazard Ratio (IV, Fixed, 95% CI)	0.65 [0.56, 0.74]
10.1.1 3-weekly platinum	9	1906	Hazard Ratio (IV, Fixed, 95% CI)	0.71 [0.59, 0.85]
10.1.2 2-weekly platinum	1	143	Hazard Ratio (IV, Fixed, 95% CI)	0.31 [0.14, 0.70]
10.1.3 Weekly platinum	3	1298	Hazard Ratio (IV, Fixed, 95% CI)	0.58 [0.45, 0.74]
10.2 Overall survival	12	3229	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.58, 0.83]
10.2.1 3-weekly platinum	8	1791	Hazard Ratio (IV, Fixed, 95% CI)	0.79 [0.64, 0.99]
10.2.2 2-weekly platinum	1	143	Hazard Ratio (IV, Fixed, 95% CI)	0.14 [0.04, 0.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2.3 Weekly platinum	3	1295	Hazard Ratio (IV, Fixed, 95% CI)	0.55 [0.39, 0.78]
10.3 Pathological complete response	16	3148	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.33, 1.61]
10.3.1 3-weekly platinum	11	1837	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.38, 1.87]
10.3.2 Weekly platinum	5	1311	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.19, 1.52]

Analysis 10.1. Comparison 10: Schedule of platinum agent, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
10.1.1 3-weekly platinum						
Ando 2014 (1)	-1.514128	0.667094	37	28	1.2%	0.22 [0.06 , 0.81]
BrighTNess comparison 1 (2)	-0.462035	0.194031	316	79	13.7%	0.63 [0.43 , 0.92]
BrighTNess comparison 2 (2)	-0.562119	0.236571	160	79	9.2%	0.57 [0.36 , 0.91]
CALGB 40603 (3)	-0.061875	0.17299	225	218	17.2%	0.94 [0.67 , 1.32]
Nasr 2015 (4)	-0.198451	0.235707	78	80	9.3%	0.82 [0.52 , 1.30]
NeoCART (5)	-0.274437	0.67686	44	44	1.1%	0.76 [0.20 , 2.86]
Wu 2018 (6)	-1.560648	0.783339	62	63	0.8%	0.21 [0.05 , 0.97]
Zhang 2016 (7)	-0.820981	0.402808	43	42	3.2%	0.44 [0.20 , 0.97]
Zheng 2022 (8)	-0.18633	0.258992	154	154	7.7%	0.83 [0.50 , 1.38]
Subtotal (95% CI)			**1119**	**787**	**63.4%**	**0.71 [0.59 , 0.85]**
Heterogeneity: Chi² = 11.53, df = 8 (P = 0.17); I² = 31%						
Test for overall effect: Z = 3.82 (P = 0.0001)						
10.1.2 2-weekly platinum						
Li 2020 (9)	-1.171183	0.417558	70	73	3.0%	0.31 [0.14 , 0.70]
Subtotal (95% CI)			**70**	**73**	**3.0%**	**0.31 [0.14 , 0.70]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.80 (P = 0.005)						
10.1.3 Weekly platinum						
ADAPT-TN (10)	-0.653926	0.201141	154	182	12.8%	0.52 [0.35 , 0.77]
GeparSixto (11)	-0.579818	0.256698	158	157	7.8%	0.56 [0.34 , 0.93]
PATTERN (12)	-0.430783	0.199024	325	322	13.0%	0.65 [0.44 , 0.96]
Subtotal (95% CI)			**637**	**661**	**33.6%**	**0.58 [0.45 , 0.74]**
Heterogeneity: Chi² = 0.64, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
Total (95% CI)			**1826**	**1521**	**100.0%**	**0.65 [0.56 , 0.74]**
Heterogeneity: Chi² = 17.16, df = 12 (P = 0.14); I² = 30%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.98, df = 2 (P = 0.08), I² = 59.9%						

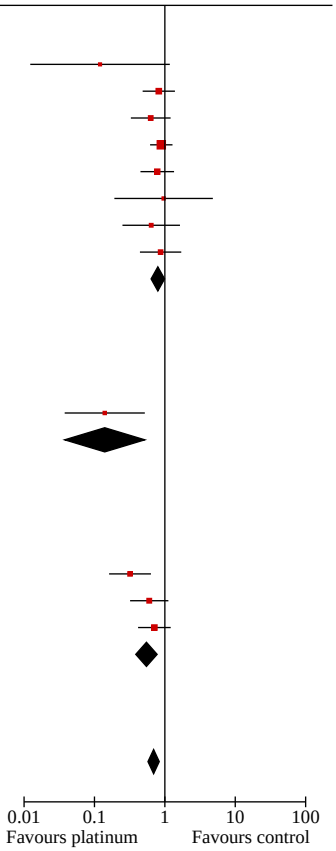


Footnotes

(1) Median follow-up 6.6 years
(2) Median follow-up 4.5 years
(3) Median follow-up 7.9 years
(4) Median follow-up 52 months
(5) Median follow-up 37 months
(6) Median follow-up not reported
(7) Median follow-up 55 months. Included relapse events only
(8) Median follow-up 97.6 months
(9) Median follow-up 57.3 months
(10) Median follow-up 36 months
(11) Median follow-up 47.3 months
(12) Median follow-up 62 months

Analysis 10.2. Comparison 10: Schedule of platinum agent, Outcome 2: Overall survival

