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Platinum-containing regimens for metastatic breast cancer (Review)

Egger SJ, Willson ML, Morgan J, Walker HS, Carrick S, Gherzi D, Wilcken N

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Platinum-containing regimens for metastatic breast cancer (Review)

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[Intervention Review]

Platinum-containing regimens for metastatic breast cancer

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ABSTRACT

Background

Studies have reported high tumour response rates for platinum-containing regimens in the treatment of women with metastatic breast cancer. Most of these studies were conducted prior to the 'intrinsic subtype' era, and did not specifically focus on metastatic triple-negative breast cancers (mTNBCs).

Objectives

To identify and review the evidence from randomised trials comparing platinum-containing chemotherapy regimens with regimens not containing platinum in the management of women with metastatic breast cancer.

Search methods

For this review update, we searched the Cochrane Breast Cancer Group's Specialised Register, CENTRAL, MEDLINE, Embase, the World Health Organization's International Clinical Trials Registry Platform and ClinicalTrials.gov on 28 May 2015. We identified further potentially relevant studies from handsearching references of previous trials, systematic reviews, and meta-analyses. Prior to this review update, the most recent search for studies was conducted in May 2003 for the original 2004 review.

Selection criteria

Randomised trials comparing platinum-containing chemotherapy regimens with regimens not containing platinum in women with metastatic breast cancer.

Data collection and analysis

At least two independent reviewers assessed studies for eligibility and quality, and extracted all relevant data from each study. Hazard ratios (HRs) were derived for time-to-event outcomes, where possible, and fixed-effect models were used for meta-analyses. Objective tumour response rates (OTRRs) and toxicities were analysed as binary (dichotomous) outcomes with risk ratios (RRs) used as measures of effects. Quality of life data were extracted where available. GRADE was used to rate the quality of evidence for survival and tumour response outcomes at the level of subgroups selected and unselected for mTNBC, and for toxicity outcomes based on combining data from selected and unselected populations.

Main results

This update includes 15 new eligible treatment-comparisons from 12 studies. In total, 28 treatment-comparisons, involving 4418 women, from 24 studies are now included in one or more meta-analyses. Of the 28 treatment-comparisons, 19 and 16 had published or provided extractable time-to-event data on overall survival (OS) or progression-free survival/time to progression (PFS/TTP), respectively. All 28 treatment-comparisons provided OTRR data that could be included in meta-analyses. Most women recruited to the studies were not selected on the basis of mTNBC status.

In a subgroup of three treatment-comparisons assessing women with mTNBC, platinum-containing regimens may have provided a survival benefit (HR 0.75, 95% CI 0.57 to 1.00; low-quality evidence). In women unselected for intrinsic subtypes such as mTNBC, there was little or no effect on survival (HR 1.01, 95% CI 0.92 to 1.12; high-quality evidence). This effect was similar to the combined analysis of survival data for both populations (HR 0.98, 95% CI 0.89 to 1.07; $I^2 = 39\%$, 1868 deaths, 2922 women; 19 trials). The difference in treatment effects between mTNBC women compared with unselected women was of borderline statistical significance ($P = 0.05$).

Data from three treatment-comparisons with mTNBC participants showed that platinum regimens may improve PFS/TTP (HR 0.59, 95% CI 0.49 to 0.72; low-quality evidence). Thirteen treatment-comparisons of unselected metastatic participants showed that there was probably a small PFS/TTP benefit for platinum recipients, although the confidence interval included no difference (HR 0.92, 95% CI 0.84 to 1.01; moderate-quality evidence). Combined analysis of data from an estimated 1772 women who progressed or died out of 2136 women selected or unselected for mTNBC indicated that platinum-containing regimens improved PFS/TTP (HR 0.85, 95% CI 0.78 to 0.93). There was marked evidence of heterogeneity ($P = 0.0004$; $I^2 = 63\%$). The larger treatment benefit in mTNBC women compared with unselected women was statistically significant ($P < 0.0001$).

There was low-quality evidence of better tumour response in both subgroups of women with mTNBC and unselected women (RR 1.33, 95% CI 1.13 to 1.56; RR 1.11, 95% CI 1.04 to 1.19, respectively). Combined analysis of both populations was closer to the effect in unselected women (RR 1.15, 95% CI 1.08 to 1.22; 4130 women). There was considerable evidence of heterogeneity ($P < 0.0001$; $I^2 = 64\%$), which may reflect between-study differences and general difficulties in assessing response, as well as the varying potencies of the comparators.

Compared with women receiving non-platinum regimens: rates of grade 3 and 4 nausea/vomiting were probably higher among women receiving cisplatin- (RR 2.65, 95% CI 2.10 to 3.34; 1731 women; moderate-quality evidence) but the effect from carboplatin-containing regimens was less certain (RR 0.77, 95% CI 0.47 to 1.26; 1441 women; moderate-quality evidence); rates of grade 3 and 4 anaemia were higher among women receiving cisplatin- (RR 3.72, 95% CI 2.36 to 5.88; 1644 women; high-quality evidence) and carboplatin-containing regimens (RR 1.72, 95% CI 1.10 to 2.70; 1441 women; high-quality evidence); rates of grade 3 and 4 hair loss (RR 1.41, 95% CI 1.26 to 1.58; 1452 women; high-quality evidence) and leukopenia (RR 1.38, 95% CI 1.21 to 1.57; 3176 women; moderate-quality evidence) were higher among women receiving platinum-containing regimens (regardless of platinum agent).

Authors' conclusions

In women with metastatic breast cancer who do not have triple-negative disease, there is high-quality evidence of little or no survival benefit and excess toxicity from platinum-based regimens. There is preliminary low-quality evidence of a moderate survival benefit from platinum-based regimens for women with mTNBC. Further randomised trials of platinum-based regimens in this subpopulation of women with metastatic breast cancer are required.

PLAIN LANGUAGE SUMMARY

Platinum-containing regimens for metastatic breast cancer

What is the issue? Metastatic breast cancer occurs when the cancer has spread to areas of the body beyond the breast and nearby lymph nodes. Although metastatic breast cancer is generally not curable, it is widely accepted that women with metastatic disease should receive some form of chemotherapy to help ease the severity of disease symptoms, while hopefully extending survival time. Chemotherapy containing platinum is known to be effective for treating a number of cancer types including lung, testicular, head and neck, bladder and ovarian cancers, but it also known to cause more adverse effects (such as nausea and vomiting, hair loss, anaemia, kidney damage and leukopenia (low white blood cells)) than other chemotherapy options. The two platinum agents most commonly used for treating metastatic breast cancer are carboplatin and cisplatin.

The original version of this review (2004) concluded that chemotherapy containing platinum did not increase survival time for women treated for metastatic breast cancer. Since then, however, researchers have discovered that there are a variety of subtypes of breast cancer which may respond differently to different types of chemotherapy. One of these subtypes — triple-negative breast cancer (TNBC) — makes up approximately 12 to 17% of breast cancers and is associated with shorter survival and higher likelihood that the cancer returns. Some researchers have speculated that chemotherapy containing platinum might be more effective in treating metastatic TNBC (mTNBC) than other chemotherapy options.

Why does it matter? There are at least two reasons why it is important to update the evidence on this topic. First, it is important to assess whether our 2004 conclusions — based on 12 early studies — are representative of the 24 studies who have now published or provided

results through to 2015. Second, it is important to assess whether chemotherapy containing platinum increases survival for women with mTNBC more than other chemotherapy options.

We asked whether chemotherapy treatments containing a platinum agent are more or less effective for treating women with metastatic breast cancer than chemotherapy treatments not containing a platinum agent. We also asked the same question, but with a focus on women with mTNBC.

We found 24 studies involving 4418 women. The evidence is current to May 2015. Five of the 24 studies specifically assessed women with mTNBC while the other 19 studies assessed women with metastatic breast cancer in general (mainly women without mTNBC). This review found that, compared to chemotherapy without platinum, chemotherapy with platinum did not increase survival time by any important degree for women with metastatic breast cancer in general (mainly women without mTNBC). The quality of the evidence for this was considered to be high, meaning that we are confident about the results. For women with mTNBC, however, this review found that chemotherapy containing platinum may increase survival time over chemotherapy without platinum, but the quality of the evidence for this is low at this point in time (largely due to the small number of studies that have assessed mTNBC). This review also found that chemotherapy including platinum reduced the number of breast cancer recurrences compared to chemotherapy that did not contain platinum in women with mTNBC, however these findings also currently come from low-quality evidence. There was no difference in the number of breast cancer recurrences for women receiving platinum or non-platinum chemotherapy for metastatic breast cancer in general. Chemotherapy with platinum was more likely to shrink tumours compared to chemotherapy without platinum, but this result needs to be considered cautiously.

Compared with women receiving chemotherapy without platinum, women receiving chemotherapy with platinum experienced higher rates of nausea/vomiting, anaemia, leukopenia and hair loss.

This means it is difficult to justify using chemotherapy containing platinum for the treatment of metastatic breast cancer that is not mTNBC, given that similarly effective but less toxic chemotherapy is commonly available. Chemotherapy containing platinum may provide a survival benefit to mTNBC participants of sufficient magnitude to justify its use, but the quality of the evidence for this is low at this point in time. Further studies are required before a more definitive conclusion can be made.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Platinum-containing regimens for women with metastatic breast cancer unselected for triple-negative disease

Platinum compared to non-platinum chemotherapy regimens for women with metastatic breast cancer unselected for triple-negative disease

Patient or population: women with metastatic breast cancer unselected for triple-negative breast cancer (TNBC)

Setting: hospital

Intervention: platinum

Comparison: non-platinum chemotherapy regimens

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (treatment- comparisons)	Quality of the evidence (GRADE)	Comments
	Risk with non-platinum chemotherapy regimens	Risk with platinum				
Overall survival - trials of metastatic breast cancer participants unselected for TNBC	1-year risk of death		HR 1.01 (0.92 to 1.12)	2531 (16)	⊕⊕⊕⊕ HIGH ³	Heterogeneity: P = 0.09, I ² =34%
	310 per 1,000 ¹	313 per 1,000 (289 to 340) ²				
	2-year risk of death					
	540 per 1,000 ¹	543 per 1,000 (510 to 581) ²				
Progression-free survival/time to progression (randomised participants) - trials of metastatic breast cancer participants unselected for TNBC	1-year risk of progression or death		HR 0.92 (0.84 to 1.01)	1745 (13)	⊕⊕⊕⊖ MODERATE ⁴	Heterogeneity: P = 0.08, I ² =38%
	737 per 1,000 ¹	707 per 1,000 (674 to 740) ²				
	2-year risk of progression or death					
	891 per 1,000 ¹	869 per 1,000 (844 to 893) ²				
Objective tumour response rate (assessable participants) - trials of metastatic breast cancer participants unselected for TNBC	493 per 1,000 ⁵	547 per 1,000 (512 to 586)	RR 1.11 (1.04 to 1.19)	3252 (23)	⊕⊕⊖⊖ LOW ^{4,6}	Heterogeneity: P = 0.0002, I ² =58%

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

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

1 Estimated from the average of non-platinum group Kaplan-Meier probabilities from the three highest weighted non-TNBC treatment-comparisons for this outcome

2 Estimated as $1000 \times (1 - S(t)^{HR})$ where $S(t)$ is the estimated probability of survival for non-platinum participants and HR is the pooled hazard ratio (Davies 1998)

3 Quality of evidence for OS was not downgraded for blinding because this outcome is unlikely to be affected by non-blinding.

4 Downgraded quality of evidence one level for 'indirectness' because this outcome is a surrogate endpoint of questionable validity for assessing the more important outcome of OS in the context of metastatic breast cancer (Burzykowski 2008)

5 Estimated from all 23 non-TNBC treatment-comparisons in the review

6 Downgraded quality of evidence one level for 'inconsistency' because there was substantial evidence of heterogeneity across studies ($P < 0.05$)

Summary of findings 2. Platinum-containing regimens for women with metastatic triple-negative breast cancer

Platinum compared to non-platinum chemotherapy regimens for women with metastatic triple-negative breast cancer

Patient or population: women with metastatic triple-negative breast cancer (mTNBC)

Setting: hospital

Intervention: platinum

Comparison: non-platinum chemotherapy regimens

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (treatment-comparisons)	Quality of the evidence (GRADE)	Comments
	Risk with non-platinum chemotherapy regimens	Risk with platinum				
Overall survival - trials of mTNBC participants	1-year risk of death		HR 0.75 (0.57 to 1.00)	391 (3)	⊕⊕⊕⊖ LOW ^{3,4,5}	Heterogeneity: $P = 0.23$, $I^2 = 32\%$
	485 per 1,000 ¹	392 per 1,000 (315 to 485) ²				
	2-year risk of death					

	655 per 1,000 ¹	550 per 1,000 (455 to 655) ²				
Progression-free survival/time to progression (randomised participants) - trials of mTNBC participants	1-year risk of death		HR 0.59 (0.49 to 0.72)	391 (3)	⊕⊕⊕⊕ LOW ^{4,6}	Heterogeneity: P = 0.07, I ² = 67%
	894 per 1,000 ¹	733 per 1,000 (667 to 801) ²				
	2-year risk of death					
	987 per 1,000 ¹	922 per 1,000 (879 to 955) ²				
Objective tumour response rate (assessable participants) - trials of mTNBC participants	354 per 1,000 ⁷	470 per 1,000 (400 to 552)	RR 1.33 (1.13 to 1.56)	878 (5)	⊕⊕⊕⊕ LOW ^{6,8}	Heterogeneity: P = 0.0010, I ² = 78%

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

CI: Confidence interval; RR: Risk ratio; HR: Hazard ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Estimated from the average of non-platinum group Kaplan-Meier probabilities from the three TNBC treatment-comparisons contributing data for pooling on this outcome

² Estimated as $1000 \times (1 - S(t)^{HR})$ where S(t) is the estimated probability of survival for non-platinum participants and HR is the pooled hazard ratio (Davies 1998)

³ Downgraded quality of evidence one level for 'imprecision' because the confidence interval for the pooled estimate is wide and crosses or nearly crosses unity

⁴ Downgraded quality of evidence one level for 'suspected publication bias' because Tutt 2014 is a large study with 376 participants but has so far only reported median OS/PFS times. As a consequence, the study did not contribute to the pooled HR estimates for OS or PFS/TTP. The reported median OS/PFS times in Tutt 2014 were similar between platinum and non-platinum regimens. Hence, it seems likely that if HRs from Tutt 2014 were able to be included in pooled HR estimates, these pooled estimates would be considerably closer to the null.

⁵ Quality of evidence for OS was not downgraded for blinding because this outcome is unlikely to be affected by non-blinding.

⁶ Downgraded quality of evidence one level for 'indirectness' because this outcome is a surrogate endpoint of questionable validity for assessing the more important outcome of OS in the context of metastatic breast cancer (Burzykowski 2008)

⁷ Estimated from all five TNBC treatment-comparisons in the review

⁸ Downgraded quality of evidence one level for 'inconsistency' because there was substantial evidence of heterogeneity across studies (P < 0.05)

Summary of findings 3. Platinum-containing regimens and toxicity profile

Platinum compared to non-platinum chemotherapy regimens for nausea/vomiting, anaemia, hair loss and leukopenia

Patient or population: women with metastatic breast cancer

Setting: hospital

Intervention: platinum

Comparison: non-platinum chemotherapy regimens

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (treatment-comparisons)	Quality of the evidence (GRADE)	Comments
	Risk with non-platinum chemotherapy regimens	Risk with platinum				
Nausea/vomiting* grade 3 or 4 (safety population) by type of platinum agent in platinum regimen	Carboplatin		(RR 0.77, 95% CI 0.47 to 1.26)	1441 (7)	⊕⊕⊕⊖ MODERATE ²	Test for carboplatin/cisplatin subgroup difference: P < 0.0001 Heterogeneity among carboplatin studies: P = 0.30, I ² = 17%
	80 per 1,000 ¹	62 per 1,000 (59 to 101)				
	Cisplatin		(RR 2.65, 95% CI 2.10 to 3.34)	1747 (14)	⊕⊕⊕⊖ MODERATE ³	Heterogeneity among cisplatin studies: P = 0.010, I ² = 32%
	80 per 1,000 ¹	210 per 1,000 (167 to 266)				
Anaemia grade 3 or 4 (safety population) by type of platinum agent in platinum regimen	Carboplatin		(RR 1.72, 95% CI 1.10 to 2.70)	1441 (7)	⊕⊕⊕⊕ HIGH	Test for carboplatin/cisplatin subgroup difference: P = 0.02 Heterogeneity among carboplatin studies: P = 0.67, I ² = 0%
	33 per 1,000 ¹	57 per 1,000 (36 to 89)				
	Cisplatin		(RR 3.72, 95% CI 2.36 to 5.88)	1644 (13)	⊕⊕⊕⊕ HIGH	Heterogeneity among cisplatin studies: P = 0.50, I ² = 0%
	33 per 1,000 ¹	123 per 1,000 (78 to 194)				
Hair loss grade 3 or 4 (safety population)	Carboplatin or cisplatin		(RR 1.41, 95% CI 1.26 to 1.58)	1452 (13)	⊕⊕⊕⊕ HIGH	Test for carboplatin/cisplatin subgroup difference: P = 0.23 Heterogeneity: P = 0.10, I ² = 40%
	264 per 1,000 ¹	372 per 1,000 (333 to 417)				
Leukopenia** grade 3 or 4 (safety population)	Carboplatin or cisplatin		(RR 1.38, 95% CI 1.21 to 1.57)	3176 (22)	⊕⊕⊕⊖ MODERATE ³	Test for carboplatin/cisplatin subgroup difference: P = 0.22

Heterogeneity: $P = 0.0002$, $I^2 = 60\%$

179 per 1,000¹   247 per 1,000 (217 to 281)

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

CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

¹ Estimated from all treatment-comparisons (cisplatin and carboplatin) contributing data for pooling for this outcome

² Downgraded quality of evidence one level for 'imprecision' because the confidence interval for the pooled estimate is wide and does not rule out 'no effect'

³ Downgraded quality of evidence one level for 'inconsistency' because there was substantial evidence of heterogeneity across studies ($P < 0.05$)

*data on vomiting was included if data on nausea/vomiting was reported separately

**data on neutropenia was included if data on leukopenia was not reported

BACKGROUND

Description of the condition

Breast cancer is both the most common type of cancer in women and the most common cause of cancer death in women (Ferlay 2013). In 2012, there was an estimated 1.67 million estimated new cases and approximately 522,000 deaths from breast cancer worldwide, with an age standardised death rate (ASR) of 12.9 per 100,000 (Ferlay 2013). ASRs of 25 or greater were recorded that same year in Fiji (28.4), Bahamas (26.3), Nigeria (25.9), Former Yugoslav Republic (FYR) Macedonia (25.5) and Pakistan (25.2) (Ferlay 2013).

The stage of breast cancer at the time of diagnosis is an important indicator of prognosis. Once breast cancer becomes metastatic, it is not generally considered curable and most women with metastatic disease do not survive beyond five years from the time of their metastatic diagnosis (Clements 2012). Another important predictor of prognosis is the biological subtype of breast cancer. One of these subtypes — triple-negative breast cancer (TNBC) — is characterised by a lack of expression of oestrogen and progesterone receptors (ER and PgR) and human epidermal receptor 2 (HER2). TNBC comprises approximately 12 to 17% of breast cancers and is associated with shorter survival and higher likelihood of recurrence (Foulkes 2010). The median survival time for women diagnosed with metastatic TNBC (mTNBC) is about one year from their metastatic diagnosis (Kassam 2009).

Although there is no evidence from randomised trials comparing chemotherapy with observation (no chemotherapy) in women with metastatic breast cancer, it is widely accepted that women with metastatic disease should receive some form of systemic therapy at some time during the course of their metastatic disease. Chemotherapy is considered by many to be the appropriate first treatment option for women with multiple sites of recurrence or where visceral disease is not easily treated by local modalities (Hayes 1995; Beslija 2009). Chemotherapy is also considered to be useful in women whose cancer is hormone refractory or is expected to be hormone resistant (Hortobagyi 1996).

Description of the intervention

Platinum compound, an alkylating agent, has been known to be active in metastatic breast cancer since clinical trials in the 1970s. However, it is more toxic and difficult to administer than other chemotherapy agents. The three most widely used platinum agents for treating breast cancer are cisplatin, carboplatin (both divalent complexes) and oxaliplatin (a tetravalent complex) (Sikov 2015). Cisplatin and carboplatin have demonstrated benefits in treating a number of cancer types including lung, testicular, head and neck, bladder and ovarian cancers. Oxaliplatin is often used to treat cisplatin- and carboplatin-resistant tumours because it is commonly believed that cross-resistance between oxaliplatin and cisplatin or carboplatin is incomplete (Mani 2002). More recent evidence suggests that the benefits of oxaliplatin may be due to its low toxicity and ability to be combined with other drugs rather than incomplete cross-resistance with other platinum agents (Stordal 2007).

The use of oxaliplatin for treating breast cancers is much less common than the use of cisplatin or carboplatin, both in normal clinical practice and as an intervention in clinical

trials (Sikov 2015). Cisplatin and carboplatin have been used and studied extensively as first-line metastatic therapy in combination with other older pharmacological agents including 5-fluorouracil and etoposide, and more recently with doxorubicin, epirubicin, vinorelbine, paclitaxel, docetaxel, cyclophosphamide, methotrexate and gemcitabine. The potential benefits of cisplatin or carboplatin as monotherapy for metastatic breast cancer, rather than as combination therapy, are rarely studied in clinical trials.

Although platinum agents have been shown to be efficacious in the treatment of a number of cancer types, their use is often associated with a variety of side effects. The known side effects of platinum agents include nausea, vomiting, myelosuppression (thrombocytopenia, leukopenia, neutropenia and anaemia), peripheral neuropathy (symptoms include tingling in fingers and toes), nephrotoxicity, ototoxicities (hearing loss and tinnitus), hypomagnesaemia and anaphylaxis. Carboplatin is reported to be more tolerable than cisplatin with less nausea and vomiting, nephrotoxicity, ototoxicity and neurotoxicity, but worse myelosuppression, especially thrombocytopenia (Sikov 2015).

How the intervention might work

The exact mechanism of action of platinum agents is not known but deoxyribonucleic acid (DNA) adducts are formed (Sikov 2015). These complexes are believed to inhibit DNA synthesis, replication and transcription by forming interstrand and intrastrand cross-linking of DNA molecules. Interstrand cross-links that remain intact can produce cell death, and it is this cytotoxic effect, when successful, that forms the mechanistic basis of action for cancer cell death by platinum agents (Noll 2006). For TNBC, it has been additionally hypothesised that a dysfunctional BRCA1 pathway in some TNBCs may make them more sensitive to platinum agents that selectively target cells deficient in homologous recombination DNA repair (Foulkes 2010).

Why it is important to do this review

There are a number of reasons for updating this review. First, this review was originally published in 2004 (Carrick 2004) and was based on 12 studies (13 treatment-comparisons) identified from a May 2003 search of the literature. Although there have since been some updates to this review containing minor amendments, no new searches for relevant studies have been conducted since 2003. In the current review update, the number of included studies has increased from 12 in the original version of this review to 24 (28 treatment-comparisons). This allows effects to be estimated with greater precision than before and provides an opportunity to conduct new subgroup analyses corresponding to emerging evidence and new hypotheses. Second, all 12 studies included in the original version of this review were conducted prior to the 'intrinsic subtype' era and thus did not specifically focus on TNBC (a term first mentioned in the medical literature in October 2006) (Foulkes 2010). Since 2009, however, five randomised control trials have published data specifically on the effects of platinum-based regimens on survival, progression or tumour response in mTNBC participants; the inclusion of these five trials in this review update represents the first meta-analysis of such trials. Third, some interest remains in the use of platinum agents for the treatment of women with metastatic breast cancer in general (i.e. unselected for intrinsic subtypes such as mTNBC) (Shamseddine 2012). This is notwithstanding the primary conclusion contained in the original version of this review that "...in view of the significant excess

toxicity, lack of progression or survival benefit and the availability of less toxic active agents it is difficult to justify the use of platinum-containing regimens, particularly as first-line treatment for women with metastatic breast cancer in routine clinical practice."

OBJECTIVES

To identify and review the evidence from randomised trials comparing platinum-containing chemotherapy regimens with regimens not containing platinum in the management of women with metastatic breast cancer.

Additional objectives of this review were to investigate whether or not women in selected subgroups of studies benefited more or less from platinum-based chemotherapy. Some subgroup analyses included in this review update were conducted in the original version of this review, while others have been added in response to new hypotheses and the availability of new subgroups.

METHODS

Criteria for considering studies for this review

Types of studies

Properly randomised controlled clinical trials (i.e. where the trial report asserts that the trial was randomised and there was no evidence to suggest otherwise).

Types of participants

Women with advanced (metastatic) breast cancer, either newly diagnosed or recurrent. Treatment-comparisons that included both women with metastatic disease and women with locoregionally recurrent disease only were eligible for inclusion if it was possible to distinguish between the two groups (i.e. data were reported separately) or if women with isolated locoregional recurrence were less than 20% of the total group. There were no age restrictions.

