National Institute for Health and Care Excellence

Early and locally advanced breast cancer: diagnosis and management

[P] Neoadjuvant chemotherapy for people with HER2 positive breast cancer

NICE guideline NG101

Evidence reviews underpinning recommendations 1.11.2 to 1.11.3 and research recommendations in the NICE guideline

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Draft for consultation

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1.1 Review question

What is the clinical and cost effectiveness of a neoadjuvant chemotherapy regimen containing a platinum and a taxane compared to a regimen containing an anthracycline and a taxane in people with HER2 positive invasive breast cancer?

1.1.1 Introduction

The 2018 update of the guideline recommends offering neoadjuvant chemotherapy to people with HER2-positive invasive breast cancer but does not specify the chemotherapy regimen. It cross refers to NICE technology appraisal TA424 on Pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer and the chemotherapy regimens that can be used with this treatment are listed in the Cancer Drug Fund list. These include platinum and taxane based regimens and anthracycline and taxane based regimens.

There is ongoing uncertainty around which neoadjuvant chemotherapy regimens should be used for people with HER2-positive invasive breast cancer and this is associated with variation in practice. The 2023 surveillance review of this guideline identified some evidence relating to the use of carboplatin, a platinum-based chemotherapy, for these people. Anthracycline-based regimens may not be suitable for some people with HER2-positive invasive breast cancer because of an increased risk of cardiotoxicity, particularly if they are having trastuzumab or pertuzumab with trastuzumab as recommended by NICE technology appraisal TA424. This review aims to determine whether there is evidence to support recommending one neoadjuvant chemotherapy regimen over the other.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	**Inclusion:** • Adults (18 and over) who have HER2 positive invasive breast cancer. HER2 positive status is defined as immunohistochemistry (IHC) 3+ or IHC 2+ and positive on fluorescence in-situ hybridisation (FISH). **Exclusion:** • Adults (18 and over) who have invasive breast cancer that is not HER2 positive. • Adults (18 and over) with newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Adults (18 and over) with Paget's disease of the breast with no invasive component.
Intervention	Neoadjuvant chemotherapy regimen containing a platinum and a taxane (without an anthracycline) Platinums of interest: • Carboplatin

	• Cisplatin The neoadjuvant chemotherapy regimen may also include anti-HER2 treatments in both arms.
Comparator	Neoadjuvant chemotherapy regimen containing an anthracycline and a taxane (without a platinum) Anthracyclines of interest: • Epirubicin • Doxorubicin Taxanes of interest: • paclitaxel (including nab-paclitaxel) • docetaxel The neoadjuvant chemotherapy regimen may also include anti-HER2 treatments in both arms.

Outcomes	**Primary outcomes (critical outcomes)**
	• Pathological complete response
	• Overall survival
	• Disease-free survival
	
	Secondary outcomes (important outcomes)
	• Breast cancer mortality
	• Quality of life
	• Adverse events
	  ○ treatment-related mortality
	  ○ treatment-related morbidity including short -term adverse events and long-term consequences of treatment
	• Adherence to or completion of treatment regimens (early cessation of treatment)
	• Local and/or locoregional recurrence
	• Breast conservation rate

Study type	RCT or systematic reviews of RCTs

For the full protocol see appendix A.

1.1.3 Methods and process

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

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

The following methods were specific for this evidence review:

1. A list of the most important adverse events relevant to this evidence review was determined by committee consensus. The committee agreed that some adverse events were likely to be shorter term occurring during treatment or shortly afterwards, while others were likely to be longer term consequences of treatment that could persist after treatment was completed. Adverse events were classified by committee consensus as short term and/ or long term prior to data extraction (see Table 20 for a list of these adverse events). All grade 3 and 4 adverse events were reported irrespective of being

short term or long term. Grade 2 short term adverse events were only reported if the frequency was 5% or more. There was no threshold for extracting data on grade 2 alopecia (a short-term adverse event) because alopecia was considered to be particularly important for people undergoing chemotherapy by the committee. Short term adverse events without stating the grade were included with the 5% frequency threshold. Short term adverse events reported as pooled grade 1 and 2 were not extracted. Where a study reported an adverse event at grade 2 and 3 to 4 only the data for grade 3 to 4 was extracted.

2. Adverse events we had classified as short term were reported as pooled grade 1 and 2 by Huang et al. (2015). Therefore, these were not extracted.

3. We planned to carry out subgroup analysis for all critical outcomes. We were able to do this for pathological complete response, but we were unable to do it for overall survival and disease-free survival because none of the included studies reported any data for the subgroups of interest for these 2 critical outcomes.

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

5. In the protocol for all dichotomous outcomes, any statistically significant difference was deemed to be clinically important, and we used the line of no effect as one of the downgrades for imprecision. The quality of the outcome was therefore downgraded once for imprecision if either end of the 95% confidence interval crossed the line of no effect. To be consistent with previous work on this guideline from 2018, we planned to use an event size of 300 events for the second downgrade based on 2018 optimal information size calculations that suggested that at least 300 events were needed to adequately detect an effect. If this information was not readily available, we planned to use sample size instead to ensure that all studies would have the potential to be downgraded twice. As information about the number of events was not available for all outcomes in this review the evidence was downgraded a second time in cases where the number of participants for an outcome was less than 500. This sample size was selected to allow for the possibility of 300 events.

6. For adverse events, when meta-analyses included 2 or more studies but some of these studies reported zero events in both arms and only 1 study reported events in either arm, the evidence for that adverse event was downgraded 1 level for inconsistency. This meant that data on that adverse event was considered as only available from 1 study. In these situations, the absolute risk was calculated using only data from the study reporting adverse events in either arm.

7. The TRYPHAENA trial (Schneeweiss at al. 2018) was a 3-arm study. For dichotomous outcomes where data on numbers of events were available, we divided the number of participants and events in the platinum and taxane containing neoadjuvant chemotherapy regimen arm (the control arm for our analyses) in half to allow for a comparison with the 2 different neoadjuvant chemotherapy regimens containing an anthracycline and a taxane (anthracycline and taxane with HER2 treatment, and anthracycline followed by taxane and HER2 treatment). Therefore, in the forest plots and analyses the TRYPHAENA trial was regarded as a single study with 2 comparisons that differ based on when the taxane was delivered.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 04 07 2024. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Cochrane Database of Systematic Reviews (CDSR); Embase (Ovid); Epistemonikos; Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 11 07 2024. The following databases were searched: Embase (Ovid); Econlit (Ovid); International Health Technology Assessment Database (INAHTA), NHS EED (CRD) and Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. The QA procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.3.2 Protocol deviations

- The results for overall survival and disease-free survival were not available as hazard ratios and we could not calculate them from the information provided in the paper (TRYPHAENA: Schneeweiss et al. 2018). Instead we used data on the number of people who had events at 3 years and the total number of participants to calculate risk ratios (RRs) for all-cause mortality (deaths from any cause) and the combined outcome of recurrence or death following a recurrence.

- Subgroup analyses were carried out for critical outcomes regardless of whether there was significant heterogeneity. This was because the committee were still interested to see subgroups in the TNBC review (evidence review O) so this was applied to all evidence reviews for consistency.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 2288 references (see appendix B for the literature search strategy). Evidence from the 2023 surveillance review (1 reference) was also reviewed.

In total 2289 references were screened at title and abstract level against the review protocol, with 2264 excluded at this level. 10% of references were screened separately by two reviewers with 99% agreement. Discrepancies were resolved by discussion.

The full texts of 14 systematic reviews and 11 RCTs were ordered for closer inspection. Three RCTs reported in 4 publications met the criteria specified in the review protocol (appendix A). For a summary of the 3 included studies see Table 2.

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

See section 1.1.14 References – included studies for the full references of the included studies.

1.1.4.2 Excluded studies

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

1.1.5 Summary of studies included in the effectiveness evidence

Table 2 Summary of studies included in the effectiveness evidence

Study details	Location Total sample size Follow up time	Median age Key inclusion/exclusion criteria	Intervention	Comparison	Outcomes	Risk of bias Applicability
Gao (2021) neoCARH	China N=135 Follow up time: not reported (surgery within 6 weeks after final dose of neoadjuvant chemotherapy)	Median age: 50 years (range: 23 to 68) Key inclusion criteria: • Female • Aged ≥18 years • HER2 positive invasive breast cancer • IHC 3+ or 2+ and positive for FISH • Clinical stage II–III C • ECOG performance status 0 or 1 • Normal organ and heart function Key exclusion criteria: • Stage IV breast cancer • Bilateral breast cancer	Docetaxel (75 mg/m²) plus carboplatin (AUC 6 mg/ml per min) every 3 weeks for 6 cycles concurrently with trastuzumab. Trastuzumab was initially administered at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks to complete 1 year of trastuzumab treatment	4 cycles of epirubicin (90 mg/m²), and cyclophosphamide (600 mg/m²) intravenously, followed by 4 cycles of docetaxel (100 mg/m²) and trastuzumab every 3 weeks. Trastuzumab was initially administered at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks to complete 1 year of trastuzumab treatment	• Pathological complete response • Adverse events: treatment-related morbidity • Adherence (early cessation of treatment) • Breast conservation rate	Moderate (all outcomes) Directly applicable

Study details	Location Total sample size Follow up time	Median age Key inclusion/exclusion criteria	Intervention	Comparison	Outcomes	Risk of bias Applicability
		• Other malignancies • Inadequate organ function • Impaired cardiac function • Uncontrolled hypertension • Previous systemic therapy for the treatment or prevention of breast cancer • Previous excisional biopsy of a primary tumour or axillary lymph node				
Huang (2015)	China N=100 Follow up time: not reported (surgery at 2 to 4 weeks after the last neoadjuvant	Median age: 47.5 years (range: 29 to 65) Key inclusion criteria: • ECOG performance status 0 or 1 • Untreated patients with histologically confirmed stage II-III breast cancer	Trastuzumab (4 mg/kg loading dose followed by 2 mg/kg) and paclitaxel (75 mg/m2) weekly combined with carboplatin (AUC = 2) weekly. Patients were given at least 4 cycles but no more than 6 cycles under discretion	Trastuzumab (4 mg/kg loading dose followed by 2 mg/kg) and paclitaxel (75 mg/m2) weekly combined with epirubicin (75 mg/m2) every 3 weeks. Patients were given at least 4 cycles but no more than 6 cycles under discretion of physicians. One year of	• Pathological complete response • Adverse events: treatment-related morbidity	High (objective outcomes) Low (adverse events) Directly applicable

Study details	Location Total sample size Follow up time	Median age Key inclusion/exclusion criteria	Intervention	Comparison	Outcomes	Risk of bias Applicability
	chemotherapy dose)	• HER2 positive breast cancer • IHC 3+ or FISH positive status • Age between 18–70 years • Infiltrating primary breast cancer with the longest clinical diameter of more than 3.0 cm • Assessable tumour in the breast without evidence of distant metastasis • Left ventricular ejection fraction ≥55% • Adequate hematopoietic function • Adequate hepatic and renal function • Aspartate aminotransferase and alanine	of physicians. One year of trastuzumab in total was recommended for all patients	trastuzumab in total was recommended for all patients	• Adherence (early cessation of treatment) • Breast conservation rate	

Study details	Location Total sample size Follow up time	Median age Key inclusion/exclusion criteria	Intervention	Comparison	Outcomes	Risk of bias Applicability
		aminotransferase <2.5xULN) Key exclusion criteria: none reported				
Schneeweiss (2013) Schneeweiss (2018) TRYPHAENA	Multicentre across 44 centres in 19 countries N=225 Follow up time: median 60.9 months (IQR: 57.4 to 62.0)	Median age: 49 years (range: 24 to 81) Key inclusion criteria: Female • Aged ≥18 years • ECOG performance status 0 or 1 • HER2 positive breast cancer • Left ventricular ejection fraction ≥55% • Untreated, operable, locally advanced or inflammatory breast cancer, with a primary tumour >2 cm Key exclusion criteria: • Bilateral breast cancer	Docetaxel plus carboplatin for six cycles, with pertuzumab plus trastuzumab in all cycles: trastuzumab (8 mg/kg initial dose, then 6 mg/kg), pertuzumab (840 mg then 420 mg), carboplatin dosed at AUC 6, docetaxel (75 mg/m2)	• FEC for three cycles followed by three cycles of docetaxel, with pertuzumab plus trastuzumab in all cycles: trastuzumab (8 mg/kg initial dose, then 6 mg/kg), pertuzumab (840 mg then 420 mg), FEC (5-fluorouracil 500 mg/m2, epirubicin 100 mg/m2 and cyclophosphamide 600 mg/m2) docetaxel (75 mg/m2 ; escalated to 100 mg/m2 if no dose-limiting toxicity before cycle 4) • FEC for three cycles followed by three cycles of docetaxel, with pertuzumab and trastuzumab in cycles 4 to 6 only (i.e. with	• Pathological complete response • All-cause mortality (proxy for overall survival) • Recurrence or death following a recurrence (proxy for disease-free survival) • Adverse events: treatment-related morbidity • Adherence (early cessation of treatment)	Low (all outcomes) Directly applicable

Study details	Location Total sample size Follow up time	Median age Key inclusion/exclusion criteria	Intervention	Comparison	Outcomes	Risk of bias Applicability
		• Other malignancies • Uncontrolled hypertension • Metastatic breast cancer • Any previous local or systemic breast cancer treatment • Inadequate bone marrow • Inadequate liver or kidney function • History of myocardial infarction within the previous 6 months		docetaxel): trastuzumab (8 mg/kg initial dose, then 6 mg/kg), pertuzumab (840 mg then 420 mg), FEC (5-fluorouracil 500 mg/m2, epirubicin 100 mg/m2 and cyclophosphamide 600 mg/m2) docetaxel (75 mg/m2 ; escalated to 100 mg/m2 if no dose-limiting toxicity before cycle 4)	• Breast conservation rate	

AUC: area under the plasma concentration/time curve; ECOG: Eastern Cooperative Oncology Group; FEC: 5-fluorouracil, epirubicin and cyclophosphamide; FISH: fluorescence in-situ hybridisation; IHC: immunohistochemistry; IQR: interquartile range

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Interpreting the effectiveness evidence

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

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

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

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

Pathological complete response

Table 3 Pathological complete response

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
Pathological complete response (RR greater than 1 favours platinum and taxane)	496 per 1,000	575 per 1,000 (481 to 690)	RR 1.16 (0.97 to 1.39)	447 (3 RCTs)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; RR: risk ratio.

Survival outcomes

Table 4 Survival outcomes

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
All-cause mortality (proxy for overall survival) (RR less than 1 favours platinum and taxane)	81 per 1,000	130 per 1,000 (58 to 287)	RR 1.60 (0.72 to 3.54)	225 (1 RCT)	Very low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
Recurrence or death following a recurrence (proxy for disease-free survival) (RR less than 1 favours platinum and taxane)	132 per 1,000	152 per 1,000 (77 to 306)	RR 1.15 (0.58 to 2.31)	208 (1 RCT)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; RR: risk ratio.

Adherence (early cessation of treatment)

Table 5 Adherence (early cessation of treatment)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
Adherence (early cessation of treatment) (RR less than 1 favours platinum and taxane)	87 per 1,000	79 per 1,000 (43 to 148)	RR 0.91 (0.49 to 1.70)	458 (3 RCTs)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; RR: risk ratio.

Breast conservation rate

Table 6 Breast conservation rate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
Breast conservation rate (RR greater than 1 favours platinum and taxane)	175 per 1,000	248 per 1,000 (162 to 379)	RR 1.42 (0.93 to 2.17)	339 (3 RCTs)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; RR: risk ratio.

Short term adverse events

Table 7 Short term adverse events

All extracted for grade 3 to 4, apart from alopecia, which was reported for all grades.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
Alopecia - RR less than 1 favours platinum and taxane	503 per 1,000	539 per 1,000 (413 to 700)	RR 1.07 (0.82 to 1.39)	223 (1 RCT)	Very low	Could not differentiate
Anaemia - RR less than 1 favours platinum and taxane – Random effects model (I2>50%)	42 per 1,000	115 per 1,000 (39 to 345)	RR 2.77 (0.93 to 8.29)	458 (3 RCTs)	Very low	Could not differentiate
Diarrhoea - RR less than 1 favours platinum and taxane	34 per 1,000	63 per 1,000 (28 to 143)	RR 1.84 (0.81 to 4.19)	458 (3 RCTs)	Low	Could not differentiate
Liver function problems - RR less than 1 favours platinum and taxane	Not estimable**	Not estimable**	RR 9.06 (1.56 to 52.79)	323 (2 RCTs)	Moderate	Effect favours platinum based neoadjuvant chemotherapy
Nausea or vomiting - RR less than 1 favours platinum and taxane	9 per 1,000	31 per 1,000 (8 to 125)	RR 3.37 (0.85 to 13.42)	358 (2 RCTs)	Low	Could not differentiate
Neutropenia - RR less than 1 favours platinum and taxane	394 per 1,000	370 per 1,000 (299 to 461)	RR 0.94 (0.76 to 1.17)	458 (3 RCTs)	Low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
Neutropenic sepsis - RR less than 1 favours platinum and taxane	137 per 1,000	140 per 1,000 (81 to 244)	RR 1.02 (0.59 to 1.78)	323 (2 RCTs)	Low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Absolute effects could not be estimated because there were 0 events in one of the arms. ***See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; RR: risk ratio.

Long term adverse events

Table 8 Long term adverse events

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
Fatigue (any grade or grade 1/2) - RR less than 1 favours platinum and taxane	341 per 1,000	351 per 1,000 (273 to 450)	RR 1.03 (0.80 to 1.32)	458 (3 RCTs)	Very low	Could not differentiate
Fatigue (grades 3 to 4) - RR less than 1 favours platinum and taxane	5 per 1,000	13 per 1,000 (3 to 54)	RR 2.63 (0.65 to 10.65)	323 (2 RCTs)	Very low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with Anthracycline and taxane	Risk with Platinum and taxane				
LVEF (over 10% reduction after 2 cycles of neoadjuvant treatment) - RR less than 1 favours platinum and taxane	60 per 1,000	1000 per 1,000 (25 to 396)	RR 1.67 (0.42 to 6.60)	100 (1 RCT)	Very low	Could not differentiate
LVEF (over 10% reduction during or after 4 cycles of neoadjuvant treatment) - RR less than 1 favours platinum and taxane	45 per 1,000	48 per 1,000 (20 to 115)	RR 1.05 (0.43 to 2.53)	458 (3 RCTs)	Low	Could not differentiate
Symptomatic left ventricular systolic dysfunction (grade 3 or more) - RR less than 1 favours platinum and taxane	27 per 1,000	10 per 1,000 (1 to 211)	RR 0.39 (0.02 to 7.92)	113 (1 RCT)	Very low	Could not differentiate
Peripheral neuropathy (any grade or grade 1/2) - RR less than 1 favours platinum and taxane	85 per 1,000	119 per 1,000 (55 to 257)	RR 1.39 (0.64 to 3.01)	235 (2 RCTs)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **See full GRADE tables (appendix F) for reasons for downgrading the evidence. CI: confidence interval; RR: risk ratio.

See appendix F for full GRADE tables.

1.1.7 Economic evidence

A literature search was conducted to identify published economic evaluations of relevance to this review question (see Appendix B – Literature search strategies). This search retrieved 662 studies, and based on title and abstract two studies were included but were excluded at full text screening on applicability (see Appendix G – Economic evidence study selection).

1.1.7.1 Included studies

No studies were included for this review question.

1.1.7.2 Excluded studies

Two studies were excluded at full text review on applicability as both were set in a US healthcare payer perspective for costs and outcomes (see Appendix J – Excluded studies).

1.1.8 Economic model

No economic modelling was conducted for this review question.