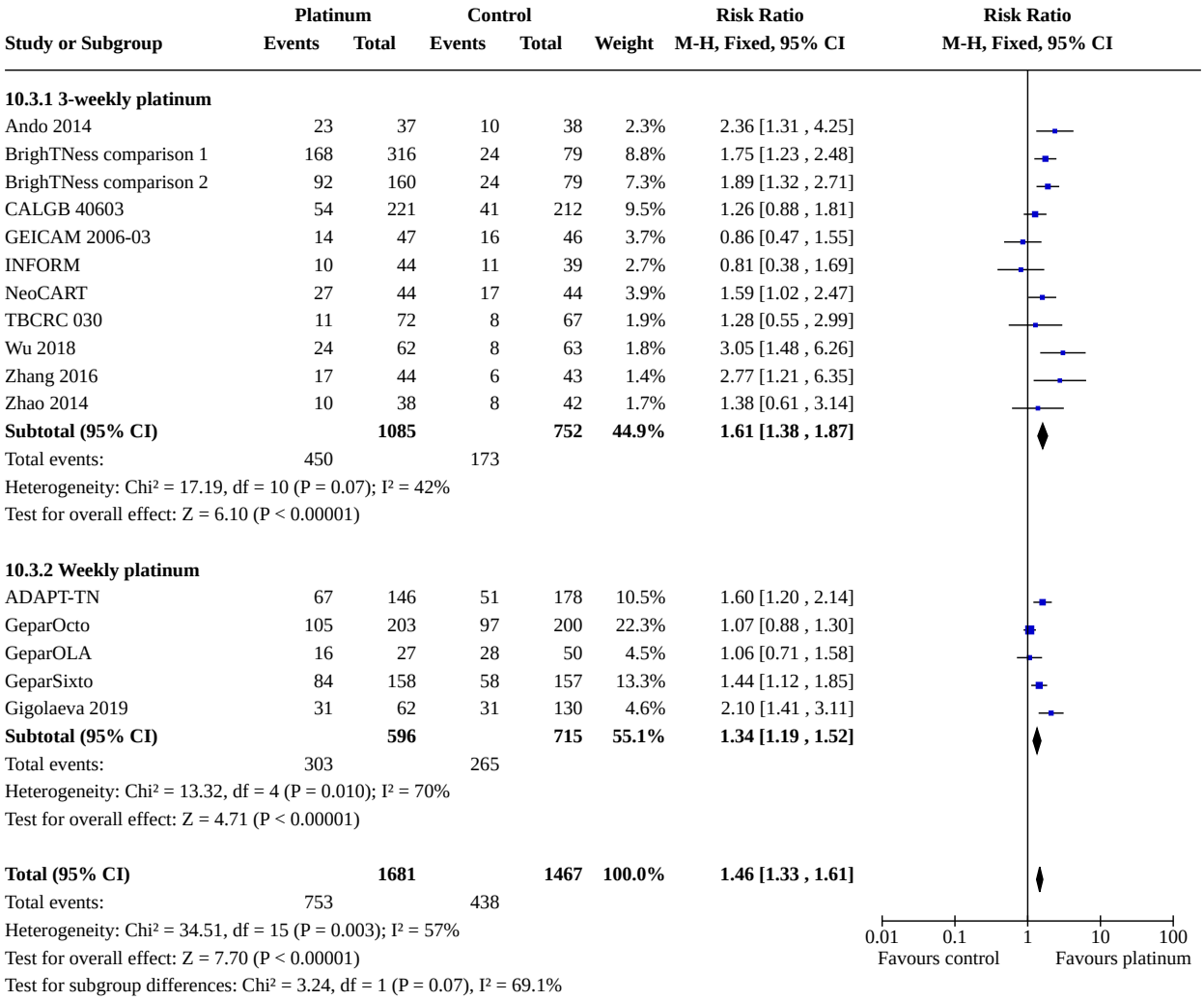
Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
10.2.1 3-weekly platinum						
Ando 2014 (1)	-2.120264	1.164396	37	38	0.7%	0.12 [0.01 , 1.18]
BrighTNess comparison 1 (2)	-0.198451	0.269406	316	79	12.2%	0.82 [0.48 , 1.39]
BrighTNess comparison 2 (2)	-0.462035	0.331456	160	79	8.1%	0.63 [0.33 , 1.21]
CALGB 40603 (3)	-0.116534	0.186911	225	218	25.3%	0.89 [0.62 , 1.28]
Nasr 2015 (4)	-0.248461	0.280263	78	80	11.3%	0.78 [0.45 , 1.35]
NeoCART (5)	-0.040822	0.821693	44	44	1.3%	0.96 [0.19 , 4.81]
Zhang 2016 (6)	-0.446287	0.479853	43	42	3.8%	0.64 [0.25 , 1.64]
Zheng 2022 (7)	-0.139262	0.344804	154	154	7.4%	0.87 [0.44 , 1.71]
Subtotal (95% CI)			**1057**	**734**	**70.1%**	**0.79 [0.64 , 0.99]**
Heterogeneity: Chi² = 3.84, df = 7 (P = 0.80); I² = 0%						
Test for overall effect: Z = 2.04 (P = 0.04)						
10.2.2 2-weekly platinum						
Li 2020 (8)	-1.966113	0.668645	70	73	2.0%	0.14 [0.04 , 0.52]
Subtotal (95% CI)			**70**	**73**	**2.0%**	**0.14 [0.04 , 0.52]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.94 (P = 0.003)						
10.2.3 Weekly platinum						
ADAPT-TN (9)	-1.139434	0.349056	154	182	7.3%	0.32 [0.16 , 0.63]
GeparSixto (10)	-0.510826	0.319588	158	154	8.7%	0.60 [0.32 , 1.12]
PATTERN (11)	-0.34249	0.272033	325	322	12.0%	0.71 [0.42 , 1.21]
Subtotal (95% CI)			**637**	**658**	**27.9%**	**0.55 [0.39 , 0.78]**
Heterogeneity: Chi² = 3.36, df = 2 (P = 0.19); I² = 41%						
Test for overall effect: Z = 3.38 (P = 0.0007)						
Total (95% CI)			**1764**	**1465**	**100.0%**	**0.69 [0.58 , 0.83]**
Heterogeneity: Chi² = 16.16, df = 11 (P = 0.14); I² = 32%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
Test for subgroup differences: Chi² = 8.96, df = 2 (P = 0.01), I² = 77.7%						



Footnotes

(1) Median follow-up 6.6 years
(2) Median follow-up 4.5 years
(3) Median follow-up 7.9 years
(4) Median follow-up 52 months
(5) Median follow-up 37 months
(6) Median follow-up 55 months
(7) Median follow-up 97.6 months
(8) Median follow-up 57.3 months
(9) Median follow-up 36 months
(10) Median follow-up 47.3 months
(11) Median follow-up 62 months

Analysis 10.3. Comparison 10: Schedule of platinum agent, Outcome 3: Pathological complete response



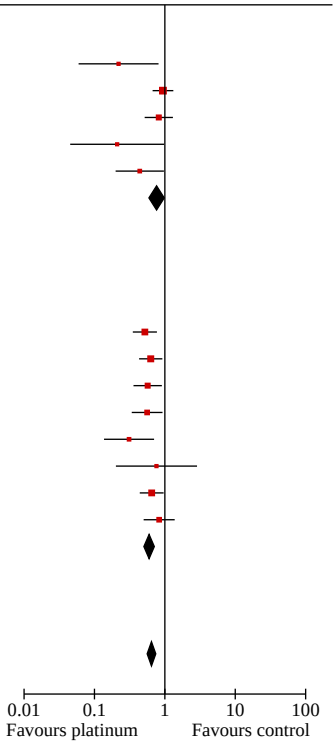
Comparison 11. Triple negative definition – hormone receptor immunohistochemistry cut-off

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Disease-free survival	13	3347	Hazard Ratio (IV, Fixed, 95% CI)	0.65 [0.56, 0.74]
11.1.1 Hormone receptor > 1% or not defined	5	876	Hazard Ratio (IV, Fixed, 95% CI)	0.76 [0.59, 0.98]
11.1.2 Hormone receptor < 1%	8	2471	Hazard Ratio (IV, Fixed, 95% CI)	0.60 [0.50, 0.71]
11.2 Overall survival	12	3229	Hazard Ratio (IV, Fixed, 95% CI)	0.69 [0.58, 0.83]
11.2.1 Hormone receptor > 1% or not defined	4	761	Hazard Ratio (IV, Fixed, 95% CI)	0.81 [0.60, 1.07]
11.2.2 Hormone receptor < 1%	8	2468	Hazard Ratio (IV, Fixed, 95% CI)	0.62 [0.49, 0.79]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Pathological complete response	16	3148	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.33, 1.61]
11.3.1 Hormone receptor > 1% or not defined	9	1307	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.30, 1.90]
11.3.2 Hormone receptor < 1%	7	1841	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.26, 1.58]