In the protocol for this review, it was proposed that treatment-comparisons would be included if the women randomised to receive chemotherapy, were to receive it as first-line treatment (i.e. no previous chemotherapy given except as adjuvant therapy). As few treatment-comparisons assessing first-line treatment were identified for inclusion in the original version of this review, those meeting the remaining eligibility criteria but which involved participants who were not first-line naive were included. This modification of the inclusion criteria was maintained for this review update, with subgroup analysis by treatment being performed (treatment-comparisons with first-line therapy for > 80% of participants vs other treatment lines).

Types of interventions

Interventions were any chemotherapy regimen containing a platinum agent (see [Table 1](#) and [Table 2](#)). Comparators were any chemotherapy regimen without a platinum agent. Endocrine therapy may also have been given to participants if it was planned to be given to both treatment groups.

Studies may or may not have specified recommended treatment upon disease progression or initial treatment failure or both. This recommended treatment may have included cross-over to the alternative treatment arm of the treatment-comparison.

Types of outcome measures

Primary outcomes

- Overall survival (OS)
- Progression-free survival/time to progression (PFS/TTP)

Secondary outcomes

- Time to treatment failure (TTF)
- Objective tumour response rate (OTRR)
- Toxicity rates (multiple condition-specific outcomes)
- Quality of life measures (multiple outcomes)

The definitions of some outcomes varied slightly across studies included in this review. Outcomes were commonly defined as:

1. Overall survival (OS): time elapsed between randomisation (or study enrolment or treatment initiation) to date of death from any cause.
2. Progression-free survival (PFS): time elapsed between randomisation (or study enrolment or treatment initiation) and event, with event defined as disease progression or death from any cause.
3. Time to progression (TTP): time elapsed between randomisation (or study enrolment or treatment initiation) and event, with event defined as disease progression (which sometimes included cause-specific death from the study disease).
4. Time to treatment failure (TTF): time elapsed between randomisation (or study enrolment or treatment initiation) to treatment discontinuation for any reason, including disease progression, treatment toxicity, participant preference, or death.
5. Objective tumour response rate (OTRR): the proportion of participants who experienced a complete or partial tumour response (versus stable disease or no response).
6. Toxicity rates (multiple condition-specific outcomes): the proportions of participants who experienced a grade 3 or 4 adverse event of nausea and vomiting, nephrotoxicity, anaemia, hair loss and leukopenia based on WHO criteria or individual protocol-based definitions. We also investigated treatment-related death which, for the purpose of this review, was defined as death due to the toxicity of the drug and not to disease progression. If an individual trial did not include their definition of a treatment-related death but used the terms 'toxic death' or 'lethal toxicity', then these deaths were still included in the pooled analysis of treatment related deaths.
7. Quality of life measures (QoL) (multiple outcomes): various validated instruments for measuring various quality of life domains.

For the purposes of this review, PFS and TTP were analysed as the same outcome (referred to as PFS/TTP), with preference given to PFS for studies reporting both PFS and TTP extractable data.

Search methods for identification of studies

Electronic searches

For this update of the review, we searched the following databases and registries on the 28 May 2015.

(a) The Cochrane Breast Cancer Specialised Register maintained by the Cochrane Breast Cancer Group (searched 1 June 2015). Details of the search strategies used by the Cochrane Breast Cancer Group for the identification of studies and the procedure used to code references are outlined in their module (www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Trials coded with the key words 'advanced', 'Cisplatin', 'cisplatinum', 'carboplatin', 'carboplatinum', 'platin', 'platinum', 'platinum diamminodichloride', 'cis-diamminedichloroplatinum', 'cis-dichlorodiammineplatinum', 'biocisplatinum', 'dichlorodiammineplatinum', 'nsc-119875', 'platidiam', 'platino', 'Platinol', 'cis-diamminedichloroplatinum', 'cis-platinum', 'cis-diammine (cyclobutanedicarboxylato) platinum', 'cbdca', 'jm-8', 'nsc-241240', 'paraplatin' were extracted for consideration.

(b) Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 4) in the Cochrane Library (searched 28 May 2015). See [Appendix 1](#).

(c) MEDLINE (via OvidSP; July 2008 to 28 May 2015). Searches were conducted from 2008 due to the Cochrane Breast Cancer Group's Specialised Register being out-of-date for an interim period. See [Appendix 2](#).

(d) Embase (Via Embase.com; July 2008 to 28 May 2015). Searches were conducted from 2008 due to the Cochrane Breast Cancer Group's Specialised Register being out-of-date for an interim period. See [Appendix 3](#).

(e) The WHO International Clinical Trials Registry Platform (ICTRP) search portal (<http://apps.who.int/trialsearch/Default.aspx>) for all prospectively registered and ongoing trials. See [Appendix 4](#).

(f) ClinicalTrials.gov (<http://clinicaltrials.gov/ct2/home>). See [Appendix 5](#).

No restrictions were applied based on language.

Searching other resources

In addition, we searched the reference lists of other, related literature reviews.

Data collection and analysis

Selection of studies

In the original version of this review and in this review update, two reviewers applied the selection criteria (including the quality of randomisation) to each reference identified by the search strategy while masked to the study results. Any discrepancies regarding eligibility or quality were resolved by consensus or adjudication from a third reviewer. Studies that may appear to have met the eligibility criteria, but which were deemed ineligible are listed in the [Characteristics of excluded studies](#) table.

Data extraction and management

In the original version of this review and in this review update, data on the relevant outcomes were extracted by at least two reviewers, with discrepancies resolved by consensus or adjudication from another reviewer. Data were also extracted on information relating to outcome definitions, study accrual, randomisation methods, baseline characteristics of participants (e.g. age, first-line/second-line treatment, prior anthracyclines/anthracycline-naïve), chemotherapy regimens (number of cycles and duration), follow-up time and analytical methods used. Where available, multiple publications on the same study were obtained

and the most complete report was assigned as the primary reference. In instances where a more recent publication was used in this review update for a study that was included in the original version of this review, the year of the reference ID was also updated. Data were entered into the Cochrane Review Manager 5.3 ([RevMan 5.3](#)) software, and [RevMan 5.3](#) was used for most statistical analyses.

Assessment of risk of bias in included studies

In this review update, potential sources of bias for all included studies (including those in the original version of this review) were assessed using Cochrane's 'Risk of bias' assessment tool ([Higgins 2011](#)). Risk of bias for each treatment-comparison was evaluated independently by at least two reviewers and discrepancies were resolved by consensus or adjudication from an additional reviewer. Clarification from authors was sought if the published data provided inadequate information for the review. The 'risk of bias' domains that were assessed were 'random sequence generation', 'allocation concealment', 'blinding of participants and personnel', 'blinding of outcome assessment', 'incomplete outcome data', 'selective reporting' and 'other bias'. For each included study, ratings of 'high', 'low', or 'unclear' risk of bias were assigned for each risk of bias domain following criteria outlined in the 'Risk of bias' assessment tool ([Higgins 2011](#)).

Open-label studies are common in phase III oncology trials because it is often difficult to conceal treatments from participants, care-providers and outcome assessors (due to differences in toxicities and treatment schedules of various treatments, for example). However, because a lack of blinding can affect risk of bias in different ways for different outcomes, we assessed 'blinding of outcome assessment' by dividing outcomes into two outcome classes: 1) OS and 2) outcomes other than OS and quality of life. This division was made because, unlike other outcomes, assessment of OS is unlikely to be affected by non-blinding.

We also divided the 'incomplete outcome data' risk of bias domain into two outcome classes: 1) time-to-event outcomes and 2) binary (i.e. dichotomous) outcomes. For time-to-event outcomes, risk of bias was deemed low, unclear, and high risk if time-to-event analysis was intention-to-treat (ITT), modified intention-to-treat (mITT) or per-protocol, respectively. For the binary outcomes (OTRRs and toxicity rates), risk of bias was deemed low, unclear, and high risk if the highest percentage of randomised participants excluded from effect estimation was less than 10%, between 10% and 15%, or more than 15%, respectively.

For 'risk of bias' domains that were divided into outcome classes, assessments were made for all studies known to be measuring the outcomes, regardless of results being reported in sufficient detail to be included in meta-analysis or reported at all (e.g. a study might specify OS as an outcome in the study protocol but not report any results).

Measures of treatment effect

OS, PFS/TTP and TTF were analysed as time-to-event outcomes, for which the hazard ratio (HR) is the most appropriate measure of treatment effect. If reported, the HR and associated variance were extracted directly from the trial publication(s), and these were used to calculate observed (O) minus expected (E) numbers of events and logrank variance (V) for each treatment-comparison using the methods described by [Tierney 2007](#) or [Parmar 1998](#). If not reported,

O - E and V were obtained indirectly from other available summary statistics or from data extracted from published Kaplan-Meier curves using the methods described by [Tierney 2007](#) or [Parmar 1998](#). For studies that did not report the relevant effect estimates and required curve extraction, the numbers at risk were based on reported minimum and maximum follow-up times. If these were not reported, minimum follow-up was estimated as the time taken to complete treatment, and maximum follow-up was estimated using the last event reported in the relevant time-to-event curve. These follow-up estimates were recorded in the [Characteristics of included studies](#) table under 'Notes'. For the purposes of data extraction, preference was given to time-to-event effect estimates derived from ITT analysis, followed by mITT analysis, then per-protocol analysis.

Pooled HRs and 95% confidence intervals (CIs) were obtained from the O - E and V statistics for each treatment-comparison using the fixed-effect model ([Yusuf 1985](#)). The pooled HR represented the instantaneous risk of an event (such as death, disease progression or treatment failure) for women receiving platinum divided by the corresponding risk for those not receiving platinum. HRs less than 1.00 favoured the platinum-containing regimens and values greater than 1.00 favoured non-platinum regimens.

Toxicity rates and OTRRs were analysed as proportions using the risk ratio (RR) as the measure of treatment effect. OTRRs were most often calculated by trialists using only participants that were assessable for tumour response. These 'assessable participants' were generally defined as participants whose tumour response could be assessed according to prespecified criteria such as RECIST ([Eisenhauer 2009](#)), but this definition was sometimes extended to additionally exclude participants who had not received a specified minimum dose of chemotherapy. In this review update and in the original version of this review, we calculated OTRRs using the numbers of assessable participants in the OTRR denominators, but we also separately calculated OTRRs using the numbers of randomised participants in the denominators. In this review update, however, only the results from the assessable participants analyses were reported as there was almost no difference between the results obtained using assessable and randomised participant denominators (the latter are available on request). Toxicity rates were most often calculated by trialists using a 'safety population' of participants who received a specified minimum dose of chemotherapy. We calculated toxicity rates for each study using the population used by that study.

Pooled RRs and 95% confidence intervals were obtained through Mantel-Haenszel fixed-effect analysis. The pooled RR represented the cumulative risk of an event for participants receiving platinum divided by the corresponding risk for those not receiving platinum. RRs greater than 1.00 favoured platinum-containing regimens and values less than 1.00 favoured non-platinum regimens.

Quality of life was generally reported as a continuous outcome. Hence, if sufficient quality of life data become available for meta-analysis in future review updates, the effect measure would most likely be the mean difference (MD) or standardised mean difference (SMD), depending on whether the same or different validated questionnaires (respectively) were employed.

Unit of analysis issues

Treatment-comparisons were the unit of analysis in this review and corresponded to pairwise comparisons of platinum and non-platinum regimens. Individual studies assessing more than one platinum-based regimen or more than one non-platinum regimen (or both) contributed more than one treatment-comparison to the review. Consequently, there were more treatment-comparisons in this review than there were studies.

Two studies each contained two non-platinum regimen (control) groups for comparison against a single platinum-based regimen (intervention) group. This was taken into account when treatment effect statistics were calculated by splitting each study into two treatment-comparisons ([Stemmler 2011 A](#), [Stemmler 2011 B](#) and [Fountzilas 2009 A](#), [Fountzilas 2009 B](#)) and halving the number of participants in their intervention groups (for odd numbered group sizes, the additional participant was arbitrarily distributed to the treatment-comparison with label ending with 'A'). Another study contained two platinum-based regimen (intervention) groups for comparison against a single non-platinum (control) group. This study was split into two treatment-comparisons ([Xu 2011 A](#), [Xu 2011 B](#)) with treatment effect statistics calculated by halving the number of participants in the control group (with additional participants again arbitrarily distributed to treatment-comparisons with label ending with 'A'). One other study was a four-armed trial and was also reported as two separate treatment-comparisons ([Berruti 2002 A](#), [Berruti 2002 B](#)). For these two treatment-comparisons, no adjustments to participant numbers were required as their control and intervention groups were unique to each comparison. These methods for correcting for multiple intervention and/or control groups were suggested in the Cochrane Handbook ([Higgins 2011](#)).

Dealing with missing data

Attempts were made to contact a number of trial investigators for additional information. Three trialists (Cocconi, Costanza and Fountzilas) provided additional time-to-event data which allowed HRs to be extracted.

Assessment of heterogeneity

Heterogeneity between trial results was assessed using the Chi² test statistic and the I² statistic. The Chi² test statistic assesses the amount of variation in a set of trials. Small P values for the Chi² test statistic suggest that there is more heterogeneity present than would be expected by chance. Chi² is not a particularly sensitive test: a cut-off of P value less than 0.10 is often used to indicate significance, but lack of statistical significance does not mean there is no heterogeneity. I² is the proportion of variation that is due to heterogeneity rather than chance. In conjunction with the Chi² test, we used the I² statistic to assess heterogeneity using the rule of thumb guide outlined in the Cochrane Handbook ([Higgins 2011](#)) (i.e. I² between 0% to 40% might not be important; between 30% to 60% may represent moderate heterogeneity; between 50% to 90% may represent substantial heterogeneity; and between 75% to 100% considerable heterogeneity).

Assessment of reporting biases

In addition to assessing each treatment-comparison individually for 'selective reporting' using the Cochrane Collaboration's 'Risk of bias' assessment tool (see [Assessment of risk of bias in included studies](#) above), publication bias and/or small-study effects were

assessed for the outcomes OS, PFS/TTP and OTRR by visual inspection of funnel plot asymmetry. Egger's statistical test was used to formally assess the degree of asymmetry (Egger 1997).

Data synthesis

For time-to-event outcomes, RevMan 5.3 was used to estimate pooled HRs and 95% CIs using fixed-effect models of the derived or reported observed (O) and expected (E) number of events and the variance of the log-rank statistic (V) for each trial. For binary outcomes, RevMan 5.3 was used to estimate pooled RRs and 95% CIs using the fixed-effect Mantel-Haenszel method.

The standard GRADE system (Guyatt 2011) was used to rate the quality of evidence relating to the estimated treatment effects on OS, PFS/TTP, OTRR, nausea/vomiting, anaemia, hair loss and leukopenia. GRADE criteria for assessing quality of evidence include 'study design', 'risk of bias', 'inconsistency', 'indirectness', 'imprecision', 'suspected publication bias' and 'other considerations'. Assessments of these criteria and corresponding justifications are provided in three 'Summary of findings' tables largely created using GRADEproGDT (GradeProGDT). GRADE assessments were performed separately for selected subgroups related to effect estimate heterogeneity (or 'inconsistency' as labelled in the GRADE assessment criteria).

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were performed to determine whether the results differed by:

1. mTNBC status: (a) mTNBC participants, (b) participants unselected for mTNBC;
2. type of regimen comparison: (a) regimen A + platinum vs regimen A, (b) regimen A + platinum vs regimen B, (c) single agent platinum vs regimen C; (note that we allowed "regimen A" to differ in dosage by small amounts between intervention and control arms)
3. type of platinum agent in platinum arm: (a) cisplatin, (b) carboplatin, (c) oxaliplatin;
4. first-line therapy: (a) first-line therapy for > 80% of participants, (b) second- or third-line therapy for ≥ 20% of participants;
5. anthracycline in regimens: (a) no anthracycline in platinum or non-platinum regimens, (b) platinum + anthracycline vs non-platinum + anthracycline regimen, (c) platinum + anthracycline vs non-platinum + non-anthracycline regimens;
6. taxane in regimens: (a) no taxane in platinum or non-platinum regimens, (b) platinum + taxane vs non-platinum + taxane regimens, (c) platinum + non-taxane vs non-platinum + taxane regimens;
7. trastuzumab in regimens: (a) no trastuzumab in platinum or non-platinum regimens, (b) platinum + trastuzumab vs non-platinum + trastuzumab regimens

Possible subgroup differences were assessed using Chi² tests.

Of the above seven subgroup analyses:

- Subgroup analysis 2 was the only 'a priori' subgroup analysis pre-specified in the review protocol; all other subgroup analyses were 'post hoc'.
- Subgroup analyses 2, 4, 5 and 6 were conducted in the original review, although additional subgroups have been added for

some of these analyses (eg. the conjugate subgroup 'second- or third-line therapy for ≥ 20% of participants' has been added to the 'first-line therapy' analysis).

- In order to reduce the number of forest plots in this review update, toxicity rates were only assessed overall and by subgroup analysis 3 (as 'type of platinum agent' is known to be related to toxicity). Analyses of toxicity rates by other subgroups are available on request.

In this review update, the subgroupings of a few studies have been corrected from the original version of the review. Furthermore, the subgroup analysis 'first-line therapy' was incorrectly labelled '100% firstline trials' in the original version of the review and the actual cut-off that was applied was first-line therapy for > 80% of participants.

Sensitivity analysis

Sensitivity analyses were performed to assess whether apparent inconsistencies in results relating to OS, PFS/TTP and OTRR were more likely to be due to differences in the underlying nature of these outcomes, or an artefact of the different treatment-comparisons available for the meta-analysis of each outcome. First, the pooled effect estimate for OTRR was recalculated restricting the meta-analysis to the 19 treatment-comparisons with extractable data on OS. Second, the pooled effect estimates for PFS/TTP and OS were recalculated restricting both meta-analyses to the 12 treatment-comparisons with extractable data on both OS and PFS/TTP.

In additional sensitivity analyses, PFS/TTP estimates were stratified according to whether the outcome was PFS or TTP. For these analyses, estimates were classified as PFS if the event of interest was defined as disease progression or death from any cause. Estimates were classified as TTP if the event of interest was defined as disease progression, which may also include cause-specific death from breast cancer. In instances where the event of interest was ambiguously defined or not defined at all, we relied on the authors label of the outcome for classifying as PFS or TTP.

Lastly, to assess the sensitivity of our primary results to our choice of analytical method, we repeated Analysis 1.1, Analysis 1.2 and Analysis 1.3 but using random-effects rather than fixed-effect methods.

RESULTS

Description of studies

Results of the search

For the 2016 review update, we reviewed 1644 unique records identified by the May 2015 database searches (Figure 1). Of these, 1610 could be excluded based on information in the title or abstract, and nine records from trial registries or protocol publications were considered to be potentially relevant ongoing studies yet to publish results (see Characteristics of ongoing studies). For the remaining 25 records, we retrieved full-text articles or abstracts for further examination. Eight of the 25 articles or abstracts were excluded because they were reviews (but these were still used to search for further studies by handsearching the bibliographies) and three other full-text articles were excluded for reasons outlined in the Characteristics of excluded studies table.

Figure 1. Review update 2016: study flow diagram.

Included studies

Fourteen studies containing 17 treatment-comparisons with sufficient data to be included in one or more pooled analyses were identified by this review update. Of these 17 treatment-comparisons, two had been included in the original review but had since published updated results (Icli 2002 and Fountzilas 2002 in the original review were renamed Icli 2005 and Fountzilas 2004 in this review update), and 15 were new to the review (Amadori 2013; Bhattacharyya 2009; Carey 2012; Fan 2012; Delaloge 2004; Fountzilas 2009 A; Fountzilas 2009 B; Hu 2015; Robert 2006; Stemmler 2011 A; Stemmler 2011 B; Tutt 2014; Valero 2011; Xu 2011 A; Xu 2011 B). Overall, the review now includes results from 24 studies corresponding to 28 treatment-comparisons (see [Characteristics of included studies](#)).

Of the 28 treatment-comparisons included in this review update ([Table 3](#)):

- 17 (61%) used cisplatin, 10 (36%) used carboplatin and one (4%) used oxaliplatin as the platinum agent in the intervention arm;
- 9 (32%) compared 'regimen A + platinum vs regimen A', 18 (64%) compared 'regimen A + platinum vs regimen B' and one (4%) compared single agent platinum vs regimen C' ([Table 4](#));
- 20 (71%) had more than 80% of participants receiving first-line therapy;
- 5 (18%) were designed to assess participants with mTNBC;
- 18 (64%) had no anthracycline in the platinum or non-platinum regimens, six (21%) had an anthracycline in both regimens, and four (14%) had an anthracycline in the platinum regimen only;
- 17 (61%) had no taxane in the platinum or non-platinum regimens; six (21%) had a taxane in both regimens and five (18%) had a taxane in the non-platinum regimen only;
- 26 (93%) had no trastuzumab in the platinum or non-platinum regimens and two (7%) had a trastuzumab in both regimens.

Not all the studies provided sufficient information on all outcomes for inclusion in meta-analyses. Of the 28 treatment-comparisons:

- 19 (68%), 16 (57%) and 28 (100%) had sufficient data to be included in the meta-analyses of effect estimates for OS, PFS/TTP and OTRR, respectively ([Table 3](#) and [Figure 1](#));
- 15 (54%), 21 (75%), 5 (18%), 20 (71%), 12 (43%) and 22 (79%) had sufficient data to be included in the meta-analyses of effect estimates for treatment-related death, nausea/vomiting, nephrotoxicity, anaemia, hair loss, and leukopenia, respectively ([Table 5](#) and [Figure 1](#)).

Three studies reported treatment effects on various quality of life domains (Fountzilas 2004; Fountzilas 2009: Fountzilas 2009 A & Fountzilas 2009 B; Amadori 2013) but these results could not be pooled in a meta-analysis. Three studies reported TTF results (Amadori 2013; Fountzilas 2004; Xu: Xu 2011 A & Xu 2011 B), but these data were only extractable for Fountzilas 2004.

Excluded studies

In this review update, seven studies may have appeared to have met the eligibility criteria, but were deemed ineligible for reasons given in the [Characteristics of excluded studies](#) table. Of these seven excluded studies: two were registered trials that were previously listed as 'ongoing studies' in the original review but were reclassified as 'excluded' in this review update because the principal investigator had informed us that the trials never commenced (Perez 2001; Perez 2002); two were 'excluded studies' in the original review and remained so in this review update (Cartei 1996; Hogdall 1993); and three were newly identified in this review update (Crump 2008; Somlo 2015; Wang 2008). Two other studies listed as 'excluded' in the original review ('Eisen' and 'Ryberg 1998') were removed from the excluded studies section altogether in this review update as they referred to earlier reports of studies that were actually included in the original review (Eisen 1998; Nielsen 2000).

Risk of bias in included studies

[Figure 2](#) shows a summary of the 'Risk of bias' judgements for each 'Risk of bias' domain of the included treatment-comparisons. Reasons for each judgement are detailed for each treatment-comparison in the [Characteristics of included studies](#) table. For each 'risk of bias' domain, a summary of the general risk of bias for results of the included studies was as follows.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (overall survival)	Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Incomplete outcome data (attrition bias) (time-to-event outcomes)	Incomplete outcome data (attrition bias) (binary outcomes)	Selective reporting (reporting bias)	Other bias
Amadori 2013	?	?	+	+	?	+	+	?	+
Berruti 2002 A	?	?	?	+	?	?	+	?	+
Berruti 2002 B	?	?	?	+	?	+	+	?	+
Bhattacharyya 2009	+	?	?	+	?	+	?	+	+
Carey 2012	+	?	+	+	+	?	?	+	?
Cocconi 1991	?	+	?	+	+	+	+	?	+
Cocconi 1996	?	?	?	+	?	?	?	?	+
Cocconi 1999	?	+	?	+	+	?	+	?	+
Costanza 1999	?	?	?	+	?	+	?	?	+
Creagan 1984	?	?	?	+	?	?	+	?	+
Delaloge 2004	?	?	?	+	?	+	?	?	+
Fiorani 1998	?	?	?	+	?	+	?	?	?

Figure 2. (Continued)

Delaighe 2004	?	?	?	+	?	+	?	?	+
Eisen 1998	?	?	?	+	?	+	?	?	?
Fan 2012	?	?	-	+	?	+	+	-	+
Fountzilas 2004	+	+	?	+	+	?	+	?	?
Fountzilas 2009 A	?	+	?	+	?	?	?	?	+
Fountzilas 2009 B	?	+	?	+	?	?	-	?	+
Hu 2015	+	+	-	+	?	?	+	+	?
Icli 2005	?	+	-	+	+	?	+	?	+
Kolaric 1985	?	?	?	+	?	-	+	?	+
Kolaric 1989	?	?	?	+	?	-	?	?	+
Nielsen 2000	?	+	?	+	?	-	?	?	+
Robert 2006	?	?	?	+	?	+	+	?	+
Stemmler 2011 A	?	?	-	+	?	+	-	+	+
Stemmler 2011 B	?	?	-	+	?	+	-	+	+
Tutt 2014	?	?	-	+	?	+	?	-	?
Valero 2011	+	?	-	+	?	+	+	?	+
Xu 2011 A	?	?	-	+	?	?	+	+	+
Xu 2011 B	?	?	-	+	?	+	+	+	+

Allocation

All 24 studies, relating to 28 treatment-comparisons, were described as randomised (this being an inclusion criterion of the review). The method of random sequence generation was described sufficiently to be judged at low risk of bias for this domain in 5 treatment-comparisons (Bhattacharyya 2009; Carey 2012; Fountzilas 2004; Hu 2015; Valero 2011). The remaining 23 treatment-comparisons were judged to be at unclear risk of bias for random sequence generation as the information available was insufficient to accurately assess this domain.