1.1.9 Unit costs

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

Table 9 Cost of neoadjuvant chemotherapy regimens for HER2+ breast cancer

Regimen	Dosing	Cost per cycle	Total cost
Docetaxel, Carboplatin, Trastuzumab and Pertuzumab	Cycle 1: Docetaxel: 75mg/m^2, Carboplatin AUC 6, Pertuzumab 840mg, Trastuzumab 8mg/kg Cycles 2-6: Docetaxel: 75mg/m^2, Carboplatin AUC 6, Pertuzumab 420mg, Trastuzumab 6mg/kg Cycles 7 to 18: Pertuzumab 420mg, Trastuzumab 6mg/kg	Cycle 1: £6,346 Cycle 2-6: £3,584 Cycle 8-21: £3,422	£65,324
Epirubicin and Cyclophosphamide then Docetaxel, Pertuzumab and Trastuzumab	Cycles 1-3: Epirubicin 100mg/m^2, Cyclophosphamide 500mg/m^2 Cycle 4: Pertuzumab 840mg, Trastuzumab 8mg/kg, Docetaxel 75mg/m^2 Cycles 5-7: Pertuzumab 420mg, Trastuzumab 6mg/kg, Docetaxel 75mg/m^2 Cycles 8 to 21: Pertuzumab 420mg, Trastuzumab 6mg/kg	Cycle 1-3: £38.94 Cycle 4: £6,201 Cycle 5-7: £3,440 Cycle 8-21: £3,422	£64,540
Fluorouracil, Epirubicin and Cyclophosphamide then Docetaxel, Pertuzumab and Trastuzumab	Cycles 1-3: Epirubicin 100mg/m^2, Fluorouracil 500mg/m^2, Cyclophosphamide 500mg/m^2 Cycle 4: Pertuzumab 840mg, Trastuzumab 8mg/kg, Docetaxel 75mg/m^2 Cycles 5-7: Pertuzumab 420mg, Trastuzumab 6mg/kg, Docetaxel 75mg/m^2 Cycles 8 to 21: Pertuzumab 420mg, Trastuzumab 6mg/kg	Cycle 1-3: £41.98 Cycle 4: £6,201 Cycle 5-7: £3,440 Cycle 8-21: £3,422	£64,549

Source of drug costs: eMIT/BNF; Source of dosing regimens: Protocols Archive - SWAG Cancer Alliance. Costs assume no vial sharing. Pertuzumab has confidential discount (not applied above).

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

Table 10 Cost of managing recurrence

Treatment	Unit cost	Non-metastatic recurrence	Metastatic recurrence
Radiotherapy	£3,115[(a)]	67%[(c)]	35%[(c)]
Surgery for non-metastatic BC	£5,383[(a)]	89%[(c)]	0%[(c)]
Surgery for metastatic BC	£2,122[(a)]	0%[(c)]	19%[(c)]
Drug therapy	£18,803[(b)]	34%[(c)]	56%[(c)]
Average		**£13,271**	**£12,023[(d)]**

a) NICE TA886
b) Assumed to be 18 cycles of docetaxel + trastuzumab (NICE TA569)
c) National Disease Registration Service (NDRS)
d) End-of-life care costs not included

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1. The outcomes that matter most

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

In addition, the committee acknowledged the importance of other outcomes including mortality due to breast cancer, local and/or locoregional recurrence, and quality of life in decision making. Breast cancer mortality and quality of life were not expected to be widely reported and therefore they were considered important but not critical to decision making. Quality of life can be severely affected by neoadjuvant chemotherapy. The risk of local and/or locoregional recurrence may be expected to be reduced after neoadjuvant chemotherapy if it is effective.

The committee also noted that the risk of adverse events and types of adverse events that people with human epidermal growth factor receptor 2 (HER2) positive breast cancer may experience with different neoadjuvant chemotherapy regimens will play an important role in their decision making about which treatment to accept and whether to continue with it should side effects occur. Therefore, the committee agreed that adverse events (both shorter term on treatment and longer term) and cessation of treatment were also important outcomes for decision making. These outcomes were especially important given the lack of evidence about effects of treatment on quality of life.

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

1.1.10.2 The quality of the evidence

Overall, the outcomes ranged from low to very low quality (with 1 being moderate) with the main reasons for downgrading being due to risk of bias, inconsistency and imprecision of the evidence. Studies were judged to be at moderate (neoCARH [Gao et al. 2021] risk of bias for both objective outcome and adverse events) or high (Huang et al. 2015 risk of bias for objective outcomes) risk of bias due to poor reporting or due to unbalanced exclusion of participants from their analysis. Downgrading for inconsistency was because there was high variability in the results of some outcomes between studies or evidence came from a single study. Some of the evidence was rated as imprecise as the 95% confidence interval crossed the line of no effect (in this case represented by the value of 1.0). All included studies had a sample size of less than 500 participants and were also downgraded a second time for imprecision as there were likely to be too few participants to reliably detect an effect. These small sample sizes may have led to there not being a high enough number of events to detect a difference between the effects of platinum and taxane based regimens and anthracycline and taxane based neoadjuvant chemotherapy regimens for most of the outcomes of interest.

The 3 included studies reported data on: pCR, treatment adherence, breast conservation rate, and short- and long-term adverse events. DFS (reported as the number of events of recurrence or death following a recurrence) and OS (reported as all-cause mortality) were only reported by the TRYPHAENA trial (Schneeweiss at al. 2018). There was no evidence found on quality of life or breast cancer mortality.

The committee had specified that a number of subgroup analyses be carried out to help them with drafting recommendations (see below for results of these analyses). We were unable to carry out subgroup analysis by age, hormone receptor status, and lymph node status for the survival outcomes as the data was not available for these analyses.

The committee highlighted that in current practice neoadjuvant chemotherapy regimens for people with HER2 positive breast cancer are used alongside anti-HER2 treatment. All included studies reported evidence for the use of neoadjuvant chemotherapy regimens with anti-HER2 treatments. The TRYPHAENA trial (Schneeweiss at al. 2018) included both pertuzumab and trastuzumab. The other 2 trials (Huang et al. 2015; neoCARH [Gao et al. 2021]) only included trastuzumab.

Two of the trials specified that participants were women (neoCARH [Gao et al. 2021]; TRYPHAENA [Schneeweiss et al. 2018]), and it is likely that the third trial (Huang et al. 2015) solely recruited people with female reproductive organs. (To be consistent with terminology used in the review on ovarian function suppression [see review Q] when we mention people with female reproductive organs, we mean this to cover women, trans men and non-binary people who currently have ovaries.) The committee highlighted that evidence came from studies recruiting relatively young women (median age in the included studies ranged from 47.5 to 50 years; age ranging from 23 to 81).

1.1.10.3 Benefits and harms

The committee looked at the evidence comparing the use of a platinum and taxane based neoadjuvant chemotherapy regimen to an anthracycline and taxane based regimen for people with HER2 positive breast cancer. They noted that it was not possible from the evidence to differentiate between the 2 neoadjuvant regimens for any of the outcomes: pCR (low quality evidence), OS (reported as all-cause mortality; very low quality evidence), DFS (reported as recurrence or death following a recurrence; very low quality evidence), treatment adherence (low quality evidence), breast conservation rate (very low quality evidence), and all adverse events (low to very low quality evidence) apart from liver function problems (see below).

Subgroup analyses were carried out for pCR, OS (reported as all-cause mortality) and DFS (reported as recurrence or death following a recurrence) where data was available (timing of anthracyclines delivery, age, hormone receptor status, and lymph node status). No subgroup differences were detected for any of the subgroup analyses.

The committee also noted that there was an increased risk of having liver function problems with platinum and taxane containing regimens compared to anthracycline and taxane containing regimens (Figure 16). They noted that although the evidence was of moderate quality, there remained high uncertainty around this outcome because the confidence intervals were wide. This was likely due to very few events in the studies, with some having zero events in the anthracycline arms.

The committee were aware of the results of the TRAIN-2 trial, which looked at the effectiveness of neoadjuvant chemotherapy with or without anthracyclines in the presence of

dual HER2 blockade for HER2-positive breast cancer. The TRAIN-2 trial was found within the NICE search for this evidence review but it was excluded after looking at the full text because all participants received platinum at some point during the neoadjuvant chemotherapy regimen and as a result the intervention and comparator did not match the inclusion criteria for this review. The committee also highlighted that the neoadjuvant chemotherapy regimens in the TRAIN-2 trial are not used in UK clinical practice. Therefore, the TRAIN-2 trial was kept as an excluded study.

Drafting of recommendations

The committee concluded that there was insufficient evidence to recommend one of the neoadjuvant chemotherapy regimens over the other. They agreed that neoadjuvant chemotherapy should be offered to people with HER2-positive invasive breast cancer in line with the commissioning criteria for any related technology appraisals. They also included a cross reference to NICE technology appraisal guidance on pertuzumab for the neoadjuvant treatment of HER2-positive breast cancer (TA424).

The committee noted that neoadjuvant therapy is not necessary for some small HER2-positive tumours, and that people who neoadjuvant therapy is suitable for are identified in line with criteria set out in related NICE technology appraisals (TA). Although there is only one related TA at time of publication (TA424), the committee agreed the recommendation should make allowances for other options as they become available in future.

The committee agreed that this recommendation covers people with male reproductive organs because the biological mechanism of neoadjuvant chemotherapy is expected to be the same as for people with female reproductive organs. (To be consistent with terminology used in the review on testicular function suppression [see review R] when we mention people with male reproductive organs, we mean this to cover men, trans women and non-binary people who currently have testes.)

1.1.10.4 Cost effectiveness and resource use

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

The committee were presented with costs of different neoadjuvant regimens for HER2-positive early breast cancer. Anthracycline-based regimens had similar overall costs to platinum-based regimens, and the cost of the anthracyclines and platinum chemotherapy elements themselves formed a small part of the overall cost. Therefore, these cost differences are unlikely to drive the potential relative cost effectiveness of each regimen.

The clinical review found that there was no real difference in the expected rate of recurrence between different regimens for HER2-positive early breast cancer, so downstream costs of managing these events would be largely equivalent.

The committee also considered the difference in adverse event profile and whether this would lead to a difference in the resources required to manage people on each treatment strategy. There was a statistically significant impact on liver function problems but the committee considered this to be highly uncertain outcome due to the low numbers of events, and therefore unlikely to have any impact on resources. The committee also noted how neutropenia and febrile neutropenia were significantly associated with anthracycline-containing regimens in the TRAIN-2 trial, a study earlier described as being out of scope.

Febrile neutropenia is expensive to manage, with the cost estimated as £11,532 per hospitalisation episode (inflated from 2016 cost reported in TA509).

Both anthracycline- and platinum-based neoadjuvant regimens are available on the NHS and many clinicians are using these regimens in routine practice. Therefore, it is not expected that the recommendation to offer a neoadjuvant chemotherapy regimen for people with HER2 positive invasive breast cancer will increase resource use.

1.1.10.5 Other factors the committee took into account

The committee noted that the equality and health inequalities assessment that accompanies this review highlighted a large number of issues that could act as barriers to people with HER2 positive breast cancer, constraining their decisions about whether to have neoadjuvant chemotherapy with regimens containing a taxane and a platinum or regimens containing a taxane and an anthracycline. However, they noted that many of these issues were societal and not within the committee's ability to address. For example, problems associated with being able to afford to take time off work and having access to affordable transport to take them to appointments or limited availability of healthcare facilities and long waiting times in their local areas. However, they noted that there are local initiatives in some places that provide free transport and extended or weekend hours that may help those who require this type of support.

The committee discussed similar issues in more detail when they looked at the evidence on neoadjuvant regimens for people with triple negative breast cancer (see section 1.1.11.5 within evidence review O). A cross referral to key sections of 2 core NICE guidelines has been added to the start of the section on systemic anti-cancer therapy planning to facilitate the decision-making process and ensure that patients are able to fully participate. These were the sections on enabling patients to actively participate in their care in the NICE guideline on patient experience in adult NHS services, and communicating risks, benefits and consequences in the NICE guideline on shared decision making. These guidelines apply to all conversations related to systemic anti-cancer therapy.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.11.2 to 1.11.3.

1.1.12 References – included studies

1.1.12.1 Effectiveness

Gao, Hong-Fei, Wu, Zhiyong, Lin, Ying et al. (2021) Anthracycline-containing versus carboplatin-containing neoadjuvant chemotherapy in combination with trastuzumab for HER2-positive breast cancer: the neoCARH phase II randomized clinical trial. Therapeutic advances in medical oncology 13: 17588359211009003

Huang, Liang, Chen, Sheng, Yang, Wentao et al. (2015) Efficacy and safety analysis of trastuzumab and paclitaxel based regimen plus carboplatin or epirubicin as neoadjuvant therapy for clinical stage II-III, HER2-positive breast cancer patients: a phase 2, open-label, multicenter, randomized trial. Oncotarget 6(21): 18683-92

Schneeweiss, A, Chia, S, Hickish, T et al. (2013) Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Annals of oncology : official journal of the European Society for Medical Oncology 24(9): 2278-84

Schneeweiss, Andreas, Chia, Stephen, Hickish, Tamas et al. (2018) Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. European journal of cancer (Oxford, England : 1990) 89: 27-35

1.1.12.2 Economic

No economic studies were included in this evidence review.

1.1.13 References – other

van Ramshorst, Mette S, van der Voort, Anna, van Werkhoven, Erik D et al. (2018) Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. The Lancet. Oncology 19(12): 1630-1640

Appendices

Appendix A – Review protocols

Review protocol for platinum and taxane containing neoadjuvant chemotherapy regimens compared to anthracycline and taxane regimens in people with HER2 positive breast cancer

ID	Field	Content
1.	Review title	RQ 1.3 Platinum and taxane containing neoadjuvant chemotherapy regimens compared to anthracycline and taxane regimens in people with HER2 positive breast cancer
2.	Review question	RQ 1.3 What is the clinical and cost effectiveness of a neoadjuvant chemotherapy regimen containing a platinum and a taxane compared to a regimen containing an anthracycline and a taxane in people with HER2 positive invasive breast cancer?
3.	Objective	To assess the clinical and cost effectiveness of a neoadjuvant chemotherapy regimen containing a platinum and a taxane compared to a regimen containing an anthracycline and a taxane in people with HER2 positive invasive breast cancer.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistimonikos • MEDLINE ALL For the economics review the following databases will be searched: • Embase • MEDLINE ALL • Econlit • INAHTA • NHS EED Searches will be restricted by: • English language • Human studies • Abstracts, conference presentations, and theses will be excluded.

		• Systematic reviews and RCTs The searches will be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion. The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Human epidermal growth factor receptor 2 (HER2) positive invasive breast cancer that is of any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0).
6.	Population	Inclusion: • Adults (18 and over) who have HER2 positive invasive breast cancer. HER2 positive status is defined as Immunohistochemistry (IHC) 3+ or IHC 2+ and positive on fluorescence in-situ hybridisation (FISH). Exclusion: • Adults (18 and over) who have invasive breast cancer that is not HER2 positive. • Adults (18 and over) with newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Adults (18 and over) with Paget's disease of the breast with no invasive component.
7.	Intervention	Neoadjuvant chemotherapy regimen containing a platinum and a taxane (without an anthracycline) Platinums of interest: • Carboplatin • Cisplatin The neoadjuvant chemotherapy regimen may also include anti-HER2 treatments in both arms.
8.	Comparator	Neoadjuvant chemotherapy regimen containing an anthracycline and a taxane (without a platinum) Anthracyclines of interest: • Epirubicin • Doxorubicin

		Taxanes of interest: • paclitaxel (including nab-paclitaxel) • docetaxel The neoadjuvant chemotherapy regimen may also include anti-HER2 treatments in both arms.
9.	Types of study to be included	• Systematic reviews/meta-analyses of RCTs • RCTs
10.	Other exclusion criteria	• Abstracts, conference presentations, theses and narrative reviews • Non-human studies • Non-English language studies • Studies where more than 20% of the participants do not have HER2 positive breast cancer or where subgroup data is not available.
11.	Context	There are no recommendations in the current guideline on the use of platinum in neoadjuvant chemotherapy regimens for people with HER2-positive breast cancer. Anthracycline-based regimens may not be suitable for some people in this group because of an increased risk of cardiotoxicity, particularly if they are having trastuzumab or pertuzumab with trastuzumab, as is recommended by NICE technology appraisal TA424. The 2023 surveillance review identified some evidence relating to the use of carboplatin, a platinum-based treatment, for people with HER2-positive breast cancer. Intelligence gathering suggests there is currently variation in practice in this area, and there may be a benefit in reviewing the evidence for platinum-based regimens as an alternative to anthracycline-based neoadjuvant regimens for this group.
12.	Primary outcomes (critical outcomes)	• Pathological complete response (dichotomous outcome) • Overall survival (time to event data) • Disease-free survival (time to event data) **Minimal important differences** Any statistically significant difference will be used for all critical outcomes.
13.	Secondary outcomes (important outcomes)	• Breast cancer mortality (time to event data) • Quality of life (using validated measures such as the EQ-5D; MID: values from the literature where available) • Adverse events (dichotomous outcome) ○ treatment-related mortality

		○ treatment-related morbidity including short -term adverse events and long-term consequences of treatment • Adherence to or completion of treatment regimens (early cessation of treatment; dichotomous outcome) • Local and/or locoregional recurrence (dichotomous outcome) • Breast conservation rate (dichotomous outcome) **Minimal important differences** Quality of life MID values from the literature: • FACT-G total: 3-7 points • FACT-B total: 7-8 points • TOI (trial outcome index) of FACT-B: 5-6 points • BCS of FACT-B: 2-3 points • WHOQOL-100: 1 point Any statistically significant difference will be used for the rest of important outcomes. **Time points** The longest follow-up periods will be prioritised for survival and recurrence outcomes if multiple time points are reported.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias for RCTs and systematic reviews will be assessed using the Cochrane Risk of Bias v.2.0 or ROBIS respectively, as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions. Hazard ratios will be pooled using the generic inverse-variance method. Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting

		numbers of people having an event. Absolute risks will be presented where possible. Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met: Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%. GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.
17.	Analysis of sub-groups	For critical outcomes only, where there is significant heterogeneity and disambiguation of the results using the following subgroups reduces this then these analyses will be carried out: • Age (under 50, 50 to 70, over 70; if these subgroups are not reported, under and over 50; age and range will be added to evidence tables) • HR status (ER positive and/or PR positive versus ER negative and PR negative) • Lymph node status (positive/negative) • Timing of anthracyclines delivery (together with monoclonal antibody or sequentially)
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English
20.	Country	England
21.	Anticipated or actual start date	July 2024

22.	Anticipated completion date	March 2025		
23.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact Centre for Guidelines, NICE. 5b Named contact e-mail breastcancerupdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team		
25.	Review team members	From the Guideline Development Team: Marie Harrisingh, Technical adviser Sarah Boyce, Senior technical analyst Yolanda Martinez, Technical analyst Nancy Pursey, Assistant technical analyst Lindsay Claxton, Health economics adviser Alfredo Mariani, Senior health economist Andrea Heath, Senior information specialist		
26.	Funding sources/sponsor	This systematic review is being completed by the NICE Guideline Development Team which receives funding from NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: early and locally advanced breast cancer: diagnosis and management - Neoadjuvant chemotherapy and ovarian function suppression (update) .
29.	Other registration details	None
30.	Reference/URL for published protocol	None
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	HER2 positive breast cancer; neoadjuvant chemotherapy; platinum; taxane; anthracycline.
33.	Details of existing review of same topic by same authors	Not applicable
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

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Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The effectiveness searches were run on 04 July 2024 and the cost effectiveness searches were run on 11 July 2024.

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

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

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

Review management

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

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies
- Editorials, letters and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

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

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

Date limits

No date limits were applied, in adherence to the review protocol. A date limit of 2010 to date was applied for the cost-effectiveness search.