Analysis 11.1. Comparison 11: Triple negative definition – hormone receptor immunohistochemistry cut-off, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
11.1.1 Hormone receptor > 1% or not defined						
Ando 2014 (1)	-1.514128	0.667094	37	28	1.2%	0.22 [0.06 , 0.81]
CALGB 40603 (2)	-0.061875	0.17299	225	218	17.2%	0.94 [0.67 , 1.32]
Nasr 2015 (3)	-0.198451	0.235707	78	80	9.3%	0.82 [0.52 , 1.30]
Wu 2018 (4)	-1.560648	0.783339	62	63	0.8%	0.21 [0.05 , 0.97]
Zhang 2016 (5)	-0.820981	0.402808	43	42	3.2%	0.44 [0.20 , 0.97]
Subtotal (95% CI)			**445**	**431**	**31.7%**	**0.76 [0.59 , 0.98]**
Heterogeneity: Chi² = 9.60, df = 4 (P = 0.05); I² = 58%						
Test for overall effect: Z = 2.12 (P = 0.03)						
11.1.2 Hormone receptor < 1%						
ADAPT-TN (6)	-0.653926	0.201141	154	182	12.8%	0.52 [0.35 , 0.77]
BrighTNess comparison 1 (7)	-0.462035	0.194031	316	79	13.7%	0.63 [0.43 , 0.92]
BrighTNess comparison 2 (7)	-0.562119	0.236571	160	79	9.2%	0.57 [0.36 , 0.91]
GeparSixto (8)	-0.579818	0.256698	158	157	7.8%	0.56 [0.34 , 0.93]
Li 2020 (9)	-1.171183	0.417558	70	73	3.0%	0.31 [0.14 , 0.70]
NeoCART (10)	-0.274437	0.67686	44	44	1.1%	0.76 [0.20 , 2.86]
PATTERN (11)	-0.430783	0.199024	325	322	13.0%	0.65 [0.44 , 0.96]
Zheng 2022 (12)	-0.18633	0.258992	154	154	7.7%	0.83 [0.50 , 1.38]
Subtotal (95% CI)			**1381**	**1090**	**68.3%**	**0.60 [0.50 , 0.71]**
Heterogeneity: Chi² = 5.04, df = 7 (P = 0.66); I² = 0%						
Test for overall effect: Z = 5.93 (P < 0.00001)						
Total (95% CI)			**1826**	**1521**	**100.0%**	**0.65 [0.56 , 0.74]**
Heterogeneity: Chi² = 17.16, df = 12 (P = 0.14); I² = 30%						
Test for overall effect: Z = 6.10 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.51, df = 1 (P = 0.11), I² = 60.2%						

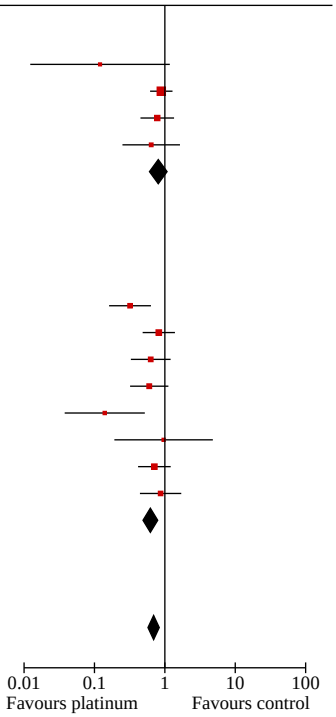


Footnotes

(1) Median follow-up 6.6 years
(2) Median follow-up 7.9 years
(3) Median follow-up 52 months
(4) Median follow-up not reported
(5) Median follow-up 55 months. Included relapse events only
(6) Median follow-up 36 months
(7) Median follow-up 4.5 years
(8) Median follow-up 47.3 months
(9) Median follow-up 57.3 months
(10) Median follow-up 37 months
(11) Median follow-up 62 months
(12) Median follow-up 97.6 months

Analysis 11.2. Comparison 11: Triple negative definition – hormone receptor immunohistochemistry cut-off, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
11.2.1 Hormone receptor > 1% or not defined						
Ando 2014 (1)	-2.120264	1.164396	37	38	0.7%	0.12 [0.01 , 1.18]
CALGB 40603 (2)	-0.116534	0.186911	225	218	25.3%	0.89 [0.62 , 1.28]
Nasr 2015 (3)	-0.248461	0.280263	78	80	11.3%	0.78 [0.45 , 1.35]
Zhang 2016 (4)	-0.446287	0.479853	43	42	3.8%	0.64 [0.25 , 1.64]
Subtotal (95% CI)			**383**	**378**	**41.1%**	**0.81 [0.60 , 1.07]**
Heterogeneity: Chi² = 3.20, df = 3 (P = 0.36); I² = 6%						
Test for overall effect: Z = 1.47 (P = 0.14)						
11.2.2 Hormone receptor < 1%						
ADAPT-TN (5)	-1.139434	0.349056	154	182	7.3%	0.32 [0.16 , 0.63]
BrighTNess comparison 1 (6)	-0.198451	0.269406	316	79	12.2%	0.82 [0.48 , 1.39]
BrighTNess comparison 2 (6)	-0.462035	0.331456	160	79	8.1%	0.63 [0.33 , 1.21]
GeparSixto (7)	-0.510826	0.319588	158	154	8.7%	0.60 [0.32 , 1.12]
Li 2020 (8)	-1.966113	0.668645	70	73	2.0%	0.14 [0.04 , 0.52]
NeoCART (9)	-0.040822	0.821693	44	44	1.3%	0.96 [0.19 , 4.81]
PATTERN (10)	-0.34249	0.272033	325	322	12.0%	0.71 [0.42 , 1.21]
Zheng 2022 (11)	-0.139262	0.344804	154	154	7.4%	0.87 [0.44 , 1.71]
Subtotal (95% CI)			**1381**	**1087**	**58.9%**	**0.62 [0.49 , 0.79]**
Heterogeneity: Chi² = 11.13, df = 7 (P = 0.13); I² = 37%						
Test for overall effect: Z = 3.87 (P = 0.0001)						
Total (95% CI)			**1764**	**1465**	**100.0%**	**0.69 [0.58 , 0.83]**
Heterogeneity: Chi² = 16.16, df = 11 (P = 0.14); I² = 32%						
Test for overall effect: Z = 3.91 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.83, df = 1 (P = 0.18), I² = 45.5%						

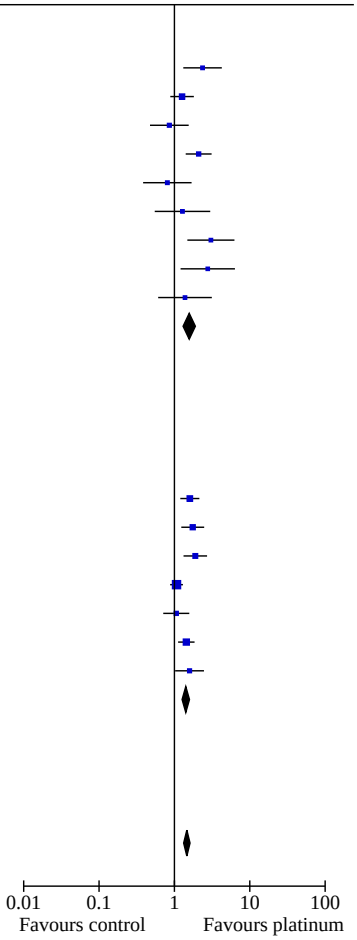


Footnotes

(1) Median follow-up 6.6 years
(2) Median follow-up 7.9 years
(3) Median follow-up 52 months
(4) Median follow-up 55 months
(5) Median follow-up 36 months
(6) Median follow-up 4.5 years
(7) Median follow-up 47.3 months
(8) Median follow-up 57.3 months
(9) Median follow-up 37 months
(10) Median follow-up 62 months
(11) Median follow-up 97.6 months

Analysis 11.3. Comparison 11: Triple negative definition – hormone receptor immunohistochemistry cut-off, Outcome 3: Pathological complete response