Eight of the 28 treatment-comparisons described central randomisation systems and were thus judged to be at low risk of bias for treatment allocation concealment (Cocconi 1991; Cocconi 1999; Fountzilas 2004; Fountzilas 2009 A; Fountzilas 2009 B; Hu 2015; Icli 2005; Nielsen 2000). The remaining 20 treatment-comparisons did not adequately describe methods of concealment and were thus judged as having unclear risk of bias for this domain.

Blinding

Eleven treatment-comparisons were described as 'nonblinded', 'not blinded', 'single blind' or 'open-label' (Amadori 2013; Carey 2012; Fan 2012; Hu 2015; Icli 2005; Stemmler 2011 A; Stemmler 2011 B; Tutt 2014; Valero 2011; Xu 2011 A; Xu 2011 B). These 11 'unblinded' treatment-comparisons were judged to be at high risk

of 'performance bias' due to the lack of blinding of participants and personnel to the treatment being administered. The remaining 17 treatment-comparisons were judged as at unclear risk of 'performance bias' because of a lack of information needed to make a firm conclusion. It seemed highly likely, however, that a number of these 17 treatment-comparisons would have also been 'unblinded', as open-label studies are common in phase III oncology trials.

All 27 treatment-comparisons known to have OS as a study outcome (including 8 not included in OS meta-analyses but excluding Amadori 2013 which did not assess OS as an outcome) were judged to be at low risk of bias from a lack of blinding of outcome assessors, regardless of actual blinding. This is because death certification was unlikely to be affected by any lack of blinding.

For outcomes other than OS and QoL, five treatment-comparisons were judged to be at low risk of bias from a lack of blinding of outcome assessors due to these outcomes being measured/confirmed through formal assessments including imaging, biochemical tests and/or the involvement of an independent clinical or radiological review group (Carey 2012; Cocconi 1991; Cocconi 1999; Fountzilas 2004; Icli 2005). The remaining 23 treatment-comparisons provided insufficient detail on outcome

assessments and were thus classified as having an unclear risk of bias.

Incomplete outcome data

Three treatment-comparisons were judged to be at high risk of attrition bias for time-to-event outcomes because participants who did not receive a specified number of cycles of chemotherapy were excluded from time-to-event analyses (a form of per-protocol analysis) (Kolaric 1985; Kolaric 1989; Nielsen 2000). Eleven treatment-comparisons excluded randomised participants who never started treatment or who were subsequently found to have been 'ineligible' from time-to-event analyses (mITT analyses) (Berruti 2002 A; Carey 2012; Cocconi 1999; Cocconi 1996; Creagan 1984; Fountzilas 2004; Fountzilas 2009 A; Fountzilas 2009 B; Hu 2015; Icli 2005; Xu 2011 A). These 11 treatment-comparisons were judged to be at unclear risk of attrition bias for time-to-event outcomes. The remaining 14 treatment-comparisons were judged to be at low risk of attrition bias for time-to-event outcomes because all randomised participants were analysed in the groups to which they were randomised (ITT analysis).

Four treatment-comparisons had more than 15% of participants not assessed/assessable for at least one binary outcome and were thus judged to be at high risk of attrition bias for binary outcomes (Amadori 2013; Fountzilas 2009 B; Stemmler 2011 A; Stemmler 2011 B;). Fourteen treatment-comparisons had less than 10% of participants not assessed/assessable for all binary outcomes and were thus judged to be at low risk of attrition bias for binary outcomes (Berruti 2002 A; Berruti 2002 B; Cocconi 1991; Cocconi 1999; Creagan 1984; Fan 2012; Fountzilas 2004; Hu 2015; Icli 2005; Kolaric 1985; Robert 2006; Valero 2011; Xu 2011 A; Xu 2011 B). The remaining 10 treatment-comparisons were judged to be at unclear risk of attrition bias for binary outcomes (10 to 15% of participants not assessed/assessable for at least one binary outcome or it was unclear what proportion were not assessed).

Selective reporting

The assessment of risk of bias from selective reporting included crosschecking the outcomes for which there were published results against the stated outcomes reported in trial registers (WHO ICTRP and ClinicalTrials.gov) and published protocols. In our assessment of risk of bias from selective reporting, studies that began recruiting participants on or after July 1, 2005 were expected have a clinical registration or published protocol specifying the study outcome or they were deemed to be at high risk of bias from selective reporting. We chose July 1, 2005 as our cut-off date because the International Committee of Medical Journal Editors (ICMJE) made

a seminal announcement in September 2004 that clinical trials that begin recruiting on or after July 1, 2005 would not be considered for publication unless they were included on a clinical trials registry (De Angelis 2005). Studies included in this review which began recruiting participants before July 1, 2005 and which did not have a trial registration or published protocol prespecifying study outcomes, were assumed to be at unclear risk of bias from selective reporting, unless additional evidence suggested otherwise.

Six treatment-comparisons from four studies were judged to be at low risk of bias from the selective reporting of outcomes (Carey 2012; Hu 2015; Stemmler 2011 A; Stemmler 2011 B; Xu 2011 A; Xu 2011 B). Each of these studies was included on a clinical trials registry and their prespecified outcomes either matched those in the trial reports or non-matches were considered to be relatively minor. Three treatment-comparisons were judged to be at high risk of bias from the selective reporting of outcomes. The first of these was Tutt 2014 which specified TTP, TTF and toxicity as outcomes in the trial registration, but did not report on these outcomes in either of two conference abstracts (future publications may report in more detail and this 'risk of bias' assessment may change). The second was Fan 2012 which did not have a trial registration or published protocol and did not report the date that participants were first enrolled. However, given that Fan 2012 was first published in December 2012 and that there were only 53 study participants, it seemed highly likely that recruitment began after July 1, 2005. Consequently, there was a high expectation of trial registration which this study failed to undertake. The third of these was Bhattacharyya 2009 in which the abstract indicated that toxicity was recorded but no results were reported. In addition, for Bhattacharyya 2009, there was no trial registration or published protocol containing prespecified outcomes. The date that participant recruitment began was not reported, but given that this was first published in September 2009, it seemed likely that recruitment began after July 1, 2005. As of April 2015, there had been no further results published other than those in the conference abstract. The remaining 19 treatment-comparisons were judged to be at unclear risk of bias from the selective reporting of outcomes either because the trial was unregistered with recruitment starting before July 1, 2005 or the stated outcomes in the registry did not match those in the trial reports, but it was unclear if these non-matches posed a high risk of bias.

Egger's tests for funnel plot asymmetry did not identify evidence consistent with the presence of publication bias or small-study effects, or both, for OS (P value = 0.98; Figure 3), PFS/TTP (P value = 0.36) or OTRR (P value = 0.45).

Figure 3. Funnel plot 1: Overall survival (OS). Assessing publication bias and/or small-study effects. Plot includes all treatment-comparisons with extractable data for OS. The plot does not show asymmetry (Egger's test P value = 0.98)

Other potential sources of bias

Five treatment-comparisons were judged to be at unclear risk of 'other bias' (Carey 2012; Eisen 1998; Fountzilas 2004; Hu 2015; Tutt 2014) for various reasons outlined in the Characteristics of included studies table. The remaining 23 treatment-comparisons were judged to be at low risk of 'other bias'.

Effects of interventions

See: [Summary of findings for the main comparison](#) Platinum-containing regimens for women with metastatic breast cancer unselected for triple-negative disease; [Summary of findings 2](#) Platinum-containing regimens for women with metastatic triple-negative breast cancer; [Summary of findings 3](#) Platinum-containing regimens and toxicity profile

Refer to [Summary of findings for the main comparison](#); [Summary of findings 2](#); [Summary of findings 3](#).

Overall survival (OS)

Twenty-seven of the 28 included treatment-comparisons assessed OS as an outcome; 19 provided sufficient OS data for pooling in meta-analyses. From these 19 treatment-comparisons, 2922 of 2956 randomised participants were analysed representing 99% of randomised participants in these treatment-comparisons (and there were about 1868 deaths). There was no statistically significant difference in survival between platinum-containing regimens or non-platinum regimens with a HR of 0.98 (95% CI 0.89 to 1.07, $P = 0.64$) with some heterogeneity identified across trials ($P = 0.04$; $I^2 = 39\%$) ([Analysis 1.1](#); [Figure 4](#)).

Figure 4. Forest plot of comparison: 1 Platinum vs non-platinum regimens (subgroup analysis 1: by treatment-comparisons assessing mTNBC), outcome: 1.1 Overall survival.

Subgroup analysis showed a marginally significant survival benefit in favour of platinum-containing regimens for three treatment-comparisons assessing women with metastatic triple-negative breast cancer (mTNBC) only (HR 0.75, 95% CI 0.57 to 1.00; $P = 0.05$; low-quality evidence) (Analysis 1.1; Figure 4). The difference between this pooled HR of 0.75 and that from 16 treatment-comparisons assessing participants unselected for TNBC (HR 1.01, 95% CI 0.92 to 1.12; high-quality evidence) was marginally significant ($P = 0.05$); heterogeneity was not large in either subgroup ($P = 0.23$, $I^2 = 32\%$ and $P = 0.09$, 34% respectively). The six other subgroup analyses showed no evidence of subgroup differences (P values ranged from $P = 0.09$ to $P = 0.86$; see Analysis 2.1; Analysis 3.1; Analysis 4.1; Analysis 5.1; Analysis 6.1; Analysis 7.1).

Progression-free survival/time to progression (PFS/TTP)

Twenty-four of the 28 included treatment-comparisons assessed PFS or TTP, or both, as an outcome; 16 provided sufficient data for pooling in meta-analyses of the composite outcome of PFS/TTP. From these 16 treatment-comparisons, 2136 out of 2162 (99%) randomised participants were analysed (and there were about 1772 events). There was a statistically significant difference in favour of platinum-containing regimens (HR 0.85, 95% CI 0.78 to 0.93, $P = 0.0002$), although there was marked evidence of heterogeneity ($P = 0.0004$; $I^2 = 63\%$) (Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Platinum vs non-platinum regimens (subgroup analysis 1: by treatment-comparisons assessing mTNBC), outcome: 1.2 Progression-free survival/time to progression.

Significant differences in the pooled HRs of subgroups were found in three of the seven subgroup analyses involving PFS/TTP. Specifically, there were significant differences in the pooled HRs for subgroups of treatment-comparisons:

- assessing participants with mTNBC (HR 0.59, 95% CI 0.49 to 0.72; heterogeneity P = 0.07, I² = 62%; n = 3; low-quality evidence) and unselected for mTNBC (HR 0.92, 95% CI 0.84 to 1.01; heterogeneity P = 0.08, I² = 38%; n = 13; moderate-quality evidence) (P < 0.0001 for subgroup difference) ([Analysis 1.2](#); [Figure 5](#)).
- with > 80% of participants receiving first-line therapy (HR 0.93, 95% CI 0.83 to 1.03; heterogeneity P = 0.003, I² = 63%; n = 11) and > 20% of participants receiving second- or third-line therapy (HR 0.75, 95% CI 0.65 to 0.86; heterogeneity P = 0.12, I² = 45%; n = 5) (P = 0.01 for subgroup difference) ([Analysis 4.2](#)).
- with no anthracycline in the platinum or non-platinum regimens (HR 0.80, 95% CI 0.73 to 0.88; heterogeneity P = 0.001, I² = 65%; n = 11), an anthracycline in both the platinum and non-platinum regimens (HR 1.05, 95% CI 0.86 to 1.27; heterogeneity P = 0.35, I² = 8%; n = 4) and an anthracycline in the platinum regimen only (HR 1.23, 95% CI 0.75 to 2.03; n = 1) (P = 0.02 for subgroup difference) ([Analysis 5.2](#)).

The four other subgroup analyses showed no evidence of subgroup differences (P values ranged from P = 0.34 to P = 0.88; see [Analysis 3.2](#); [Analysis 6.2](#); [Analysis 7.2](#); [Analysis 8.2](#)).

Time to treatment failure (TTF)

Three of the 28 included treatment-comparisons assessed TTF as an outcome but only one provided sufficient data for extraction ([Fountzilas 2004](#): HR 0.88, 95% CI 0.69 to 1.13).

Objective Tumour Response Rate (OTRR) — assessable participants

All 28 included treatment-comparisons assessed OTRR as an outcome and provided sufficient data for extraction. From the 28 treatment-comparisons, 4130 out of 4475 (92%) randomised participants were assessable for tumour response (and 2017 had a complete or partial response). There was a statistically significant difference in OTRRs in favour of platinum-containing regimens (RR 1.15, 95% CI 1.08 to 1.22, P < 0.0001), but there was also considerable evidence of heterogeneity (P < 0.0001; I² = 64%) ([Analysis 1.3](#); [Figure 6](#)).

Figure 6. Forest plot of comparison: 1 Platinum vs non-platinum regimens (subgroup analysis 1: by treatment-comparisons assessing mTNBC), outcome: 1.3 Objective tumour response rate (assessable participants).

Footnotes

(1) 97% of Tutt 2014 participants were TNBC

Significant differences in the pooled RRs of subgroups were found in five of the seven OTRR subgroup analyses. Specifically, there were significant differences in the pooled RRs for subgroups of treatment-comparisons:

- assessing participants with mTNBC (RR 1.33, 95% CI 1.13 to 1.56; heterogeneity P = 0.0010, I² = 78%; n = 5; low-quality evidence) and unselected for mTNBC (RR 1.11, 95% CI 1.04 to 1.19; heterogeneity P = 0.0002, I² = 58%; n = 23; low-quality evidence) (P = 0.05 for subgroup difference) (Analysis 1.3; Figure 6).

- comparing 'regimen A + platinum vs regimen A' (RR 1.10, 95% CI 1.01 to 1.21; heterogeneity P = 0.009, I² = 61%; n = 9), 'regimen A + platinum vs regimen B' (RR 1.22, 95% CI 1.12 to 1.33; heterogeneity P = 0.0002, I² = 63%; n = 18) and 'single agent platinum vs regimen C' (RR 0.88, 95% CI 0.66 to 1.17; n = 1) (P = 0.05 for subgroup difference) (Analysis 2.3).
- using cisplatin (RR 1.35, 95% CI 1.24 to 1.46; heterogeneity P = 0.006, I² = 53%; n = 17), carboplatin (RR 0.88, 95% CI 0.86 to 1.04; heterogeneity P = 0.10, I² = 38%; n = 10) and oxaliplatin (RR 0.85, 95% CI 0.48 to 1.52; n = 1) as the platinum agent in the platinum regimen (P < 0.0001 for subgroup difference) (Analysis 3.3).

- with no anthracycline in their platinum or non-platinum regimens (RR 1.10, 95% CI 1.02 to 1.20; heterogeneity $P < 0.0001$, $I^2 = 65\%$; $n = 18$), an anthracycline in both the platinum and non-platinum regimens (RR 1.09, 95% CI 0.97 to 1.22; heterogeneity $P = 0.12$, $I^2 = 42\%$; $n = 6$) and an anthracycline in the platinum regimen only (RR 1.49, 95% CI 1.28 to 1.74; heterogeneity $P = 0.38$, $I^2 = 2\%$; $n = 4$) ($P = 0.002$ for subgroup difference) ([Analysis 5.3](#)).
- with no taxane in the platinum or non-platinum regimens (RR 1.25, 95% CI 1.15 to 1.36; heterogeneity $P = 0.009$, $I^2 = 51\%$; $n = 17$), a taxane in both platinum and non-platinum regimens (RR 1.01, 95% CI 0.90 to 1.12; heterogeneity $P = 0.002$, $I^2 = 74\%$; $n = 6$) and a taxane in the non-platinum regimen only (RR 1.11, 95% CI 0.94 to 1.30; heterogeneity $P = 0.02$, $I^2 = 67\%$; $n = 5$) ($P = 0.007$ for subgroup difference) ([Analysis 6.3](#)).

The two other subgroup analyses showed no evidence of subgroup differences ($P = 0.55$, [Analysis 4.3](#); and $P = 0.94$, [Analysis 7.3](#)).

Toxicity – safety populations

Treatment-related death

Fifteen of the 28 included treatment-comparisons assessed treatment-related death and provided sufficient data for extraction. Of these 15 treatment-comparisons, five had non-estimable RRs due to no treatment-related deaths and, consequently, did not contribute to the pooled estimates. For the 10 remaining treatment-comparisons, 1688 out of 1759 (96%) randomised women were included in the safety populations, with 32 treatment-related deaths. There was no significant difference between platinum and non-platinum regimens in terms of treatment-related death but the confidence interval was wide (RR 1.42, 95% CI 0.73 to 2.76; [Analysis 3.4](#)). There was no evidence of heterogeneity ($P = 0.94$, $I^2 = 0\%$).

No significant differences in pooled RRs were found according to the type of platinum agent used ($P = 0.61$).

Nausea/vomiting

Twenty-one of the 28 included treatment-comparisons assessed grade 3 and 4 nausea/vomiting with sufficient data for extraction. One treatment-comparison had a non-estimable RR due to there being no grade 3 or 4 cases. For the 20 remaining treatment-comparisons, 3101 out of 3192 (97%) randomised women were included in the safety populations with 364 cases of grade 3 or 4 nausea/vomiting. Risk of grade 3 or 4 nausea/vomiting was significantly higher among women receiving platinum-containing regimens (RR 2.07, 95% CI 1.69 to 2.54, $P < 0.0001$) but there was also considerable evidence of heterogeneity ($P = 0.0003$, $I^2 = 60\%$) ([Analysis 3.5](#)).

Subgroup analysis indicated that the increased risk of grade 3 or 4 nausea/vomiting for platinum recipients (compared to non-platinum recipients) was primarily driven by cisplatin rather than carboplatin use. Specifically, there was a significant difference in the pooled RR for treatment-comparisons using cisplatin (RR 2.65, 95% CI 2.10 to 3.34; $n = 14$; moderate-quality evidence) rather than carboplatin (RR 0.77, 95% CI 0.47 to 1.26; $n = 6$; moderate-quality evidence) in their platinum-containing regimens ($P < 0.0001$ for subgroup difference). There was evidence of heterogeneity in the cisplatin ($P = 0.008$, $I^2 = 54\%$) but not the carboplatin ($P = 0.30$, $I^2 = 17\%$) subgroup.

Nephrotoxicity

Five of the 28 included treatment-comparisons assessed grade 3 and 4 nephrotoxicity and reported sufficient data for extraction. One treatment-comparison had a non-estimable RR due to there being no grade 3 or 4 cases. For the four remaining treatment-comparisons, 557 out of 571 (98%) randomised women were included in the safety populations, with 11 cases of grade 3 or 4 nephrotoxicity. Risk of grade 3 or 4 nephrotoxicity was more than three-fold higher among women receiving platinum-containing regimens, but this increase in risk was not significant (RR 3.06, 95% CI 0.86 to 10.84, $P = 0.08$) ([Analysis 3.6](#)). There was no evidence of heterogeneity ($P = 0.92$, $I^2 = 0\%$).

No significant differences in pooled RRs were found according to the type of platinum agent used ($P = 0.65$).

Anaemia

Twenty of the 28 included treatment-comparisons assessed grade 3 and 4 anaemia with sufficient data for extraction. One treatment-comparison had a non-estimable RR due to there being no grade 3 or 4 anaemia cases. For the 19 remaining treatment-comparisons, 3032 out of 3107 (98%) randomised women were included in the safety populations, with 176 cases of grade 3 or 4 anaemia. Risk of grade 3 or 4 anaemia was significantly higher among women receiving platinum-containing regimens (RR 2.61, 95% CI 1.90 to 3.58, $P < 0.0001$) ([Analysis 3.7](#)). There was no evidence of heterogeneity ($P = 0.41$, $I^2 = 4\%$).

Subgroup analysis indicated that the increased risk of grade 3 or 4 anaemia for platinum recipients (compared to non-platinum recipients) was worse for cisplatin recipients compared to carboplatin recipients. Specifically, there was a significant difference between the pooled RRs for treatment-comparisons using cisplatin (RR 3.72, 95% CI 2.36 to 5.88; $n = 12$; high-quality evidence) rather than carboplatin (RR 1.72, 95% CI 1.10 to 2.70; $n = 7$; high-quality evidence) in their platinum-containing regimens ($P = 0.02$ for subgroup difference). There was no evidence of heterogeneity in the cisplatin or carboplatin subgroups ($P = 0.50$ and $P = 0.67$, respectively; $I^2 = 0\%$ and $I^2 = 0\%$, respectively).

Hair Loss

Twelve of the 28 included treatment-comparisons assessed grade 3 and 4 hair loss and reported sufficient data for extraction. Three treatment-comparisons had a non-estimable RR due to there being no grade 3 or 4 cases. For the nine remaining treatment-comparisons, 1080 out of 1089 (99%) randomised women were included in the safety populations, with 469 cases of grade 3 or 4 hair loss. Risk of grade 3 or 4 hair loss was significantly higher among women receiving platinum-containing regimens (RR 1.41, 95% CI 1.26 to 1.58, $P < 0.0001$; high-quality evidence) ([Analysis 3.8](#)). There was some indication of heterogeneity ($P = 0.10$, $I^2 = 40\%$).

No significant differences in pooled RRs were found according to the type of platinum agent used ($P = 0.23$).

Leukopenia

Twenty-two of the 28 included treatment-comparisons assessed grade 3 and 4 leukopenia and reported sufficient data for extraction. One treatment-comparison had a non-estimable RR due to there being no grade 3 or 4 cases of leukopenia. For the 21 remaining treatment-comparisons, 3123 out of 3222 (97%)

randomised women were included in the safety populations, with 628 cases of grade 3 or 4 leukopenia. Risk of grade 3 or 4 leukopenia was significantly higher among women receiving platinum-containing regimens (RR 1.38, 95% CI 1.21 to 1.57, $P < 0.0001$; moderate-quality evidence) but with evidence of heterogeneity ($P = 0.0002$, $I^2 = 62\%$) ([Analysis 3.9](#)).

No significant differences in pooled RRs were found according to the type of platinum agent used ($P = 0.21$).

Quality of life

Three studies reported treatment effects on quality of life; [Fountzilias 2004](#) (EORTC QLQ-C30), [Fountzilias 2009](#) ([Fountzilias 2009 A](#); [Fountzilias 2009 B](#)) (EUROQOL EQ5D and EQ VAS) and [Amadori 2013](#) (EORTC QLQ-C30). However, quality of life results could not be pooled in a meta-analysis because only one quality of life domain was common to two treatment-comparisons (the EORTC QLQ-C30 'global' domain reported by [Fountzilias 2004](#) and [Amadori 2013](#)) and only one reported sufficient data for extraction ([Amadori 2013](#)).

[Fountzilias 2004](#) found paclitaxel/carboplatin was associated with an improvement both in the emotional functioning scale and in sleep disturbance symptoms compared with paclitaxel/epirubicin, but did not find significant group differences in any other quality of life domains assessed (physical role, cognitive, social, global quality of life, fatigue, nausea and vomiting, pain, dyspnoea, appetite loss, constipation, diarrhoea, financial impact). [Fountzilias 2009](#) ([Fountzilias 2009 A](#); [Fountzilias 2009 B](#)) found that changes in quality across time did not differ significantly between groups for the domains reported (EQ5D index and EQ VAS score). [Amadori 2013](#) found that pemetrexed/carboplatin participants had significantly greater deterioration in global health status scores (follow-up minus baseline scores) than vinorelbine/gemcitabine participants, but there was no significance difference in body image scores between groups.

Sensitivity analyses

Restricting the OTRR meta-analysis to the 19 treatment-comparisons with extractable data on OS had little impact on the pooled RR estimate (RR = 1.15 and RR = 1.13 in the original and sensitivity analyses, respectively). Restricting the OS and PFS/TTP meta-analyses to the 12 treatment-comparisons with extractable data on both OS and OS and PFS/TTP lowered the pooled HR estimate from HR = 0.98 to HR = 0.92 for OS, and from 0.85 to 0.80 for PFS/TTP. This represented a 6% reduction in the HR estimates for both OS and PFS/TTP and suggested that the relative difference between OS and PFS/TTP results was unlikely to be due to the different treatment-comparisons available for the meta-analysis of each outcome.