Search filters and classifiers

Effectiveness searches

Randomised controlled trials filter

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

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

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

Cost effectiveness searches

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

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

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

Key decisions

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

Effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	04/07/2024	Wiley	Cochrane Central Register of Controlled Trials Issue 7 of 12, July 2024	1149

Cochrane Database of Systematic Reviews (CDSR)	04/07/2024	Wiley	Cochrane Database of Systematic Reviews Issue 7 of 12, July 2024	7
Embase	04/07/2024	Ovid	Embase <1974 to 2024 July 03>	1615
Epistemonikos	04/07/2024	Epistemonikos		181
MEDLINE ALL	04/07/2024	Ovid	Ovid MEDLINE(R) ALL <1946 to July 03, 2024>	1149

Search strategy history

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

Searches		
#1	MeSH descriptor: [Breast Neoplasms] explode all trees	20302
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees	1013
#3	MeSH descriptor: [Carcinoma, Lobular] this term only	219
#4	MeSH descriptor: [Carcinoma, Medullary] this term only	21
#5	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only	309
#6	{OR #1-#5}	20609
#7	MeSH descriptor: [Breast] explode all trees	1156
#8	breast*:ti,ab	62188
#9	#7 or #8	62297
#10	(breast NEXT milk):ti,ab	2788
#11	(breast NEXT tender*):ti,ab	270
#12	#10 or #11	3057
#13	#9 not #12	59240
#14	MeSH descriptor: [Neoplasms] explode all trees	125512
#15	#13 and #14	20646
#16	(breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab	44499
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab	290
#18	{OR #15-#17}	45532
#19	#6 or #18	46953
#20	MeSH descriptor: [Receptor, ErbB-2] this term only	1634
#21	MeSH descriptor: [Genes, erbB-2] this term only	73
#22	human epidermal growth factor receptor 2 positive*:ti,ab	2488
#23	(human epidermal growth factor receptor2*):ti,ab	2

Searches	
#24	(HER2* or HER-2* or HERII* or HER-II*):ti,ab 8737
#25	(erbB2* or erbB-2* or erythroblastic oncogene B*):ti,ab 421
#26	(neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*):ti,ab 46
#27	(CD340* or CD-340*):ti,ab 1
#28	{OR #20-#27} 9576
#29	#19 and #28 8101
#30	MeSH descriptor: [Neoadjuvant Therapy] this term only 2641
#31	(neoadjuvant* or neo-adjuvant* or neo* NEXT adjuvant*):ti,ab 12331
#32	(primary near/3 (chemotherap* or therap* or treatment*)):ti,ab 30527
#33	(induct* near/3 (chemotherap* or therap* or treatment*)):ti,ab 10617
#34	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) near/3 (chemotherap* or therap* or treatment*)):ti,ab 5793
#35	{OR #30-#34} 56471
#36	MeSH descriptor: [Cisplatin] this term only 6392
#37	MeSH descriptor: [Carboplatin] this term only 3303
#38	MeSH descriptor: [Platinum Compounds] this term only 145
#39	MeSH descriptor: [Platinum] this term only 385
#40	((platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*) near/3 (chemotherap* or therap* or treatment*)):ti,ab 11620
#41	(nsc-119875 or nsc-241240 or cbdca or jm-8):ti,ab 263
#42	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum):ti,ab 78
#43	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum):ti,ab 306
#44	{OR #36-#43} 17923
#45	MeSH descriptor: [Taxoids] explode all trees 7856
#46	(taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*):ti,ab 20838
#47	#45 or #46 21878
#48	MeSH descriptor: [Anthracyclines] explode all trees 7114
#49	(anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*):ti,ab 15355
#50	#48 or #49 17025
#51	#44 and #47 5595
#52	#47 and #50 4468
#53	#51 or #52 9430
#54	#35 or #53 62768
#55	#29 and #54 in Cochrane Reviews, Cochrane Protocols 7
#56	#29 and #54 in Trials 3459
#57	((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an524201
#58	"conference":pt 245616

Searches		
#59	#57 or #58	769817
#60	#56 not #59	1149

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

Searches	
#1	MeSH descriptor: [Breast Neoplasms] explode all trees 20302
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 1013
#3	MeSH descriptor: [Carcinoma, Lobular] this term only 219
#4	MeSH descriptor: [Carcinoma, Medullary] this term only 21
#5	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 309
#6	{OR #1-#5} 20609
#7	MeSH descriptor: [Breast] explode all trees 1156
#8	breast*:ti,ab 62188
#9	#7 or #8 62297
#10	(breast NEXT milk):ti,ab 2788
#11	(breast NEXT tender*):ti,ab 270
#12	#10 or #11 3057
#13	#9 not #12 59240
#14	MeSH descriptor: [Neoplasms] explode all trees 125512
#15	#13 and #14 20646
#16	(breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 44499
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 290
#18	{OR #15-#17} 45532
#19	#6 or #18 46953
#20	MeSH descriptor: [Receptor, ErbB-2] this term only 1634
#21	MeSH descriptor: [Genes, erbB-2] this term only 73
#22	human epidermal growth factor receptor 2 positive*:ti,ab 2488
#23	(human epidermal growth factor receptor2*):ti,ab 2
#24	(HER2* or HER-2* or HERII* or HER-II*):ti,ab 8737
#25	(erbB2* or erbB-2* or erythroblastic oncogene B*):ti,ab 421
#26	(neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*):ti,ab 46
#27	(CD340* or CD-340*):ti,ab 1
#28	{OR #20-#27} 9576
#29	#19 and #28 8101
#30	MeSH descriptor: [Neoadjuvant Therapy] this term only 2641
#31	(neoadjuvant* or neo-adjuvant* or neo* NEXT adjuvant*):ti,ab 12331
#32	(primary near/3 (chemotherap* or therap* or treatment*)):ti,ab 30527
#33	(induct* near/3 (chemotherap* or therap* or treatment*)):ti,ab 10617

Searches	
#34	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) near/3 (chemotherap* or therap* or treatment*)):ti,ab 5793
#35	{OR #30-#34} 56471
#36	MeSH descriptor: [Cisplatin] this term only 6392
#37	MeSH descriptor: [Carboplatin] this term only 3303
#38	MeSH descriptor: [Platinum Compounds] this term only 145
#39	MeSH descriptor: [Platinum] this term only 385
#40	((platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*) near/3 (chemotherap* or therap* or treatment*)):ti,ab 11620
#41	(nsc-119875 or nsc-241240 or cbdca or jm-8):ti,ab 263
#42	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum):ti,ab 78
#43	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum):ti,ab 306
#44	{OR #36-#43} 17923
#45	MeSH descriptor: [Taxoids] explode all trees 7856
#46	(taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*):ti,ab 20838
#47	#45 or #46 21878
#48	MeSH descriptor: [Anthracyclines] explode all trees 7114
#49	(anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*):ti,ab 15355
#50	#48 or #49 17025
#51	#44 and #47 5595
#52	#47 and #50 4468
#53	#51 or #52 9430
#54	#35 or #53 62768
#55	#29 and #54 in Cochrane Reviews, Cochrane Protocols 7

1 **Database name: Embase**

Searches		
1	exp breast cancer/	601450
2	exp breast carcinoma/	100199
3	exp medullary carcinoma/	13060
4	ductal breast carcinoma in situ/	3403
5	exp breast tumor/	683555
6	lobular carcinoma/	3579
7	or/1-6	695047
8	exp breast/	130096
9	breast*.ti,ab,kw.	808267
10	8 or 9	841409
11	(breast adj milk).ti,ab,kw.	20791
12	(breast adj tender*).ti,ab,kw.	781
13	11 or 12	21566

Searches	
14	10 not 13 819843
15	exp neoplasm/ 5792446
16	14 and 15 624358
17	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 623105
18	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 44361
19	16 or 17 or 18 699936
20	7 or 19 827404
21	human epidermal growth factor receptor 2 positive breast cancer/ 13284
22	human epidermal growth factor receptor 2 positive*.ti,ab. 1285
23	(human epidermal growth factor receptor2 adj positive*).ti,ab. 6
24	(HER2* or HER-2* or HERII* or HER-II*).ti,ab. 91891
25	(erbB2* or erbB-2* or erythroblastic oncogene B*).ti,ab. 18817
26	(neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*).ti,ab. 1002
27	(CD340* or CD-340*).ti,ab. 63
28	or/21-27 109744
29	20 and 28 81721
30	exp neoadjuvant therapy/ 59385
31	(neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 101216
32	(primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 127349
33	(induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 62499
34	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 43019
35	or/30-34 329474
36	cisplatin/ or cisplatin derivative/ 229328
37	carboplatin/ 91752
38	platinum derivative/ or platinum/ 53719
39	((platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 68935
40	(nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 1420
41	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 3102
42	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 5237
43	or/36-42 326759
44	taxoid/ 2745
45	paclitaxel/ or docetaxel/ or taxane derivative/ 197636
46	(taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 110957
47	or/44-46 213388
48	exp anthracycline antibiotic agent/ 309291

Searches		
49	(anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab.	139529
50	48 or 49	325318
51	43 and 47	89752
52	47 and 50	59731
53	51 or 52	121742
54	35 or 53	427220
55	29 and 54	19372
56	random:.tw.	2087131
57	placebo:.mp.	541200
58	double-blind:.tw.	253384
59	or/56-58	2371146
60	55 and 59	3830
61	limit 60 to english language	3789
62	nonhuman/ not human/	5476167
63	61 not 62	3772
64	(conference abstract* or conference review or conference paper or conference proceeding or editorial or letter).db,pt,su.	8127691
65	63 not 64	1630
66	case report/	3015244
67	65 not 66	1615

1 Database name: Epistimonikos

Searches
(advanced_title_en:((breast* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*))) OR advanced_abstract_en:((breast* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)) OR (mammar* AND (neoplasm* OR cancer* OR tumo?r* OR carcinoma* OR adenocarcinoma* OR sarcoma* OR leiomyosarcoma* OR duct* OR infiltrat* OR intraduct* OR lobul* OR medullary OR tubular OR malignan*)))) AND (advanced_title_en:((human epidermal growth factor receptor 2 positive*) OR (her2* OR her-2*)) OR advanced_abstract_en:((human epidermal growth factor receptor 2 positive*) OR (her2* OR her-2*))) AND (advanced_title_en:((neoadjuvant* OR neo-adjuvant* OR neo* AND adjuvant*) OR (primary AND (chemotherap* OR therap* OR treatment*)) OR (induct* AND (chemotherap* OR therap* OR treatment*))) OR advanced_abstract_en:((neoadjuvant* OR neo-adjuvant* OR neo* AND adjuvant*) OR (primary AND (chemotherap* OR therap* OR treatment*)) OR (induct* AND (chemotherap* OR therap* OR treatment*)))) [Filters: classification=systematic-review]

2 **Database name: MEDLINE ALL**

Searches		
1	exp Breast Neoplasms/	355625

Searches	
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/ 48319
3	Carcinoma, Lobular/ 6173
4	Carcinoma, Medullary/ 3423
5	Carcinoma, Intraductal, Noninfiltrating/ 10873
6	or/1-5 375969
7	exp Breast/ 54812
8	breast*.ti,ab,kw. 583855
9	7 or 8 593861
10	(breast adj milk).ti,ab,kw. 16338
11	(breast adj tender*).ti,ab,kw. 596
12	10 or 11 16931
13	9 not 12 576930
14	exp Neoplasms/3990764
15	13 and 14 373424
16	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 434220
17	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 37224
18	or/15-17 491002
19	6 or 18 549019
20	Receptor, ErbB-2/ 30411
21	Genes, erbB-2/ 3086
22	human epidermal growth factor receptor 2 positive*.ti,ab. 1061
23	(human epidermal growth factor receptor2 adj positive*).ti,ab. 3
24	(HER2* or HER-2* or HERII* or HER-II*).ti,ab. 46958
25	(erbB2* or erbB-2* or erythroblastic oncogene B*).ti,ab. 12484
26	(neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*).ti,ab. 825
27	(CD340* or CD-340*).ti,ab. 43
28	or/20-27 61976
29	19 and 28 43576
30	Neoadjuvant Therapy/ 30708
31	(neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 53133
32	(primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 83594
33	(induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 32223
34	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 28582
35	or/30-34 193705
36	Cisplatin/ 60054
37	Carboplatin/ 13347
38	Platinum Compounds/ or Platinum/ 14148
39	((platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 41666

Searches
40 (nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 969
41 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 2883
42 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 4640
43 or/36-42 101693
44 exp Taxoids/ 45019
45 (taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 65206
46 44 or 45 71157
47 exp Anthracyclines/ 80225
48 (anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab. 96287
49 47 or 48 119447
50 43 and 46 14619
51 46 and 49 11256
52 50 or 51 23969
53 35 or 52 212217
54 29 and 53 6528
55 exp Randomized Controlled Trial/ 617872
56 randomi?ed.mp. 1127858
57 placebo.mp. 257786
58 or/55-57 1195850
59 54 and 58 1189
60 limit 59 to english language 1166
61 Animals/ not (Animals/ and Humans/) 5202832
62 60 not 61 1165
63 limit 62 to (case reports or clinical conference or comment or consensus development conference or consensus development conference, nih or editorial or letter) 16
64 62 not 63 1149

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	11/07/24	Ovid	Embase <1974 to 2024 July 10>	514
Econlit	11/07/24	Ovid	Econlit <1886 to June 27, 2024>	5
INAHTA	11/07/24	INAHTA		106
NHS EED	11/07/24	CRD		21

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Medline ALL	11/07/24	Ovid	Ovid MEDLINE(R) ALL <1946 to July 10, 2024>	186

1 **Search strategy history**

2 **Database name: Embase**

Searches		
1	exp breast cancer/	602110
2	exp breast carcinoma/	100271
3	exp medullary carcinoma/	13077
4	ductal breast carcinoma in situ/	3428
5	exp breast tumor/	684254
6	lobular carcinoma/	3581
7	or/1-6	695761
8	exp breast/	130136
9	breast*.ti,ab,kw.	809020
10	8 or 9	842175
11	(breast adj milk).ti,ab,kw.	20798
12	(breast adj tender*).ti,ab,kw.	781
13	11 or 12	21573
14	10 not 13	820602
15	exp neoplasm/	5797754
16	14 and 15	624991
17	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	623752
18	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw.	44383
19	16 or 17 or 18	700610
20	7 or 19	828217
21	human epidermal growth factor receptor 2 positive breast cancer/	13319
22	human epidermal growth factor receptor 2 positive*.ti,ab.	1290
23	(human epidermal growth factor receptor2 adj positive*).ti,ab.	6
24	(HER2* or HER-2* or HERII* or HER-II*).ti,ab.	91991
25	(erbB2* or erbB-2* or erythroblastic oncogene B*).ti,ab.	18839
26	(neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*).ti,ab.	1003
27	(CD340* or CD-340*).ti,ab.	63
28	or/21-27	109875
29	20 and 28	81816

Searches	
30	exp neoadjuvant therapy/ 59532
31	(neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 101345
32	(primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 127493
33	(induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 62539
34	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 43070
35	or/30-34 329866
36	cisplatin/ or cisplatin derivative/ 229519
37	carboplatin/ 91853
38	platinum derivative/ or platinum/ 53777
39	((platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 69001
40	(nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 1420
41	(biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 3103
42	(cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 5238
43	or/36-42 327072
44	taxoid/ 2745
45	paclitaxel/ or docetaxel/ or taxane derivative/ 197825
46	(taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 111046
47	or/44-46 213588
48	exp anthracycline antibiotic agent/ 309532
49	(anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab. 139621
50	48 or 49 325563
51	43 and 47 89858
52	47 and 50 59777
53	51 or 52 121868
54	35 or 53 427698
55	29 and 54 19398
56	exp Health Economics/ 1082377
57	exp "Health Care Cost"/ 355380
58	exp Pharmacoeconomics/ 244161
59	Monte Carlo Method/ 54122
60	Decision Tree/ 25106
61	econom$.tw. 530220
62	cba.tw. 14598
63	cea.tw. 43332
64	cua.tw. 1986
65	markov$.tw. 42229
66	(monte adj carlo).tw. 64658
67	(decision adj3 (tree$ or analys$)).tw. 43400

Searches
68 (cost or costs or costing$ or costly or costed).tw. 1055736
69 (price$ or pricing$).tw. 77443
70 budget$.tw. 49736
71 expenditure$.tw. 95144
72 (value adj3 (money or monetary)).tw. 4524
73 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 9946
74 or/56-73 2383694
75 55 and 74 1118
76 limit 75 to dc=20100101-20240717 1000
77 limit 76 to english language 983
78 nonhuman/ not human/ 5481144
79 77 not 78 980
80 (conference abstract* or conference review or conference paper or conference proceeding or editorial or letter).db,pt,su. 8130463
81 79 not 80 514

1 **Database name: Econlit**

Searches
1 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 403
2 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 1
3 (duct* carcinoma* in situ or DCIS).ti,ab,kw. 3
4 or/1-3 405
5 human epidermal growth factor receptor*.ti,ab,kw. 2
6 (HER2* or HER-2* or HERII* or HER-II*).ti,ab,kw. 27
7 (erbB2* or erbB-2* or erythroblastic oncogene B*).ti,ab,kw. 0
8 (neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*).ti,ab,kw. 0
9 (CD340* or CD-340*).ti,ab,kw. 0
10 or/5-9 27
11 4 and 10 6
12 limit 11 to yr="2010 -Current" 5

2 **Database name: INAHTA**

Searches
((((((mammar* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ((breast* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ("Carcinoma, Intraductal, Noninfiltrating"[mh]) OR ("Carcinoma, Medullary"[mh]) OR ("Carcinoma, Lobular"[mh]) OR ("Neoplasms, Ductal, Lobular, and Medullary"[mhe]) OR

Searches
("Breast Neoplasms"[mhe])))))) AND (((Receptor, ErbB-2)[mh]) OR ((Genes, erbB-2)[mh]) OR (human epidermal growth factor receptor*) OR (HER2* or HER-2* or HERII* or HER-II*) OR (erbB-2* or erythroblastic oncogene B*) OR (neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*) OR (CD340* or CD-340*))) AND (((Receptor, ErbB-2)[mh]) OR ((Genes, erbB-2)[mh]) OR (human epidermal growth factor receptor*) OR (HER2* or HER-2* or HERII* or HER-II*) OR (erbB-2* or erythroblastic oncogene B*) OR (neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*) OR (CD340* or CD-340*)) FROM 2010 TO 2024 [Applied English language limit]

1 **Database name: NHS EED**

Searches
1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
3 MESH DESCRIPTOR Carcinoma, Lobular
4 MESH DESCRIPTOR Carcinoma, Medullary
5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating
6 #1 or #2 or #3 or #4 or #5
7 MESH DESCRIPTOR Breast EXPLODE ALL TREES
8 breast*
9 #7 or #8
10 (breast NEXT milk)
11 (breast NEXT tender*)
12 #10 or #11
13 #9 not #12
14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
15 #13 and #14
16 (breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
17 (mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
18 #15 or #16 or #17
19 #6 or #18
20 MESH DESCRIPTOR Receptor, ErbB-2
21 MESH DESCRIPTOR Genes, erbB-2
22 human epidermal growth factor receptor 2 positive*
23 (human epidermal growth factor receptor2*)
24 (HER2* or HER-2* or HERII* or HER-II*)
25 (erbB2* or erbB-2* or erythroblastic oncogene B*)
26 (neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*)
27 (CD340* or CD-340*)
28 #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
29 #19 and #28
30 (#29) IN NHSEED FROM 2010 TO 2024