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.3.1 Hormone receptor > 1% or not defined						
Ando 2014	23	37	10	38	2.3%	2.36 [1.31 , 4.25]
CALGB 40603	54	221	41	212	9.5%	1.26 [0.88 , 1.81]
GEICAM 2006-03	14	47	16	46	3.7%	0.86 [0.47 , 1.55]
Gigolaeva 2019	31	62	31	130	4.6%	2.10 [1.41 , 3.11]
INFORM	10	44	11	39	2.7%	0.81 [0.38 , 1.69]
TBCRC 030	11	72	8	67	1.9%	1.28 [0.55 , 2.99]
Wu 2018	24	62	8	63	1.8%	3.05 [1.48 , 6.26]
Zhang 2016	17	44	6	43	1.4%	2.77 [1.21 , 6.35]
Zhao 2014	10	38	8	42	1.7%	1.38 [0.61 , 3.14]
Subtotal (95% CI)		**627**		**680**	**29.5%**	**1.57 [1.30 , 1.90]**
Total events:	194		139			
Heterogeneity: Chi² = 17.85, df = 8 (P = 0.02); I² = 55%						
Test for overall effect: Z = 4.74 (P < 0.00001)						
11.3.2 Hormone receptor < 1%						
ADAPT-TN	67	146	51	178	10.5%	1.60 [1.20 , 2.14]
BrighTNess comparison 1	168	316	24	79	8.8%	1.75 [1.23 , 2.48]
BrighTNess comparison 2	92	160	24	79	7.3%	1.89 [1.32 , 2.71]
GeparOcto	105	203	97	200	22.3%	1.07 [0.88 , 1.30]
GeparOLA	16	27	28	50	4.5%	1.06 [0.71 , 1.58]
GeparSixto	84	158	58	157	13.3%	1.44 [1.12 , 1.85]
NeoCART	27	44	17	44	3.9%	1.59 [1.02 , 2.47]
Subtotal (95% CI)		**1054**		**787**	**70.5%**	**1.42 [1.26 , 1.58]**
Total events:	559		299			
Heterogeneity: Chi² = 15.04, df = 6 (P = 0.02); I² = 60%						
Test for overall effect: Z = 6.06 (P < 0.00001)						
Total (95% CI)		**1681**		**1467**	**100.0%**	**1.46 [1.33 , 1.61]**
Total events:	753		438			
Heterogeneity: Chi² = 34.51, df = 15 (P = 0.003); I² = 57%						
Test for overall effect: Z = 7.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.89, df = 1 (P = 0.35), I² = 0%						



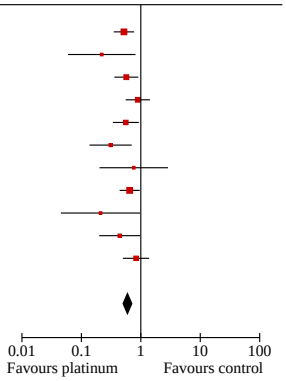
Comparison 12. Platinum-based chemotherapy versus platinum free chemotherapy without Nasr 2015 or BrigTNess comparison 1, and using bevacizumab-free CALGB

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Disease-free survival	11	2572	Hazard Ratio (IV, Fixed, 95% CI)	0.60 [0.50, 0.71]
12.2 Overall survival	10	2454	Hazard Ratio (IV, Fixed, 95% CI)	0.64 [0.52, 0.79]
12.3 Pathological complete response	15	2959	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.35, 1.63]

Analysis 12.1. Comparison 12: Platinum-based chemotherapy versus platinum free chemotherapy without Nasr 2015 or BrigTNess comparison 1, and using bevacizumab-free CALGB, Outcome 1: Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
ADAPT-TN (1)	-0.653926	0.201141	154	182	18.6%	0.52 [0.35 , 0.77]
Ando 2014 (2)	-1.514128	0.667094	37	28	1.7%	0.22 [0.06 , 0.81]
BrighTNess comparison 2 (3)	-0.562119	0.236571	160	79	13.4%	0.57 [0.36 , 0.91]
CALGB 40603 – comparison 1 (without bevacizumab) (4)	-0.116534	0.240164	113	108	13.0%	0.89 [0.56 , 1.43]
GeparSixto (5)	-0.579818	0.256698	158	157	11.4%	0.56 [0.34 , 0.93]
Li 2020 (6)	-1.171183	0.417558	70	73	4.3%	0.31 [0.14 , 0.70]
NeoCART (7)	-0.274437	0.67686	44	44	1.6%	0.76 [0.20 , 2.86]
PATTERN (8)	-0.430783	0.199024	325	322	19.0%	0.65 [0.44 , 0.96]
Wu 2018 (9)	-1.560648	0.783339	62	63	1.2%	0.21 [0.05 , 0.97]
Zhang 2016 (10)	-0.820981	0.402808	43	42	4.6%	0.44 [0.20 , 0.97]
Zheng 2022 (11)	-0.18633	0.258992	154	154	11.2%	0.83 [0.50 , 1.38]
Total (95% CI)			**1320**	**1252**	**100.0%**	**0.60 [0.50 , 0.71]**

Heterogeneity: Chi² = 12.32, df = 10 (P = 0.26); I² = 19%
Test for overall effect: Z = 5.98 (P < 0.00001)
Test for subgroup differences: Not applicable

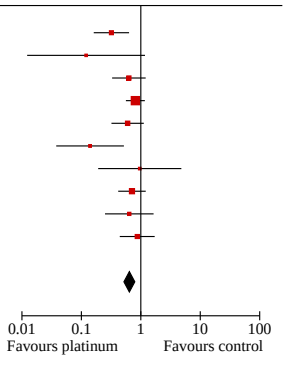


Footnotes
(1) Median follow-up 36 months
(2) Median follow-up 6.6 years
(3) Median follow-up 4.5 years
(4) Median follow-up 7.9 years
(5) Median follow-up 47.3 months
(6) Median follow-up 57.3 months
(7) Median follow-up 37 months
(8) Median follow-up 62 months
(9) Median follow-up not reported
(10) Median follow-up 55 months. Included relapse events only
(11) Median follow-up 97.6 months

Analysis 12.2. Comparison 12: Platinum-based chemotherapy versus platinum free chemotherapy without Nasr 2015 or BrigTNess comparison 1, and using bevacizumab-free CALGB, Outcome 2: Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Platinum Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
ADAPT-TN (1)	-1.139434	0.349056	154	182	9.5%	0.32 [0.16 , 0.63]
Ando 2014 (2)	-2.120264	1.164396	37	38	0.9%	0.12 [0.01 , 1.18]
BrighTNess comparison 2 (3)	-0.462035	0.331456	160	79	10.5%	0.63 [0.33 , 1.21]
CALGB 40603 – comparison 1 (without bevacizumab) (4)	-0.210721	0.18724	113	108	33.0%	0.81 [0.56 , 1.17]
GeparSixto (5)	-0.510826	0.319588	158	154	11.3%	0.60 [0.32 , 1.12]
Li 2020 (6)	-1.966113	0.668645	70	73	2.6%	0.14 [0.04 , 0.52]
NeoCART (7)	-0.040822	0.821693	44	44	1.7%	0.96 [0.19 , 4.81]
PATTERN (8)	-0.34249	0.272033	325	322	15.6%	0.71 [0.42 , 1.21]
Zhang 2016 (9)	-0.446287	0.479853	43	42	5.0%	0.64 [0.25 , 1.64]
Zheng 2022 (10)	-0.139262	0.344804	154	154	9.7%	0.87 [0.44 , 1.71]
Total (95% CI)			**1258**	**1196**	**100.0%**	**0.64 [0.52 , 0.79]**