Stratifying PFS/TTP estimates according to whether the outcome was PFS or TTP suggested that platinum chemotherapy was more beneficial in terms of TTP than PFS, although the difference was not statistically significant ($P = 0.06$). Repeating [Analysis 1.1](#), and [Analysis 1.2](#) using random-effects methods did not appreciably change the point estimates for OS or PFS/TTP, but did produce slightly wider confidence intervals ([Analysis 10.1](#); [Analysis 10.2](#)). Repeating [Analysis 1.3](#) using a random-effects model did not appreciably change the OTRR point estimate for participants unselected for mTNBC, but did increase the point estimate for mTNBC participants (from 1.33 to 1.60).

DISCUSSION

Summary of main results

In this review update and consistent with the findings of the original review, our results did not show an OS benefit from platinum-containing regimens compared to non-platinum regimens for women with metastatic breast cancer 'in general' (i.e. without regard to subgroups). The confidence limits for the OS pooled HR estimate suggested that platinum-containing regimens were unlikely to confer more than a 11% reduction in the risk of death and might increase the risk by up to 7%. The lack of an OS benefit for platinum-containing regimens was somewhat at odds with the significant PFS/TTP and OTRR benefits observed in this review. Compared to women receiving non-platinum regimens, those receiving platinum-containing regimens had a 15% lower rate of progression or death (as measured by PFS/TTP) and a 15% higher rate of complete or partial tumour response. Sensitivity analyses indicated that the discrepancies between the OS and OTRR findings, and between the OS and PFS/TTP findings, were unlikely to be due to the different sets of treatment-comparisons used in the various meta-analyses of OS, PFS/TTP and OTRR. Rather, these discrepancies seemed more likely to be related to PFS/TTP and OTRR being somewhat poor surrogate outcomes for OS in metastatic breast cancer research ([Burzykowski 2008](#)), and perhaps also related to general difficulties in measuring tumour response. Given that OS is generally regarded as the outcome of choice for assessing treatment efficacy in metastatic breast cancer research ([Burzykowski 2008](#)) and given that this review now has a sufficient number of included studies to estimate the effects of treatments on OS with relatively high precision, we think that considerably more weight should be given to the OS results than the PFS/TTP or OTRR results.

In the absence of subgroup analyses, heterogeneity of effect estimates was observed for PFS/TTP, OTRR and, to a lesser degree, OS. With regards to OS and PFS/TTP, heterogeneity was explained to a large extent by the triple-negative status of study participants. More specifically for OS, data from three treatment-comparisons assessing mTNBC participants showed a 25% reduction in the risk of death for recipients of platinum-containing regimens compared to recipients of non-platinum regimens ($P = 0.05$). In absolute terms, this 25% risk ratio reduction corresponded to about 93 fewer deaths at one year after metastatic diagnosis for every 1000 mTNBC participants who received platinum-containing chemotherapy, and about 105 fewer deaths at two years ([Summary of findings 2](#)). In contrast, data from 16 treatment-comparisons, assessing participants unselected for TNBC, showed similar risks of death among platinum and non-platinum recipients (HR = 1.01). In relation to PFS/TTP, platinum-containing regimens reduced the risk of death or progression, or both, by about 41% for mTNBC participants ($P < 0.0001$) but only by about 8% for participants unselected for mTNBC ($P = 0.10$). The difference between the pooled effect estimates of the mTNBC and 'unselected for mTNBC' subgroups was significant for PFS/TTP ($P < 0.0001$) and on the margins of statistical significance for OS ($P = 0.05$) and OTRR ($P = 0.05$).

While we also found a number of other statistically significant subgroup differences for OTRR and PFS/TTP (see [Effects of interventions](#)), it is difficult to judge the importance or reliability of these findings, given that similar differences were not observed in relation to OS.

Assessments of toxicity showed that women receiving platinum-containing regimens experienced higher rates of grade 3 and 4 nausea/vomiting, anaemia, leukopenia and hair loss than women receiving non-platinum regimens. Subgroup analysis indicated that the higher rate of grade 3 and 4 nausea/vomiting was associated with cisplatin but not carboplatin use, and the increased risk of grade 3 and 4 anaemia was higher for cisplatin recipients than for carboplatin recipients.

Overall completeness and applicability of evidence

This review now includes data from 24 studies relating to 28 treatment-comparisons, with publications years ranging from 1984 to 2014. Of the 28 treatment-comparisons, 19 (68%) and 16 (57%) provided sufficient time-to-event data to be included in OS and PFS/TTP meta-analyses, respectively. All 28 treatment-comparisons provided OTRR data that could be included in meta-analyses. A majority of treatment-comparisons had sufficient data on treatment-related death ($n=15$; 54%), nausea/vomiting ($n=21$; 75%), anaemia ($n=20$; 71%) and leukopenia ($n=22$; 79%) for inclusion in meta-analyses. Five (18%) and 12 (43%) treatment-comparisons had sufficient data on nephrotoxicity and hair loss for pooling, respectively. The evidence relating to treatment effects on quality of life remained almost wholly incomplete, with only three studies reporting quality of life results that could not be pooled in meta-analysis.

Although data for the most important outcome (OS) was extractable for 68% of treatment-comparisons, the evidence would clearly be more complete if OS data were extractable for all 28 treatment-comparisons. Nonetheless, it is somewhat reassuring that sensitivity analyses restricting the OTRR meta-analysis to the 19 treatment-comparisons with extractable OS data did not appreciably change the OTRR pooled estimate of effect ($RR=1.15$ and $RR=1.13$ in the original and sensitivity analyses, respectively). This provides some evidence that the 'overall' pooled effect estimate for OS was unlikely to have changed substantively if OS data were extractable for all 28 treatment-comparisons. It is important to note, however, that although the 'overall' pooled estimate of effect for OS appeared robust to the missing treatment-comparisons, this may not be the case for smaller subgroups. For example, our finding of a significant OS benefit for mTNBC participants receiving platinum-containing regimens — based on data from only three treatment-comparisons — may have been different if we were able to include OS data from [Tutt 2014](#) in the meta-analysis. In this relatively large treatment-comparison of mainly mTNBC participants, median OS times were similar in the platinum and non-platinum groups.

The evidence in this review appeared to be generally applicable to the current practice of the treatment of metastatic breast cancer for a number of reasons. First, the platinum and non-platinum regimens used in the included trials contained most chemotherapy drugs currently used in clinical practice to treat metastatic breast cancer, including cyclophosphamide, methotrexate, fluorouracil (CMF), trastuzumab and various anthracyclines and taxanes. Second, the review included trials of women receiving first-line treatment and women receiving treatment after failure of previous anthracycline or taxane regimens. Third, the review was well populated with trials using the two most commonly used platinum agents for treating metastatic breast cancer — carboplatin and cisplatin. While the review had only one trial using oxaliplatin as the platinum agent, oxaliplatin is not widely

used in clinical practice for treating breast cancers. Fourth, this review update is the first to use meta-analysis to synthesise the evidence on an issue of considerable interest and importance to clinical practice; namely, whether platinum-based chemotherapies improved survival outcomes for mTNBC participants.

Quality of the evidence

Quality of evidence ratings relating to OS, PFS/TTP and OTRR effect estimates were graded separately for the subgroups of treatment-comparisons with women unselected for mTNBC ([Summary of findings for the main comparison](#)) and with mTNBC ([Summary of findings 2](#)). We identified no problems using the GRADE assessment criteria in relation to the OS effect estimate for the 'unselected' subgroup; hence, the quality of the evidence for this estimate was rated 'high'. For the 'mTNBC' subgroup, the quality of the evidence rating for the OS effect estimate was downgraded two levels to 'low' for 'imprecision' (because the confidence interval for the pooled estimate was wide and close to the null) and for 'suspected publication bias' (because of the absence of [Tutt 2014](#) from the OS meta-analysis). The quality of the evidence ratings for PFS/TTP and OTRR effect estimates ranged from 'low' to 'moderate' across the 'unselected' and 'mTNBC' subgroups for reasons including 'indirectness', 'imprecision', 'inconsistency' and 'suspected publication bias' (see [Summary of findings for the main comparison](#) and [Summary of findings 2](#) for details).

Treatment effect estimates for four key toxicity outcomes were graded for quality of evidence ([Summary of findings 3](#)). Gradings were stratified by 'type of platinum agent' (cisplatin or carboplatin) for nausea/vomiting and anaemia and not stratified for hair loss and leukopenia (because hair loss and leukopenia were not significantly related to 'type of platinum agent'). The quality of the evidence ratings were 'high' for hair loss and for anaemia (both cisplatin and carboplatin subgroups), and downgraded one level to 'moderate' for nausea/vomiting (both cisplatin and carboplatin subgroups) and leukopenia due to either 'imprecision' or 'inconsistency' (see [Summary of findings 3](#) for details).

Potential biases in the review process

Although it is possible that we may not have identified every eligible study with published results, study protocol or clinical trial registration, this seemed unlikely given our highly sensitive search strategies, including access to the Cochrane Breast Cancer Specialised Register maintained by the Cochrane Breast Cancer Group. A related but more insidious problem, however, was the risk of reporting bias arising from completed studies that never published their (largely) negative findings. While non-publication of negative findings probably has occurred less frequently in recent years (due to increasing pressures to preregister clinical trials and publish results within reasonable time-frames), many systematic reviews remain vulnerable to historical reporting bias. In this review, many of the included studies were conducted in an era when non-publication of negative findings was more likely, but it seemed unlikely that this would have substantively affected our OS main finding, given that this finding was itself negative.

Agreements and disagreements with other studies or reviews

[Petrelli 2016](#) recently published a systematic review and meta-analysis of randomised trials to assess the efficacy and safety of therapy with platinum salts in participants with locally advanced

or metastatic breast cancer. In their review, Petrelli reported overall pooled effect estimates similar to our estimates in terms of OS (HR = 0.91 vs HR = 0.98, respectively), PFS/TTP (HR = 0.84 vs HR = 0.85, respectively) and OTRR (odds ratio = 1.27 vs odds ratio = 1.33, respectively after recalculating our relative risk estimate into an odds ratio). It is important to note, however, that while the overall results of the two systematic reviews are similar, [Petrelli 2016](#) included studies with 100% locally advanced participants whereas our review excluded studies with more than 20% of participants having isolated locoregional recurrence. In addition, our review extended the work of Petrelli through the inclusion of multiple additional subgroup analyses.

To our knowledge, there has been only one other systematic review of randomised trials comparing the effects of platinum and non-platinum-containing regimens among participants with mTNBC ([Guan 2015](#)). That review, however, only performed meta-analyses of tumour response rates and not time-to-event outcomes. The OTRR meta-analysis in [Guan 2015](#) was comprised of three of the five mTNBC treatment-comparisons included in the current review ([Bhattacharyya 2009](#); [Carey 2012](#); [Fan 2012](#)); the additional inclusion of [Tutt 2014](#) and [Hu 2015](#) in the current review resulted in a pooled OTRR estimate of effect (RR 1.33, 95% CI 1.13 to 1.56), significantly lower than that of [Guan 2015](#) (RR 2.42, 95% CI 1.66 to 3.53).

AUTHORS' CONCLUSIONS

Implications for practice

In view of the excess toxicity and limited survival benefits from platinum-based regimens, it is difficult to justify their use over commonly-available less toxic active agents as first-line treatment for metastatic patients without mTNBC. On the other hand, this review update found preliminary low-quality evidence of a moderate survival benefit for women with mTNBC. Consequently, although the evidence may be premature to recommend widespread use of platinum-based regimens for

mTNBC patients, some women and clinicians may consider platinum-based regimens worth trying. While evidence from this review suggested that carboplatin was generally associated with less toxicity than cisplatin, it is not yet clear whether the possible benefits for women with mTNBC are related to the type of platinum agent.

Implications for research

It seems unlikely that the inclusion of additional randomised trials could alter our conclusion that platinum-containing regimens offer little or no survival benefit for women with metastatic breast cancer that is not confirmed to be mTNBC. In contrast, however, our finding of a moderate survival benefit for women with mTNBC was based on low-quality evidence from only three trials; hence, additional randomised trials are necessary to confirm this finding. It is also worth noting that [Tutt 2014](#) did not find an OS, PFS or OTRR advantage for women with mTNBC receiving carboplatin (vs docetaxel). However, in subgroup analysis restricted to 43 [BRCA1/2](#) positive participants, [Tutt 2014](#) found carboplatin was associated with significantly better OTRRs, perhaps suggesting a useful line of future research.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Amadori 2013

Methods	Multicentre, randomised, two-stage, open-label, noncomparative, parallel-group phase II study conducted between June 2006 and April 2010.
Participants	135 adult females with a histologic or cytologic diagnosis of advanced breast cancer previously treated with anthracycline and taxanes. Median age 52 and 51.5 years in platinum and control arms, respectively. Age range 29 to 77 years. 100% advanced breast cancer. 30% 1st-line, 70% 2nd-line. 100% previously treated with anthracycline and taxanes.
Interventions	Pemetrexed and carboplatin vs vinorelbine and gemcitabine. ARM A: Pemetrexed 600 mg/m ² (intravenously for 10 min on day 1) and carboplatin (given over approximately 30 min beginning after the end of the pemetrexed infusion for target area under the curve (AUC) 5.0) on day 1, after pretreatment with folic acid, vitamin B12 and dexamethasone.

Amadori 2013 (Continued)

ARM B: Vinorelbine 30 mg/m² (given over approximately 6 to 10 min) and gemcitabine 1,200 mg/m² (given over approximately 30 min) were administered on day 1 and day 8.

Outcomes	Response. Time to progressive disease (TTPD; Kaplan-Meier curve) defined as "the time from the date of study enrolment to the first documented date of progressive disease or death from study disease". Time to treatment failure (TTTF; presented as medians in months; not extractable for hazard ratio calculation) defined as the time from date of study enrolment to the first documented date of death from any cause, progressive disease, or study treatment discontinuation due to adverse event. Grades 3 and 4 adverse events (only reported when event occurred in ≥ 10% of participants in each treatment group). QoL (EORTC questionnaires, QLQ-C30 global health status, and QLQ-BR23 body image).
Notes	Data for TTTF was not extractable because only event numbers and median TTFs were reported (i.e. pemetrexed and carboplatin: events/total = 60/69, median TTTF = 4.8 months; vinorelbine and gemcitabine: events/total = 58/66, median TTTF = 5.1 months). Data for some adverse event types such as anaemia were not extractable because event data were only reported for event types which occurred in ≥ 10% of participants in each treatment group. Estimated min follow-up = 0.3 months (based on first censoring tick on TTP curve). Estimated max follow-up = 22 months (based on last censoring tick on TTP curve). QoL: Pemetrexed/carboplatin participants had significantly greater deterioration in global health status scores (follow-up minus baseline scores) than vinorelbine/gemcitabine participants. There was no significance difference in body image scores between groups. Median TTPD was 5.1 (95% CI: 4.1 to 8.0) months for pemetrexed/carboplatin arm and 5.6 months (95% CI: 4.2 to 7.5) months for vinorelbine/gemcitabine arm. This study was sponsored by Eli Lilly and Company, Indianapolis, IN, USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were "randomised either to Arm A ...or to Arm B..."; no additional details were provided on how random assignment was achieved in the trial report.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Open-label study but not clear if outcome assessors were blinded to intervention. For tumour response rates, radiological assessments performed before treatment at every other cycle. No further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 69 and 66 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).

Amadori 2013 (Continued)

Incomplete outcome data (attrition bias) (binary outcomes)	High risk	12 of 69 and 10 of 66 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (16.3% of all randomised participants). 4 of 69 and 0 of 66 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (3.0% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	Quality of life was not included in ClinicalTrials.gov record (https://clinicaltrials.gov/ct2/show/NCT00325234) but was included in the trial report. All other outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa.
Other bias	Low risk	None identified.

Berruti 2002 A

Methods	RCT multicentre phase III trial. Randomisation method not reported. Accrual October 1995 to April 1999. Baseline comparability: no significant imbalance apparent or reported.
Participants	186 women with histologically confirmed metastatic breast cancer (1 ineligible -185 entered trial) in the treatment-comparison Berruti 2002 A (186 participants also for Berruti 2002 B). Median age 58. Age range 28 to 75. 100% metastatic breast cancer. 100% first-line. All participants anthracycline-naïve.
Interventions	EPI vs EPI + CDDP. ARM A: Epirubicin 60 mg/m ² on days 1 and 2 every 21 days. ARM B: EPI + CDDP: Epirubicin 60 mg/m ² IV on days 1 and 2 + platinum 30 mg/m ² IV on day 1 and 2 every 21 days.
Outcomes	Overall survival measured from the date of randomisation until death (insufficient OS data reported to calculate hazard ratio for pooling). Time to progression (Kaplan-Meier curve), defined as "the time elapsed from randomisation until disease progression or death" (this would usually be called progression-free survival because death from any cause is treated as an event). Response. Toxicity.
Notes	The trial was part of a factorial 2 x 2 design (4 arms n = 371) to answer two questions. IT IS INCLUDED IN THIS REVIEW AS TWO TRIALS: Berruti (a) and Berruti (b). Intention-to-treat analyses used for overall survival and time to progression. Toxic deaths n = 6, due to either hematologic toxicity, pulmonary thromboembolism, congestive heart failure, arrhythmia, hepatorenal syndrome, or sudden death. Estimated min follow-up = 4.5 months (based on the median number of cycles received). Estimated max follow-up = 64 months (based on last event on the curve). Last follow-up reported as March 2001. Median TTP: 10.8 to 12.2 months LND arms; 9.9 to 8.6 months non-LND arms. Median survival: 28.8 CDDP arms; 29.5 non-CDDP arms; 29.8 LND arms 27.3 non-LND arms (insufficient OS data reported to calculate hazard ratio for pooling).

Berruti 2002 A (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in detail.
Allocation concealment (selection bias)	Unclear risk	Not reported - stated as "randomized" only.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Standard criteria used for classifying tumour response; physical examination or radiography took place. No further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	92 of 93 and 93 of 93 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis (modified intent-to-treat).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	8 of 93 and 5 of 93 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (7.5% of all randomised participants). 3 of 93 and 1 of 93 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (2.2% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of registration or published protocol was low.
Other bias	Low risk	None identified.

Berruti 2002 B

Methods	RCT multicentre phase III trial. Randomisation method not reported. Accrual October 1995 to April 1999. Baseline comparability: no significant imbalance apparent or reported.
Participants	186 women with histologically confirmed metastatic breast cancer. Median age 58. Age range 35 to 74. 100% metastatic breast cancer. 100% first-line. All participants anthracycline-naïve.

Berruti 2002 B (Continued)

Interventions	EPI + LND vs EPI + CDDP + LND. ARM A: EPI + LND: Epiubicin 60 mg/m² IV on days 1 and 2 every 21 days and Lonidamine 450 mg po every day. ARM B: EPI + CDDP + LND: Epiubicin 60 mg/m² IV on days 1 and 2 + cisplatin 30 mg/m² IV on days 1 and 2 every 21 days + lonidamine 450 mg po every day. LND was pursued until progression. Remaining chemotherapy was delivered up to a maximum of 6 weeks.
Outcomes	Overall survival measured from the date of randomisation until death. Time to progression (Kaplan-Meier curve), defined as "the time elapsed from randomisation until disease progression or death" (this would usually be called progression-free survival because death from any cause is treated as an event). Response. Toxicity.
Notes	Toxic deaths n = 5, due to either hematologic, toxicity, pulmonary thromboembolism, congestive heart failure, arrhythmia, hepatorenal syndrome or sudden death. Estimated min follow-up = 4.5 months (based on the median number of cycles received). Estimated max follow-up = 64 months (based on last event on the curve). Last follow-up reported as March 2001. Median TTP: 10.8 to 12.2 months LND arms; 9.9 to 8.6 months non-LND arms. Median survival: 28.8 CDDP arms; 29.5 non-CDDP arms; 29.8 LND arms; 27.3 non-LND arms (insufficient OS data reported to calculate hazard ratio for pooling).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in detail.
Allocation concealment (selection bias)	Unclear risk	Not reported - stated as "randomized" only.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Standard criteria used for classifying tumour response; physical examination or radiography took place. No further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 93 and 93 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	8 of 93 and 5 of 93 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (8.6% of all randomised participants). 3 of 93 and 2 of 93 participants randomised to

Berruti 2002 B (Continued)

		intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (2.7% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Bhattacharyya 2009

Methods	Randomised phase III trial.
Participants	126 mTNBC participants between age group of 38 to 72 years and who had already received anthracyclines and taxanes and had relapsed and could not afford ixabepilone and/or avastin.
Interventions	'No platinum' arm: endoxan 50 mg per day at 10 am and methotrexate 2.5 mg twice a day at 9 am and 5 pm. Platinum arm: Same as above but with 'cisplatinum'.
Outcomes	Response. Overall survival (insufficient OS data reported to calculate hazard ratio for pooling). Time to progression (insufficient TTP data reported to calculate hazard ratio for pooling). Toxicity (no results reported).
Notes	Abstract only. Median follow-up not stated. Median TTP: Platinum arm 13 months vs 'no platinum' arm 7 months (insufficient TTP data reported to calculate hazard ratio for pooling). Median OS: Platinum arm 16 months vs 'no platinum' arm 12 months (insufficient OS data reported to calculate hazard ratio for pooling).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified on more than one factor. Quote: "Patients were randomised to either... stratified by number of sites of metastasis and with or without visceral metastasis with or without bisphosphonates."
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in the abstract.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided in the abstract.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information provided in the abstract. Unlikely that assessment of overall survival would be influenced by lack of blinding.

Bhattacharyya 2009 (Continued)

Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	No information provided in the abstract.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 60 and 66 participants randomised to intervention and control groups, respectively, appear to have been analysed in time-to-event analyses (intent-to-treat analyses), but only median times were reported (hence no extractable time-to-event data).
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	All randomised participants appear to have been assessed/assessable for tumour response. This was not entirely clear though, as it was not explicitly stated and they may have simply used randomised participant denominators.
Selective reporting (reporting bias)	High risk	The abstract mentions that toxicity was recorded but no results were reported. In addition, there was no trial registration or published protocol containing prespecified outcomes. The date when participant recruitment began was not reported, but given that this was first published in September 2009, it seemed likely that recruitment began after July 1, 2005. As of April 2015, there has been no further results published other than those in the conference abstract.
Other bias	Low risk	None identified.

Carey 2012

Methods	Multicentre randomised phase II study. Participants were randomised to control or platinum arms, with control participants additionally receiving platinum upon progression.
Participants	112 women with stage IV triple-negative metastatic breast cancer measurable by RECIST criteria and negative for ER, PR, and HER2 (0 or 1 on immunohistochemistry and/or normal gene copy number by fluorescence in situ hybridisation), of which 102 were treated and included in time-to-event analyses. Median age 52 and 49 years in platinum and control arms, respectively. Age range 28 to 33 years. 100% metastatic breast cancer. Of the 102 participants analysed: 55 (54%) were treated in the second- or third-line setting, but not with previous EGFR inhibitor or platinum for metastatic disease; 84 (98%) had received an anthracycline; 65 (76%) had also received a taxane.
Interventions	Ce vs Ce + C. ARM 1: Cetuximab (400 mg/m ² load then 250 mg/m ² per week intravenously (IV)) alone, with carboplatin (area under the curve of 2, once per week IV) added after progression. ARM 2: Cetuximab (400 mg/m ² load then 250 mg/m ² per week intravenously and with carboplatin (area under the curve of 2, once per week IV).
Outcomes	Response. Overall survival (Kaplan-Meier curve). Time to progression, defined as "treatment initiation to documented progression" (Kaplan-Meier curve; y-axis label typo "Progression-free survival"). Toxicity (data not extractable because results for Arm 2 were combined with Arm 1 participants after progression).

Platinum-containing regimens for metastatic breast cancer (Review)

Carey 2012 (Continued)

Notes

Estimated min follow-up = 0.25 months (based on first censoring tick on TTP curve).

Estimated max follow-up = 38.3 months (based on last censoring tick on TTP curve).

Median OS was 7.5 months (95% CI, 5.0 to 11.6) for arm one and 10.4 months (95% CI, 7.7 to 13.1) for arm 2.

Study supported by Bristol-Myers Squibb, University of North Carolina Breast Cancer Specialized Program of Research, Avon Partners-for-Progress awards and by National Institutes of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quotes: "Patients were randomly assigned..." and "Constrained block randomizations (block size 21 plus 21) kept the imbalance between the arms to four at most".
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single Blind (Outcomes Assessor)" at https://clinicaltrials.gov/show/NCT00232505 implying that participants and personnel were aware of treatment allocation.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Single Blind (Outcomes Assessor). Assessment of overall survival was unlikely to be influenced by no or incomplete blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Low risk	Cyclical evaluations including biochemical tests, CT or MRI imaging every 8 weeks, in addition to an independent evaluation of OTRR by "investigators blinded to treatment arms and not involved in the study".
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	102 of 112 randomised participants were analysed in time-to-event analyses (modified ITT). The 10 excluded participants were excluded after enrolment but before treatment, but no information was provided on the randomised groups of these excluded participants.
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	10 of 112 randomised participants were excluded from all analyses, with no information provided on the randomised groups of these excluded participants. In addition to these 10 excluded participants: 6 of 71 and 0 of 31 participants in the (known) intervention and control groups, respectively, were not assessed/assessable for tumour response (14.3% of all randomised participants); 6 of 71 and 0 of 31 participants in the (known) intervention and control groups, respectively, were excluded from the safety population for evaluating toxicities (14.3% of all randomised participants) (toxicity data were not extractable because results for Arm 2 were combined with Arm 1 participants after progression).
Selective reporting (reporting bias)	Low risk	Toxicity was not listed under 'outcomes' in ClinicalTrials.gov record (https://clinicaltrials.gov/show/NCT00232505), but it was mentioned in the 'secondary objectives' section of the record. All other outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa.
Other bias	Unclear risk	26 participants in the control arm were additionally given carboplatin after progression. This may have attenuated any differences between treatment arms in overall survival.