1 **Database name: Medline ALL**

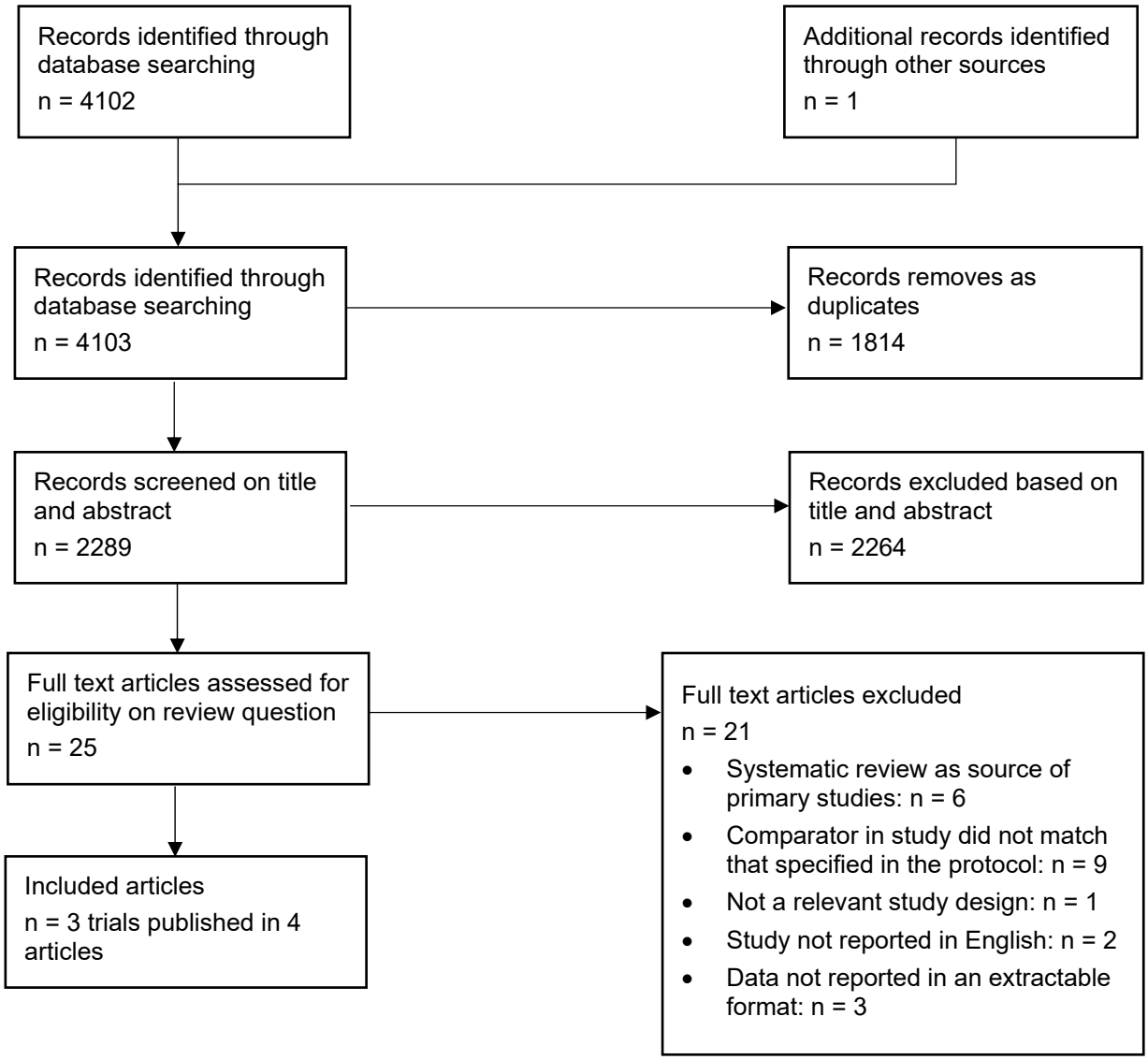
Searches	
1	exp Breast Neoplasms/ 355738
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/ 48352
3	Carcinoma, Lobular/ 6172
4	Carcinoma, Medullary/ 3424
5	Carcinoma, Intraductal, Noninfiltrating/ 10876
6	or/1-5 376114
7	exp Breast/ 54813
8	breast*.ti,ab,kw. 584289
9	7 or 8 594295
10	(breast adj milk).ti,ab,kw. 16344
11	(breast adj tender*).ti,ab,kw. 596
12	10 or 11 16937
13	9 not 12 577358
14	exp Neoplasms/3992339
15	13 and 14 373564
16	(breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 434556
17	(mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 37230
18	or/15-17 491336
19	6 or 18 549385
20	Receptor, ErbB-2/ 30425
21	Genes, erbB-2/ 3086
22	human epidermal growth factor receptor 2 positive*.ti,ab. 1063
23	(human epidermal growth factor receptor2 adj positive*).ti,ab. 3
24	(HER2* or HER-2* or HERII* or HER-II*).ti,ab. 47008
25	(erbB2* or erbB-2* or erythroblastic oncogene B*).ti,ab. 12489
26	(neu-gene* or neugene* or proto-oncogene Neu* or protooncogene Neu*).ti,ab. 825
27	(CD340* or CD-340*).ti,ab. 43
28	or/20-27 62029
29	19 and 28 43611
30	Neoadjuvant Therapy/ 30775
31	(neoadjuvant* or neo-adjuvant* or neo* adjuvant*).ti,ab. 53241
32	(primary adj3 (chemotherap* or therap* or treatment*)).ti,ab. 83690
33	(induct* adj3 (chemotherap* or therap* or treatment*)).ti,ab. 32259
34	((perioperat* or peri-operat* or perisurg* or peri-surg* or preoperat* or pre-operat* or presurg* or pre-surg*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 28621
35	or/30-34 193976
36	Cisplatin/ 60074
37	Carboplatin/ 13354

Searches
38 Platinum Compounds/ or Platinum/ 14155
39 ((platin* or cisplatin* or platinol* or carboplatin* or paraplatin* or platidiam*) adj3 (chemotherap* or therap* or treatment*)).ti,ab. 41711
40 (nsc-119875 or nsc-241240 or cbdca or jm-8).ti,ab. 970
41 (biocisplatinum or dichlorodiammineplatinum or diamminedichloroplatinum).ti,ab. 2882
42 (cis-diamminedichloroplatinum or cis-dichlorodiammineplatinum or cis-platinum).ti,ab. 4639
43 or/36-42 101767
44 exp Taxoids/ 45050
45 (taxane* or taxoid* or docetaxel* or Taxotere* or paclitaxel* or Taxol*).ti,ab. 65269
46 44 or 45 71222
47 exp Anthracyclines/ 80242
48 (anthracycline* or Daunorubicin* or Cerubidine* or DaunoXome* or Doxorubicin* or Adriamycin* or Doxil* or Epirubicin* or Ellence* or Idarubicin* or Idamycin* or Mitoxantrone* or Valrubicin*).ti,ab. 96344
49 47 or 48 119507
50 43 and 46 14636
51 46 and 49 11265
52 50 or 51 23990
53 35 or 52 212497
54 29 and 53 6541
55 Economics/ 27536
56 exp "Costs and Cost Analysis"/ 271690
57 Economics, Dental/ 1922
58 exp Economics, Hospital/ 25890
59 exp Economics, Medical/ 14440
60 Economics, Nursing/ 4013
61 Economics, Pharmaceutical/ 3143
62 Budgets/ 11830
63 exp Models, Economic/ 16398
64 Markov Chains/ 16271
65 Monte Carlo Method/ 33046
66 Decision Trees/ 12268
67 econom$.tw. 438313
68 cba.tw. 11411
69 cea.tw. 28036
70 cua.tw. 1509
71 markov$.tw. 33542
72 (monte adj carlo).tw. 61911
73 (decision adj3 (tree$ or analys$)).tw. 32803
74 (cost or costs or costing$ or costly or costed).tw. 796178
75 (price$ or pricing$).tw. 56848
76 budget$.tw. 37720

Searches		
77	expenditure$.tw.	72102
78	(value adj3 (money or monetary)).tw.	3383
79	(pharmacoeconomic$ or (pharmaco adj economic$)).tw.	4642
80	or/55-79	1526887
81	54 and 80	222
82	limit 81 to ed=20100101-20240717	144
83	limit 81 to dt=20100101-20240717	197
84	82 or 83	198
85	limit 84 to english language	191
86	Animals/ not (Animals/ and Humans/)	5203943
87	85 not 86	191
88	limit 87 to (case reports or clinical conference or comment or consensus development conference or consensus development conference, nih or editorial or letter)	5
89	87 not 88	186

1
2

Appendix C – Effectiveness evidence study selection



1 Appendix D – Effectiveness evidence

2 Gao, 2021

Bibliographic Reference	Gao, Hong-Fei; Wu, Zhiyong; Lin, Ying; Song, Xiang-Yang; Cao, Yin; Chen, Qian-Jun; Zhang, Gangling; Fu, Peifen; Liu, Zhenzhen; Zhang, Liu-Lu; Yang, Ci-Qiu; Yang, Mei; Zhu, Teng; Ji, Fei; Li, Jie-Qing; Cheng, Min-Yi; Wang, Kun; Anthracycline-containing versus carboplatin-containing neoadjuvant chemotherapy in combination with trastuzumab for HER2-positive breast cancer: the neoCARH phase II randomized clinical trial.; Therapeutic advances in medical oncology; 2021; vol. 13; 17588359211009003

3 Study details

Trial registration number and/or trial name	neoCARH / NCT03140553
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Hospital
Study dates	May 2017 to November 2019
Sources of funding	Study was supported by grants from Science and Technology Planning Project of Guangzhou City, Science and Technology Special Fund of Guangdong Provincial People's Hospital, National Natural Science Foundation of China, CSCO-Hengrui Cancer Research Fund, Guangdong Provincial Department of Education Characteristic Innovation Project, Guangdong Basic and Applied Basic Research Foundation and Guangdong Medical Science and Technology Research Fund.
Inclusion criteria	Female Aged ≥18 years HER2 positive invasive breast cancer Tumours had to be HER2 immunohistochemistry 3+ or 2+ and positive for fluorescence in-situ hybridization (FISH) Clinical stage II–III C Eastern Cooperative Oncology Group performance status 0 or 1 Normal organ and heart function
Exclusion criteria	Stage IV breast cancer Bilateral breast cancer Other malignancies Inadequate organ function Impaired cardiac function Uncontrolled hypertension

	Previous systemic therapy for the treatment or prevention of breast cancer Previous excisional biopsy of a primary tumour or axillary lymph node
Intervention(s)	Carboplatin, docetaxel and trastuzumab
Comparator	Epirubicin, cyclophosphamide, docetaxel and trastuzumab
Outcome measures	Pathological complete response Percentage of pathological complete response (ypT0/is, ypN0), which was defined as the absence of any residual invasive cancer in both the breast and axillary lymph nodes. Adverse events: treatment-related morbidity Adverse events were assessed with each cycle of treatment according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Early cessation of treatment Number of people who discontinued treatment Breast conservation rate Number of people who underwent breast conserving surgery
Number of participants	135
Duration of follow-up	Not reported
Methods of analysis	Modified intention-to-treat analysis
Additional comments	Study authors noted that due to the lack of sufficient follow-up for most patients, results on event-free survival were not shown. Study reports subgroup analyses (age, hormone receptor status, and lymph node status) for pathological complete response. Study authors did not report follow-up time but reported that patients underwent surgery within 6 weeks after their final dose of chemotherapy. Therefore, 6 weeks were taken as the follow-up time to report outcomes.

Study arms

Platinum and taxane (N = 68)

Loss to follow-up	2 participants discontinued treatment, reasons: 1 participant because of adverse event 1 participant on patient's decision

Docetaxel (75 mg/m²) plus carboplatin (area under the curve, 6 mg/ml per min) administered every 3 weeks for six cycles concurrently with trastuzumab. Trastuzumab was initially administered at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks to complete 1 year of trastuzumab treatment.

Anthracycline and taxane (N = 67)

Loss to follow-up	2 participants discontinued because of adverse event

Four cycles of epirubicin (90 mg/m²), and cyclophosphamide (600 mg/m²) intravenously, followed by four cycles of docetaxel (100 mg/m²) and trastuzumab every 3 weeks. Trastuzumab was initially administered at a loading dose of 8 mg/kg, followed by 6 mg/kg every 3 weeks to complete 1 year of trastuzumab treatment.

Characteristics

Arm-level characteristics

Characteristic	Platinum and taxane (N = 68)	Anthracycline and taxane (N = 67)
Median age (years (median and range)) Custom value	50.5 years (23 to 68)	50 years (25 to 68)
ECOG performance status: 0 No of events	n = 64 ; % = 91.4	n = 63 ; % = 94
ECOG performance status: 1 No of events	n = 4 ; % = 5.9	n = 4 ; % = 6
Tumour stage T1 No of events	n = 3 ; % = 4.4	n = 3 ; % = 4.5
Tumour stage T2 No of events	n = 43 ; % = 63.2	n = 44 ; % = 65.7
Tumour stage T3 No of events	n = 17 ; % = 25	n = 17 ; % = 25.3
Tumour stage T4 No of events	n = 5 ; % = 7.4	n = 3 ; % = 4.5
Lymph node status: N0 No of events	n = 26 ; % = 38.2	n = 22 ; % = 32.8
Lymph node status: N1 No of events	n = 29 ; % = 42.6	n = 33 ; % = 49.3
Lymph node status N2 No of events	n = 9 ; % = 13.2	n = 9 ; % = 13.4
Lymph node status: N3 No of events	n = 4 ; % = 5.9	n = 3 ; % = 4.5
ER negative and PR negative No of events	n = 34 ; % = 50	n = 33 ; % = 49.3
ER positive and/or PR positive No of events	n = 34 ; % = 50	n = 34 ; % = 50.7

Outcomes

Study timepoints

- 6 week (Timepoint is based on the following statement from the trial: Patients underwent surgery within 6 weeks after their final dose of chemotherapy.)

Pathological complete response

Outcome	Platinum and taxane vs Anthracycline and taxane, 6 week, N = 68	Platinum and taxane vs Anthracycline and taxane, 6 week, N = 67
Pathological complete response No of events	n = 38; % = 55.9	n = 25; % = 37.3

Pathological complete response - Polarity - Higher values are better

Breast conservation rate

Outcome	Platinum and taxane, 6 week, N = 67	Anthracycline and taxane, 6 week, N = 66
Breast conservation rate No of events	n = 23 ; % = 34.3	n = 15 ; % = 22.7

Breast conservation rate - Polarity - Higher values are better

Early cessation of treatment

Outcome	Platinum and taxane, 6 week, N = 68	Anthracycline and taxane, 6 week, N = 67
Early cessation of treatment No of events	n = 2 ; % = 2.9	n = 2 ; % = 3

Early cessation of treatment - Polarity - Lower values are betterShort term adverse events: treatment-related morbidity (grade 3 and 4)

Outcome	Platinum and taxane, 6 week, N = 68	Anthracycline and taxane, 6 week, N = 67
Anaemia No of events	n = 3 ; % = 4.4	n = 3 ; % = 4.5
Diarrhoea No of events	n = 0 ; % = 0	n = 1 ; % = 1.5
Increased alanine aminotransferase (liver function test) No of events	n = 0 ; % = 0	n = 0 ; % = 0

Outcome	Platinum and taxane, 6 week, N = 68	Anthracycline and taxane, 6 week, N = 67
Nausea or vomiting Nausea and vomiting were reported separately in the trial publication No of events	n = 1 ; % = 1.5	n = 0 ; % = 0
Neutropenia No of events	n = 4 ; % = 5.9	n = 3 ; % = 4.5
Febrile neutropenia No of events	n = 0 ; % = 0	n = 0 ; % = 0

1 Anaemia - Polarity - Lower values are better
2 Diarrhoea - Polarity - Lower values are better
3 Increased alanine aminotransferase (liver function test) - Polarity - Lower values are better
4 Nausea or vomiting - Polarity - Lower values are better
5 Neutropenia - Polarity - Lower values are better
6 Febrile neutropenia - Polarity - Lower values are better
7 Grade 3 and 4 extracted for short term adverse events

8 **Long term adverse events: treatment-related morbidity**

Outcome	Platinum and taxane, 6 week, N = 68	Anthracycline and taxane, 6 week, N = 67
Fatigue Any grade No of events	n = 9 ; % = 13.2	n = 15 ; % = 22.4
Fatigue Grades 3 and 4 No of events	n = 0 ; % = 0	n = 0 ; % = 0
Peripheral sensory neuropathy Any grade No of events	n = 8 ; % = 11.8	n = 3 ; % = 4.5
Peripheral sensory neuropathy Grades 3 and 4 No of events	n = 0 ; % = 0	n = 0 ; % = 0
LVEF Non-CTCAE definition of LVEF decline of 10% or more and LVEF below 50% No of events	n = 3 ; % = 4.4	n = 3 ; % = 4.5

9 Fatigue - Polarity - Lower values are better
10 Fatigue - Polarity - Lower values are better
11 Peripheral sensory neuropathy - Polarity - Lower values are better
12 Peripheral sensory neuropathy - Polarity - Lower values are better
13 LVEF - Polarity - Lower values are better
14 All grades extracted for long term adverse events

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

RoB for objective outcomes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (No information about concealment of the allocation sequence)
Overall bias and Directness	Overall Directness	Directly applicable

RoB for adverse events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns (No information about concealment of the allocation sequence)
Overall bias and Directness	Overall Directness	Directly applicable

Huang, 2015

Bibliographic Reference	Huang, Liang; Chen, Sheng; Yang, Wentao; Xu, Binghe; Huang, Tao; Yang, Hongjian; Zheng, Hong; Wang, Yongsheng; Song, Erwei; Zhang, Jin; Cui, Shude; Pang, Da; Tang, Lili; Lei, Yutao; Geng, Cuizhi; Shao, Zhiming; Efficacy and safety analysis of trastuzumab and paclitaxel based regimen plus carboplatin or epirubicin as neoadjuvant therapy for clinical stage II-III, HER2-positive breast cancer patients: a phase 2, open-label, multicenter, randomized trial.; Oncotarget; 2015; vol. 6 (no. 21); 18683-92

Study details

Trial registration number and/or trial name	NCT01428414
Study type	Randomised controlled trial (RCT)
Study location	China
Study setting	Cancer centres
Study dates	Aug 2011 to May 2012
Sources of funding	This study was supported by Shanghai Roche Pharmaceuticals Limited and China Breast Cancer Clinical Study Group.

Inclusion criteria	Eastern Cooperative Oncology Group performance status 0 or 1 Untreated patients with histologically confirmed stage II-III breast cancer HER2 positive breast cancer HER2 positivity was determined by IHC 3+ or fluorescence in situ hybridization (FISH) positive status. Age between 18–70 years Infiltrating primary breast cancer with the longest clinical diameter of more than 3.0 cm Assessable tumour in the breast without evidence of distant metastasis measured by breast mammogram, magnetic resonance imaging, chest computed tomography scan, abdominal ultrasound and bone scan Left ventricular ejection fraction ≥55% Adequate hematopoietic function (absolute neutrophil count≧1.5x10^9 /L, platelet count≧100x10^9 /L, and haemoglobin level≧100g/L) Adequate hepatic and renal function (Serum total bilirubin and Serum creatinine, <1.5xULN (upper limit of normal) Aspartate aminotransferase and alanine aminotransferase<2.5xULN)
Exclusion criteria	None reported
Intervention(s)	Carboplatin, paclitaxel and trastuzumab
Comparator	Epirubicin, paclitaxel and trastuzumab
Outcome measures	Pathological complete response pCR in the breast was defined as the disappearance of residual invasive disease (residual ductal carcinoma in situ allowed) by pathologic examination, and pCR in the axilla was assessed as the absence of positive lymph nodes by haematoxylin and eosin staining. Adverse events: treatment-related morbidity Toxicity was evaluated at every cycle and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Early cessation of treatment Number of people who did not complete at least 4 cycles chemotherapy because of AE, disease progression, withdrawal of consent or immediate surgery. Breast conservation rate Number of people undergoing breast conserving surgery
Number of participants	100
Duration of follow-up	Not reported
Methods of analysis	Not specified but most likely to be per protocol analysis
Additional comments	Study reports subgroup analyses (age, hormone receptor status, and lymph node status) for pathological complete response. Study authors did not report follow-up time but reported that surgery was performed 2–4 weeks after the last chemotherapy dose. Therefore, 4 weeks were taken as the follow-up time to report outcomes.

Study arms

Platinum and taxane (N = 50)

Loss to follow-up	4 participants were lost to follow-up: 3 withdrew after randomisation (1 allergic reaction, 1 pneumonia, 1 patient's decision) 1 withdrew after treatment (refused surgery)

Trastuzumab (4 mg/kg loading dose followed by 2 mg/kg) and paclitaxel (75 mg/m2) weekly combined with carboplatin (AUC = 2) weekly. Patients were given at least 4 cycles but no more than 6 cycles under discretion of physicians. One year of trastuzumab in total was recommended for all patients.

Anthracycline and taxane (N = 50)

Loss to follow-up	9 participants were lost to follow-up: 7 withdrew after randomisation (1 liver function damage, 1 pneumonia, 1 disease progression, 1 protocol violation, 1 stop chemo early and proceeded to surgery, 2 patients' decision) 2 withdrew after treatment (1 refused surgery, 1 opted out before surgery)

Trastuzumab (4 mg/kg loading dose followed by 2 mg/kg) and paclitaxel (75 mg/m2) weekly combined with epirubicin (75 mg/m2) every 3 weeks. Patients were given at least 4 cycles but no more than 6 cycles under discretion of physicians. One year of trastuzumab in total was recommended for all patients.

Characteristics

Arm-level characteristics

Characteristic	Platinum and taxane (N = 50)	Anthracycline and taxane (N = 50)
Median age (years (median and range)) Custom value	48 years (29 to 65)	47.5 years (30 to 63)
Clinical tumour stage: cT1 No of events	n = 1 ; % = 2	n = 1 ; % = 2
Clinical tumour stage: cT2 No of events	n = 32 ; % = 64	n = 34 ; % = 68
Clinical tumour stage: cT3 No of events	n = 13 ; % = 26	n = 12 ; % = 24
Clinical tumour stage: cT4 No of events	n = 4 ; % = 8	n = 3 ; % = 6
Clinical lymph node stage: cN0 No of events	n = 7 ; % = 14	n = 8 ; % = 16
Clinical lymph node stage: cN1 No of events	n = 21 ; % = 42	n = 27 ; % = 54
Clinical lymph node stage: cN2	n = 15 ; % = 30	n = 9 ; % = 18

Characteristic	Platinum and taxane (N = 50)	Anthracycline and taxane (N = 50)
No of events		
Clinical lymph node stage: cN3 No of events	n = 6 ; % = 12	n = 6 ; % = 12
Oestrogen receptor positive No of events	n = 26 ; % = 52	n = 19 ; % = 38
Oestrogen receptor negative No of events	n = 23 ; % = 46	n = 29 ; % = 58
Progesterone receptor positive No of events	n = 20 ; % = 40	n = 16 ; % = 32
Progesterone receptor negative No of events	n = 29 ; % = 58	n = 32 ; % = 64
LVEF (Median (range)) Custom value	67 (58 to 79)	65 (56.5 to 83)

Outcomes

Study timepoints

- 4 week (Timepoint is based on the following statement from the trial: surgery was performed 2 to 4 weeks after the last chemotherapy dose.)