Heterogeneity: Chi² = 13.98, df = 9 (P = 0.12); I² = 36%
Test for overall effect: Z = 4.12 (P < 0.0001)
Test for subgroup differences: Not applicable



Footnotes
(1) Median follow up 36 months
(2) Median follow-up 6.6 years
(3) Median follow-up 4.5 years
(4) Median follow-up 7.9 years
(5) Median follow-up 47.3 months
(6) Median follow-up 57.3 months
(7) Median follow-up 37 months
(8) Median follow-up 62 months
(9) Median follow-up 55 months
(10) Median follow-up 97.6 months

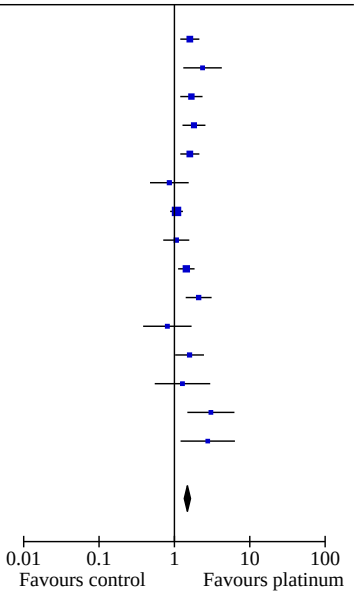
Analysis 12.3. Comparison 12: Platinum-based chemotherapy versus platinum free chemotherapy without Nasr 2015 or BrigTNess comparison 1, and using bevacizumab-free CALGB, Outcome 3: Pathological complete response

Study or Subgroup	Platinum Events	Platinum Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ADAPT-TN	67	146	51	178	10.5%	1.60 [1.20 , 2.14]
Ando 2014	23	37	10	38	2.3%	2.36 [1.31 , 4.25]
BrighTNess comparison 1	168	316	25	79	9.1%	1.68 [1.20 , 2.36]
BrighTNess comparison 2	92	160	25	79	7.6%	1.82 [1.28 , 2.58]
CALGB 40603	67	146	51	178	10.5%	1.60 [1.20 , 2.14]
GEICAM 2006-03	14	47	16	46	3.7%	0.86 [0.47 , 1.55]
GeparOcto	105	203	97	200	22.3%	1.07 [0.88 , 1.30]
GeparOLA	16	27	28	50	4.5%	1.06 [0.71 , 1.58]
GeparSixto	84	158	58	157	13.3%	1.44 [1.12 , 1.85]
Gigolaeva 2019	31	62	31	130	4.6%	2.10 [1.41 , 3.11]
INFORM	10	44	11	39	2.7%	0.81 [0.38 , 1.69]
NeoCART	27	44	17	44	3.9%	1.59 [1.02 , 2.47]
TBCRC 030	11	72	8	67	1.9%	1.28 [0.55 , 2.99]
Wu 2018	24	62	8	63	1.8%	3.05 [1.48 , 6.26]
Zhang 2016	17	44	6	43	1.4%	2.77 [1.21 , 6.35]
Total (95% CI)		**1568**		**1391**	**100.0%**	**1.49 [1.35 , 1.63]**
Total events:	756		442			

Heterogeneity: Chi² = 33.72, df = 14 (P = 0.002); I² = 58%

Test for overall effect: Z = 8.19 (P < 0.00001)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Summary of the included treatment comparisons

Trial	Year recruitment started	Intervention (platinum-containing)	Control	Platinum agent	Same backbone?	Adjuvant or neoadjuvant	Hormone receptor IHC cut-off
ADAPT-TN	2013	Nab-paclitaxel 125 mg/m^2 + carboplatin AUC2 days 1 and 8 every 3 weeks for 4 cycles	Nab-paclitaxel 125 mg/m^2 + gemcitabine 1000 mg/m^2 days 1 and 8 every 3 weeks for 4 cycles	Carboplatin AUC2 every week (days 1 and 8 every 21 days)	No	Neoadjuvant	< 1%
Ando 2014	2010	Carboplatin AUC5 every 3 weeks for 4 cycles + paclitaxel 80 mg/m^2 days 1, 8, 15 for 4 cycles, followed by 4 cycles of cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2 and fluorouracil 500 mg/m^2 every 3 weeks	Paclitaxel 80 mg/m^2 days 1, 8, 15 for 4 cycles followed by 4 cycles of cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2 and fluorouracil 500 mg/m^2 every 3 weeks	Carboplatin AUC5 every 3 weeks	Yes	Neoadjuvant	< 10%
BrighTNess comparison 1	2014	Paclitaxel 80 mg/m^2 weekly + carboplatin AUC6 every 3 weeks for 12 weeks + veliparib 50 mg twice a day, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles	Paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles	Carboplatin AUC6 every 3 weeks	Yes	Neoadjuvant	< 1%
BrighTNess comparison 2	2014	Paclitaxel 80 mg/m^2 weekly + carboplatin AUC6 every 3 weeks for 12 weeks, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles	Paclitaxel 80 mg/m^2 weekly for 12 weeks, followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles	Carboplatin AUC6 every 3 weeks	Yes	Neoadjuvant	< 1%
CALGB 40603	2009	Paclitaxel 80 mg/m^2 weekly + carboplatin AUC6 every 3 weeks for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles ± bevacizumab 10 mg/kg every 2 weeks for 9 cycles	Paclitaxel 80 mg/m^2 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles ± bevacizumab 10 mg/kg every 2 weeks for 9 cycles	Carboplatin AUC6 every 3 weeks	Yes	Neoadjuvant	< 10%

Table 1. Summary of the included treatment comparisons *(Continued)*

GEICAM 2006-03	2007	Epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by docetaxel 75 mg/m^2 + carboplatin AUC6 every 3 weeks for 4 cycles	Epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by docetaxel 75 mg/m^2 every 3 weeks for 4 cycles	Carboplatin AUC6 every 3 weeks	Yes	Neoadjuvant	Not described
GeparOcto	2014	Paclitaxel 80 mg/m^2 + non-pegylated liposomal doxorubicin 20 mg/m^2 + carboplatin AUC1.5 weekly for 18 weeks	Epirubicin 150 mg/m^2 + paclitaxel 225 mg/m^2 + cyclophosphamide 2000 mg/m^2 every 2 weeks for 3 cycles	Carboplatin AUC1.5 every week	No	Neoadjuvant	< 1%
GeparOLA	2016	Paclitaxel 80 mg/m^2 + carboplatin AUC2 weekly for 12 weeks followed by epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles	Paclitaxel 80 mg/m^2 weekly + olaparib 100 mg twice a day for 12 weeks followed by epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles	Carboplatin AUC2 every week	No	Neoadjuvant	< 1%
GeparSixto	2011	Carboplatin AUC2 or 1.5 + paclitaxel 80 mg/m^2 + non-pegylated liposomal doxorubicin 20 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks for 18 weeks	Paclitaxel 80 mg/m^2 + non-pegylated liposomal doxorubicin 20 mg/m^2 weekly + bevacizumab 15 mg/kg every 3 weeks for 18 weeks	Carboplatin AUC1.5 or 2 every week	Yes	Neoadjuvant	< 1%
Gigolaeva 2019	NR	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by carboplatin AUC2 weekly + eribulin 1.4 mg/m^2 or paclitaxel 175 mg/m^2 every 3 weeks for 12 weeks	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by paclitaxel 80 mg/m^2 for 12 weeks	Carboplatin AUC2 every week	No	Neoadjuvant	Not described
INFORM	2012	Cisplatin 75 mg/m^2 every 3 weeks for 4 cycles	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2–3 weeks for 4 cycles	Cisplatin 75 mg/m^2 every 3 weeks	No	Neoadjuvant	< 10%
I-SPY2	2010	Paclitaxel 80 mg/m^2 weekly + veliparib 50 mg twice daily + carboplatin AUC6 every 3 weeks for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophos-	Paclitaxel 80 mg/m^2 weekly for 12 weeks followed by doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles	Carboplatin AUC6 every 3 weeks	No	Neoadjuvant	< 5%