Cocconi 1991

Methods	National, multicentre, RCT, Accrual May 1985 to April 1988. Randomisation - telephone call to central office. Treatment allocation by randomly permuted blocks of two. Baseline comparability: no significant imbalance apparent or reported.
Participants	140 women with histologically confirmed metastatic breast cancer. Median age 57. Age range 32 to 75. 100% metastatic breast cancer. 100% first-line. Unclear whether the prior adjuvant therapy received by 22% of participants included anthracyclines.
Interventions	CMF vs PE. ARM A: Cyclophosphamide 100 mg/m ² , orally days 1 to 14; Methotrexate 40 mg/m ² IV days 1 and 8; Fluorouracil 600 mg/m ² IV days 1 and 8 repeated every 4 weeks; ARM B: Cisplatin 100 mg/m ² IV day 1 (with hydration and mannitol forced diuresis); etoposide 100 mg/m ² IV days 1, 3 and 5 repeated every 3 weeks.
Outcomes	Overall survival (curve). Time to progression (calculated from beginning of chemotherapy; insufficient TTP data reported to calculate hazard ratio for pooling). Response (calculated from beginning of chemotherapy). Toxicity.
Notes	Min follow-up: 12 months (reported). Max follow-up: 48 months (reported). Median TTP: 8 m CMF, 7.7 m PE (P = 0.84) (insufficient TTP data reported to calculate hazard ratio for pooling). Median survival: 18.7 m CMF, 19 months PE (P = 0.86). Treatment suspended in 5 participants due to toxicity. Study supported by Associazione Italiens per la Ricerca sul Cancro and in part by Progetto Finalizzato Oncologia of Consiglio Nazionale delle Ricerche.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in sufficient detail.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than	Low risk	Tumour response rate evaluated every 3 cycles and every 3 months after suspension of treatment and were assessed "by an extramural review committee for response to treatment" (p. 666).

Cocconi 1991 (Continued)

overall survival and quality of life)

Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	70 of 70 and 70 of 70 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	5 of 70 and 5 of 70 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (7.1% of all randomised participants). 0 of 70 and 2 of 70 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (1.4% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Cocconi 1996

Methods	National multicentre RCT. Randomisation and treatment allocation methods not reported. Baseline comparability: no significant imbalance apparent or reported.
Participants	186 (183 eligible) women with metastatic breast cancer. Median age 57. Age range 32 to 75. 100% metastatic breast cancer. 100% first-line. Unclear whether the prior adjuvant therapy received by about 45% of participants included anthracyclines.
Interventions	CMF vs MPEPIV or MPEMI. ARM A: CMF: Cyclophosphamide 600 mg/m ² days 1 to 8; methotrexate 40 mg/m ² days 1 to 8; Fluorouracil 600 mg/m ² days 1 to 9; every 4 weeks. ARM B: MPEPIV: Methotrexate 100 mg/m ² days 1 to 8, + leucovorin rescue; cisplatin (P) 70 mg/m ² , day 1; epirubicin 70 mg/m ² day 1 + vincristine 1.4 mg/m ² days 1 to 8; every 3 weeks. MPEMI: Methotrexate 100 mg/m ² days 1 to 8 + rescue; cisplatin 70 mg/m ² day 2; etoposide (E) 100 mg/m ² days 1 to 2; mitomycin (MI) 6 mg/m ² day 1; every 3 weeks.
Outcomes	Time to progression (insufficient TTP data reported to calculate hazard ratio for pooling). Survival (insufficient OS data reported to calculate hazard ratio for pooling). Response. Toxicity (no extractable data).
Notes	Conference abstract (1996). Median TTP: 10.7 CMF, 9.5 MPEPIV or MPEMI (insufficient TTP data reported to calculate hazard ratio for pooling). Median survival: 28.7 months CMF, 31.2 MPEPIV or MPEMI (insufficient OS data reported to calculate hazard ratio for pooling). Follow-up could not be estimated. Toxicity data was not extractable. The study reported that the platinum regimen "... was substantially more toxic than CMF, but tolerable, with no toxic deaths: the toxicities platelet, haemoglobin, vomiting, diarrhoea and mucositis were significantly more frequent in..." the platinum arm.

Cocconi 1996 (Continued)

Study "Supported by CNR FInalyzed Project ACRO and by AIRC."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in sufficient detail. Stated as "randomised" only.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided in the abstract.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in abstract. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	No details provided in the abstract.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	91 of 93 and 92 of 93 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis (modified intent-to-treat), but only median times were reported (hence, no extractable time-to-event data).
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	5 of 93 and 9 of 93 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (9.1% of all randomised participants). It is not clear how many participants were included in the safety population, but toxicity data were not extractable anyway.
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Cocconi 1999

Methods	National, multicentre, RCT, accrual July 1988 to June 1991. Randomisation was by telephone to a central office in blocks of two. Treatment allocation not reported. Baseline comparability: no significant imbalance apparent or reported.
Participants	109 (105 eligible) women with histologically confirmed metastatic breast cancer. Median age 53/57. Age range 26 to 72. 100% metastatic breast cancer. 100% first-line.

Cocconi 1999 (Continued)

Unclear whether the prior adjuvant therapy received by 58% of participants included anthracyclines.

Interventions	CMF vs PE + CMF + AL. ARM A: Cyclophosphamide 100 mg/m² po days 1 to 14 + methotrexate 40 mg/m² IV bolus days 1 and 8 + 5-FU 6000 mg/m² IV bolus days 1 and 8, 4 weekly cycles. ARM B: Cisplatin 100 mg/m² i.v. infusion for 30 minutes on day 1; etoposide 100 mg/m² i.v. infusion for 15 minutes on days 1, 3, and 5, 3 week intervals. Cyclophosphamide 100 mg/m² po days 1 to 14 + methotrexate 40 mg/m² IV bolus days 1 and 8 + 5-FU 6000 mg/m² IV bolus days 1 and 8, 4 weekly cycles. Doxorubicin 60 mg/m² i.v. bolus on day 2; leucovorin 500 mg/m² i.v. infusion for 2 hours on days 1 and 8; 5-FU 600 mg/m² i.v. bolus 1 hour after the beginning of leucovorin infusion on days 1 and 8; allopurinol, 900 mg 24 hours after each 5-FU dose, 3 week intervals.
Outcomes	Overall survival (Kaplan-Meier curve). Time to progression, calculated from the date of randomisation to the date of the last progression occurring during the administration of the whole program (insufficient TTP data reported to calculate hazard ratio for pooling). Response. Toxicity.
Notes	The trial included 2 complex protocol treatments, rotational crossing and sequential intensification. The rotational crossing protocol was not included because of the difficulty in separating the cisplatin-related outcomes. Intent-to-treat for survival, TTP and toxicity on all eligible participants. Estimated min follow-up: 6 months (calculated from planned months of treatment per patient). Estimated max follow-up: 132 months (calculated from date of randomisation to date of submission for publication). Reported med follow-up: 78 months. Median TTP: 6.55 months CMF, 15 months PE + CMF + AL (P = 0.0004) (insufficient TTP data reported to calculate hazard ratio for pooling). Median survival: 27.5 months CMF, 27.2 months PE + CMF + AL. No toxic deaths reported. Study "Supported by Assoc. Ital. Ricerca sul Cancro (AIRC) and by PF ACRO of the Consiglio Nazionale Delle Ricerche (CNR)."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in sufficient detail.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than	Low risk	Tumour response rate evaluated every 2 cycles and every 3 months after suspension of treatment and were assessed "by an extramural treatment response review committee".

Cocconi 1999 (Continued)

overall survival and quality of life)

Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	105 of 109 randomised participants were analysed in time-to-event analyses (modified ITT). The randomised groups of the 4 excluded participants were not clear. Potential bias reported as participants with progression on CMF were immediately withdrawn.
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	4 of 109 randomised participants were excluded from all analyses, with no information provided on the randomised groups of these excluded participants (7.3% of all randomised participants). In addition to these 10 excluded participants: 3 of 50 and 1 of 55 participants in the (known) intervention and control groups, respectively, were not assessed/assessable for tumour response; no participants in the (known) intervention and control groups, respectively, were excluded from the safety population for evaluating toxicities (3.7% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Costanza 1999

Methods	Randomised unblinded phase II study. Randomisation was 1:2 ratio of standard to experimental arm. Baseline comparability: no significant imbalance apparent or reported.
Participants	221 (193 eligible) women with histologically confirmed metastatic breast cancer. Age range < 40 to 70+. 100% metastatic breast cancer. 100% first-line. Unclear whether the prior adjuvant therapy received by some participants included anthracyclines.
Interventions	CAF vs C + CAF ARM A: CAF: cyclophosphamide 600 mg/m ² IV day 1, doxorubicin 45 mg/m ² IV day 1, fluorouracil 500 mg/m ² IV days 1 and 8, every 4 weeks. Following a total doxorubicin dose of 540 mg/m ² (including any adjuvant doxorubicin), methotrexate was substituted at 40 mg/m ² IV days 1 and 8 (30 mg/m ² for participants 60 or older). ARM B: C: Carboplatin 400 mg/m ² IV bolus escalated by 50 mg/m ² depending on day 1 nadir counts. Repeated every 28 days for up to 4 cycles followed by standard CAF.
Outcomes	Overall survival (Kaplan-Meier, data from trialist). Response. Toxicity.
Notes	Participants randomised to the phase II arm (n = 178) were randomised to CAF alone or to one of 5 phase II agents including carboplatin followed by CAF. Carboplatin data (from the published paper) only is included in the review (n = 49). 2 participants did not receive any protocol treatment, 23 were ineligible (unexplained). Only eligible participants were included in the published analysis. Min follow-up: 16 months (provided by trialist). Max follow-up: 136 months (provided by trialist). Median survival: 19.6 months CAF, 14.9 months C + CAF. 3 toxic deaths on CAF arm attributed to treatment-induced sepsis.

Costanza 1999 (Continued)

For time-to-event analyses, intent-to-treat data and numbers of participants randomised and included as eligible were provided by the trialist (ITT).

Study "Supported in part by National Institutes of Health grants."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. Stated as "randomised" only.
Allocation concealment (selection bias)	Unclear risk	Not reported - stated as "randomised" only.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Blood tests and scans completed; no further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 52 and 169 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	3 of 52 and 25 of 169 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (12.7% of all randomised participants). 3 of 52 and 25 of 169 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (12.7% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Creagan 1984

Methods	Single centre, prospective cross-over RCT. Randomisation by dynamic allocation. Accrual not detailed. Baseline comparability: no significant imbalance apparent or reported.
Participants	88 (86 eligible) postmenopausal women with histologically confirmed metastatic breast cancer. Median age 58. 100% metastatic breast cancer. 92% first-line.

Creagan 1984 (Continued)

All participants anthracycline-naïve.

Interventions	CFP vs CFP + CAP ARM A: CFP: Cyclophosphamide 150 mg/m² per day; 5-Fluorouracil 300 mg/m² per day IV infusion on days 1 through 5 every 5 weeks; prednisone 30 mg/d po days 1 through 14, 20 mg/d days 15 through 21; then 10 mg daily. ARM B: CAP: Cyclophosphamide 400 mg/m² and adriamycin 40 mg/m² on single day IV. Cis-dichlor-diammine platinum (CDDP) 40 mg/m² in 500 mL 5% dextrose/0.5 normal saline 1 hour IV infusion for 4 cycles then cross over to CFP as above.
Outcomes	Overall survival (Kaplan-Meier curve from time of first treatment). Time to progression (Kaplan-Meier curve suggests breast cancer deaths and disease progression are defined events). Response. Toxicity.
Notes	Abstract. Estimated min follow-up: 4 months (based on number of intervention cycles). Estimated max follow-up: 55 months OS, 44 months TTP (based on last event on curves). Median TTP: 9.3 months CFP, 6 months CFP + CAP. Median survival: 18.2 months CFP, 11.4 months CFP + CAP (follow-up for survival was continued for participants with disease progression for whom the trial was terminated). Trialists reported bias may have been introduced by the time to progression of 7 participants who refused further treatment and were censored at time off the study. No toxic deaths reported. Trial terminated before projected accrual due to the therapeutic trend in favour of CFP. 86 of 88 randomised participants were analysed in time-to-event analyses (modified ITT). Study supported in part by National Cancer Institute, National Institutes of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in sufficient detail.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Standard criteria used for classifying tumour response; no further details provided.

Creagan 1984 (Continued)

Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	86 of 88 randomised participants were analysed in time-to-event analyses (modified ITT). No information was provided on the randomised groups of the 2 excluded participants.
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	2 of 88 randomised participants were excluded from all analyses, with no information provided on the randomised groups of these excluded participants. Apart from the 2 excluded participants (2.3% of all randomised participants), there were no missing data for tumour response; 1 of 45 and 2 of 41 participants in the (known) intervention and control groups, respectively, were excluded from the safety population for evaluating toxicities (5.7% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Delaloge 2004

Methods	Multicentre prospective randomised controlled trial. Participant characteristics at baseline: no differences reported.
Participants	137 women with progressing metastatic breast cancer with at least one measurable target lesion and at least one previous chemotherapy agent.
Interventions	OXA + FU vs VIN + FU Arm A: OXA + FU: Oxaliplatin 130 mg/m ² 2 hours IV on day 1 plus 5-fluorouracil 750 mg/m ² daily by continuous IV infusion days 1 to 5 q 3 weeks. Arm B: VIN + FU: Vinorelbine 25 mg/m ² IV bolus plus 5-fluorouracil 750 mg/m ² daily by continuous IV infusion days 1 to 5 q 3 weeks.
Outcomes	Overall survival (insufficient OS data reported to calculate hazard ratio for pooling). Progression-free survival (insufficient PFS data reported to calculate hazard ratio for pooling). Response rate. Toxicity (grade-specific data not reported).
Notes	Abstract. Follow-up could not be estimated. Efficacy was evaluated by radiological assessment every 6 weeks; responses were confirmed at least 4 weeks later. Median PFS: 19.1 weeks OXA + FU, 22.9 weeks VIN + FU (P = 0.26) (insufficient PFS data reported to calculate hazard ratio for pooling). Median survival: 61.7 weeks OXA + FU, 71 weeks VIN + FU (P = 0.26) (insufficient OS data reported to calculate hazard ratio for pooling). The study was prematurely discontinued due to accrual difficulty related to competitive drugs introduced (Capecitabine) in the same clinical setting.

Delalage 2004 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. Stated as "randomised" only.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information provided in the 2 abstracts.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information provided in the 2 abstracts. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Quote: "Efficacy was evaluated by radiological assessment every 6 wks; responses are confirmed at least 4 wks later" (abstract from 2004). No further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 68 and 69 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses), but only median times were reported (hence no extractable time-to-event data)
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	All randomised participants appear to have been assessed/assessable for tumour response and included in the safety population for evaluating toxicities (only toxic death data extractable as grade-specific data not reported for other conditions). This was not entirely clear though, as it was not explicitly stated and the authors may have simply used randomised participant denominators.
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Eisen 1998

Methods	Phase II RCT. Allocation assigned to intervention in a 2:1 randomisation. Accrual February 1994 to January 1997. Baseline comparability: no significant imbalance apparent or reported.
Participants	59 women with cytologically or histologically confirmed metastatic/advanced inoperable breast cancer. Median age 47/48. Age range 28 to 73. 61% metastatic breast cancer. 39% locally advanced. 83% first-line. All participants anthracycline-naïve.

Eisen 1998 (Continued)

Interventions	ECycloF vs ECisF. ARM A: ECycloF: 5-Fluorouracil 200 mg/m² continuous IV every 24 hours + epirubicin 60 mg/m² by IV bolus every 3 weeks for 6 courses + Cyclophosphamide 600 mg/m² by IV bolus every 3 weeks for 6 courses. ARM B: ECisF: 5-Fluorouracil 200 mg/m² IV every 24 hours + epirubicin 60 mg/m² by IV bolus every 3 weeks for 6 courses + cisplatin 60 mg/m² IV every 3 weeks for 6 courses.
Outcomes	Overall survival, measured from start of treatment (insufficient OS data reported to calculate hazard ratio for pooling). Progression-free survival, endpoints not defined (Kaplan-Meier curve, measured from start of treatment). Time to progression, endpoints not defined (medians only). Response. Toxicity.
Notes	Metastatic and locoregional results reported separately for response. Combined metastatic and locoregional toxicity data as published, were included in the review on the assumption that stage of disease might not influence toxicity. 2 not assessable for toxicity due to death (cause unexplained) following 1 treatment. 4 participants crossed from cisplatin to carboplatin, as per protocol, due to tinnitus (n = 2) and poor renal function (n = 2); unclear if participants had metastatic breast cancer or locally advanced. Min follow-up: 4 months (reported). Max follow-up: 32 months (reported), 23 months PFS (based on last event on curve). Median TTP: 7 months. Median survival: 10 m ECisF, 13 m ECycloF (insufficient OS data reported to calculate hazard ratio for pooling). All 59 randomised metastatic participants were analysed in time-to-event PFS analysis (ITT).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. Stated as "randomised" only.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Standard criteria used for classifying tumour response; no further details provided.

Eisen 1998 (Continued)

Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 21 and 38 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	The study reported "Patients who received at least two cycles of chemotherapy were assessable for response... ", but they did report how many metastatic participants completed at least 2 cycles. The study calculated response rates using the numbers of randomised participants as denominators, which may or may not mean that all metastatic participants completed at least 2 cycles. Combined metastatic and locoregional toxicity data were included in this review on the assumption that stage of disease might not influence toxicity. All 96 metastatic and locoregional participants randomised to intervention and control groups, respectively, were included in the safety population for evaluating toxicities.
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Unclear risk	None identified.

Fan 2012

Methods	A prospective, open-label, randomised phase II clinical trial carried out in the Cancer Hospital, Chinese Academy of Medical Sciences.	
Participants	53 metastatic triple-negative breast cancer (mTNBC) participants aged ≥ 18 years with histologically confirmed ER-, PR-, and HER2- primary breast cancer. Median age 48 and 49 years in platinum and control arms, respectively. Age range 27 to 71 years. 100% mTNBC. 100% 1st-line. No prior treatment of advanced disease. All the participants had received anthracyclines while 66.7% of participants in the TP arm and 57.7% of participants in the TX arm received paclitaxel in the adjuvant/neoadjuvant setting..	
Interventions	TP vs TX. TP ARM: Docetaxel 75 mg/m² plus cisplatin 75 mg/m² IV infusion day 1. TX ARM: Docetaxel 75 mg/m² IV infusion day 1 plus capecitabine 1000 mg/m² bid, 2 weeks on, 1 week off.	
Outcomes	Response. Overall survival (Kaplan-Meier curve). Progression-free survival, defined as "the time from the start of the treatment until disease progression or death" (Kaplan-Meier curve). Common adverse events.	
Notes	Estimated min follow-up = 6 months (based on first event on OS curve). Estimated max follow-up = 42 months (based on last event on OS curve). Median PFS time: Docetaxel + cisplatin arm 10.9 months, docetaxel + capecitabine arm 4.8 months, $P < 0.001$.	

Fan 2012 (Continued)

Median survival time: Docetaxel + cisplatin arm 32.8 months, docetaxel + capecitabine arm 21.5 months, $P = 0.027$.

All 53 randomised participants were analysed in time-to-event analyses (ITT).

Funding grant: AVON China breast cancer research grant and the National Natural Science Foundation of China.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized..."; no additional details were provided on how random assignment was achieved in the trial report.
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Not clear if outcome assessors were blinded to allocated intervention. Tumour response rates evaluated by CT or MRI every two cycles; no further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 27 and 26 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	All randomised participants were assessed/assessable for tumour response. All randomised participants appear to have been included in the safety population for evaluating toxicities.
Selective reporting (reporting bias)	High risk	No trial registration or published protocol containing prespecified outcomes could be found. The date when participant recruitment began was not reported, but given that this was first published in December 2012 and that there were only 53 participants, it seems highly likely that recruitment began after July 1, 2005. Consequently, there was a high expectation of trial registration.
Other bias	Low risk	Baseline characteristics similar across groups except for histological grade, where the docetaxel-platinum arm had a greater number of grade III tumours than the docetaxel-capecitabine arm.

Fountzilas 2004

Methods	Prospective RCT. Central randomisation and stratification. Baseline comparability: no significant imbalance apparent or reported.
Participants	327 eligible women (5 excluded) with histologically confirmed metastatic breast cancer.

Platinum-containing regimens for metastatic breast cancer (Review)

Fountzilas 2004 (Continued)

100% metastatic breast cancer.
100% first-line.
54% anthracycline-naive.

Interventions	PE vs PCb. ARM A: PE: 6 cycles epirubicin 80 mg/m² followed by paclitaxel 175 mg/m². ARM B: PCb: 6 cycles of paclitaxel 175 mg/m² in a 3-hour infusion immediately followed by carboplatin 6 AUC. All cycles given every 3 weeks.
Outcomes	Overall survival (Kaplan-Meier curve). Time to treatment failure (Kaplan-Meier curve) calculated from the randomisation date to the date progression of the disease was documented (participants who discontinued their treatment for any reason or probably died from disease-related causes were considered at that time, as treatment failures). Response. Toxicity. Quality of life (EORTC QLQ-C30).
Notes	Estimated min follow-up: 3 months. Estimated max follow-up: 36 months TTF, 36 months OS (based on last event on curves). Median TTF: not reported. Median survival: not reported. QoL: PCb was associated with an improvement both in the emotional functioning scale and in sleep disturbance symptoms compared with PE. No other QoL differences were found. No toxic deaths reported. 327 of 332 randomised participants were analysed in time-to-event analyses (modified ITT) Note that 'Fountzilas 2004' was labelled 'Fountzilas 2002' in the original version of this review and its TTF estimate was incorrectly included in PFS/TTP meta-analyses. This has been corrected in the 2016 review update. Study "Supported by a Hellenic Cooperative Oncology Group research grant (HE R-11b/99). Dr George Fountzilas received research support from Bristol-Myers Squibb, Aventis and AstraZeneca."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized centrally at the HeCOG Data Office in Athens and stratified according to the history of previous adjuvant chemotherapy and risk category in a modified version of that used by Cavalli et al."
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Low risk	Images for tumour response were reviewed by an "independent radiological response review committee", 83% were reviewed by this committee (p. 1518).

Fountzilas 2004 (Continued)

(outcomes other than overall survival and quality of life)

Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	327 of 332 randomised participants were analysed in time-to-event analyses (modified ITT). No information was provided on the randomised groups of the 5 excluded participants.
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	5 of 332 randomised participants were excluded from all analyses, with no information provided on the randomised groups of these excluded participants. In addition to these 5 excluded participants: 14 of 164 and 10 of 163 participants in the (known) intervention and control groups, respectively, were not assessed/assessable for tumour response (8.7% of all randomised participants); 4 of 164 and 1 of 163 participants in the (known) intervention and control groups, respectively, were excluded from the safety population for evaluating toxicities (3.0% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Unclear risk	None identified.

Fountzilas 2009 A

Methods	Prospective RCT. Central stratified block randomisation. Baseline comparability - all characteristics equal with the exception of performance status and the incidence of osseous metastases at study entry.
Participants	Total of 437 women with histologically confirmed metastatic breast cancer 'entered' the study (this included participants in both treatment-comparisons Fountzilas 2009 A and Fountzilas 2009 B). 21 were found 'ineligible' leaving 416 'eligible' participants, of which 272 were in Fountzilas 2009 A . 100% metastatic breast cancer. 100% first-line.
Interventions	Pw vs PCb. ARM A: Pw: Paclitaxel 80 mg/m ² for 12 weeks. ARM B: PCb: Paclitaxel 175 mg/m ² + carboplatin 6 AUC for 6 (3 week) cycles.
Outcomes	Overall survival. Time to progression (insufficient TTP data reported to calculate hazard ratio for pooling). Response. Toxicity. Quality of life (EUROQOL questionnaire).
Notes	The effective number of intervention participants allocated to Fountzilas 2009 A for calculating treatment effects was halved because Fountzilas 2009 A and Fountzilas 2009 B shared a common intervention group. Minimum reported follow-up 0.01 months. Maximum reported follow-up 56.9 months. No toxic deaths reported.

Fountzilas 2009 A (Continued)

Median TTP: 11.5 months PCb (0.01 to 54.6), 11.4 months Pw (0.92 to 56.9) (insufficient TTP data reported to calculate hazard ratio for pooling).