Pathological complete response

Outcome	Platinum and taxane vs Anthracycline and taxane, 4 week, N = 46	Platinum and taxane vs Anthracycline and taxane, 4 week, N = 41
Pathological complete response No of events	n = 18 ; % = 39.1	n = 20 ; % = 48.8

Pathological complete response - Polarity - Higher values are better

Early cessation of treatment

Outcome	Platinum and taxane, 4 week, N = 50	Anthracycline and taxane, 4 week, N = 50
Early cessation of treatment No of events	n = 3 ; % = 6	n = 7 ; % = 14

Early cessation of treatment - Polarity - Lower values are better

Breast conservation rate

Outcome	Platinum and taxane, 4 week, N = 46	Anthracycline and taxane, 4 week, N = 41
Breast conservation rate No of events	n = 2 ; % = 4.3	n = 2 ; % = 4.9

Breast conservation rate - Polarity - Higher values are better

Short term adverse events: treatment-related morbidity

Outcome	Platinum and taxane, 4 week, N = 50	Anthracycline and taxane, 4 week, N = 50
Anaemia No of events	n = 7 ; % = 14	n = 5 ; % = 10
Diarrhoea No of events	n = 1 ; % = 2	n = 1 ; % = 2
Liver function tests Increased ALT, AST, and ALP No of events	n = 5 ; % = 10	n = 0 ; % = 0
Nausea or vomiting Nausea and vomiting reported separately No of events	n = 0 ; % = 0	n = 0 ; % = 0
Neutropenia No of events	n = 28 ; % = 56	n = 35 ; % = 70
Febrile neutropenia No of events	n = 4 ; % = 8	n = 7 ; % = 14

Anaemia - Polarity - Lower values are better

Diarrhoea - Polarity - Lower values are better

Liver function tests - Polarity - Lower values are better

Nausea or vomiting - Polarity - Lower values are better

Neutropenia - Polarity - Lower values are better

Febrile neutropenia - Polarity - Lower values are better

Long term adverse events: treatment-related morbidity

Outcome	Platinum and taxane, 4 week, N = 50	Anthracycline and taxane, 4 week, N = 50
Fatigue (grade 1/2) No of events	n = 24 ; % = 48	n = 22 ; % = 44
Fatigue (grade 3/4) No of events	n = 0 ; % = 0	n = 1 ; % = 2

Outcome	Platinum and taxane, 4 week, N = 50	Anthracycline and taxane, 4 week, N = 50
LVEF Over 10% reduction in LVEF after 2 cycles of neoadjuvant treatment No of events	n = 5 ; % = 11.9	n = 3 ; % = 7.7
LVEF Over 10% reduction in LVEF after 4 cycles of neoadjuvant treatment No of events	n = 3 ; % = 7.3	n = 1 ; % = 2.7
Peripheral neuropathy (grade 1/2) No of events	n = 6 ; % = 12	n = 7 ; % = 14
Peripheral neuropathy (grade 3/4) No of events	n = 0 ; % = 0	n = 0 ; % = 0

Fatigue (grade 1/2) - Polarity - Lower values are better

Fatigue (grade 3/4) - Polarity - Lower values are better

LVEF - Polarity - Lower values are better

LVEF - Polarity - Lower values are better

Peripheral neuropathy (grade 1/2) - Polarity - Lower values are better

Peripheral neuropathy (grade 3/4) - Polarity - Lower values are better

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

RoB objective outcomes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (Per-protocol analysis with participants excluded from analysis (5% in the platinum and taxane arm and 18% in the anthracycline and taxane arm))
Overall bias and Directness	Overall Directness	Directly applicable

RoB for adverse events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low (Intention-to-treat analysis for adverse events)
Overall bias and Directness	Overall Directness	Directly applicable

1 **TRYPHAENA**

2 **Schneeweiss, 2013**

Bibliographic Reference	Schneeweiss, A; Chia, S; Hickish, T; Harvey, V; Eniu, A; Hegg, R; Tausch, C; Seo, J H; Tsai, Y-F; Ratnayake, J; McNally, V; Ross, G; Cortes, J; Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA).; Annals of oncology : official journal of the European Society for Medical Oncology; 2013; vol. 24 (no. 9); 2278-84

3 **Schneeweiss, 2018**

Bibliographic Reference	Schneeweiss, Andreas; Chia, Stephen; Hickish, Tamas; Harvey, Vernon; Eniu, Alexandru; Waldron-Lynch, Maeve; Eng-Wong, Jennifer; Kirk, Sarah; Cortes, Javier; Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: Evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer.; European journal of cancer (Oxford, England : 1990); 2018; vol. 89; 27-35

4 **Study details**

Trial registration number and/or trial name	TRYPHAENA / NCT00976989
Study type	Randomised controlled trial (RCT)
Study location	Multicentre across 44 centres in 19 countries: (Bahamas, Bosnia and Herzegovina, Brazil, Canada, Croatia, Germany, Greece, Italy, Republic of Korea, Mexico, New Zealand, Portugal, Romania, Serbia, South Africa, Spain, Sweden, Switzerland, Taiwan, United Kingdom).
Study setting	Multicentre
Study dates	December 2009 and January 2011
Sources of funding	F. Hoffmann-La Roche Ltd funded the study.
Inclusion criteria	Female Aged ≥18 years Eastern Cooperative Oncology Group performance status 0 or 1 HER2 positive breast cancer Left ventricular ejection fraction ≥55% Untreated, operable, locally advanced or inflammatory breast cancer, with a primary tumour >2 cm
Exclusion criteria	Bilateral breast cancer Other malignancies

	except for carcinoma in situ of the cervix, basal cell carcinoma or squamous cell carcinoma of the skin Uncontrolled hypertension Metastatic breast cancer Any previous local or systemic breast cancer treatment Inadequate bone marrow Inadequate liver or kidney function History of myocardial infarction within the previous 6 months
Intervention(s)	Docetaxel plus carboplatin for six cycles, with pertuzumab plus trastuzumab in all cycles.
Comparator	Comparator A: 5-fluorouracil, epirubicin and cyclophosphamide (FEC) for three cycles followed by three cycles of docetaxel, with pertuzumab plus trastuzumab in all cycles. Comparator B: FEC for three cycles followed by three cycles of docetaxel, with pertuzumab and trastuzumab in cycles 4 to 6 only (i.e. with docetaxel).
Outcome measures	Pathological complete response Assessed locally at the time of surgery and defined as the absence of invasive neoplastic cells during microscopic assessment of the primary tumour in the breast and axilla (ypT0/Tis, ypN0) Overall survival Defined as the time from randomisation to death from any cause Disease-free survival Defined as the time from the first date of no disease i.e. date of surgery, to the first documentation of progressive disease (defined as the recurrence of ipsilateral invasive or non-invasive breast cancer, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer [excluding contralateral disease in situ], a distant disease recurrence or death) Adverse events: treatment-related morbidity Adverse events were monitored continuously and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Symptomatic left ventricular systolic dysfunction was reported as a serious adverse event Early cessation of treatment Withdrawal from neoadjuvant treatment Breast conservation rate Rate of breast-conserving surgery for patients for whom mastectomy was planned before treatment (T2−3)
Number of participants	225
Methods of analysis	Intention-to-treat analysis for pathological complete response, disease-free survival and overall survival
Additional comments	Trial authors reported that a substantial number of patients did not complete the 5-year post-randomisation follow-up at the time of clinical cut-off, therefore, they reported survival rates at 3 years to ensure the robustness of the data.

Study arms

Platinum and taxane (pertuzumab plus trastuzumab in all cycles) (N = 77)

Duration of follow-up	Median 60.9 months (interquartile range: 57.4 to 62.0)	Median 60.9 months (interquartile range: 57.4 to 62.0)
Loss to follow-up	2	2

Docetaxel plus carboplatin for six cycles, with pertuzumab plus trastuzumab in all cycles. All study drugs were administered intravenously, given consecutively on the same day in the sequence: trastuzumab (8 mg/kg initial dose, then 6 mg/kg), pertuzumab (840 mg then 420 mg), carboplatin dosed at AUC 6, docetaxel (75 mg/m2). Dose modifications of trastuzumab or pertuzumab were not permitted; docetaxel could be reduced to 75 mg/m2 and 60 mg/m2 (re-escalation not permitted). Carboplatin reductions were performed according to the local prescribing information.

Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles) (N = 73)

Duration of follow-up	Median 61.1 months (interquartile range: 59.4 to 61.8)	Median 61.1 months (interquartile range: 59.4 to 61.8)
Loss to follow-up	3	3

5-fluorouracil, epirubicin and cyclophosphamide (FEC) for three cycles followed by three cycles of docetaxel, with pertuzumab plus trastuzumab in all cycles. All study drugs were administered intravenously, given consecutively on the same day in the sequence: trastuzumab (8 mg/kg initial dose, then 6 mg/kg), pertuzumab (840 mg then 420 mg), FEC (5-fluorouracil 500 mg/m2, epirubicin 100 mg/m2 and cyclophosphamide 600 mg/m2) docetaxel (75 mg/m2 ; escalated to 100 mg/m2 if no dose-limiting toxicity before cycle 4). Dose modifications of trastuzumab or pertuzumab were not permitted; docetaxel could be reduced to 75 mg/m2 and 60 mg/m2 (re-escalation not permitted). FEC reductions were performed according to the local prescribing information.

Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6) (N = 75)

Duration of follow-up	Median 61.8 months (interquartile range: 59.4 to 63.6)	Median 61.8 months (interquartile range: 59.4 to 63.6)
Loss to follow-up	2	2

FEC for three cycles followed by three cycles of docetaxel, with pertuzumab and trastuzumab in cycles 4 to 6 only (i.e. with docetaxel). All study drugs were administered intravenously, given consecutively on the same day in the sequence: trastuzumab (8 mg/kg initial dose, then 6 mg/kg), pertuzumab (840 mg then 420 mg), FEC (5-fluorouracil 500 mg/m2, epirubicin 100 mg/m2 and cyclophosphamide 600 mg/m2) docetaxel (75 mg/m2 ; escalated to 100 mg/m2 if no dose-limiting toxicity before cycle 4). Dose modifications of trastuzumab or pertuzumab were not permitted; docetaxel could be reduced to 75 mg/m2 and 60 mg/m2 (re-escalation not permitted). FEC reductions were performed according to the local prescribing information.

1 **Characteristics**

2 **Arm-level characteristics**

Characteristic	Platinum and taxane (pertuzumab plus trastuzumab in all cycles) (N = 77)	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles) (N = 73)	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6) (N = 75)
Median age (years (median and range)) Custom value	50.0 years (30 to 81)	49.0 years (27 to 77)	49.0 years (24 to 75)
Race: Black No of events	n = 2 ; % = 2.6	n = 4 ; % = 5.5	n = 3 ; % = 4
Race: white No of events	n = 64 ; % = 83.1	n = 56 ; % = 76.7	n = 52 ; % = 69.3
Race Oriental No of events	n = 11 ; % = 14.3	n = 12 ; % = 16.4	n = 18 ; % = 24
Race: Other No of events	n = 0 ; % = 0	n = 1 ; % = 1.4	n = 0 ; % = 0
ECOG PS 0 No of events	n = 68 ; % = 88.3	n = 66 ; % = 90.4	n = 66 ; % = 88
ECOG PS 1 No of events	n = 9 ; % = 11.7	n = 6 ; % = 8.2	n = 9 ; % = 12
ECOG PS unknown No of events	n = 0 ; % = 0	n = 1 ; % = 1.4	n = 0 ; % = 0
Histological grade: well differentiated No of events	n = 2 ; % = 2.6	n = 3 ; % = 4.1	n = 2 ; % = 2.7
Histological grade: moderately differentiated No of events	n = 32 ; % = 41.6	n = 28 ; % = 38.4	n = 34 ; % = 45.3
Histological grade: poorly differentiated No of events	n = 27 ; % = 35.1	n = 25 ; % = 34.2	n = 26 ; % = 34.7
Histological grade: unknown No of events	n = 16 ; % = 20.8	n = 17 ; % = 23.3	n = 13 ; % = 17.3
Primary tumour size at baseline (mm (median and range)) by clinical breast examination	Median 50 mm (15 to 200)	Median 53 mm (10 to 220)	Median 49 mm (19 to 120)

Characteristic	Platinum and taxane (pertuzumab plus trastuzumab in all cycles) (N = 77)	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles) (N = 73)	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6) (N = 75)
Custom value			
ER positive and/or PR positive No of events	n = 40 ; % = 51.9	n = 39 ; % = 53.4	n = 35 ; % = 46.7
ER negative and PR negative No of events	n = 37 ; % = 48.1	n = 34 ; % = 46.6	n = 40 ; % = 53.3
LVEF (Central readings (median range)) Data not available for all randomised participants Sample size	n = 76	n = 72	n = 75
LVEF (Central readings (median range)) Data not available for all randomised participants Custom value	Median 72.9 (51 to 88)	Median 71.6 (55 to 89)	Median 72.0 (50 to 88)

Outcomes

Study timepoints

- 18 week (Pathological complete response was assessed at surgery after 18 weeks (6 cycles) of neoadjuvant treatment.)
- 3 year (Survival rates at 3 years)
- 28 day (Adverse events and serious adverse events were reportable during study treatment and up to 28 days after the last dose of study medication but not during post-treatment follow-up.)

Pathological complete response (after neoadjuvant chemotherapy, at surgery)

Outcome	Platinum and taxane (pertuzumab plus trastuzumab in all cycles), N = 77	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles), N = 73	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6), N = 75
Pathological complete response No of events	n = 49 ; % = 63.6	n = 41 ; % = 56.2	n = 41 ; % = 54.7

Pathological complete response - Polarity - Higher values are better

Data extracted from Schneeweiss et al. (2013). ypT0/is ypN0: no invasive tumour residues in the breast and lymph nodes, DCIS/LCIS in the breast at surgery allowed

Survival outcomes (follow-up 3 years)

Outcome	Platinum and taxane (pertuzumab plus trastuzumab in all cycles), N = 77	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles), N = 73	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6), N = 75
Overall survival No of events	n = 10; % = 13.0	n = 5; % = 6.8	n = 7; % = 9.3
Disease-free survival Sample size	**N = 72**	**N = 69**	**N = 67**
Disease-free survival No of events	n = 11; % = 15.3	n = 10; % = 14.5	n = 8; % = 11.9

Overall survival - Polarity - Higher values are better

Disease-free survival - Polarity - Higher values are better

Data extracted from Schneeweiss et al. (2018)

Early cessation of treatment (at the end of neoadjuvant chemotherapy)

Outcome	Platinum and taxane (pertuzumab plus trastuzumab in all cycles), N = 76	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles), N = 72	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6), N = 75
Early cessation of treatment Totals are number of people who entered neoadjuvant treatment No of events	n = 9 ; % = 11.8	n = 4 ; % = 5.6	n = 10 ; % = 13.3

Early cessation of treatment - Polarity - Lower values are better

Data extracted from Schneeweiss et al. (2013)

Breast conservation rate (after neoadjuvant chemotherapy, at surgery)

Outcome	Platinum and taxane (pertuzumab plus trastuzumab in all cycles), N = 37	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles), N = 46	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6), N = 36
Breast conserving surgery Among people who were planned for mastectomy	n = 10 ; % = 27	n = 10 ; % = 21.7	n = 6 ; % = 16.7

Outcome	Platinum and taxane (pertuzumab plus trastuzumab in all cycles), N = 37	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles), N = 46	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6), N = 36
No of events			

Breast conserving surgery - Polarity - Higher values are better

Data extracted from Schneeweiss et al. (2013)

Short term adverse events: treatment-related morbidity (grade 3 or more; during study treatment and up to 28 days after the last dose of study medication)

Outcome	Platinum and taxane (pertuzumab plus trastuzumab in all cycles), N = 76	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles), N = 72	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6), N = 75
Alopecia All grades No of events	n = 41 ; % = 53.9	n = 35 ; % = 48.6	n = 39 ; % = 52
Anaemia No of events	n = 13 ; % = 17.1	n = 1 ; % = 1.4	n = 2 ; % = 2.7
Diarrhoea No of events	n = 9 ; % = 11.8	n = 3 ; % = 4.2	n = 4 ; % = 5.3
Liver function tests ALT No of events	n = 3 ; % = 3.9	n = 0 ; % = 0	n = 0 ; % = 0
Vomiting No of events	n = 4 ; % = 5.3	n = 0 ; % = 0	n = 2 ; % = 2.7
Neutropenia No of events	n = 35 ; % = 46.1	n = 34 ; % = 47.2	n = 32 ; % = 42.7
Febrile neutropenia No of events	n = 13 ; % = 17.1	n = 13 ; % = 18.1	n = 7 ; % = 9.3

Alopecia - Polarity - Lower values are better

Anaemia - Polarity - Lower values are better

Diarrhoea - Polarity - Lower values are better

Liver function tests - Polarity - Lower values are better

Vomiting - Polarity - Lower values are better

Neutropenia - Polarity - Lower values are better

Febrile neutropenia - Polarity - Lower values are better

Data extracted from Schneeweiss et al. (2013). All short term adverse events are grade 3 or more apart from alopecia.

Long term adverse events: treatment-related morbidity (during study treatment and up to 28 days after the last dose of study medication)

Outcome	Platinum and taxane (pertuzumab plus trastuzumab in all cycles), N = 76	Anthracycline and taxane (pertuzumab plus trastuzumab in all cycles), N = 72	Anthracycline and taxane (pertuzumab plus trastuzumab in cycles 4 to 6), N = 75
Fatigue All grades No of events	n = 32 ; % = 42.1	n = 26 ; % = 36.1	n = 27 ; % = 36
Fatigue Grade 3 and more No of events	n = 3 ; % = 3.9	n = 0 ; % = 0	n = 0 ; % = 0
LVEF (grade not reported) decline 10% or more points from baseline to less than 50% No of events	n = 3 ; % = 3.9	n = 4 ; % = 5.6	n = 4 ; % = 5.3
Symptomatic left ventricular systolic dysfunction Grade 3 or more No of events	n = 0 ; % = 0	n = 0 ; % = 0	n = 2 ; % = 2.7

Fatigue - Polarity - Lower values are better

Fatigue - Polarity - Lower values are better

LVEF - Polarity - Lower values are better

Symptomatic left ventricular systolic dysfunction - Polarity - Lower values are better

Data extracted from Schneeweiss et al. (2013).