Table 1. Summary of the included treatment comparisons *(Continued)*

		phamide 600 mg/m^2 every 2 or 3 weeks for 4 cycles					
Li 2020	2011	Paclitaxel 150 mg/m^2 + carboplatin AUC3 every 2 weeks for 8 cycles	Epirubicin 80 mg/m^2 and cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles followed by paclitaxel 175 mg/m^2 every 2 weeks for 4 cycles	Carboplatin AUC3 every 2 weeks	No	Adjuvant	< 1%
Nasr 2015	2008	5-fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 every 3 weeks for 3 cycles then docetaxel 80 mg/m^2 + carboplatin AUC5 every 3 weeks for 3 cycles, followed by postoperative radiotherapy, followed by cyclophosphamide 50 mg daily and methotrexate 2.5 mg twice daily on days 1, 2 of each week for 1 year	5-fluorouracil 500 mg/m^2 + epirubicin 100 mg/m^2 + cyclophosphamide 500 mg/m^2 every 3 weeks for 3 cycles then docetaxel 80 mg/m^2 every 3 weeks for 3 cycles	Carboplatin AUC5 every 3 weeks	No	Adjuvant	Not described
NeoCART	2016	Docetaxel 75 mg/m^2 + carboplatin AUC6 every 3 weeks for 6 cycles	Epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles followed by docetaxel 100 mg/m^2 every 3 weeks for 4 cycles	Carboplatin AUC6 every 3 weeks	No	Neoadjuvant	< 1%
PATTERN	2011	Paclitaxel 80 mg/m^2 + carboplatin AUC2 days 1, 8, 15, every 28 days for 6 cycles	Cyclophosphamide 500 mg/m^2 + epirubicin 100 mg/m^2 + fluorouracil 500 mg/m^2 every 3 weeks for 3 cycles followed by docetaxel 100 mg/m^2 every 3 weeks for 3 cycles	Carboplatin AUC2 every week (days 1, 8, 15 every 28 days)	No	Adjuvant	< 1%
TBCRC 030	2014	Cisplatin 75 mg/m^2 every 3 weeks for 4 cycles	Doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 2 weeks for 4 cycles	Cisplatin 75 mg/m^2 every 3 weeks	No	Neoadjuvant	< 5%
Wu 2018	2014	Lobaplatin 30 mg/m^2 for 4 cycles + epirubicin 80 mg/m^2 + docetaxel 75 mg/m^2 every 3 weeks	Epirubicin 80 mg/m^2 for 4 cycles + docetaxel 75 mg/m^2 every 3 weeks presurgery and 2 cycles postsurgery	Lobaplatin 30 mg/m^2 every 3 weeks	Yes	Both	< 10%

Table 1. Summary of the included treatment comparisons *(Continued)*

		presurgery and 2 cycles post-surgery					
Zhang 2016	2006	Paclitaxel 175 mg/m^2 + carboplatin AUC5 every 3 weeks for 4–6 cycles	Epirubicin 75 mg/m^2 + paclitaxel 175 mg/m^2 every 3 weeks for 4–6 cycles	Carboplatin AUC5 every 3 weeks	No	Neoadjuvant	< 10%
Zhao 2014	Not provided in translation	Paclitaxel 175 mg/m^2 day 1, carboplatin AUC5 day 2, every 3 weeks for 2 cycles	Epirubicin 75 mg/m2 day 1, paclitaxel 175 mg/m^2 day 2, every 3 weeks for 2 cycles	Carboplatin AUC5 every 3 weeks	No	Neoadjuvant	Not provided in translation
Zheng 2022	2009	Docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 + carboplatin AUC5 every 3 weeks for 6 cycles	Epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 weeks for 4 cycles, followed by docetaxel 75 mg/m^2 or paclitaxel 175 mg/m^2 every 3 weeks for 4 cycles	Carboplatin AUC5 every 3 weeks	No	Adjuvant	< 1%

AUC: area under the curve; IHC: immunohistochemistry.

Table 2. Number of treatment comparisons by subgroup and efficacy outcomes

	Outcome			
	Treatment comparisons n (%)	**DFS n (%)**	**OS n (%)**	**pCR n (%)**
Overall	21	13 (62%)	12 (57%)	16 (76%)
Treatment setting				
Neoadjuvant	16 (76%)	8 (38%)	8 (38%)	16 (76%)
Adjuvant	4 (19%)	4 (19%)	4 (19%)	0
Both	1 (5%)	1 (5%)	0	1 (5%)
Subgroups				
BRCA mutation subgroup reported	6 (29%)	4 (19%)	0	6 (29%)
HRD status subgroup reported	1 (5%)	1 (5%)	0	1 (5%)
Lymph node positive reported	3 (14%)	3 (14%)	0	3 (14%)
Type of platinum agent				
Carboplatin	18 (%)	12 (57%)	12 (57%)	13 (62%)
Cisplatin	2 (10%)	0	0	2 (10%)
Lobaplatin	1 (5%)	1 (5%)	0	1 (5%)
Type of regimen				
Different backbone	14 (67%)	7 (33%)	7 (33%)	9 (%)
Same backbone	7 (33%)	6 (29%)	5 (24%)	7 (%)
Anthracycline content in intervention arm				
Anthracycline present	12 (57%)	7 (33%)	6 (29%)	10 (47%)
Anthracycline free	9 (43%)	6 (29%)	6 (29%)	6 (29%)
Schedule of platinum agent				
3-weekly	14 (67%)	9 (43%)	8 (38%)	11 (57%)
2-weekly	1 (5%)	1 (5%)	1 (5%)	0
Weekly	5 (24%)	3 (14%)	3 (%)	5 (24%)
Hormone receptor IHC cut-off				
> 1% or not reported	11 (57%)	5 (24%)	4 (19%)	9 (43%)

Table 2. Number of treatment comparisons by subgroup and efficacy outcomes *(Continued)*

< 1%	10 (47%)	8 (38%)	8 (38%)	7 (33%)

DFS: disease-free survival; HRD: homologous recombination deficiency; IHC: immunohistochemistry; n: number; OS: overall survival; pCR: pathological complete response.