Changes in QoL (EQ-5D index and EQ VAS Score) across time did not differ significantly between groups.

21 participants in Arms A, B and C were excluded after they 'entered' the study as they were found to be ineligible.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in sufficient detail.
Allocation concealment (selection bias)	Low risk	Centralised.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Response assessed by blood and biochemistry tests, CT scans during and after treatment but "central evaluation of imaging material pertinent to tumor response was not performed in this study" and it was unclear whether or not the study was open-label.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	21 randomised participants were excluded from time-to-event analyses across all three treatment arms before the commencement of treatment (modified intent-to-treat). No information was provided on the randomised groups of the 21 excluded participants.
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	21 randomised participants were excluded from all analyses, with no information provided on the randomised groups of these excluded participants. In addition to these 21 excluded participants: 17 of 136 and 16 of 136 participants in the (known) intervention and control groups, respectively, were not assessed/assessable for tumour response (11.8% of all randomised participants); 5 of 136 and 3 of 136 in the (known) intervention and control groups, respectively, were excluded from the safety population for evaluating toxicities (2.5% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Fountzilas 2009 B

Methods   Prospective RCT. Central stratified block randomisation.

Fountzilas 2009 B (Continued)

Baseline comparability - all characteristics equal with the exception of performance status and the incidence of osseous metastases at study entry.

Participants	Total of 437 women with histologically confirmed metastatic breast cancer 'entered' the study (this included participants in both treatment-comparisons Fountzilas 2009 A and Fountzilas 2009 B). 21 were found 'ineligible' leaving 416 'eligible' participants, of which 280 were in Fountzilas 2009 B . 100% metastatic breast cancer. 100% first-line.
Interventions	PCb vs GDoc ARM B: PCb: Paclitaxel 175 mg/m ² + carboplatin 6 AUC for 6 (3 week) cycles. ARM C: GDoc: Gemcitabine 1000 mg/m ² + docetaxel 75 mg/m ² for 6 (3 week) cycles.
Outcomes	Overall survival. Time to progression (insufficient TTP data reported to calculate hazard ratio for pooling). Response. Toxicity. Quality of life (EUROQOL questionnaire).
Notes	The effective number of intervention participants allocated to Fountzilas 2009 B for calculating treatment effects was halved because Fountzilas 2009 A and Fountzilas 2009 B shared a common intervention group. Minimum reported follow-up 0.01 months. Maximum reported follow-up 56.9 months. No toxic deaths reported. Median TTP: 11.5 months PCb (0.01 to 54.6), 10.4 months GDoc (0.01 to 51.4) (insufficient TTP data reported to calculate hazard ratio for pooling). Changes in QoL (EQ-5D index and EQ VAS Score) across time did not differ significantly between groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in sufficient detail.
Allocation concealment (selection bias)	Low risk	Centralised.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Response assessed by blood and biochemistry tests, CT scans during and after treatment but "central evaluation of imaging material pertinent to tumor response was not performed in this study" and it was unclear whether or not the study was open-label.

Fountzilas 2009 B (Continued)

Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	21 randomised participants were excluded from time-to-event analyses across all three treatment arms (modified intent-to-treat). No information was provided on the randomised groups of the 21 excluded participants.
Incomplete outcome data (attrition bias) (binary outcomes)	High risk	21 randomised participants were excluded from all analyses, with no information provided on the randomised groups of these excluded participants. In addition to these 21 excluded participants: 17 of 136 and 30 of 144 participants in the (known) intervention and control groups, respectively, were not assessed/assessable for tumour response (18.4% of all randomised participants); 5 of 136 and 10 of 144 in the (known) intervention and control groups, respectively, were excluded from the safety population for evaluating toxicities (6.1% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Hu 2015

Methods	Prospective, open-label, multicentre, randomised, phase 3 trial at 12 institutions or hospitals in China.	
Participants	240 Chinese participants (236 analysed) with breast cancer aged 18 to 70 years who had metastatic triple-negative breast cancer (mTNBC) histologically confirmed at the primary tumour, with clinical, imaging, histological or cytological evidence of metastatic (stage IV) disease. Median age 47 and 48 years in platinum and control arms, respectively. Age interquartile range 42 to 57 and 43 to 55 years in platinum and control arms, respectively. 100% mTNBC. 100% 1st-line. 152 (64%) of the 236 participants had received anthracyclines. 195 (83%) of the 236 participants had received taxanes.	
Interventions	Cisplatin + gemcitabine vs paclitaxel + gemcitabine. Platinum ARM: Cisplatin plus gemcitabine (cisplatin 75 mg/m² on day 1; gemcitabine 1250 mg/m² on days 1 and 8) intravenously every 3 weeks for a maximum of eight cycles, or until disease progression or intolerable toxic effects developed. Control ARM: Paclitaxel plus gemcitabine (paclitaxel 175 mg/m² on day 1; gemcitabine 1250 mg/m² on days 1 and 8) intravenously every 3 weeks for a maximum of eight cycles, or until disease progression or intolerable toxic effects developed.	
Outcomes	Response. Overall survival. Progression-free survival, defined as "the time from the date of randomisation to progression or death from any cause". Adverse events.	
Notes	4 participants were randomised but not analysed for OS or PFS (i.e. modified ITT). An additional 9 participants were not assessable for response.	

Hu 2015 (Continued)

Estimated min follow-up = 3 months (based on first censoring tick on OS curve).

Estimated max follow-up = 35 months (based on last censoring tick on OS curve).

Median progression-free survival was 7.73 months (95% CI 6.16 to 9.30) in the cisplatin plus gemcitabine group and 6.47 months (5.76 to 7.18) in the paclitaxel plus gemcitabine group.

Median survival time was 22.3 months in the cisplatin plus gemcitabine group and 18.6 months in the paclitaxel plus gemcitabine group; not reported in the text of the study paper but estimated from Kaplan-Meier curve.

118 of 120 randomised metastatic participants were analysed in time-to-event PFS analyses (modified ITT).

The study was funded by Shanghai Natural Science Foundation and gemcitabine was provided by Eli Lilly.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was done centrally via a block randomisation of size eight, with no stratification factors, via an interactive web-response system."
Allocation concealment (selection bias)	Low risk	Central allocation. Quote: "Randomisation was done centrally..." and "After checking the inclusion criteria, the study coordinator sent the allocated treatment back to the investigator by fax."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	The extent and/or the effectiveness of intended blinding was not clear. Quote: "Tumour response was assessed by a team of local investigators ... and when needed, with independent central assessment, every two cycles until disease progression." Assessment of toxicity appeared to be unblinded. Quote: "Adverse events were recorded at each treatment visit, at each follow-up visit, and at the end-of-study visit."
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	118 of 120 and 118 of 120 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis (modified intent-to-treat analysis).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	8 of 120 and 5 of 120 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (5.4% of all randomised participants). 2 of 120 and 2 of 120 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (1.7% of all randomised participants).
Selective reporting (reporting bias)	Low risk	Overall survival was not listed under 'outcomes' in ClinicalTrials.gov record (https://clinicaltrials.gov/ct2/show/NCT01287624) but it was mentioned in the 'purpose' section of the record. All other outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa.
Other bias	Unclear risk	Baseline characteristics were generally similar across groups except for ECOG performance status, number of metastatic organ sites and menopausal status.

Icli 2005

Methods	Prospective randomised non-blinded multicentre phase III study. No stratification for prognostic factors or centres. Central randomisation. Baseline comparability: no significant imbalance apparent or reported.
Participants	201 women with histologically confirmed locally advanced or metastatic breast cancer previously treated with anthracyclines (193 eligible). Median age 47/49. Age range 18 to 70. 96% metastatic breast cancer. 20% first-line. 60% 2nd line. 20% 3rd line. All participants had previously received anthracycline therapy.
Interventions	T vs VP-16 + P. ARM A: Paclitaxel 175 mg/m ² IV, day 1 q3 weeks. ARM B: Cisplatin 70 mg/m ² IV, day 1 q3 weeks + oral etoposide (VP-16) 50 mg bid, po, days 1 to 7 q3 weeks.
Outcomes	Overall survival (Kaplan-Meier curve). Time to progression (Kaplan-Meier curve) defined as "the duration between the first day of study treatment and date of progression". Response. Toxicity.
Notes	Conference powerpoint slide presentation. 193 eligible: - 3 died before treatment. - 5 withdrew consent. - 1 had an accident and did not commence treatment. Participants crossed over after 2 cycles if disease progressed or there was no evidence of response: 47 crossed to Arm A; 37 crossed to Arm B. 185 assessable for response. Estimated min follow-up: 4.5 months (based on the median number of cycles received). Estimated max follow-up: 45 months TTP, 48 months OS (based on last events on curves). Median TTP: 6 months Arm B, 3.9 months Arm A. Median survival: 13 months Arm B, 10 months Arm A. 4 toxic deaths (Arm B, n = 2; Arm A, n = 3). 193 of 202 randomised metastatic participants were analysed in time-to-event PFS analyses (modified ITT). "Bristol Myers Squibb (Turkey) supplied limited number of paclitaxel for this trial".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported other than "No stratification was carried out for prognostic factors or centers."
Allocation concealment (selection bias)	Low risk	Central randomisation.

Icli 2005 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	"nonblinded study"
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Non-blinded study. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Low risk	Quote: "Responses were reviewed by two independent experts to confirm the response status blindly for treatment received" (p. 2).
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	96 of 100 and 97 of 101 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis (modified intent-to-treat analysis).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	9 of 100 and 7 of 101 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (8.0% of all randomised participants). 7 of 100 and 4 of 101 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (4.0% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Kolaric 1985

Methods	Prospective phase III RCT. Randomisation, treatment, allocation methods, and accrual not detailed. Baseline comparability: no significant imbalance apparent or reported.
Participants	128 women with metastatic breast cancer. Age range 30 to 70. 100% metastatic breast cancer. 100% first-line. All participants anthracycline-naïve.
Interventions	CMFVP vs CAP. ARM A: CMFVP: Cyclophosphamide 200 mg/m ² IV days 1, 2, 3, 4, 5 + methotrexate 20 mg/m ² IV days 2, 4 + 5-fluorouracil 500 mg/m ² IV days 1, 3, 5 + vincristine 1 mg/m ² po days 1 and 5 + prednisolone 40 mg po days 1, 2, 3, 4, 5. 3 to 4 week cycles. ARM B: CAP: cis-platinum 30 mg/m ² IV days 1, 3, 5; + adriamycin 40 mg/m ² IV day 1 + cyclophosphamide 200 mg/m ² IV days 1, 3, 5.
Outcomes	Overall survival (insufficient OS data reported to calculate hazard ratio for pooling). Response. Toxicity.
Notes	Trial analysis not intent-to-treat:

Kolaric 1985 (Continued)

- 123 evaluable following > 2 cycles.
- 5 not evaluable, unexplained..
Min follow-up: 6 months (reported).
Max follow-up: 33 months (reported).
Preliminary data reported survival in favour of CAP (33%) vs CMFVP (53%), $P < 0.05$ (insufficient OS data reported to calculate hazard ratio for pooling).
No toxic deaths reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. Stated as "randomised" only.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Standard criteria used to assess tumour response but no further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	High risk	61 of 65 and 62 of 63 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis. Excluded participants included those who did not complete more than 2 cycles of chemotherapy (per-protocol analysis), but only median times were reported (hence no extractable time-to-event data).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	4 of 65 and 1 of 63 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response or included in the safety population for evaluating toxicities (3.9% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Kolaric 1989

Methods	Prospective RCT. Stratification prior to randomisation. Randomisation and allocation methods not detailed. Accrual June 1984 to 1986.

Kolaric 1989 (Continued)

Imbalance in prominent metastatic site (prevalence of visceral metastases 21 vs 31) was created by un-evaluable participants being taken off the trial after the first cycle.

Participants	142 women with metastatic or locoregional advanced inoperable breast cancer. Median age 53. Age range 29 to 70. 58% metastatic breast cancer. 42% locally advanced non-resectable breast cancer. 100% first-line. All participants anthracycline-naïve.
Interventions	CAP vs FAC. ARM A: FAC (n = 68): 5-Fluorouracil 500 mg/m ² days 1 and 8; adriamycin 50 mg/m ² 500 mg/m ² day 1; cyclophosphamide 500 mg/m ² day 1. ARM B: CAP (n = 58): Cyclophosphamide 200 mg/m ² IV days 1,3 and 5; adriamycin 40 mg/m ² IV day 1; platinum 30 mg/m ² IV day 1,3 and 5.
Outcomes	Overall survival (Kaplan-Meier curve). Response. Toxicity.
Notes	126 evaluable for > 2 cycles. 16 withdrawn after 1 cycle: - 1 early death due to progression. - 5 further treatment refusals. - 10 lost to follow-up. Proportion of total numbers with either metastatic or locoregionally advanced disease was not reported. However, 53 reported with predominant metastatic site of soft tissue: 73 were reported with predominant site as viscera or bones; hence, an assumption made that at least 58% (73/126) were likely to have metastatic breast cancer. Min follow-up: 1 month (reported). Max follow-up: 30 months (reported). Median survival: 13 months CAP, 9 months FAC. No toxic deaths reported. 126 of 142 participants that had > 2 cycles were analysed in time-to-event OS analysis (per-protocol analysis).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not detailed.
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.

Kolaric 1989 (Continued)

Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Standard criteria used to assess tumour response but no further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	High risk	58 of 68 and 68 of 74 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis. Excluded participants included those who did not complete more than 2 cycles of chemotherapy (per-protocol analysis).
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	10 of 69 and 6 of 74 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response or included in the safety population for evaluating toxicities (11.3% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Nielsen 2000

Methods	Phase III RCT. Central randomisation registered, stratified by ECOG performance status. Accrual from July 1987 to November 1990. Baseline comparability: no significant imbalance apparent or reported.
Participants	155 women with histologically proven locally advanced or metastatic breast cancer. Median age 52/55. Age range 27 to 69. 91% metastatic breast cancer. 100% first-line. All participants anthracycline-naïve.
Interventions	EPI vs EPI + CIS. ARM A: Epirubicin 70 mg/m ² days 1 and 8 every 4 weeks. ARM B: Epirubicin 60 mg/m ² days 1 and 8 + cisplatin 100 mg/m ² day 1 every 4 weeks.
Outcomes	Overall survival (Kaplan-Meier curve). Time to progression (Kaplan-Meier curve, "calculated as the time from the drug administration to progression for both responders and nonresponders"). Response. Toxicity.
Notes	Oophorectomy performed in premenopausal participants, n = 45 (32%). Trial claimed 'intent-to-treat' analysis for all randomised participants and outcomes, although: - 10 were declared ineligible (EPI, n = 7; EPI + CIS, n = 3). - 6 refused treatment after 1 cycle (EPI + CIS arm) and were excluded. Hence, given 139 of 155 randomised participants were analysed in time-to-event analyses and 6 participants who started but did not complete treatment were excluded, this represented per-protocol analyses for time-to-event data. Epirubicin was continued until disease progression or to cumulative dose of 1000 mg/m ² . Cisplatin was discontinued after 6 cycles. Doses of epirubicin were adjusted according to WBC and platelet counts on the day of treatment. Cisplatin was adjusted according to nephrotoxicity. Reported min follow-up: 0.1 months.

Nielsen 2000 (Continued)

Reported max follow-up: 77.7 months TTP and OS.
Median TTP: 8.4 months EPI, 15.3 months EPI + CIS.
Median survival: 15.1 months, EPI; 21.5, months EPI + CIS.
5 deaths were attributed to treatment: nephrotic syndrome: n = 1, leukaemia: n = 2, congestive cardiac failure: n = 1, and thrombocytopenia: n = 1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in sufficient detail.
Allocation concealment (selection bias)	Low risk	Central randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	"evaluation of response ... was done according to WHO criteria" (p. 460) but no further details provided.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	High risk	65 of 74 and 74 of 81 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis. Excluded participants included those who did not complete more than 2 cycles of chemotherapy (per-protocol analysis).
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	9 of 74 and 7 of 81 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response or included in the safety population for evaluating toxicities (10.3% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Robert 2006

Methods	Randomised, multicentre, phase III trial. Accrual between November 1998 and May 2002. Baseline characteristics reported as well balanced between study arms.
Participants	196 women with histologically proven HER2 positive metastatic breast cancer. Median age 55/56. Age range 33 to 83. 100% metastatic breast cancer.

Robert 2006 (Continued)

100% first-line for metastatic breast cancer.

100% HER2 positive.

Interventions	TPa vs TPC. ARM A: TPa: Trastuzumab 4 mg/kg + paclitaxel 175mg/m ² . ARM B: TPC: Trastuzumab 4 mg/kg + paclitaxel 175mg/m ² + carboplatin 6 AUC.
Outcomes	Overall survival. Progression-free survival, defined as the interval between the date of first dose and the date of progression or death as a result of any cause. Response. Toxicity.
Notes	Minimum reported follow-up: < 1 month. Maximum reported follow-up: 56.8 months. No deaths due to toxicity. Randomisation procedure not stated - just reported as "randomised". Stratified by IHC score (2+ or 3+). Participants with prior adjuvant or neo-adjuvant chemotherapy: TPa, 46%; TPC, 46%. Participants were eligible provided a taxane had not been used and that cumulative doxorubicin exposure was < 360 mg/m ² . Reported hazard ratios and confidence intervals were inconsistent with the Kaplan Meier curves. For example, the text stated that the difference in OS "was not statistically significant", yet the reported 95% confidence interval was 0.88 to 0.92 (not only was the confidence interval highly statistically significant, it was far too narrow, given the cohort size). Consequently, we extracted OS and TTP data from the Kaplan-Meier curves rather than relying on the reported hazard ratios. Study "Supported by grants from Bristol-Myers Squibb Co, Princeton, NJ, and Genentech Inc, South San Francisco, CA."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in detail.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information in trial publication.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	No information in trial publication. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "Tumor assessments were performed by physical examination before every cycle, with imaging studies evaluating indicator lesions repeated every

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Robert 2006 (Continued)

(outcomes other than overall survival and quality of life)		other cycle" (p. 2787). No further details provided on whether central assessment took place.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 98 and 98 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	6 of 98 and 4 of 98 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (5.1% of all randomised participants). One randomised participant (control group) was excluded from the safety population for evaluating toxicities (0.5% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	No trial registration or published protocol prespecifying all study outcomes. Study began recruitment before July 1, 2005 so expectation of trial registration or published protocol was low.
Other bias	Low risk	None identified.

Stemmler 2011 A

Methods	Randomised multicentre phase II trial. Accrual between 2003 and 2006. Groups comparable at baseline in all regards except menopausal status.
Participants	Overall, a total of 141 participants (91 in Arm A + Arm B) with histologically confirmed metastatic breast cancer. Median age: ~ 60. 100% metastatic breast cancer. First line: ~ 36%. Anthracycline-naïve: ~ 43%.
Interventions	GemVin vs GemCis. ARM A: GemVin: Gemcitabine 1000 mg/m ² + vinorelbine 25 mg/m ² . ARM B: GemCis: Gemcitabine 1000 mg/m ² + cisplatin 30 mg/m ² . Treatment for a maximum of six (3 week) cycles.
Outcomes	Overall survival (Kaplan-Meier). Time to progression, defined as "time from the start of therapy to first evidence of progressive disease or last follow-up" (but TTP was also interchangeably referred to as PFS at various points in the paper) (Kaplan-Meier). Response rate. Toxicity. Quality of life.
Notes	No reported deaths due to toxicity. Estimated min follow-up: 1 month.

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Stemmler 2011 A (Continued)

Estimated max follow-up: 47 months.

Median PFS: 5.7 months, 95% CI: 3.9 to 8.2 (GemVin); 6.9 months, 95% CI: 5.8 to 8.8 (GemCis).

Median OS: 17.5 months, 95% CI: 12.2 to 30.0 (GemVin); 13.0 months, 95% CI: 11.0 to 19.2 (GemCis).

Randomisation procedure not stated - just reported as "randomised".

All randomised participants were analysed in time-to-event analyses (ITT).

"This study was supported by Lilly GmbH Germany."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. Stated as "randomised" only.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Registered as 'open-label' trial (https://www.clinicaltrials.gov/ct2/show/NCT00480597).
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label study. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Blood and biochemistry tests, and imaging took place during therapy. No details were provided on whether there was a central (independent) evaluation team for assessing tumour response rates.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 45 and 46 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	High risk	10 of 45 and 9 of 46 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (20.3% of all randomised participants). 0 of 45 and 4 of 46 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (5.8% of all randomised participants).
Selective reporting (reporting bias)	Low risk	All outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa (https://www.clinicaltrials.gov/ct2/show/NCT00480597).
Other bias	Low risk	None identified.

Stemmler 2011 B

Methods

Randomised multicentre phase II trial. Accrual between 2003 and 2006.

Stemmler 2011 B (Continued)

Groups comparable at baseline in all regards except menopausal status.

Participants	Overall 141 participants (95 in Arm B + Arm C) with histologically confirmed metastatic breast cancer. Median age: ~ 60 years. 100% metastatic breast cancer. First-line: ~ 36%. Anthracycline-naïve: ~ 43%.
Interventions	GemCis vs GemCap. ARM B: GemCis: Gemcitabine 1000 mg/m² + cisplatin 30 mg/m². ARM C: GemCap: Gemcitabine 1000 mg/m² + capecitabine 1.300 mg/m². Treatment for a maximum of six (3 week) cycles.
Outcomes	Overall survival (Kaplan-Meier). Time to progression, defined as "time from the start of therapy to first evidence of progressive disease or last follow-up" (but TTP was also interchangeably referred to as PFS at various points in the paper) (Kaplan-Meier). Response rate. Toxicity.
Notes	No reported deaths due to toxicity. Estimated min follow-up: 1 month. Estimated max follow-up: 47 months. Median PFS: 6.9 months, 95% CI: 5.8 to 8.8 (GemCis); and 8.3 months, 95% CI: 4.3 to 9.6 (GemCap). Median OS: 13.0 months, 95% CI: 11.0 to 19.2 (GemCis); and 19.4 months, 95% CI: 16.6 to 22.0 (GemCap). All randomised participants were analysed in time-to-event analyses (ITT). "This study was supported by Lilly GmbH Germany."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported. Stated as "randomised" only.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Registered as "open label" trial (https://www.clinicaltrials.gov/ct2/show/NCT00480597).

Stemmler 2011 B (Continued)

Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label study. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Blood and biochemistry tests, and imaging took place during therapy. No details were provided on whether there was a central (independent) evaluation team for assessing tumour response rates.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 45 and 50 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	High risk	10 of 45 and 9 of 50 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (18.1% of all randomised participants). 0 of 45 and 1 of 50 participants randomised to intervention and control groups, respectively, were not included in the safety population for evaluating toxicities (1.4% of all randomised participants).
Selective reporting (reporting bias)	Low risk	All outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa (https://www.clinicaltrials.gov/ct2/show/NCT00480597).
Other bias	Low risk	None identified.

Tutt 2014

Methods	Randomised phase III trial.
Participants	341 metastatic and 35 recurrent locally advanced triple-negative or <i>BRCA</i> 1/2 breast cancer. 43 <i>BRCA</i> + participants (29 known (i.e. 16 TNBC, 12 ER-positive, HER2-negative, 1 ER unknown, HER2-negative) & 14 research test).
Interventions	C vs D. C: Carboplatin (AUC 6 every 3 weeks for six cycles). D: Docetaxel (100 mg/m ² every 3 weeks for six cycles).
Outcomes	Response. Overall survival (insufficient OS data reported to calculate hazard ratio for pooling). Progression-free survival (insufficient PFS data reported to calculate hazard ratio for pooling). Toxicity (no results reported).
Notes	Abstracts only. Median follow-up: 11 months. Median PFS: Carboplatin 3.1 (95% CI 2.5 to 4.2) vs docetaxel 4.5 (95% CI 4.1 to 5.2) months; absolute difference -0.4 (95%CI -1.1 to 0.3), P = 0.29 (insufficient PFS data reported to calculate hazard ratio for pooling). Median OS: Carboplatin 12.4 (95% CI 10.4 to 15.3) vs docetaxel 12.3 (95% CI 10.5 to 13.6) months; absolute difference -0.2 (95% CI -1.1 to 0.8), P = 0.31 (insufficient OS data reported to calculate hazard ratio for pooling).

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Tutt 2014 (Continued)

Subgroup analysis restricted to 43 BRCA1/2+ participants showed carboplatin was associated with significantly greater proportions of objective responses (68% vs 33%; P = 0.03).

"Sponsor: Institute of Cancer Research, United Kingdom".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomized" ; no additional details were provided on how random assignment was achieved in the abstracts or ClinicalTrials.gov record (https://clinicaltrials.gov/ct2/show/NCT00532727).
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in the abstracts.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label trial. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Insufficient information provided in the available abstracts.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 188 and 188 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses), but only median times were reported (hence no extractable time-to-event data).
Incomplete outcome data (attrition bias) (binary outcomes)	Unclear risk	All randomised participants were included in response rate denominators, but it was not explicitly stated that all participants were assessed/assessable. No toxicity results reported.
Selective reporting (reporting bias)	High risk	TTP, TTF and toxicity were specified as outcomes in ClinicalTrials.gov record (https://clinicaltrials.gov/ct2/show/NCT00532727), but no results for these outcomes were provided in the abstracts.
Other bias	Unclear risk	Unable to assess from the abstracts.