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

RoB for objective outcomes

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

RoB for adverse events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E – Forest plots

Pathological complete response

Figure 1 Pathological complete response

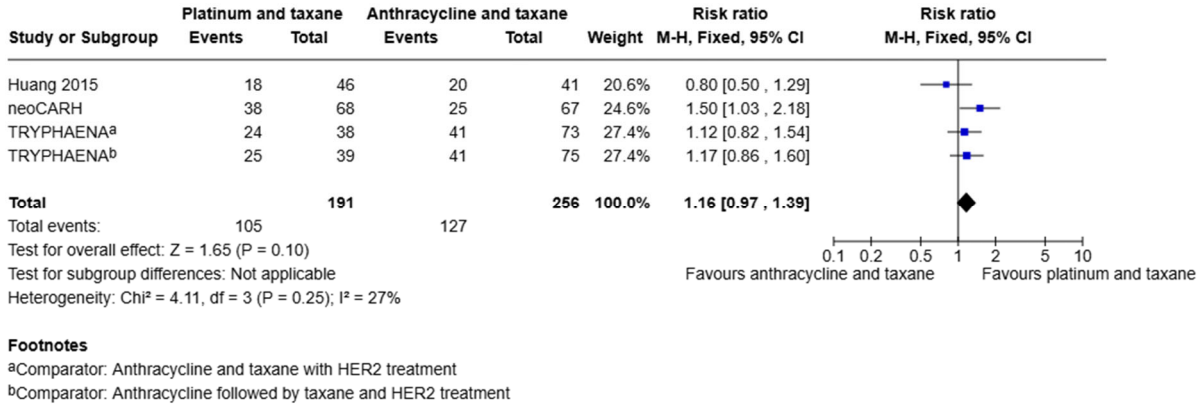


Figure 2 Pathological complete response: subgroup analysis by timing of anthracyclines delivery

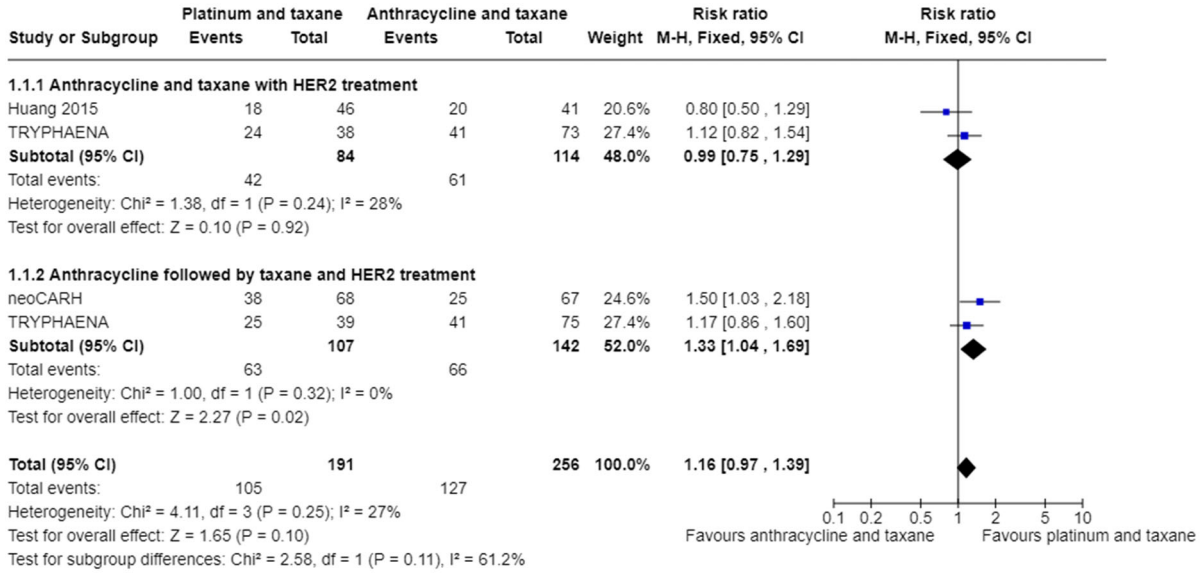
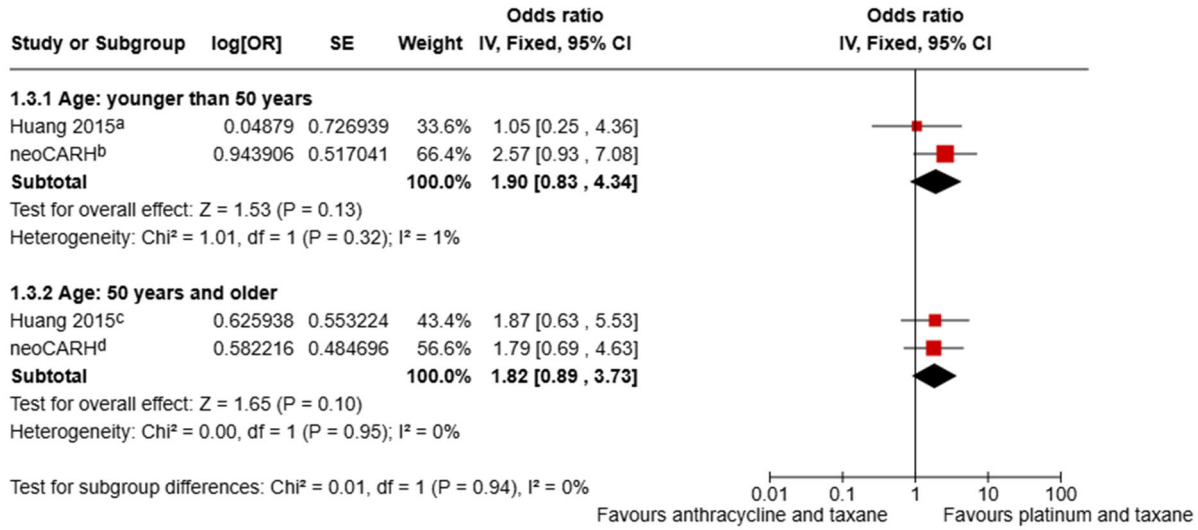


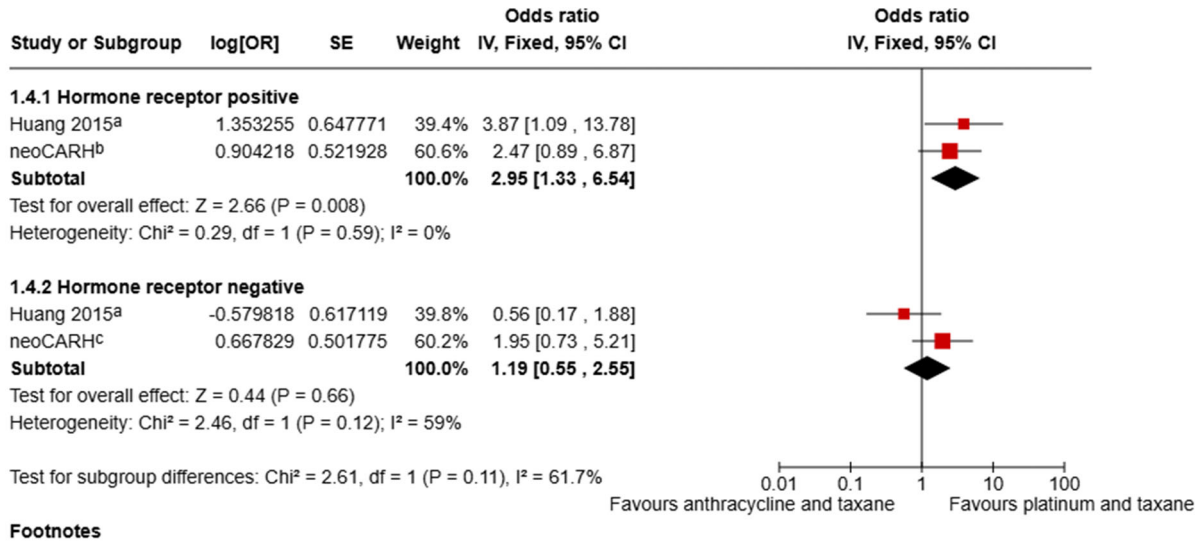
Figure 3 Pathological complete response: subgroup analysis by age



Footnotes

[a]Subgroup by age: 45 years or younger
[b]Subgroup by age: younger than 50 years
[c]Subgroup by age: over 45 years
[d]Subgroup by age: 50 years and older

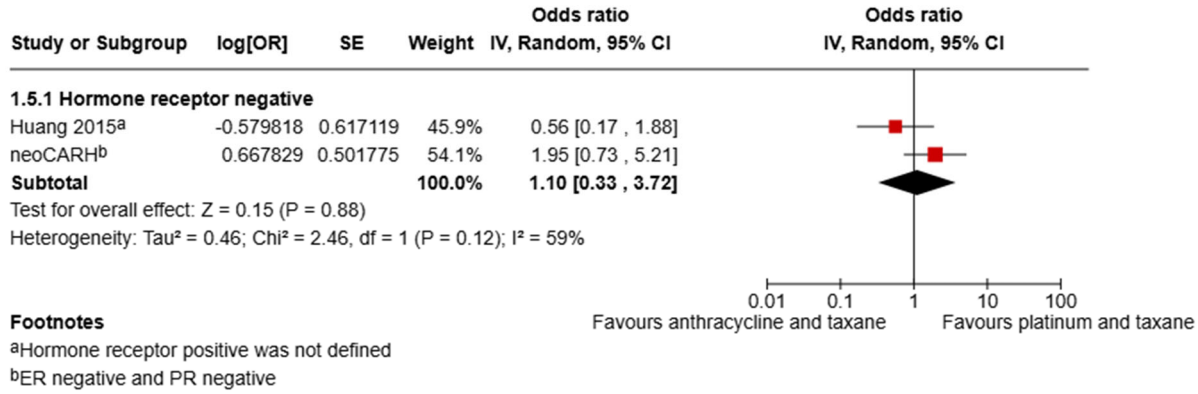
Figure 4 Pathological complete response: subgroup analysis by hormone receptor status (Fixed effect model for hormone receptor positive subgroup)



Footnotes

[a]Hormone receptor positive was not defined
[b]ER positive and/or PR positive
[c]ER negative and PR negative

Figure 5 Pathological complete response: subgroup analysis by hormone receptor status (Random effects model for hormone receptor negative subgroup)

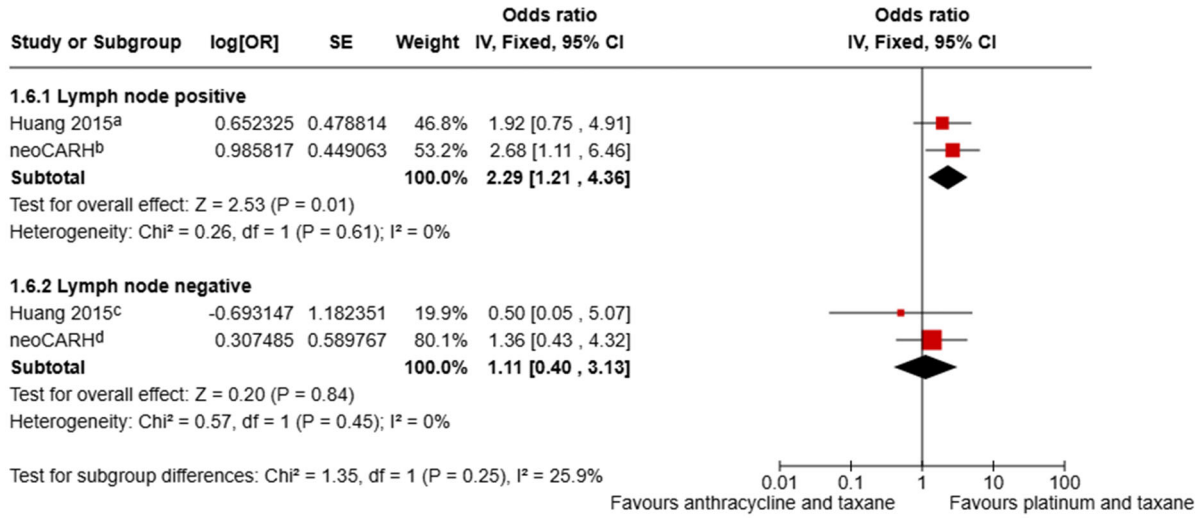


Footnotes

[a]Hormone receptor positive was not defined

[b]ER negative and PR negative

Figure 6 Pathological complete response: subgroup analysis by lymph node status



Footnotes

[a]Clinical lymph node stage (unclear which stages were regarded as positive)

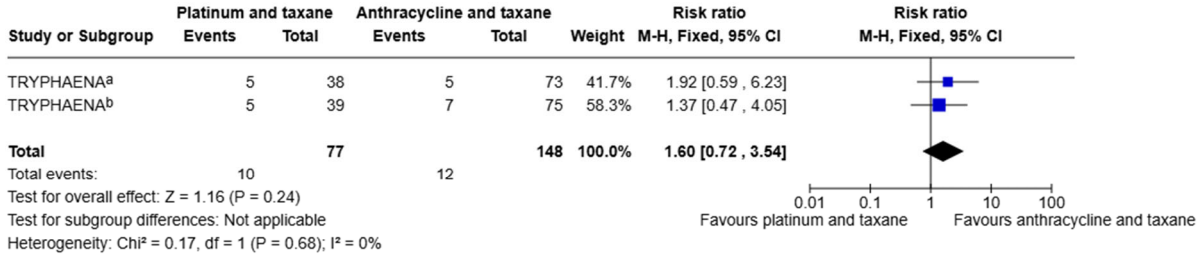
[b]Lymph node status (unclear if this was clinical or pathological and unclear which stages were regarded as positive)

[c]Clinical lymph node stage (unclear which stages were regarded as negative)

[d]Lymph node status (unclear if this was clinical or pathological and unclear which stages were regarded as negative)

Survival outcomes

Figure 7 All-cause mortality at 3 years (proxy for overall survival)

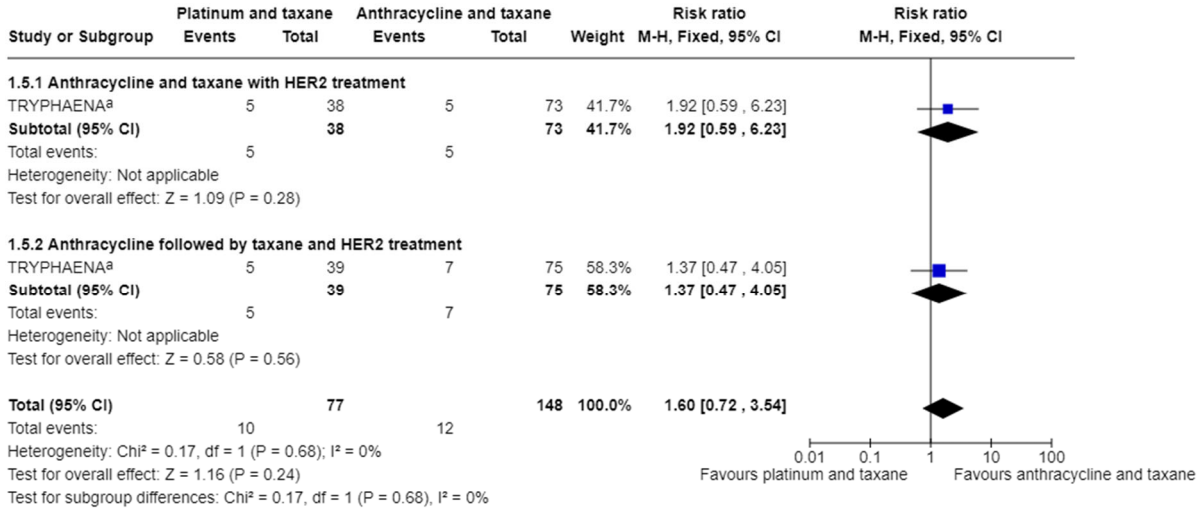


Footnotes

[a]Follow-up: 3 years. Comparator: Anthracycline and taxane with HER2 treatment

[b]Follow-up: 3 years. Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 8 All-cause mortality at 3 years (proxy for overall survival): subgroup analysis by timing of anthracyclines delivery



Footnotes

[a]Follow-up: 3 years

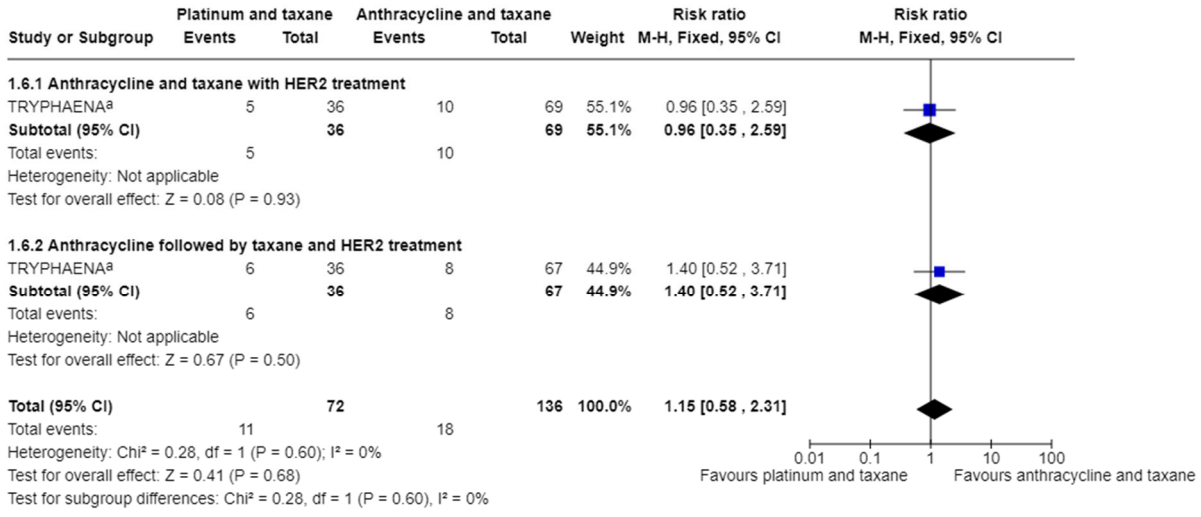
Figure 9 Recurrence or death following a recurrence (proxy for disease-free survival)

Footnotes

[a]Follow-up: 3 years. Comparator: Anthracycline and taxane with HER2 treatment

[b]Follow-up: 3 years. Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 10 Recurrence or death following a recurrence (proxy for disease-free survival): subgroup analysis by timing of anthracyclines delivery



Footnotes

[a]Follow-up: 3 years

Adherence

Figure 11 Adherence (early cessation of treatment)

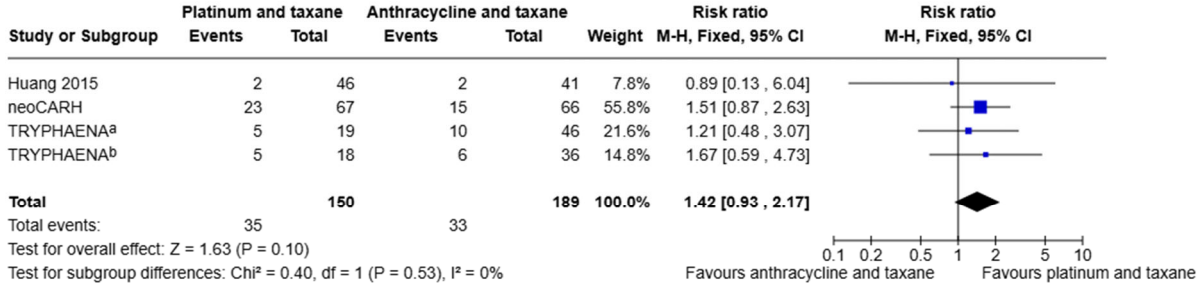
Footnotes

[a]Comparator: Anthracycline and taxane with HER2 treatment

[b]Comparator: Anthracycline followed by taxane and HER2 treatment

Breast conservation rate

Figure 12 Breast conservation rate



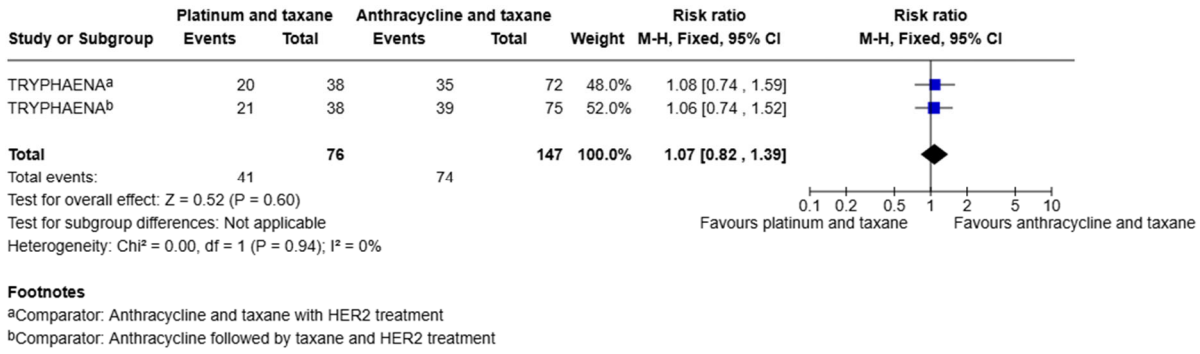
Footnotes

[a]Comparator: Anthracycline and taxane with HER2 treatment

[b]Comparator: Anthracycline followed by taxane and HER2 treatment

Short term adverse events

Figure 13 Short term adverse events: alopecia (all grades)

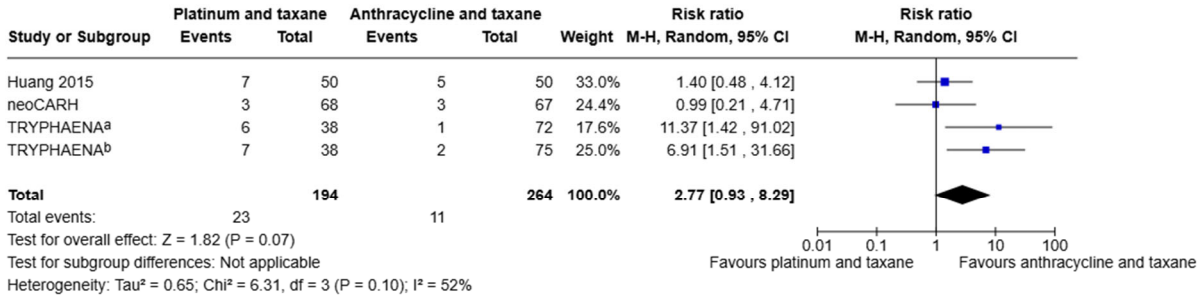


Footnotes

[a]Comparator: Anthracycline and taxane with HER2 treatment

[b]Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 14 Short term adverse events: anaemia (grades 3 to 4)