APPENDICES

Appendix 1. CENTRAL

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 triple negative breast near neoplasm*
#3 triple negative breast near carcinoma*
#4 triple negative breast near cancer*
#5 triple negative breast near tumour*
#6 triple negative breast near tumor*
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 (locally advanced near breast neoplasm*):ti
#9 (locally advanced near breast carcinoma*):ti
#10 (locally advanced near breast cancer*):ti
#11 (locally advanced near breast tumour*):ti
#12 (locally advanced near breast tumor*):ti
#13 (metasta* near breast neoplasm*):ti
#14 (metasta* near breast carcinoma*):ti
#15 (metasta* near breast cancer*):ti
#16 (metasta* near breast tumour*):ti
#17 (metasta* near breast tumor*):ti
#18 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 #7 not #18
#20 platinum or cisplatin or cisplatinum or Oxaliplatin or Carboplatin or lobaplatin or nedaplatin or eptaplatin or miboplatin or sebriplatin
#21 MeSH descriptor: [Platinum] explode all trees
#22 MeSH descriptor: [Cisplatin] explode all trees
#23 MeSH descriptor: [Platinum Compounds] explode all trees
#24 MeSH descriptor: [Carboplatin] explode all trees
#25 MeSH descriptor: [Oxaliplatin] explode all trees
#26 #20 or #21 or #22 or #23 or #24 or #25
#27 #19 and #26 in Trials

Appendix 2. MEDLINE

#	Searches
1	exp Breast Neoplasms/
2	exp Triple Negative Breast Neoplasms/
3	Triple Negative Breast cancer$.tw.
4	Triple Negative Breast neoplasm$.tw.
5	Triple Negative Breast carcinoma$.tw.
6	Triple Negative Breast tumo?r$.tw.
7	or/1-6

(Continued)

8	(local$ adj6 advance$ adj6 (breast adj6 (neoplasm$ or cancer$ or carcinoma$ or tumo?r$))).ti.
9	(metasta$ adj6 (breast adj6 (neoplasm$ or cancer$ or carcinoma$ or tumo?r$))).ti.
10	or/8-9
11	7 not 10
12	exp Cisplatin/
13	exp Carboplatin/
14	exp Organoplatinum Compounds/
15	exp Platinum/
16	exp Platinum Compounds/
17	(cisplatinum or cisplat* or cisplatin).tw.
18	(carboplatinum or carboplat* or carboplatin).tw.
19	(platinum or platin*).tw.
20	platinum compound*.tw.
21	(platinum-containing regime* or platinum containing regime*).tw.
22	(platinum-based agent* or platinum based agent*).tw.
23	(Platinol or Platinol- AQ or CDDP or CACP or platidiam or platinum diamminodichloride or cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or biocisplatinum or dichlorodi-ammineplatinum or nsc-119875 or nsc 119875 or cis-platinum or Abiplatin or AI3-62048 or AI3 62048 or Briplatin or CCRIS 221 or Cismaplat or Cisplatine or Cisplatyl or Neoplatin).tw.
24	(carboplatine or CCRIS 3404 or EINECS 255-446-0 or "EINECS 255 446 0" or HSDB 6957 or cbd-ca or jm-8 or jm8 or nsc-241240 or nsc 241240 or paraplatin or Paraplatin- AQ or NSC 201345 or NSC-201345 or cis-diammine cyclobutanedicarboxylato platinum).tw.
25	(lobaplatin or lobaplatinum or lobaplat* or D-19466 or D 19466).tw.
26	(Nedaplatin or Aqupla or CCRIS 4088 or NSC 375101D or NSC-375101D or cis-Diammine glycolato platinum).tw.
27	(Heptaplatin or Eptaplatin or NSC D644591 or NSC-D644591).tw.
28	(Oxaliplatin or oxalapatin or 1-OHP or CCRIS 9143 or Dacplat or Eloxatin or Elplat or JM-83 or JM83 or l-OHP or Lipoxal or NSC 266046 or NSC-266046 or Oxalatoplatin or Oxalatoplatinum or Oxali-platin or Oxaliplatino or Oxaliplatinum or Oxalitin or Oxaloplatine or Oxaloplatino or RP-54780 or RP54780 or SR-96669 or SR 96669).tw.
29	(miboplatin or CCRIS 5235 or DWA 2114R).tw.
30	(sebriplatin or NK 121).tw.
31	or/12-30

(Continued)

32	11 and 31
33	animals/ not humans/
34	32 not 33
35	randomized controlled trial.pt.
36	controlled clinical trial.pt.
37	randomized.ab.
38	placebo.ab.
39	Clinical Trials as Topic/
40	randomly.ab.
41	trial.ti.
42	(crossover or cross-over).tw.
43	Pragmatic Clinical Trials as Topic/
44	pragmatic clinical trial.pt.
45	or/35-44
46	34 and 45
47	remove duplicates from 46

Appendix 3. Embase

#	Searches
1	exp breast cancer/
2	exp triple negative breast cancer/
3	Triple Negative Breast cancer$.tw.
4	Triple Negative Breast neoplasm$.tw.
5	Triple Negative Breast carcinoma$.tw.
6	Triple Negative Breast tumo?r$.tw.
7	or/1-6
8	(local$ adj6 advance$ adj6 (breast adj6 (neoplasm$ or cancer$ or carcinoma$ or tumo?r$))).ti.

(Continued)

9	(metasta$ adj6 (breast adj6 (neoplasm$ or cancer$ or carcinoma$ or tumo?r$))).ti.
10	or/8-9
11	7 not 10
12	exp cisplatin/
13	exp cisplatin derivative/
14	exp carboplatin/
15	exp platinum complex/
16	exp platinum/
17	exp platinum derivative/
18	exp platinum 1,2 diaminocyclohexane bisneodecanoate/
19	exp lobaplatin/
20	exp nedaplatin/
21	exp eptaplatin/
22	exp oxaliplatin/
23	exp miboplatin/
24	exp sebriplatin/
25	(cisplatinum or cisplat* or cisplatin).tw.
26	(carboplatinum or carboplat* or carboplatin).tw.
27	(platinum or platin*).tw.
28	platinum compound*.tw.
29	(platinum-containing regime* or platinum containing regime*).tw.
30	(platinum-based agent* or platinum based agent*).tw.
31	(Platinol or Platinol- AQ or CDDP or CACP or platidiam or platinum diamminodichloride or cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or biocisplatinum or dichlorodi-ammineplatinum or nsc-119875 or nsc 119875 or cis-platinum or Abiplatin or AI3-62048 or AI3 62048 or Briplatin or CCRIS 221 or Cismaplat or Cisplatine or Cisplatyl or Neoplatin).tw.
32	(carboplatine or CCRIS 3404 or EINECS 255-446-0 or "EINECS 255 446 0" or HSDB 6957 or cbd-ca or jm-8 or jm8 or nsc-241240 or nsc 241240 or paraplatin or Paraplatin- AQ or NSC 201345 or NSC-201345 or cis-diammine cyclobutanedicarboxylato platinum).tw.
33	(lobaplatin or lobaplatinum or lobaplat* or D-19466 or D 19466).tw.