Valero 2011

Methods	Randomised multicentre phase III trial. Accrual between 11 December 2001 and 23 March 2004. Groups comparable at baseline.
Participants	263 participants with histologically confirmed metastatic breast cancer. Median age 52/51 years. 100% metastatic breast cancer.

Valero 2011 (Continued)

100% first-line.

Interventions	TH vs TCH ARM A: TH: Trastuzumab 2 mg/kg + docetaxel 100 mg/m². ARM B: TCH: Trastuzumab 2 mg/kg + docetaxel 75 mg/m² + carboplatin 6 AUC.
Outcomes	Overall survival (Kaplan-Meier curves and unadjusted HRs). Progression-free survival (Kaplan-Meier curves and unadjusted HRs) defined as "the interval from the day of random assignment to the date of disease progression, diagnosis of second primary malignancy or death" (the authors used the terms TTP and PFS interchangeably). Response rate. Toxicity (frequencies for some conditions were not grade-specific and therefore could not be used for pooling).
Notes	Estimated min follow-up: 6 months. Estimated max follow-up: 78 months. Median TTP: 11.1 and 10.4 months for TH and TCH arms, respectively. Median OS: 37.1 and 37.4 months for TH and TCH arms, respectively. Reported HRs were for Arm B as the reference group and were thus inverted. All 263 randomised participants were analysed in time-to-event analyses (ITT). Research Funding: Pfizer, Sanofi-Aventis, Roche, GlaxoSmithKline.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned... Treatment allocation was based on a dynamic minimization procedure, stratified by center and by prior neoadjuvant chemotherapy."
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Treatment was not blinded" (p.151).
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label study. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Imaging for tumour response took place before, during, and after chemotherapy. No details were provided on whether there was a central (independent) evaluation team for assessing tumour response rates.

Valero 2011 (Continued)

Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 132 and 131 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	5 of 132 and 1 of 131 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (2.3% of all randomised participants). One randomised participant (control) was excluded from the safety population for evaluating toxicities (0.3% of all randomised participants).
Selective reporting (reporting bias)	Unclear risk	Most outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa (https://clinicaltrials.gov/ct2/show/NCT00047255). However, the ClinicalTrials.gov record indicated that pathologic, molecular, genetic and biochemical markers would also be assessed, but these were not reported on in the paper.
Other bias	Low risk	None identified.

Xu 2011 A

Methods	Randomised multicentre phase II trial. Accrual between March 2005 and December 2007. Groups comparable at baseline except length of disease-free interval of > 24 months at enrolment.
Participants	Total of 147 women overall (100 in Arm 1 and Arm 3) with histologically or cytologically confirmed metastatic breast cancer. Median age 48 years. 100% metastatic breast cancer. 97.3% of participants had received neoadjuvant or adjuvant anthracycline based chemotherapy.
Interventions	GemCis vs GemPac. ARM 1: GemPac: Paclitaxel 150 mg/m ² + gemcitabine 2500 mg/m ² . ARM 3: GemCis: Gemcitabine 2500 mg/m ² + cisplatin 50 mg/m ² .
Outcomes	Overall survival (Kaplan-Meier). Progression-free survival, endpoints not stated (Kaplan-Meier). Response rate. Time to treatment failure (insufficient TTF data reported to calculate hazard ratio for pooling). Toxicity.
Notes	Estimated min follow-up: 2 months. Estimated max follow-up: 24 months. Median OS: GemPac = 15.5 months (10.4 to 26.7), GemCis = 20.1 months (12.4 to 21.6). Median PFS: GemPac = 4.8 months (4.2 to 7.0), GemCis = 4.8 months (3.7 to 8.1). Median TTF: GemPac = 5.8 months (4.2 to 5.8), GemCis = not calculable. 99 of 100 randomised participants analysed in time-to-event analyses (modified ITT).

Platinum-containing regimens for metastatic breast cancer (Review)

Xu 2011 A (Continued)

"This study was sponsored by Eli Lilly and Company".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in detail other than stratified on one factor only. Quote: "Eligible patients were randomly assigned in a 1:1:1 ratio, stratified by country..."
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label study. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Quote: "Tumor assessments were performed at baseline (within 4 weeks of enrolment) and at the end of cycles 4 and 8" (p. 205) and during follow-up. No mention of a central (independent, blinded) adjudication team for assessing tumour response.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Unclear risk	50 of 51 and 49 of 49 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analysis (modified intent-to-treat analysis).
Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	3 of 51 and 5 of 49 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (7.9% of all randomised participants). One randomised participant (intervention) was excluded from the safety population for evaluating toxicities (1.3% of all randomised participants).
Selective reporting (reporting bias)	Low risk	All outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa (https://clinicaltrials.gov/ct2/show/study/NCT00191854).
Other bias	Low risk	None identified.

Xu 2011 B

Methods	Randomised multicentre phase II trial. Accrual between March 2005 and December 2007. Groups comparable at baseline except length of disease-free interval of > 24 months at enrolment.
Participants	Total of 147 women overall (96 in Arm 1 and Arm 2) with histologically or cytologically confirmed metastatic breast cancer. Median age 48 years. 100% metastatic breast cancer. 97.3% of participants had received neoadjuvant or adjuvant anthracycline-based chemotherapy.

Xu 2011 B (Continued)

Interventions	GemCarb vs GemPac. ARM 1: GemPac: Paclitaxel 150 mg/m² + gemcitabine 2500 mg/m². ARM 2: GemCarb: Gemcitabine 2500 mg/m² + carboplatin 2.5 AUC.
Outcomes	Overall survival (Kaplan-Meier). Progression-free survival, endpoints not stated (Kaplan-Meier). Response rate. Time to treatment failure (insufficient TTF data reported to calculate hazard ratio for pooling). Toxicity.
Notes	Estimated min follow-up: 2 months. Estimated max follow-up: 24 months. Median OS: GemPac = 15.5 months (10.4 to 26.7), GemCarb = 22.8 months (13.3 – not calculable). Median PFS: GemPac = 4.8 months (4.2 to 7.0), GemCarb = 4.3 months (3.7 to 5.9). Median TTF: GemPac = 5.8 months (4.2 to 5.8), GemCarb = 4.3 months (3.7 – not calculable). All 96 randomised participants analysed in time-to-event analyses (ITT). "This study was sponsored by Eli Lilly and Company".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not reported in detail other than stratified on one factor only. Quote: "Eligible patients were randomly assigned in a 1:1:1 ratio, stratified by country..."
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label trial.
Blinding of outcome assessment (detection bias) (overall survival)	Low risk	Open-label study. Unlikely that assessment of overall survival would be influenced by lack of blinding.
Blinding of outcome assessment (detection bias) (outcomes other than overall survival and quality of life)	Unclear risk	Quote: "Tumor assessments were performed at baseline (within 4 weeks of enrolment) and at the end of cycles 4 and 8" (p. 205) and during follow-up. No mention of a central (independent, blinded) adjudication team for assessing tumour response.
Incomplete outcome data (attrition bias) (time-to-event outcomes)	Low risk	All 47 and 49 participants randomised to intervention and control groups, respectively, were analysed in time-to-event analyses (intent-to-treat analyses).

Xu 2011 B (Continued)

Incomplete outcome data (attrition bias) (binary outcomes)	Low risk	3 of 47 and 5 of 49 participants randomised to intervention and control groups, respectively, were not assessed/assessable for tumour response (7.0% of all randomised participants). No participants were excluded from the safety population for evaluating toxicities.
Selective reporting (reporting bias)	Low risk	All outcomes in the trial report were listed in the ClinicalTrials.gov record and vice versa (https://clinicaltrials.gov/ct2/show/study/NCT00191854).
Other bias	Low risk	None identified.

5-FU:5-fluorouracil

AL: doxorubicin, leucovorin, 5-fluorouracil, allopurinol

AUC: Area under the curve

bid: Twice a day

C: Carboplatin

CAF: Cyclophosphamide, doxorubicin, fluorouracil

CAP: Cyclophosphamide, adriamycin, Cis-dichloridiammine platinum

CDDP: Cis-dichloridiammine platinum

Ce: Cetuximab

CFP: Cyclophosphamide, 5-Fluorouracil, prednisone

CI: Confidence interval

CIS: Cisplatin

CMF: Cyclophosphamide, methotrexate, fluorouracil

CMFVP: Cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisolone

CT: X-ray image made using computerized axial tomography

D: Docetaxel

EcisF: 5-Fluorouracil, epirubicin, cisplatin

ECOG: Eastern Cooperative Oncology Group

EcycloF: 5-Fluorouracil, epirubicin, cyclophosphamide

EGFR: Epidermal growth factor receptor

EORTC: European Organisation for Research and Treatment of Cancer

EPI: Epirubicin

EQ-5D: EuroQol five dimensions questionnaire

EQ VAS: EuroQol visual analogue scale

ER: oestrogen receptor

EUROQOL: The EuroQOL research Group

FAC: 5-Fluorouracil, adriamycin, cyclophosphamide

FU: 5-fluorouracil

GemCap: Gemcitabine, capecitabine

GemCarb: Gemcitabine, carboplatin

GemCis: Gemcitabine, cisplatin

GemPac: Gemcitabine, paclitaxel

GemVin: Gemcitabine, vinorelbine

GDoc: Gemcitabine, docetaxel

HeCOG: Hellenic Cooperative Oncology Group

HER2: Human epidermal growth factor receptor 2

HR: Hazard ratio

IHC: Immunohistochemistry

ITT: Intention-to-treat

IV: Intravenous

LND: Lonidamine

Max: Maximum

Min: Minimum

MPEMI: Methotrexate + rescue, cisplatin, etoposide, mitomycin

MPEIV: Methotrexate+ leucovorin rescue; cisplatin, epirubicin, vincristine

MRI: Magnetic resonance imaging

mTNBC: metastatic triple-negative breast cancer

OS: overall survival

OXA: Oxaliplatin

P: Cisplatin
 p.: Page
 PCb: Paclitaxel, carboplatin
 PE: Cisplatin, etoposide
 PFS: progression-free survival
 po: by mouth
 PR: Progesterone receptor
 Pw: Paclitaxel
 q: every
 QLQ-BR23: 23 item quality of life questionnaire
 QLQ-C30: 30 item quality of life questionnaire
 QoL: quality of life
 RECIST: Response Evaluation Criteria In Solid Tumors
 T: Paclitaxel
 TCH: Trastuzumab 2 mg/kg + docetaxel 75 mg/m² + carboplatin
 TH: Trastuzumab, docetaxel
 TP: Docetaxel, cisplatin
 TPa: Trastuzumab, paclitaxel
 TPC: Trastuzumab, carboplatin
 TTF: Time to treatment failure
 TTP: Time to progression
 TTPD: Time to progressive disease
 TTTF: Time to treatment failure
 TX: Docetaxel, capecitabine
 VIN: Vinorelbine
 VP-16: Oral etoposide
 WBC: White blood cell

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cartei 1996	Conference abstract only with insufficient data. Attempts to contact authors were unsuccessful. This study was listed as an 'excluded study' in the original version of this review.
Crump 2008	Included 38% participants with locoregional disease. Attempts to contact authors were unsuccessful.
Hogdall 1993	Trial reported only the serum tetranectin levels in relation to survival and response. This study was listed as an 'excluded study' in the original version of this review.
Perez 2001	Trial was registered but never started. Hence, this study has been moved from the 'ongoing studies' section in the original version of this review to the 'excluded studies' of this review update.
Perez 2002	Trial was registered but never started. Hence, this study has been moved from the 'ongoing studies' section in the original version of this review to the 'excluded studies' of this review update.
Somlo 2015	Participants not randomised.
Wang 2008	> 20% participants with locally advanced disease only. Data were not reported separately.

Characteristics of ongoing studies [ordered by study ID]

BRCA

Trial name or title	Carboplatin or Docetaxel in Treating Women With Metastatic Genetic Breast Cancer (BRCA Trial).

BRCA (Continued)

Methods	A randomised phase II pilot trial.
Participants	Participants with metastatic genetic breast cancer.
Interventions	Carboplatin vs docetaxel.
Outcomes	Response. Time to progression. Toxicity.
Starting date	January 2005. Estimated primary completion date: 2009.
Contact information	Andrew Tutt, King's College London, email: andrew.tutt@kcl.ac.uk.
Notes	Emails sent to the principal investigator in 2015/16 requesting a progress report on the study were not answered.

NCT00201760

Trial name or title	Gemcitabine/Trastuzumab and Gemcitabine/Cisplatin/Trastuzumab in Patients With Metastatic Breast Cancer.
Methods	Randomised phase II study.
Participants	Participants with metastatic breast cancer.
Interventions	Gemcitabine/trastuzumab vs gemcitabine/cisplatin/trastuzumab.
Outcomes	Disease-free progression. Response. Side effects.
Starting date	February 2005. Estimated study completion date: December 2012.
Contact information	Kari Kendra, MD, email: Kari.Kendra@osumc.edu.
Notes	Emails sent to the principal investigator in 2015 requesting a progress report on the study were not answered. Sponsor: Eli Lilly and Company.

NCT00717951

Trial name or title	A Randomised,Multi-Center Study of Docetaxol Plus Capecitabine or Cisplatin in Anthracycline-Pre-treated Patients With Advanced Breast Cancer.

NCT00717951 (Continued)

Methods	Randomised, phase 2, multicentre study.
Participants	Participants with advanced breast cancer.
Interventions	Docetaxel + capecitabine vs docetaxel + cisplatin.
Outcomes	Response. Time to progression. Time to treatment failure. 2 year progression-free survival. Safety. QoL.
Starting date	May 2008. Estimated study completion date: May 2010.
Contact information	Jiang Zefei, Ph.D, emails: jiangzf@hotmail.com; jiangzefei@medmail.com.cn.
Notes	Emails sent to the principal investigator in 2015 requesting a progress report on the study were not answered.

NCT01506609

Trial name or title	The Study Evaluating Efficacy And Tolerability Of Veliparib in Combination With Temozolomide or In Combination With Carboplatin and Paclitaxel Versus Placebo in Subjects With BRCA1 and BRCA2 Mutation and Metastatic Breast Cancer.
Methods	Randomised, phase 2 study.
Participants	Women with BRCA1 or BRCA2 mutation and metastatic breast cancer.
Interventions	Veliparib with temozolomide vs veliparib with carboplatin and paclitaxel vs placebo with carboplatin and paclitaxel.
Outcomes	Progression-free survival. Overall survival. Clinical benefit. Objective response. Chemotherapy-induced peripheral neuropathy.
Starting date	Study start date: January 2012. Estimated study completion date: May 2016.
Contact information	Stacie P. Shepherd, MD, AbbVie.
Notes	Sponsors and Collaborators: AbbVie (prior sponsor, Abbott).

NCT01898117

Trial name or title	Biomarker Discovery Randomized Phase IIb Trial With Carboplatin-cyclophosphamide Versus Paclitaxel With or Without Bevacizumab as First-line Treatment in Advanced Triple Negative Breast Cancer.
Methods	Randomised phase IIb trial.
Participants	Participants with advanced triple-negative breast cancer.
Interventions	Carboplatin-cyclophosphamide vs paclitaxel with or without bevacizumab.
Outcomes	Progression-free survival. Overall survival. Toxicity.
Starting date	July 2013. Estimated primary completion date: December 2019.
Contact information	Sabine C Linn, Prof, MD, email; s.linn@nki.nl.
Notes	

NCT02207335

Trial name or title	Trial of Gemcitabine_Capecitabine Versus Gemcitabine_Carboplatin in Breast Cancer.
Methods	A multicentre randomised phase III clinical trial.
Participants	Participants with triple-negative recurrent or metastatic breast cancer.
Interventions	Gemcitabine + capecitabine vs gemcitabine + carboplatin.
Outcomes	Response (RECIST 1.1).
Starting date	December 2013. Estimated study completion date: December 2016.
Contact information	Zhongsheng Tong, Master, email: 18622221181@163.com .
Notes	

NCT02207361

Trial name or title	Paclitaxel in Combination With Carboplatin Versus Paclitaxel Plus Epirubicin in Metastatic Breast Cancer.
Methods	Randomised prospective clinical trial.
Participants	Participants with metastatic breast cancer.

NCT02207361 (Continued)

Interventions	Paclitaxel + carboplatin vs paclitaxel + epirubicin.
Outcomes	Response (RECIST 1.1).
Starting date	December 2013. Estimated study completion date: December 2016.
Contact information	Zhongsheng Tong, Master, email: 18622221181@163.com .
Notes	

TnAcity

Trial name or title	TnAcity : A phase 2/3 randomised study of weekly nab-paclitaxel in combination with either gemcitabine or carboplatin vs gemcitabine/carboplatin as first-line treatment for triple-negative metastatic breast cancer.
Methods	Phase 2/3 randomised study.
Participants	Women with ER-, PR-, and HER2 negative (triple-negative) metastatic breast cancer.
Interventions	Carboplatin plus gemcitabine vs nab-paclitaxel plus carboplatin OR gemcitabine.
Outcomes	Progression-free survival. Overall survival. Response. Duration of response. Safety.
Starting date	Date of registration: 12/06/2013.
Contact information	
Notes	Sponsored by Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation.

[BRCA](#): Breast cancer susceptibility gene

ER: Oestrogen receptor

HER2: Human epidermal growth factor receptor 2

PR: Progesterone receptor

QoL: Quality of life

RECIST: Response Evaluation Criteria In Solid Tumors

DATA AND ANALYSES

Comparison 1. Platinum vs non-platinum regimens (subgroup analysis 1: by treatment-comparisons assessing mTNBC)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19	2922	HR (95% CI)	0.98 [0.89, 1.07]
1.1 Treatment-comparisons assessing patients with mTNBC	3	391	HR (95% CI)	0.75 [0.57, 1.00]
1.2 Treatment-comparisons assessing patients unselected for mTNBC	16	2531	HR (95% CI)	1.01 [0.92, 1.12]
2 Progression-free survival/time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]
2.1 Treatment-comparisons assessing patients with mTNBC	3	391	HR (95% CI)	0.59 [0.49, 0.72]
2.2 Treatment-comparisons assessing patients unselected for mTNBC	13	1745	HR (95% CI)	0.92 [0.84, 1.01]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.22]
3.1 Treatment-comparisons assessing patients with mTNBC	5	878	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.13, 1.56]
3.2 Treatment-comparisons assessing patients unselected for mTNBC	23	3252	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.04, 1.19]

Analysis 1.1. Comparison 1 Platinum vs non-platinum regimens (subgroup analysis 1: by treatment-comparisons assessing mTNBC), Outcome 1 Overall survival.

Analysis 1.2. Comparison 1 Platinum vs non-platinum regimens (subgroup analysis 1: by treatment-comparisons assessing mTNBC), Outcome 2 Progression-free survival/time to progression.

Analysis 1.3. Comparison 1 Platinum vs non-platinum regimens (subgroup analysis 1: by treatment-comparisons assessing mTNBC), Outcome 3 Objective tumour response rate (assessable participants).

Comparison 2. Platinum vs non-platinum regimens (subgroup analysis 2: by type of regimen comparison)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19	2922	HR (95% CI)	0.98 [0.89, 1.07]
1.1 Regimen A + platinum agent vs regimen A	6	1141	HR (95% CI)	1.08 [0.93, 1.26]
1.2 Regimen A + platinum agent vs regimen B	13	1781	HR (95% CI)	0.92 [0.81, 1.03]
2 Progression-free survival / time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]
2.1 Regimen A+platinum agent vs regimen A	6	1087	HR (95% CI)	0.88 [0.78, 1.00]
2.2 Regimen A+platinum agent vs regimen B	10	1049	HR (95% CI)	0.83 [0.74, 0.93]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.22]
3.1 Regimen A + platinum agent vs regimen A	9	1519	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.01, 1.21]
3.2 Regimen A + platinum agent vs regimen B	18	2235	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.12, 1.33]
3.3 Single agent platinum vs regimen C	1	376	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.66, 1.17]

Analysis 2.1. Comparison 2 Platinum vs non-platinum regimens (subgroup analysis 2: by type of regimen comparison), Outcome 1 Overall survival.

Analysis 2.2. Comparison 2 Platinum vs non-platinum regimens (subgroup analysis 2: by type of regimen comparison), Outcome 2 Progression-free survival / time to progression.

Analysis 2.3. Comparison 2 Platinum vs non-platinum regimens (subgroup analysis 2: by type of regimen comparison), Outcome 3 Objective tumour response rate (assessable participants).

Comparison 3. Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19	2922	HR (95% CI)	0.98 [0.89, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Cisplatin in platinum arm	11	1326	HR (95% CI)	0.91 [0.80, 1.05]
1.2 Carboplatin in platinum arm	8	1596	HR (95% CI)	1.04 [0.91, 1.18]
2 Progression-free survival/time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]
2.1 Cisplatin in platinum arm	11	1369	HR (95% CI)	0.85 [0.76, 0.94]
2.2 Carboplatin in platinum arm	5	767	HR (95% CI)	0.86 [0.75, 0.99]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.22]
3.1 Cisplatin in platinum arm	17	2050	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.24, 1.46]
3.2 Carboplatin in platinum arm	10	1943	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.86, 1.04]
3.3 Oxaliplatin in platinum arm	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.48, 1.52]
4 Treatment-related death (safety population)	15	2377	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.73, 2.76]
4.1 Cisplatin in platinum arm	8	1185	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.59, 3.25]
4.2 Carboplatin in platinum arm	6	1055	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.57, 6.05]
4.3 Oxaliplatin in platinum arm	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.16]
5 Nausea/vomiting (safety population)	21	3172	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [1.69, 2.54]
5.1 Cisplatin in platinum arm	14	1731	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [2.10, 3.34]
5.2 Carboplatin in platinum arm	7	1441	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.47, 1.26]
6 Nephrotoxicity (safety population)	5	632	Risk Ratio (M-H, Fixed, 95% CI)	3.06 [0.86, 10.84]
6.1 Cisplatin in platinum arm	4	561	Risk Ratio (M-H, Fixed, 95% CI)	3.46 [0.86, 13.97]
6.2 Carboplatin in platinum arm	1	71	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.07, 36.97]
7 Anaemia (safety population)	20	3085	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [1.90, 3.58]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Cisplatin in platinum arm	13	1644	Risk Ratio (M-H, Fixed, 95% CI)	3.72 [2.36, 5.88]
7.2 Carboplatin in platinum arm	7	1441	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.10, 2.70]
8 Hair loss (safety population)	12	1452	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.26, 1.58]
8.1 Cisplatin in platinum arm	9	983	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [1.15, 1.54]
8.2 Carboplatin in platinum arm	3	469	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.28, 1.84]
9 Leukopenia (safety population)	22	3176	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.21, 1.57]
9.1 Cisplatin in platinum arm	15	1866	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.23, 1.81]
9.2 Carboplatin in platinum arm	7	1310	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.07, 1.50]

Analysis 3.1. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 1 Overall survival.

Analysis 3.2. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 2 Progression-free survival/time to progression.

Analysis 3.3. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 3 Objective tumour response rate (assessable participants).

Analysis 3.4. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 4 Treatment-related death (safety population).

Analysis 3.5. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 5 Nausea/vomiting (safety population).

Analysis 3.6. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 6 Nephrotoxicity (safety population).

Analysis 3.7. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 7 Anaemia (safety population).

Analysis 3.8. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 8 Hair loss (safety population).

Analysis 3.9. Comparison 3 Platinum vs non-platinum regimens (subgroup analysis 3: by type of platinum agent in platinum arm), Outcome 9 Leukopenia (safety population).

Comparison 4. Platinum vs non-platinum regimens (subgroup analysis 4: by first-line therapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19	2922	HR (95% CI)	0.98 [0.89, 1.07]
1.1 First-line therapy for > 80% of patients	15	2486	HR (95% CI)	1.00 [0.90, 1.11]
1.2 Second- or third-line therapy for ≥20% of patients	4	436	HR (95% CI)	0.89 [0.73, 1.09]
2 Progression-free survival/time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]
2.1 First-line therapy for > 80% of patients	11	1565	HR (95% CI)	0.93 [0.83, 1.03]
2.2 Second- or third-line therapy for ≥20% of patients	5	571	HR (95% CI)	0.75 [0.65, 0.86]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.22]
3.1 First-line therapy for > 80% of patients	20	2983	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.06, 1.21]
3.2 Second- or third-line therapy for ≥20% of patients	8	1147	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.02, 1.42]

**Analysis 4.1. Comparison 4 Platinum vs non-platinum regimens
(subgroup analysis 4: by first-line therapy), Outcome 1 Overall survival.** **Analysis 4.2. Comparison 4 Platinum vs non-platinum regimens (subgroup analysis
4: by first-line therapy), Outcome 2 Progression-free survival/time to progression.**

Analysis 4.3. Comparison 4 Platinum vs non-platinum regimens (subgroup analysis 4: by first-line therapy), Outcome 3 Objective tumour response rate (assessable participants).