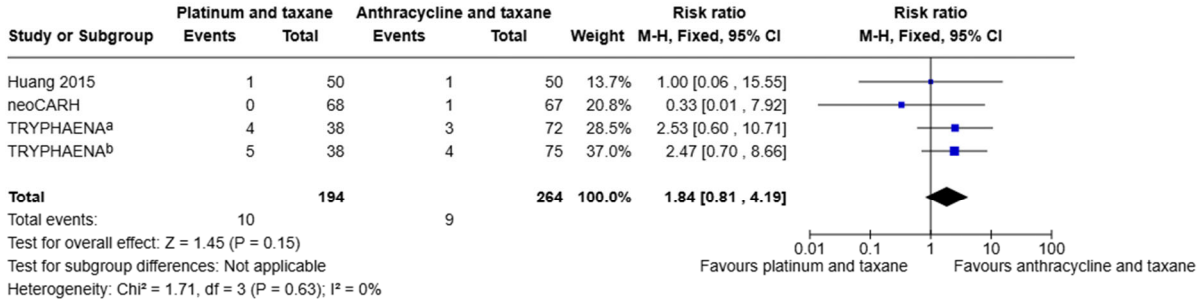


Footnotes

[a]Comparator: Anthracycline and taxane with HER2 treatment

[b]Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 15 Short term adverse events: diarrhoea (grades 3 to 4)

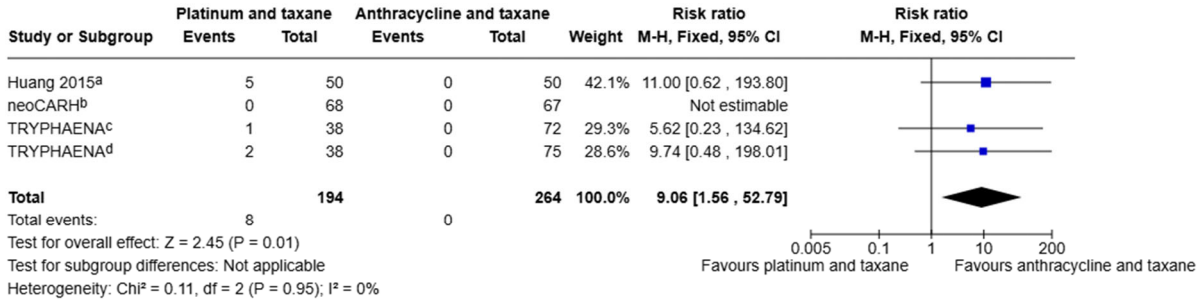


Footnotes

[a]Comparator: Anthracycline and taxane with HER2 treatment

[b]Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 16 Short term adverse events: liver function problems (combined: increased ALT, AST and ALP; grades 3 to 4)



Footnotes

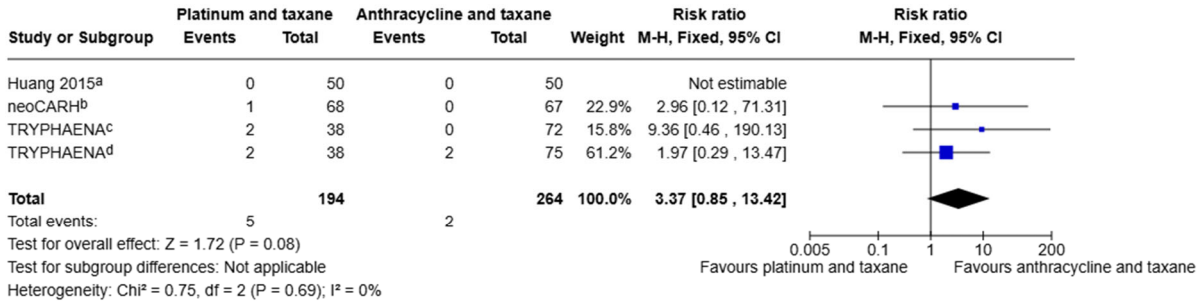
[a]Increased ALT, AST and ALP

[b]Increased ALT

[c]Increased ALT. Comparator: Anthracycline and taxane with HER2 treatment

[d]Increased ALT. Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 17 Short term adverse events: nausea and vomiting (grades 3 to 4)



Footnotes

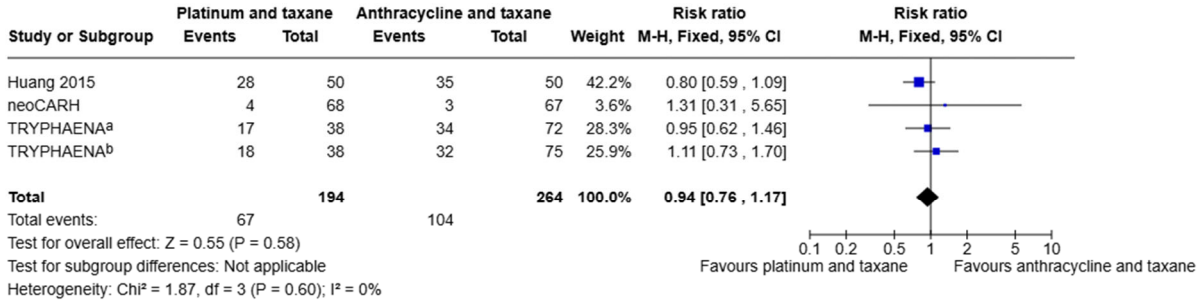
[a]Nausea and vomiting

[b]Vomiting

[c]Vomiting. Comparator: Anthracycline and taxane with HER2 treatment

[d]Vomiting. Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 18 Short term adverse events: neutropenia (grades 3 to 4)

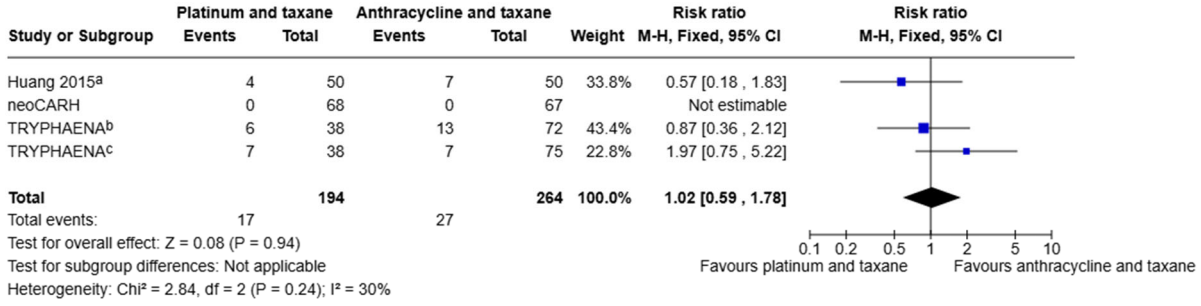


Footnotes

[a]Comparator: Anthracycline and taxane with HER2 treatment

[b]Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 19 Short term adverse events: neutropenic sepsis (grades 3 to 4)



Footnotes

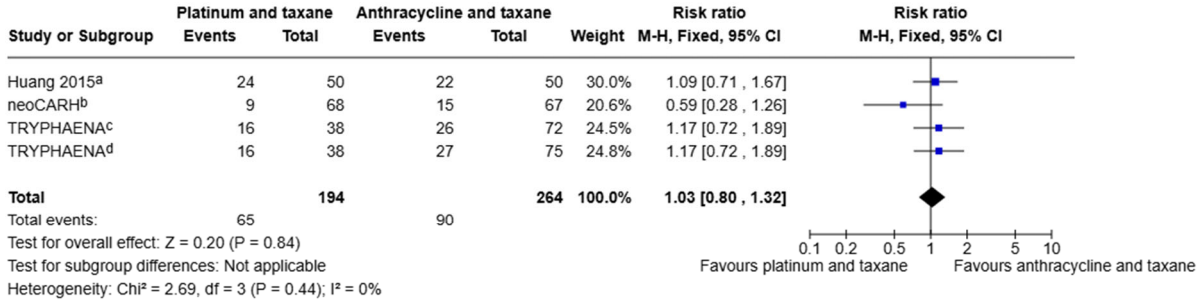
[a]Reported as febrile neutropenia

[b]Reported as febrile neutropenia. Comparator: Anthracycline and taxane with HER2 treatment

[c]Reported as febrile neutropenia. Comparator: Anthracycline followed by taxane and HER2 treatment

Long term adverse events

Figure 20 Long term adverse events: fatigue (see footnote for grades)



Footnotes

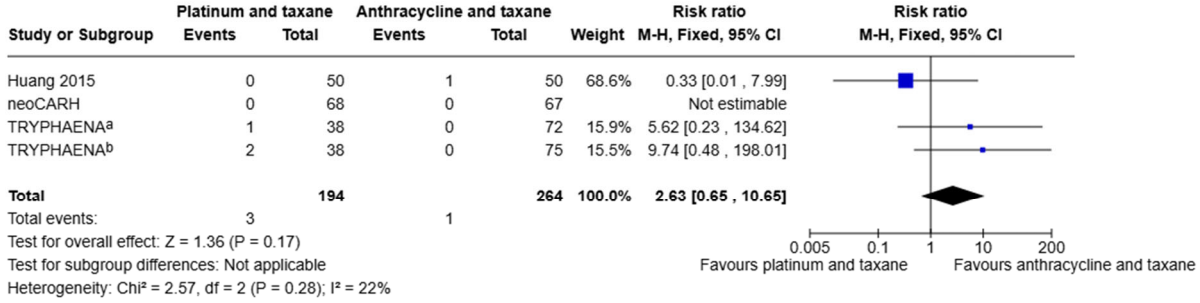
[a]Grade 1/2

[b]Any grade

[c]All grades. Comparator: Anthracycline and taxane with HER2 treatment

[d]All grades. Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 21 Long term adverse events: fatigue (grades 3 to 4)



Footnotes

[a]Comparator: Anthracycline and taxane with HER2 treatment

[b]Comparator: Anthracycline followed by taxane and HER2 treatment

Figure 22 Long term adverse events: LVEF (over 10% reduction after 2 cycles of neoadjuvant treatment; grade not reported)

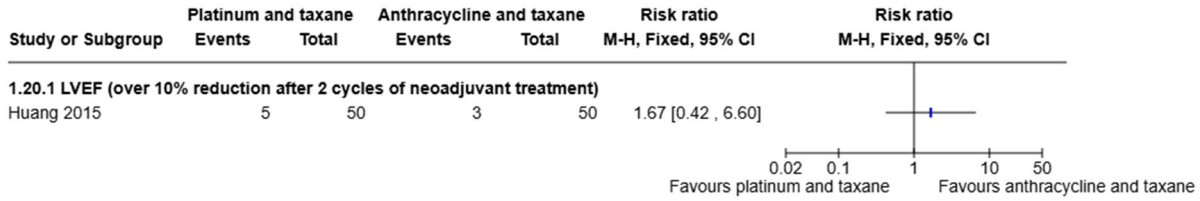
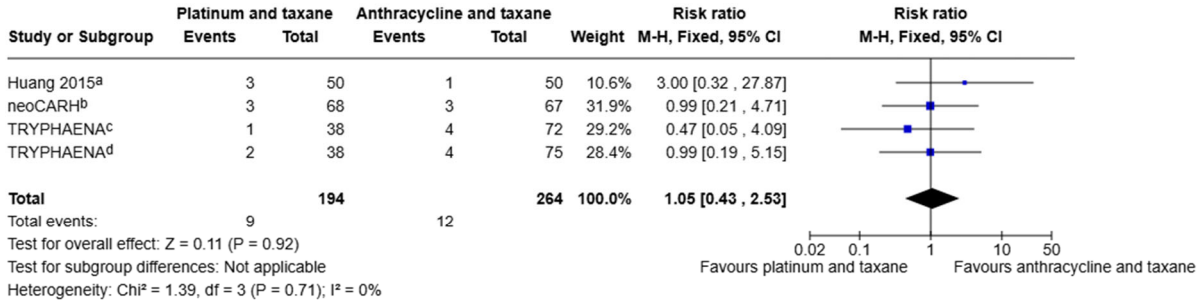


Figure 23 Long term adverse events: LVEF (over 10% reduction during or after 4 cycles of neoadjuvant treatment; CTCAE not used for this outcome so grade of severity not reported)



Footnotes

[a]Over 10% reduction of LVEF after 4 cycles of neoadjuvant treatment

[b]Decline of 10% or more and below 50% during neoadjuvant treatment

[c]Decline of 10% or more and below 50% during neoadjuvant treatment. Comparator: Anthracycline and taxane with HER2 treatment

[d]Decline of 10% or more and below 50% during neoadjuvant treatment. Comparator: Anthracycline followed by taxane and HER2 treatment

CTCAE: common terminology criteria for adverse events

Figure 24 Long term adverse events: symptomatic left ventricular systolic dysfunction (grades 3 to 4)

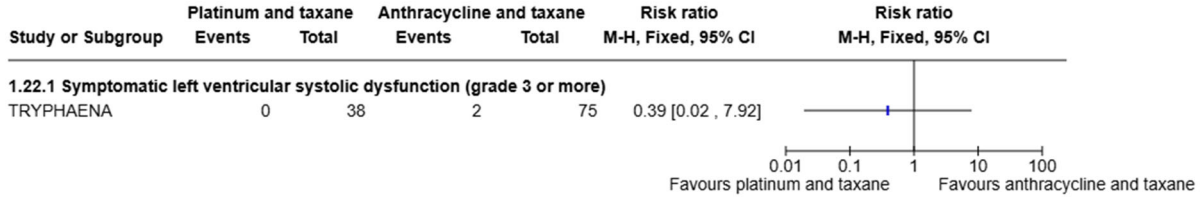
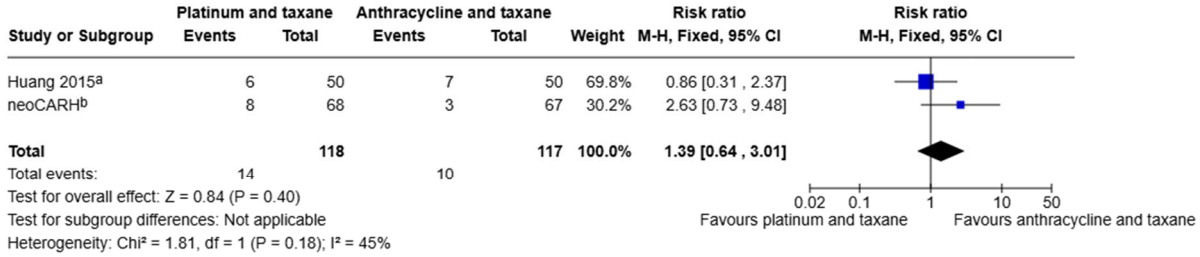


Figure 25 Long term adverse events: peripheral neuropathy (see footnote for grades)



Footnotes

[a]Grade 1/2

[b]Any grade

Appendix F – GRADE tables

Pathological complete response

Table 11 Pathological complete response

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
Pathological complete response (RR greater than 1 favours platinum and taxane)												
3	randomised trials	not serious	not serious	not serious	very serious[a]	none	105/191 (55.0%)	127/256 (49.6%)	RR 1.16 (0.97 to 1.39)	79 more per 1,000 (from 15 fewer to 193 more)	Low	CRITICAL
Pathological complete response - Subgroup by timing of delivery: Anthracycline and taxane with HER2 treatment (RR greater than 1 favours platinum and taxane)												
2	randomised trials	not serious	not serious	not serious	very serious[a]	none	42/84 (50.0%)	61/114 (53.5%)	RR 0.99 (0.75 to 1.29)	5 fewer per 1,000 (from 134 fewer to 155 more)	Low	CRITICAL
Pathological complete response - Subgroup by timing of delivery: Anthracycline followed by taxane and HER2 treatment (RR greater than 1 favours platinum and taxane)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum and taxane**	**Anthracycline and taxane**	**Relative (95% CI)**	**Absolute (95% CI)**		
2	randomised trials	not serious	not serious	not serious	serious[b]	none	63/107 (58.9%)	66/142 (46.5%)	RR 1.33 (1.04 to 1.69)	153 more per 1,000 (from 19 more to 321 more)	Moderate	CRITICAL
Pathological complete response - Subgroup by age: younger than 50 years (OR greater than 1 favours platinum and taxane)												
2	randomised trials	serious[c]	not serious	not serious	very serious[a]	none	Not reported	Not reported	OR 1.90 (0.83 to 4.34)	Not calculable	Very low	CRITICAL
Pathological complete response - Subgroup by age: 50 years and older (OR greater than 1 favours platinum and taxane)												
2	randomised trials	serious[c]	not serious	not serious	very serious[a]	none	Not reported	Not reported	OR 1.82 (0.89 to 3.73)	Not calculable	Very low	CRITICAL
Pathological complete response - Subgroup by hormone receptor status: HR positive (OR greater than 1 favours platinum and taxane)												
2	randomised trials	serious[c]	not serious	not serious	very serious[a]	none	Not reported	Not reported	OR 2.95 (1.33 to 6.54)	Not calculable	Very low	CRITICAL
Pathological complete response - Subgroup by hormone receptor status: HR negative (OR greater than 1 favours platinum and taxane) RE model (I2>50%)												
2	randomised trials	serious[c]	serious[d]	not serious	very serious[a]	none	Not reported	Not reported	OR 1.10 (0.33 to 3.72)	Not calculable	Very low	CRITICAL
Pathological complete response - Subgroup by lymph node status: Lymph node positive (OR greater than 1 favours platinum and taxane)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[c]	not serious	not serious	serious[b]	none	Not reported	Not reported	OR 2.29 (1.21 to 4.36)	Not calculable	Low	CRITICAL
Pathological complete response - Subgroup by lymph node status: Lymph node negative (OR greater than 1 favours platinum and taxane)												
2	randomised trials	serious[c]	not serious	not serious	very serious[a]	none	Not reported	Not reported	OR 1.11 (0.40 to 3.13)	Not calculable	Very low	CRITICAL

CI: confidence interval; cN: clinical node status; ER: oestrogen receptor; OR: odds ratio; PR: progesterone receptor; RR: risk ratio

Explanations

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

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

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

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

Survival outcomes

Table 12 Survival outcomes

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (proxy for overall survival) (RR less than 1 favours platinum and taxane)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	10/77 (13.0%)	12/148 (8.1%)	RR 1.60 (0.72 to 3.54)	49 more per 1,000 (from 23 fewer to 206 more)	Very low	CRITICAL
All-cause mortality (proxy for overall survival) - Subgroup by timing of delivery: Anthracycline and taxane with HER2 treatment (RR less than 1 favours platinum and taxane)												
1	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	5/38 (13.2%)	5/73 (6.8%)	RR 1.92 (0.59 to 6.23)	63 more per 1,000 (from 28 fewer to 358 more)	Very low	CRITICAL
All-cause mortality (proxy for overall survival) - Subgroup by timing of delivery: Anthracycline followed by taxane and HER2 treatment (RR less than 1 favours platinum and taxane)												
1	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	5/39 (12.8%)	7/75 (9.3%)	RR 1.37 (0.47 to 4.05)	35 more per 1,000 (from 49 fewer to 285 more)	Very low	CRITICAL
Recurrence or death following a recurrence (proxy for disease-free survival) (RR less than 1 favours platinum and taxane)												
1	randomised trials	not serious	serious[b]	not serious	very seriousa	none	11/72 (15.3%)	18/136 (13.2%)	RR 1.15 (0.58 to 2.31)	20 more per 1,000 (from 56 fewer to 173 more)	Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum and taxane**	**Anthracycline and taxane**	**Relative (95% CI)**	**Absolute (95% CI)**		
Recurrence or death following a recurrence (proxy for disease-free survival) - Subgroup by timing of delivery: Anthracycline and taxane with HER2 treatment (RR less than 1 favours platinum and taxane)												
1	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	5/36 (13.9%)	10/69 (14.5%)	RR 0.96 (0.35 to 2.59)	6 fewer per 1,000 (from 94 fewer to 230 more)	Very low	CRITICAL
Recurrence or death following a recurrence (proxy for disease-free survival) - Subgroup by timing of delivery: Anthracycline followed by taxane and HER2 treatment (RR less than 1 favours platinum and taxane)												
1	randomised trials	not serious	serious[b]	not serious	very serious[a]	none	6/36 (16.7%)	8/67 (11.9%)	RR 1.40 (0.52 to 3.71)	48 more per 1,000 (from 57 fewer to 324 more)	Very low	CRITICAL