(Continued)

34	(Nedaplatin or Aqupla or CCRIS 4088 or NSC 375101D or NSC-375101D or cis-Diammine glycolato platinum).tw.
35	(Heptaplatin or Eptaplatin or NSC D644591 or NSC-D644591).tw.
36	(Oxaliplatin or oxalapatin or 1-OHP pr CCRIS 9143 or Dacplat or Eloxatin or Elplat or JM-83 or JM83 or l-OHP or Lipoxal or NSC 266046 or NSC-266046 or Oxalatoplatin or Oxalatoplatinum or Oxaliplatin or Oxaliplatino or Oxaliplatinum or Oxalitin or Oxaloplatine or Oxaloplatino or RP-54780 or RP54780 or SR-96669 or SR 96669).tw.
37	(miboplatin or CCRIS 5235 or DWA 2114R).tw.
38	(sebriplatin or NK 121).tw.
39	or/12-38
40	Randomized controlled trial/
41	Controlled clinical study/
42	Random$.ti,ab.
43	randomization/
44	intermethod comparison/
45	placebo.ti,ab.
46	(compare or compared or comparison).ti.
47	(open adj label).ti,ab.
48	((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
49	double blind procedure/
50	parallel group$1.ti,ab.
51	(crossover or cross over).ti,ab.
52	((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab.
53	(assigned or allocated).ti,ab.
54	(controlled adj7 (study or design or trial)).ti,ab.
55	(volunteer or volunteers).ti,ab.
56	trial.ti.
57	or/40-56
58	11 and 39 and 57
59	remove duplicates from 58

(Continued)

60	limit 59 to (human and (conference abstracts or embase))

Appendix 4. WHO ICTRP

Basic Search:

Triple negative breast cancer AND platinum

Advanced Searches:

1. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: platinum

Recruitment status: All

2. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: platinum-containing regime OR platinum compound OR platinum OR cisplatin OR carboplatin OR platin OR cisplatinum OR carboplatinum OR carboplatine OR cisplatine OR lobaplatin OR nedaplatin OR heptaplatin OR oxaliplatin OR oxalapatin OR miboplatin

Recruitment status: All

3. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: sebriplatin OR platinol OR platinol- AQ OR CDDP OR CACP OR platidiam OR platinum diamminodichloride OR cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR biocisplatinum OR dichlorodiammineplatinum OR nsc-119875

Recruitment status: All

4. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention:abiplatin OR AI3-62048 OR AI3 62048 OR briplatin OR CCRIS 221 OR cismaplat OR cisplatyl OR neoplatin OR CCRIS 3404 OR EINECS 255-446-0 OR HSDB 6957 OR cbdca OR jm-8 OR nsc-241240 OR paraplatin OR paraplatin- AQ OR NSC 201345

Recruitment status: All

5. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: cis-diammine cyclobutanedicarboxylato platinum OR lobaplatinum OR D-19466 OR Aqupla OR CCRIS 4088 OR NSC 375101D OR cis-Diammine glycolato platinum OR Eptaplatin OR NSC D644591 OR CCRIS 9143 OR Dacplat OR Eloxatin OR Elplat OR JM-83 OR JM83 OR l-OHP

Recruitment status:All

6. Condition: triple negative breast cancer OR triple negative breast neoplasm

Intervention: Lipoxal OR NSC 266046 OR Oxalatoplatin OR Oxalatoplatinum OR Oxaliplatino OR Oxaliplatinum OR Oxalitin OR Oxaloplatine OR Oxaloplatino OR RP-54780 OR SR-96669 OR CCRIS 5235 OR DWA 2114R OR NK 121

Recruitment status: All

Appendix 5. ClinicalTrials.gov

Basic search:

Condition or disease: Triple negative breast cancer

Other terms: platinum

Advanced searches:

1. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: platinum-containing regime OR platinum compound OR platinum OR cisplatin OR carboplatin OR platin OR cisplatinum OR carboplatinum OR carboplatine OR cisplatine OR lobaplatin OR nedaplatin OR heptaplatin OR oxaliplatin OR oxalapatin OR miboplatin

Study type: All studies

2. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: sebriplatin OR platinol OR platinol- AQ OR CDDP OR CACP OR platidiam OR platinum diamminodichloride OR cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR biocisplatinum OR dichlorodiammineplatinum OR nsc-119875

Study type: All studies

3. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: abiplatin OR AI3-62048 OR AI3 62048 OR briplatin OR CCRIS 221 OR cismaplat OR cisplatyl OR neoplatin OR CCRIS 3404 OR EINECS 255-446-0 OR HSDB 6957 OR cbdca OR jm-8 OR nsc-241240 OR paraplatin OR paraplatin- AQ OR NSC 201345

Study type: All studies

4. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: cis-diammine cyclobutanedicarboxylato platinum OR lobaplatinum OR D-19466 OR Aqupla OR CCRIS 4088 OR NSC 375101D OR cis-Diammine glycolato platinum OR Eptaplatin OR NSC D644591 OR CCRIS 9143 OR Dacplat OR Eloxatin OR Elplat OR JM-83 OR JM83 OR l-OHP

Study type: All studies

5. Condition or disease: Triple negative breast cancer OR triple negative breast neoplasm

Intervention/treatment: Lipoxal OR NSC 266046 OR Oxalatoplatin OR Oxalatoplatinum OR Oxaliplatino OR Oxaliplatinum OR Oxalitin OR Oxaloplatine OR Oxaloplatino OR RP-54780 OR SR-96669 OR CCRIS 5235 OR DWA 2114R OR NK 121

Study type: All studies

HISTORY

Protocol first published: Issue 5, 2021

CONTRIBUTIONS OF AUTHORS

- Draft the protocol: SM, MW, AG with support of all authors
- Study selection: MW, AG, SM, the Cochrane Breast Cancer Group's Information Specialist
- Extract data from studies: SM, MW with support of AG
- Enter data into Review Manager Web: MW, SM
- Carry out the analysis: SM, MW, AG, SE with support of all authors
- Interpret the analysis: SM, AG, MW, SE, JB, RD with support of all authors
- Draft the final review: SM, MW, AG with support of all authors
- Disagreement resolution: JB, RD
- Update the review: SM, AG

DECLARATIONS OF INTEREST

SM: none.

MW: none. Melina is a member of the Cochrane Breast Cancer editorial team but was not involved in the editorial process for this review.

SE: none.

JB: none related to this review. Jane has received funding to travel to conferences from Novartis. Jane has served on advisory boards for Pfizer and Lilly for unrelated matters and payment has been made to her institution.

RD: none.

AG: none related to this review. Annabel reports consultancy/expert witness or advisory roles for Pfizer (2018, 2019) and AstraZeneca (2018) for matters unrelated to this review topic. There is no competing interest associated with funding of travel to attend an educational meeting, or to provide expertise regarding Cancer Genetic counselling in Australia. Annabel also receives ongoing funds for editorial support for manuscript writing for the EMBRACA trial (not related to this review). Annabel is also a member of the Cochrane Breast Cancer editorial team but was not involved in the editorial process for this review.

SOURCES OF SUPPORT

Internal sources

- NHMRC Clinical Trials Centre, University of Sydney, Australia

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment: we decided to employ the original Cochrane risk of bias tool (RoB 1) rather than the second version (RoB 2).

Subgroup analyses: two proposed subgroup analyses were not undertaken for the following reasons.

- BRCA was the only high-risk gene mutation stratified in the reported trials. Therefore, it was not possible to review any other 'high-risk genes' as planned.
- Most studies, except one, included a taxane in the chemotherapy regimen. Therefore, we did not conduct the planned subgroup analysis of 'platinum and taxane-containing regimen versus taxane-containing regimen'.

We added one new subgroup analysis on lymph node status as several trials stratified outcomes by this subgroup.

Sensitivity analyses: we added two sensitivity analyses that were not prespecified in the protocol. This included:

- assessing the impact of different immunohistochemical definitions for triple-negative breast cancer because the definition varied slightly across trials and
- removing adjusted estimates when a meta-analysis included both unadjusted and adjusted values. In this review, we did not use any adjusted estimates.

We did not conduct a sensitivity analysis based on risk of bias because all studies reporting on DFS and OS were at low risk of bias for most if not all domains.

INDEX TERMS

Medical Subject Headings (MeSH)

Adjuvants, Immunologic; Anthracyclines [therapeutic use]; Carboplatin; *Febrile Neutropenia; Platinum; Quality of Life; *Triple Negative Breast Neoplasms [drug therapy]

MeSH check words

Humans