CI: confidence interval; OR: odds ratio; RR: risk ratio

Explanations

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

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

Adherence (early cessation of treatment)

Table 13 Adherence (early cessation of treatment)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
Adherence (early cessation of treatment) (RR less than 1 favours platinum and taxane)												
3	randomised trials	not serious	not serious	not serious	very serious[a]	none	14/194 (7.2%)	23/264 (8.7%)	RR 0.91 (0.49 to 1.70)	8 fewer per 1,000 (from 44 fewer to 61 more)	Low	IMPORTANT

CI: confidence interval; OR: odds ratio; RR: risk ratio

Explanations

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

Breast conservation rate

Table 14 Breast conservation rate

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
Breast conservation rate (RR greater than 1 favours platinum and taxane)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
3	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	35/150 (23.3%)	33/189 (17.5%)	RR 1.42 (0.93 to 2.17)	73 more per 1,000 (from 12 fewer to 204 more)	Very low	IMPORTANT

CI: confidence interval; OR: odds ratio; RR: risk ratio

Explanations

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

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

Short term adverse events

Table 15 Short term adverse events

All extracted for grade 3 to 4, apart from alopecia, which was reported for all grades.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
Alopecia												
Alopecia (RR less than 1 favours platinum and taxane)												
1 (TRYPHAENA)	randomised trials	not serious	serious[e]	not serious	very serious[a]	none	41/76 (53.9%)	74/147 (50.3%)	RR 1.07 (0.82 to 1.39)	35 more per 1,000 (from 91 fewer to 196 more)	Very low	IMPORTANT
Anaemia												
Anaemia (RR less than 1 favours platinum and taxane) Random effects model (I2>50%)												
3 (Huang 2015, neoCARH, TRYPHAENA)	randomised trials	serious[c]	serious[d]	not serious	very serious[a]	none	23/194 (11.9%)	11/264 (4.2%)	RR 2.77 (0.93 to 8.29)	74 more per 1,000 (from 3 fewer to 304 more)	Very low	IMPORTANT
Diarrhoea												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum and taxane**	**Anthracycline and taxane**	**Relative (95% CI)**	**Absolute (95% CI)**		
Diarrhoea (RR less than 1 favours platinum and taxane)												
3 (Huang 2015, neoCARH, TRYPHAENA)	randomised trials	not serious	not serious	not serious	very serious[a]	none	10/194 (5.2%)	9/264 (3.4%)	RR 1.84 (0.81 to 4.19)	29 more per 1,000 (from 6 fewer to 109 more)	Low	IMPORTANT
Liver function												
Liver function (RR less than 1 favours platinum and taxane)												
2 (Huang 2015, TRYPHAENA)	randomised trials	not serious	not serious	not serious	serious[b]	none	8/126 (6.3%)	0/197 (0.0%)	RR 9.06 (1.56 to 52.79)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Moderate	IMPORTANT
Nausea or vomiting												
Nausea or vomiting (RR less than 1 favours platinum and taxane)												
2 (neoCARH, TRYPHAENA)	randomised trials	not serious	not serious	not serious	very serious[a]	none	5/144 (3.5%)	2/214 (0.9%)	RR 3.37 (0.85 to 13.42)	22 more per 1,000 (from 1 fewer to 116 more)	Low	IMPORTANT
Neutropenia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
Neutropenia (RR less than 1 favours platinum and taxane)												
3 (Huang 2015, neoCARH, TRYPHAENA)	randomised trials	not serious	not serious	not serious	very serious[a]	none	67/194 (34.5%)	104/264 (39.4%)	RR 0.94 (0.76 to 1.17)	24 fewer per 1,000 (from 95 fewer to 67 more)	Low	IMPORTANT
Neutropenic sepsis												
Neutropenic sepsis (RR less than 1 favours platinum and taxane)												
2 (Huang 2015, TRYPHAENA)	randomised trials	not serious	not serious	not serious	very serious[a]	none	17/126 (13.5%)	27/197 (13.7%)	RR 1.02 (0.59 to 1.78)	3 more per 1,000 (from 56 fewer to 107 more)	Low	IMPORTANT

CI: confidence interval; OR: odds ratio; RR: risk ratio

Explanations

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

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

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

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

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

Long term adverse events

Table 16 Long term adverse events

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Platinum and taxane**	**Anthracycline and taxane**	**Relative (95% CI)**	**Absolute (95% CI)**		
Fatigue												
Fatigue (any grade or grade 1/2) (RR less than 1 favours platinum and taxane)												
3	randomised trials	serious[b]	not serious	not serious	very serious[a]	none	65/194 (33.5%)	90/264 (34.1%)	RR 1.03 (0.80 to 1.32)	10 more per 1,000 (from 68 fewer to 109 more)	Very low	IMPORTANT
Fatigue (grades 3 to 4) (RR less than 1 favours platinum and taxane)												
2	randomised trials	not serious	not serious	not serious	very serious[a]	none	3/126 (2.4%)	1/197 (0.5%)	RR 2.63 (0.65 to 10.65)	8 more per 1,000 (from 2 fewer to 49 more)	Low	IMPORTANT
Left ventricular ejection fraction (LVEF)												
LVEF (over 10% reduction after 2 cycles of neoadjuvant treatment) (RR less than 1 favours platinum and taxane)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	serious[d]	not serious	very serious[a]	none	5/50 (10.0%)	3/50 (6.0%)	RR 167.00 (0.42 to 6.60)	1,000 more per 1,000 (from 35 fewer to 336 more)	Very low	IMPORTANT
LVEF (over 10% reduction during or after 4 cycles of neoadjuvant treatment) (RR less than 1 favours platinum and taxane)												
3	randomised trials	not serious	not serious	not serious	very serious[a]	none	9/194 (4.6%)	12/264 (4.5%)	RR 1.05 (0.43 to 2.53)	2 more per 1,000 (from 26 fewer to 70 more)	Low	IMPORTANT
Symptomatic left ventricular systolic dysfunction												
Symptomatic left ventricular systolic dysfunction (grade 3 or more) (RR less than 1 favours platinum and taxane)												
1	randomised trials	not serious	serious[d]	not serious	very serious[a]	none	0/38 (0.0%)	2/75 (2.7%)	RR 0.39 (0.02 to 7.92)	16 fewer per 1,000 (from 26 fewer to 185 more)	Very low	IMPORTANT
Peripheral neuropathy												
Peripheral neuropathy (any grade or grade 1/2) (RR less than 1 favours platinum and taxane)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Platinum and taxane	Anthracycline and taxane	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	not serious	serious[c]	not serious	very serious[a]	none	14/118 (11.9%)	10/117 (8.5%)	RR 1.39 (0.64 to 3.01)	33 more per 1,000 (from 31 fewer to 172 more)	Very low	IMPORTANT

CI: confidence interval; OR: odds ratio; RR: risk ratio

Explanations

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

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

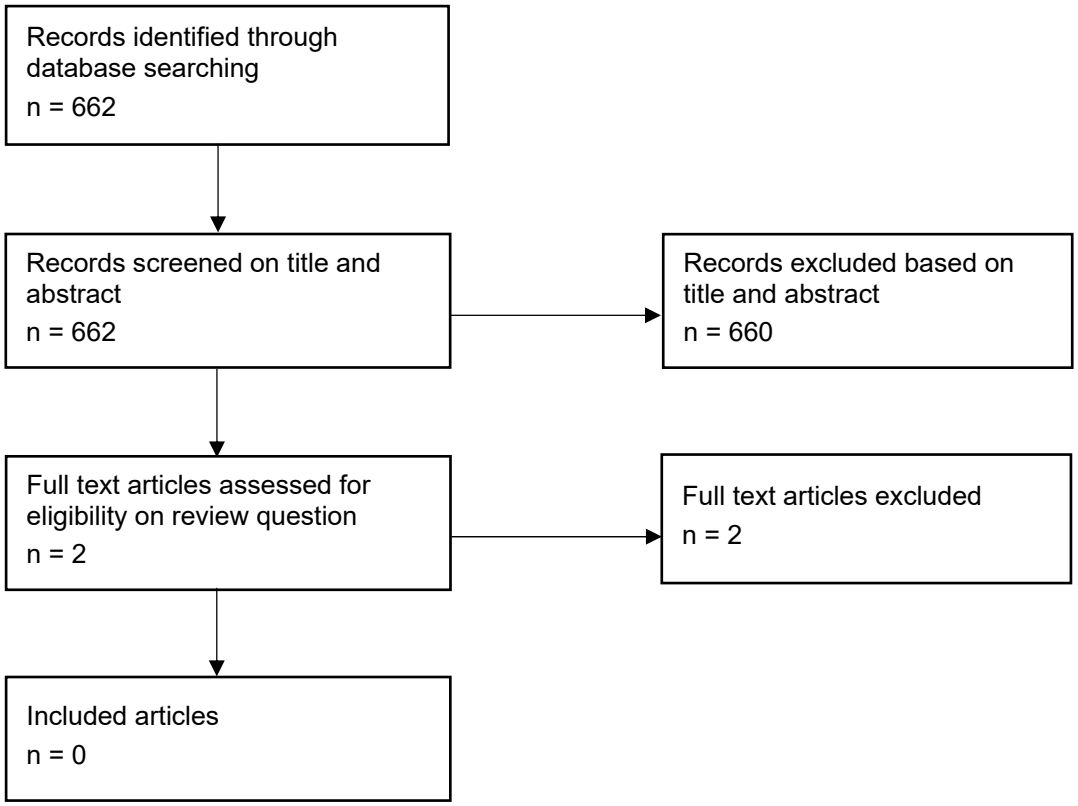
c. I2 was between 41% and 60%, outcome was downgraded one level

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

Table 17 Short and long term adverse events that were not reported by the included studies (no data reported on these adverse events at all)

Short term adverse events
• Mucositis
Long term adverse events
• Decreased cognitive function
• Incidence of new, non-breast primary cancer
• Ovarian function (fertility)

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was identified as relevant for this evidence review.

Appendix I – Health economic model

No economic modelling was conducted for this review question.

1 Appendix J – Excluded studies

2 Effectiveness studies

Study	Reason
Chen, D., Jin, L., Xu, Y. et al. (2021) ErbB inhibitors as neoadjuvant therapy for triple-positive breast cancer: A network meta-analysis. American Journal of Translational Research 13(11): 12129-12140	- Systematic review used as source of primary studies
Chen, W, He, J, Wu, H et al. (2014) Efficacy observation of TCH/TAC neoadjuvant chemotherapy in treatment of HER-2 over-expressing breast cancer. Chinese journal of clinical oncology 41(6): 373-376	- Study not reported in English Chinese
Clavarezza, Matteo, Puntoni, Matteo, Gennari, Alessandra et al. (2016) Dual Block with Lapatinib and Trastuzumab Versus Single-Agent Trastuzumab Combined with Chemotherapy as Neoadjuvant Treatment of HER2-Positive Breast Cancer: A Meta-analysis of Randomized Trials. Clinical cancer research : an official journal of the American Association for Cancer Research 22(18): 4594-603	- Comparator in study does not match that specified in protocol Trials compared neoadjuvant dual block with lapatinib and trastuzumab plus chemotherapy versus trastuzumab alone plus chemo (1 study included platinum therapy but all participants underwent treatment with platinum).
Ginzac, Angeline, Molnar, Ioana, Durando, Xavier et al. (2024) Neoadjuvant anthracycline-based (5-FEC) or anthracycline-free (docetaxel/carboplatin) chemotherapy plus trastuzumab and pertuzmab in HER2 + BC patients according to their TOP2A: a multicentre, open-label, non-randomized phase II trial. Breast cancer research and treatment 205(2): 267-279	- Not a relevant study design Non-randomised phase II trial
Gunasekara ADM, Anothaisintawee T, Youngkong S et al. (2022) Neoadjuvant Treatment with HER2-Targeted Therapies in HER2-Positive Breast Cancer: A Systematic Review and Network Meta-Analysis. Cancers 14(3)	- Comparator in study does not match that specified in protocol Some trials with neoadjuvant chemotherapy regimens containing platinum and taxane in both arms or platinum and taxane in 1 arm and no anthracycline in the comparator arm
Karakatsanis, A., Tasoulis, M.K., Warnberg, F. et al. (2018) Meta-analysis of neoadjuvant therapy and its impact in facilitating breast conservation in operable	- Systematic review used as source of primary studies

Study	Reason
breast cancer. British Journal of Surgery 105(5): 469-481	
Mittal, Abhenil, Tamimi, Faris, Molto, Consolacion et al. (2023) Three-year disease-free survival in randomized trials of neoadjuvant chemotherapy and HER2-targeted therapy in breast cancer: A meta-analysis. Critical reviews in oncology/hematology 181: 103880	- Systematic review used as source of primary studies
Nagayama, Aiko, Hayashida, Tetsu, Jinno, Hiromitsu et al. (2014) Comparative effectiveness of neoadjuvant therapy for HER2-positive breast cancer: a network meta-analysis. Journal of the National Cancer Institute 106(9)	- Comparator in study does not match that specified in protocol One trial with neoadjuvant chemotherapy regimen containing platinum and taxane in both arms
Nakashoji, Ayako, Hayashida, Tetsu, Yokoe, Takamichi et al. (2018) The updated network meta-analysis of neoadjuvant therapy for HER2-positive breast cancer. Cancer treatment reviews 62: 9-17	- Comparator in study does not match that specified in protocol Comparator in study does not match that specified in protocol (One study with platinum but all participants underwent treatment with platinum)
Pathak, M., Deo, S.V., Dwivedi, S.N. et al. (2020) Regimens of neo-adjuvant chemotherapy in the treatment of breast cancer: A systematic review & network meta-analysis with PRISMA-NMA compliance. Critical Reviews in Oncology/Hematology 153: 103015	- Comparator in study does not match that specified in protocol One study with platinum but all participants underwent treatment with anthracycline and they had TNBC
Petrelli, F., Barni, S., Bregni, G. et al. (2016) Platinum salts in advanced breast cancer: a systematic review and meta-analysis of randomized clinical trials. Breast Cancer Research and Treatment 160(3): 425-437	- Data not reported in an extractable format Data was not reported separately for people with HER2 positive breast cancer
Takano, Toshimi, Masuda, Norikazu, Ito, Mitsuya et al. (2024) Long-term outcomes of neoadjuvant trastuzumab emtansine + pertuzumab (T-DM1 + P) and docetaxel + carboplatin + trastuzumab + pertuzumab (TCbHP) for HER2-positive primary breast cancer: results of the randomized phase 2 JBCRG20 study (Neo-peaks). Breast cancer research and treatment	- Comparator in study does not match that specified in protocol Comparator regimen does not contain an anthracycline
Van Belle, H., Hurvitz, S.A., Gilbar, P.J. et al. (2021) Systematic review and meta-	- Data not reported in an extractable format

Study	Reason
analysis of febrile neutropenia risk with TCH(P) in HER2-positive breast cancer. Breast Cancer Research and Treatment 190(3): 357-372	Febrile neutropenia was not reported for the comparison in the protocol: taxane and platinum versus taxane and anthracycline
van der Voort, Anna, van Ramshorst, Mette S, van Werkhoven, Erik D et al. (2021) Three-Year Follow-up of Neoadjuvant Chemotherapy With or Without Anthracyclines in the Presence of Dual ERBB2 Blockade in Patients With ERBB2-Positive Breast Cancer: A Secondary Analysis of the TRAIN-2 Randomized, Phase 3 Trial. JAMA oncology 7(7): 978-984	- Comparator in study does not match that specified in protocol Platinum was also included in the comparator arm
van Ramshorst, Mette S, van der Voort, Anna, van Werkhoven, Erik D et al. (2018) Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual HER2 blockade for HER2-positive breast cancer (TRAIN-2): a multicentre, open-label, randomised, phase 3 trial. The Lancet. Oncology 19(12): 1630-1640	- Comparator in study does not match that specified in protocol Platinum was also included in the comparator arm
van Ramshorst, Mette S, van Werkhoven, Erik, Honkoop, Aafke H et al. (2016) Toxicity of dual HER2-blockade with pertuzumab added to anthracycline versus non-anthracycline containing chemotherapy as neoadjuvant treatment in HER2-positive breast cancer: The TRAIN-2 study. Breast (Edinburgh, Scotland) 29: 153-9	- Comparator in study does not match that specified in protocol Platinum was also included in the comparator arm
Villacampa, Guillermo, Matikas, Alexios, Oliveira, Mafalda et al. (2023) Landscape of neoadjuvant therapy in HER2-positive breast cancer: a systematic review and network meta-analysis. European journal of cancer (Oxford, England : 1990) 190: 112885	- Systematic review used as source of primary studies
Yang, Ciqiu, Li, Peiyong, Chen, Yitian et al. (2024) Pooled analysis of NeoCARH and NeoCART trials: patient-reported outcomes in patients with early-stage breast cancer receiving platinum-based or anthracycline-based neoadjuvant chemotherapy. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 32(6): 401	- Data not reported in an extractable format Data was not reported separately for HER2 positive breast cancer

Study	Reason
Zhang, Jie, Yu, Yushuai, Lin, Yuxiang et al. (2021) Efficacy and safety of neoadjuvant therapy for HER2-positive early breast cancer: a network meta-analysis. Therapeutic advances in medical oncology 13: 17588359211006948	- Systematic review used as source of primary studies
Zhou, J-M, Hu, X, Zhang, H-Q et al. (2019) Effect of trastuzumab plus anthracycline on cardiac function in her2-positive breast cancer. Chinese journal of cancer prevention and treatment 26(10): 707-712	- Study not reported in English Chinese
Zhu, Jingjin, Min, Ningning, Chen, Yizhu et al. (2023) Neoadjuvant therapy with vs. without anthracyclines for HER2-positive breast cancer: a systematic review and meta-analysis. Annals of translational medicine 11(5): 200	- Systematic review used as source of primary studies

1

2 **Economics studies**

Study	Reason
Hassett, M J, Li, H, Burstein, H J et al. (2020) Neoadjuvant treatment strategies for HER2-positive breast cancer: cost-effectiveness and quality of life outcomes. Breast cancer research and treatment 181(1): 43-51	- US healthcare payer perspective on costs and outcomes
Kunst, Natalia, Wang, Shi-Yi, Hood, Annette et al. (2020) Cost-Effectiveness of Neoadjuvant-Adjuvant Treatment Strategies for Women With ERBB2 (HER2)-Positive Breast Cancer. JAMA network open 3(11): e2027074	- US healthcare payer perspective on costs and outcomes

3

Appendix K– Research recommendations – full details

No research recommendation was drafted.

Appendix L – Methods

Reviewing research evidence

Review protocols

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

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2024 NICE guidelines manual.

Selecting studies for inclusion

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

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

Methods of combining evidence

Data synthesis for intervention studies

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

Pairwise meta-analysis

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

Random effects models were fitted when significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken. For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as I2≥50%.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with I2 < 50%) the results from these subgroups were reported using fixed effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

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

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

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

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

Minimally important differences (MIDs) and clinical decision thresholds

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

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. Clinical decision thresholds that were used in the guideline are given in Table 18 and also reported in the relevant evidence reviews.

Table 18 Identified Clinical decision thresholds

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

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 19. These criteria were used to apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 19 Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than <50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 50% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than <50% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than >50% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. Not serious: If the I^2 was less than <40%, the outcome was not downgraded. Serious: If the I^2 was between 41% and 60%, the outcome was downgraded one level or if data on the outcome was only available from one study. Very serious: If the I^2 was greater than >60%, the outcome was downgraded two levels.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was

GRADE criteria	Reasons for downgrading quality
	not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

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Appendix M – Short and long term adverse events of interest

Table 20 List of short and long term adverse events of interest

Short term adverse events
Haematological adverse events • Anaemia • Neutropenia • Neutropenic sepsis
Liver function adverse events • Liver function tests (combined): increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)
Other adverse events • Alopecia • Diarrhoea • Mucositis • Nausea or vomiting
Long term adverse events
Cardiac toxicity • Asymptomatic decreases in left ventricular ejection fraction (LVEF) • Symptomatic left ventricular systolic dysfunction
Other adverse events • Fatigue • Decreased cognitive function • Incidence of new, non-breast primary cancer • Ovarian function (fertility) • Peripheral neuropathy