Comparison 5. Platinum vs non-platinum regimens (subgroup analysis 5 by anthracycline in regimens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19	2922	HR (95% CI)	0.98 [0.89, 1.07]
1.1 No anthracycline in platinum or non-platinum regimens	14	2213	HR (95% CI)	0.94 [0.84, 1.05]
1.2 Platinum + anthracycline vs non-platinum + anthracycline regimens	3	518	HR (95% CI)	1.09 [0.88, 1.34]
1.3 Platinum + anthracycline vs non-platinum + non-anthracycline regimens	2	191	HR (95% CI)	1.12 [0.78, 1.60]
2 Progression-free survival/time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 No anthracycline in platinum or non-platinum regimens	11	1465	HR (95% CI)	0.80 [0.73, 0.88]
2.2 Platinum+anthracycline vs non-platinum+anthracycline regimens	4	585	HR (95% CI)	1.05 [0.86, 1.27]
2.3 Platinum+anthracycline vs non-platinum+non-anthracycline regimens	1	86	HR (95% CI)	1.23 [0.75, 2.03]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.22]
3.1 No anthracycline in platinum or non-platinum regimens	18	2792	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.02, 1.20]
3.2 Platinum+anthracycline vs non-platinum+anthracycline regimens	6	859	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.97, 1.22]
3.3 Platinum+anthracycline vs non-platinum+non-anthracycline regimens	4	479	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.28, 1.74]

Analysis 5.1. Comparison 5 Platinum vs non-platinum regimens (subgroup analysis 5 by anthracycline in regimens), Outcome 1 Overall survival.

Analysis 5.2. Comparison 5 Platinum vs non-platinum regimens (subgroup analysis 5 by anthracycline in regimens), Outcome 2 Progression-free survival/time to progression.

Analysis 5.3. Comparison 5 Platinum vs non-platinum regimens (subgroup analysis 5 by anthracycline in regimens), Outcome 3 Objective tumour response rate (assessable participants).

Comparison 6. Platinum vs non-platinum regimens (subgroup analysis 6: by taxane in regimens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19	2922	HR (95% CI)	0.98 [0.89, 1.07]
1.1 No taxane in platinum or non-platinum regimens	9	1092	HR (95% CI)	1.07 [0.93, 1.24]
1.2 Platinum + taxane vs non-platinum + taxane regimens	6	1255	HR (95% CI)	0.96 [0.82, 1.11]
1.3 Platinum + non-taxane vs non-platinum + taxane regimens	4	575	HR (95% CI)	0.85 [0.69, 1.04]
2 Progression-free survival / time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]
2.1 No taxane in platinum or non-platinum regimens	9	1049	HR (95% CI)	0.92 [0.80, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Platinum + taxane vs non-platinum + taxane regimens	3	512	HR (95% CI)	0.84 [0.70, 1.00]
2.3 Platinum + non-taxane vs non-platinum + taxane regimens	4	575	HR (95% CI)	0.79 [0.69, 0.91]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.22]
3.1 No taxane in platinum or non-platinum regimens	17	2054	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.15, 1.36]
3.2 Platinum + taxane vs non-platinum + taxane regimens	6	1152	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.12]
3.3 Platinum + non-taxane vs non-platinum + taxane regimens	5	924	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.94, 1.30]

Analysis 6.1. Comparison 6 Platinum vs non-platinum regimens (subgroup analysis 6: by taxane in regimens), Outcome 1 Overall survival.

Analysis 6.2. Comparison 6 Platinum vs non-platinum regimens (subgroup analysis 6: by taxane in regimens), Outcome 2 Progression-free survival / time to progression.

Analysis 6.3. Comparison 6 Platinum vs non-platinum regimens (subgroup analysis 6: by taxane in regimens), Outcome 3 Objective tumour response rate (assessable participants).

Comparison 7. Platinum vs non-platinum regimens (subgroup analysis 7: by trastuzumab in regimens)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19	2922	HR (95% CI)	0.98 [0.89, 1.07]
1.1 No trastuzumab in platinum or non-platinum regimens	17	2463	HR (95% CI)	0.97 [0.88, 1.08]
1.2 Platinum + trastuzumab vs non-platinum + trastuzumab regimens	2	459	HR (95% CI)	1.00 [0.79, 1.27]
2 Progression-free survival/time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]
2.1 No trastuzumab in platinum or non-platinum regimens	14	1677	HR (95% CI)	0.84 [0.76, 0.92]
2.2 Platinum+trastuzumab vs non-platinum+trastuzumab regimens	2	459	HR (95% CI)	0.90 [0.75, 1.08]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.08, 1.22]
3.1 No trastuzumab in platinum or non-platinum regimens	26	3687	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.07, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Platinum+trastuzumab vs non-platinum+trastuzumab regimens	2	443	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.99, 1.31]

Analysis 7.1. Comparison 7 Platinum vs non-platinum regimens (subgroup analysis 7: by trastuzumab in regimens), Outcome 1 Overall survival.

Analysis 7.2. Comparison 7 Platinum vs non-platinum regimens (subgroup analysis 7: by trastuzumab in regimens), Outcome 2 Progression-free survival/time to progression.

Analysis 7.3. Comparison 7 Platinum vs non-platinum regimens (subgroup analysis 7: by trastuzumab in regimens), Outcome 3 Objective tumour response rate (assessable participants).

Comparison 8. Platinum vs non-platinum regimens (sensitivity analysis 1: excluding selected treatment-comparisons)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival (restricted to the 12 treatment-comparisons common to OS and PFS/TTP meta-analyses)	12	1571	HR (95% CI)	0.92 [0.81, 1.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Progression-free survival/time to progression (restricted to the 12 treatment-comparisons common to OS and PFS/TTP meta-analyses)	12	1571	HR (95% CI)	0.80 [0.73, 0.88]
3 Objective tumour response rate (assessable participants- restricted to the 19 treatment-comparisons in OS meta-analyses)	19	2685	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [1.05, 1.22]

Analysis 8.1. Comparison 8 Platinum vs non-platinum regimens (sensitivity analysis 1: excluding selected treatment-comparisons), Outcome 1 Overall survival (restricted to the 12 treatment-comparisons common to OS and PFS/TTP meta-analyses).

Analysis 8.2. Comparison 8 Platinum vs non-platinum regimens (sensitivity analysis 1: excluding selected treatment-comparisons), Outcome 2 Progression-free survival/time to progression (restricted to the 12 treatment-comparisons common to OS and PFS/TTP meta-analyses).

Analysis 8.3. Comparison 8 Platinum vs non-platinum regimens (sensitivity analysis 1: excluding selected treatment-comparisons), Outcome 3 Objective tumour response rate (assessable participants- restricted to the 19 treatment-comparisons in OS meta-analyses).

Comparison 9. Platinum vs non-platinum regimens (sensitivity analysis 2: Progression-free survival vs. time to progression)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression-free survival vs time to progression	16	2136	HR (95% CI)	0.85 [0.78, 0.93]
1.1 Progression-free survival	9	1324	HR (95% CI)	0.92 [0.82, 1.03]
1.2 Time to progression	7	812	HR (95% CI)	0.78 [0.69, 0.88]

Analysis 9.1. Comparison 9 Platinum vs non-platinum regimens (sensitivity analysis 2: Progression-free survival vs. time to progression), Outcome 1 Progression-free survival vs time to progression.

Comparison 10. Platinum vs non-platinum regimens (sensitivity analysis 3: Analyses 1 repeated but with random effects approach)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Overall survival	19		Hazard Ratio (Random, 95% CI)	0.98 [0.87, 1.11]
1.1 Treatment-comparisons assessing patients with mTNBC	3		Hazard Ratio (Random, 95% CI)	0.73 [0.51, 1.04]
1.2 Treatment-comparisons assessing patients unselected for mTNBC	16		Hazard Ratio (Random, 95% CI)	1.02 [0.90, 1.16]
2 Progression-free survival/time to progression	16		Hazard Ratio (Random, 95% CI)	0.88 [0.76, 1.02]
2.1 Treatment-comparisons assessing patients with mTNBC	3		Hazard Ratio (Random, 95% CI)	0.55 [0.38, 0.78]
2.2 Treatment-comparisons assessing patients unselected for mTNBC	13		Hazard Ratio (Random, 95% CI)	0.96 [0.85, 1.09]
3 Objective tumour response rate (assessable participants)	28	4130	Risk Ratio (M-H, Random, 95% CI)	1.17 [1.05, 1.30]
3.1 Treatment-comparisons assessing patients with mTNBC	5	878	Risk Ratio (M-H, Random, 95% CI)	1.60 [1.04, 2.45]
3.2 Treatment-comparisons assessing patients unselected for mTNBC	23	3252	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.01, 1.25]

Analysis 10.1. Comparison 10 Platinum vs non-platinum regimens (sensitivity analysis 3: Analyses 1 repeated but with random effects approach), Outcome 1 Overall survival.

Analysis 10.2. Comparison 10 Platinum vs non-platinum regimens (sensitivity analysis 3: Analyses 1 repeated but with random effects approach), Outcome 2 Progression-free survival/time to progression.

Analysis 10.3. Comparison 10 Platinum vs non-platinum regimens (sensitivity analysis 3: Analyses 1 repeated but with random effects approach), Outcome 3 Objective tumour response rate (assessable participants).

ADDITIONAL TABLES

Table 1. Platinum agents

Generic name	Other names
Carboplatin	Blastocarb, Carboplat, Carboplatin Hexal, Carboplatino, Carbosin, Carbosol, Carbotec, CBDCA, Dis-plata, Ercar, Nealorin, Novoplatinum, Paraplat, Paraplatin AQ, Paraplatin, Paraplatine, Platinwas, Ribocarbo
Cisplatin	Abiplatin, Blastolem, Briplatin, CACP, CDDP, cis-DDP, cis-diamminedichloridoplatinum, cis-diamminedichloro platinum (II), cis-diamminedichloroplatinum, Cis-dichloroammine Platinum (II), Cismaplat, Cisplatina, cis-platinous diamine dichloride, cis-platinum II diamine dichloride, cis-platinum II, cis-platinum, Cisplatyl, Citoplatino, Citosin, CPDD, Cysplatyna, DDP, DDP, Lederplatin, Metaplatin, Neoplatin, PDD, Peyrone's Chloride, Peyrone's Salt, Placis, Platamine, Platiblastin, Platiblastin-S, Platinex, Platinol- AQ, Platinol, Platinol-AQ VHA Plus, Platinol-AQ, Platinoxan, platinum diamminodichloride, Platiran, Platistin, Platosin
Oxaliplatin	Ai Heng, Aiheng, diaminocyclohexane oxalatoplatinum, oxalatoplatin, oxalatoplatinum, oxaliplatin, Eloxatin, Dacotin, Dacplat, Eloxatine, 1-OHP, L-OHP, oxaliplatin medac

Table 2. Chemotherapeutic Agents (adapted from Table 1.1 in The Chemotherapy Source Book)

Type of Agent	Action	Includes
Agents that damage the DNA template	by alkylation: nitrogen mustards	cyclophosphamide, melphalan, ifosfamide, chlorambucil
	by alkylation: nitrosureas	carmustine (BCNU), lomustine (CCNU)
	by alkylation: other agents	thiotepa, mitomycin C
	by platinum coordination cross-linking	cisplatin, carboplatin

Table 2. Chemotherapeutic Agents (adapted from Table 1.1 in The Chemotherapy Source Book) (Continued)

	antibiotics	doxorubicin, daunorubicin, mitoxantrone, idarubicin, epirubicin, amsacrine
	podophyllotoxins	etoposide, teniposide
	by intercalation	dactinomycin, mithramycin
	by uncertain mechanisms	bleomycin
Spindle poisons	vinca alkaloids	vincristine, vinblastine, vendesine, vinorelbine
	taxanes	taxol, taxotere
Antimetabolites	thymidylate synthase	5-fluorouracil
	dihydrofolate reductase	methotrexate

Table 3. Number of treatment-comparisons included in meta-analyses by subgroup and three outcomes

Subgroup	Outcome			
	Treatment-comparisons N	Overall survival n (% of N)	Progression-free survival/time to progression n (% of N)	Objective response rate n (% of N)
Overall:	28	19 (68%)	16 (57%)	28 (100%)
Type of platinum agent in platinum arm:				
Cisplatin in platinum arm	17	11 (65%)	11 (65%)	17 (100%)
Carboplatin in platinum arm	10	8 (80%)	5 (50%)	10 (100%)
Oxaliplatin in platinum arm	1	(0%)	(0%)	1 (100%)
Type of regimen comparison:				
Regimen A + platinum agent vs regimen A	9	6 (67%)	6 (67%)	9 (100%)
Regimen A + platinum agent vs regimen B	18	13 (72%)	10 (56%)	18 (100%)
Single agent platinum vs regimen C	1	(0%)	(0%)	1 (100%)
First-line therapy:				
First-line therapy for > 80% of participants	20	15 (75%)	11 (55%)	20 (100%)
Second- or third-line therapy for ≥ 20% of participants	8	4 (50%)	5 (63%)	8 (100%)

Table 3. Number of treatment-comparisons included in meta-analyses by subgroup and three outcomes (Continued)

Participant selection for mTNBC:				
Participants with mTNBC	5	3 (60%)	3 (60%)	5 (100%)
Participants unselected for mTNBC	23	16 (70%)	13 (57%)	23 (100%)
Anthracycline in regimens:				
No anthracycline in platinum or non-platinum regimens	18	14 (78%)	11 (61%)	18 (100%)
Platinum + anthracycline vs non-platinum + anthracycline regimens	6	3 (50%)	4 (67%)	6 (100%)
Platinum + anthracycline vs non-platinum + non-anthracycline regimens	4	2 (50%)	1 (25%)	4 (100%)
Taxane in regimens:				
No taxane in platinum or non-platinum regimens	17	9 (53%)	9 (53%)	17 (100%)
Platinum + taxane vs non-platinum + taxane regimens	6	6 (100%)	3 (50%)	6 (100%)
Platinum + non-taxane vs non-platinum + taxane regimens	5	4 (80%)	4 (80%)	5 (100%)
Trastuzumab in regimens:				
No trastuzumab in platinum or non-platinum regimens	26	17 (65%)	14 (54%)	26 (100%)
Platinum + trastuzumab vs non-platinum + trastuzumab regimens	2	2 (100%)	2 (100%)	2 (100%)

Table 4. Summary of regimens included in the analysis

Trials ID	Arm 1 (platinum-containing)	Arm 2 (control)	First-line therapy for > 80% of participants	Majority participants anthracycline-naïve
Regimen A + platinum vs regimen A				
Berruti 2002 A	Epi + Cis (epirubicin+cisplatin)	Epi (epirubicin)	Y	Y
Berruti 2002 B	Epi + Cis + LND (epirubicin+cisplatin+lonidamine)	Epi + LND (epirubicin + lonidamine)	Y	Y
Bhattacharyya 2009	Endoxan 50 mg per day at 10 am and methotrexate 2.5 mg twice a day at 9 am and 5 pm and with 'cisplatinum'	Endoxan 50 mg per day at 10 am and methotrexate 2.5 mg twice a day at 9 am and 5 pm	N	N
Carey 2012	C + Cb (Cetuximab + carboplatin)	C (Cetuximab with carboplatin added after progression)	N	N

Table 4. Summary of regimens included in the analysis *(Continued)*

Costanza 1999	CBDA + CAF (carboplatin + cycloheximide + doxorubicin + fluorouracil + methotrexate)	CAF (cycloheximide + doxorubicin + fluorouracil) (methotrexate substituted after total doxorubicin - 540 mg)	Y	Unclear
Fountzilas 2009 A	PCb (paclitaxel + carboplatin)	Pw (paclitaxel)	Y	N
Nielsen 2000	Epi + Cis (epirubicin + cisplatin)	Epi (epirubicin)	Y	Y
Robert 2006	TPC (trastuzumab + paclitaxel + carboplatin)	TP (trastuzumab + paclitaxel)	Y	Unclear
Valero 2011	TCH (trastuzumab + docetaxel + carboplatin)	TH (trastuzumab + docetaxel)	Y	N
Regimen A + platinum vs regimen B				
Amadori 2013	(pemetrexed + carboplatin)	(vinorelbine + gemcitabine)	N	N
Cocconi 1991	MPEPIV(a) or MPEMi (b) (a: methotrexate, leucovorin, cisplatin, epirubicin, vincristine; b: methotrexate, leucovorin, cisplatin, etoposide, mitomycin)	CMF (cyclophosphamide, methotrexate, fluorouracil)	Y	Y
Cocconi 1996	Etop + Cis (etoposide + cisplatin)	CMF (cyclophosphamide, methotrexate, fluorouracil)	Y	Unclear
Cocconi 1999	PE + CMF + AL (cisplatin + etoposide + doxorubicin + cyclophosphamide, methotrexate + fluorouracil, leucovorin + allopurinol)	CMF (cyclophosphamide, methotrexate, fluorouracil)	Y	Unclear
Creagan 1984	CFP + CAP (cyclophosphamide + doxorubicin + cis-dichlorodiammine + CFP)	CFP (cyclophosphamide + fluorouracil + prednisone)	Y	Y
Delaloge 2004	OXA (oxaliplatin + 5-fluorouracil)	VIN (vinorelbine)	N	N
Eisen 1998	EcisF (5-fluorouracil + epirubicin + cisplatin)	EcycloF (5-fluorouracil + epirubicin + cyclophosphamide)	Y	Y
Fan 2012	TP (docetaxel + cisplatin)	TX (docetaxel + capecitabine)	Y	N
Fountzilas 2004	Epi + Pcb (epirubicin + carboplatin)	Epi + P (epirubicin + paclitaxel)	Y	Y (54%)
Fountzilas 2009 B	PCb (paclitaxel + carboplatin)	GDoc (docetaxel + gemcitabine)	Y	N
Hu 2015	(cisplatin + gemcitabine)	(paclitaxel + gemcitabine)	Y	N
Icli 2005	Etop + Cis (etoposide + cisplatin)	P (paclitaxel)	N	N

Table 4. Summary of regimens included in the analysis *(Continued)*

Kolaric 1985	CAP (cyclophosphamide + doxorubicin + platinum)	CMFVP (cyclophosphamide + methotrexate + 5-fluorouracil + vincristine + prednisone)	Y	Y
Kolaric 1989	CAP (cyclophosphamide + doxorubicin + platinum)	FAC (5-fluorouracil + doxorubicin + cyclophosphamide)	Y	Y
Stemmler 2011 A	GemCis (gemcitabine + cisplatin)	GemVin (gemcitabine + vinorelbine)	N	N
Stemmler 2011 B	GemCis (gemcitabine + cisplatin)	GemCap (gemcitabine + capecitabine)	N	N
Xu 2011 A	GemCis (gemcitabine + cisplatin)	GemPac (gemcitabine + paclitaxel)	Y	N
Xu 2011 B	GemCarb (gemcitabine + carboplatin)	GemPac (gemcitabine + paclitaxel)	Y	N
Single agent platinum vs regimen C				
Tutt 2014	C (carboplatin)	D (docetaxel)	N	Unclear

Table 5. Summary of outcomes for included trials

Trial ID	Extractable OS data for HR estimation ¹	Median OS time ²	Extractable PFS/TTP data for HR estimation ¹	Median PFS/TTP time ²	Overall response	Treat-ment-relat-ed deaths	Grade III & IV Toxicity	Accrual ³
Regimen A + platinum vs regimen A								
Berruti 2002 A	NR	Y	Y	Y	Y	Y	Nausea/vomiting Nephrotoxicity Anaemia Leukopenia	185
Berruti 2002 B	NR	Y	Y	Y	Y	Y	Nausea/vomiting Nephrotoxicity Anaemia Leukopenia	186
Bhattacharyya 2009	NR	Y	NR	Y	Y	NR	NR	126
Carey 2012	Y	Y	Y	NR	Y	NR	Not extractable	102
Costanza 1999	Y	Y	NR	NR	Y	Y	Nausea/vomiting Anaemia Leukopenia	221
Fountzilias 2009 A	Y	Y	NR	NR	Y	Y	Nausea/vomiting Anaemia Hair loss Leukopenia	204
Nielsen 2000	Y	Y	Y	Y	Y	Y	Nausea/vomiting Leukopenia	155

Table 5. Summary of outcomes for included trials *(Continued)*

Robert 2006	Y	Y	Y	Y	Y	NR	Nausea/vomiting Anaemia Leukopenia	196
Valero 2011	Y	Y	Y	Y	Y	Y	Nausea/vomiting Anaemia	263
Regimen A + platinum vs regimen B								
Amadori 2013	NR	NR	Y	Y	Y	Y	Leukopenia	135
Cocconi 1991	Y	Y	NR	Y	Y	NR	Anaemia Leukopenia	140
Cocconi 1999	Y	Y	NR	Y	Y	NR	Nausea/vomiting Anaemia Hair loss Leukopenia	105
Cocconi 1996	NR	Y	NR	Y	Y	DU	Not extractable	169
Creagan 1984	Y	Y	Y	Y	Y	NR	Nausea/vomiting Hair loss Leukopenia	86
Delaloge 2004	NR	Y	NR	Y	Y	Y	Not extractable	137
Eisen 1998	NR	Y	Y	Y	Y	DU	Nausea/vomiting Anaemia Hair loss Leukopenia	59
Fan 2012	Y	Y	Y	Y	Y	Y	Nausea/vomiting Anaemia	53

Table 5. Summary of outcomes for included trials *(Continued)*

							Leukopenia	
Fountzilas 2004	Y	NR	NR	NR	Y	NR	Nausea/vomiting Anaemia Leukopenia	327
Fountzilas 2009 B	Y	Y	NR	NR	Y	Y	Nausea/vomiting Anaemia Hair loss Leukopenia	212
Hu 2015	Y	NR	Y	Y	Y	Y	Nausea/vomiting Anaemia Hair loss Leukopenia	236
Icli 2005	Y	Y	Y	NR	Y	Y	Nausea/vomiting Anaemia Leukopenia	193
Kolaric 1985	NR	NR	NR	NR	Y	NR	Nausea/vomiting Nephrotoxicity Anaemia Hair loss Leukopenia	123
Kolaric 1989	Y	Y	NR	NR	Y	Y	Nausea/vomiting Anaemia Hair loss Leukopenia	142

Table 5. Summary of outcomes for included trials (Continued)

Stemmler 2011 A	Y	Y	Y	Y	Y	NR	Nausea/vomiting	69
							Anaemia	
							Hair loss	
							Leukopenia	
Stemmler 2011 B	Y	Y	Y	Y	Y	NR	Nausea/vomiting	72
							Anaemia	
							Hair loss	
							Leukopenia	
Xu 2011 A	Y	Y	Y	Y	Y	Y	Nausea/vomiting	75
							Nephrotoxicity	
							Anaemia	
							Hair loss	
							Leukopenia	
Xu 2011 B	Y	Y	Y	Y	Y	Y	Nausea/vomiting	71
							Nephrotoxicity	
							Anaemia	
							Hair loss	
							Leukopenia	
Single agent platinum vs regimen C								
Tutt 2014	NR	Y	NR	Y	Y	NR	NR	376

¹ Sufficient data reported to estimate a HR for pooling as outlined by Parmar 1998 and Tierney 2007; this includes Kaplan-Meier curve, HR and standard error/confidence interval or logrank statistics

² Trials that did not explicitly report median time were classified as NR here regardless of estimable median time from Kaplan-Meier curve

³ Accrual numbers represent the maximum numbers of participants in the trial (not study) that were included in the analyses of OS, PFS/TTP or OR (assessable participants).

*NR = not reported, DU = deaths unexplained, Y = data reported.

APPENDICES

Appendix 1. CENTRAL

1. MeSH descriptor: [Breast Neoplasms] explode all trees
2. breast near neoplasm*
3. breast near carcinoma*
4. breast near cancer*
5. breast near tumour*
6. breast near tumor*
7. #1 or #2 or #3 or #4 or #5 or #6
8. platinum or cisplatin or cisplatinum
9. MeSH descriptor: [Platinum] explode all trees
10. MeSH descriptor: [Cisplatin] explode all trees
11. MeSH descriptor: [Platinum Compounds] explode all trees
12. #8 or #9 or #10 or #11
13. #7 and #12

Appendix 2. MEDLINE (via Ovid SP)

1	randomized controlled trial.pt.
2	controlled clinical trial.pt.
3	randomized.ab.
4	placebo.ab.
5	Clinical Trials as Topic/
6	randomly.ab.
7	trial.ti.
8	(crossover or cross-over).tw.
9	Pragmatic Clinical Trials as Topic/
10	pragmatic clinical trial.pt.
11	or/1-10
12	exp Breast Neoplasms/
13	advanced breast cancer\$.tw,sh.
14	advanced breast neoplasm\$.tw,sh.
15	advanced breast carcinoma\$.tw,sh.
16	advanced breast tumor\$.tw,sh.
17	advanced breast tumour\$.tw,sh.

(Continued)

18	metastatic breast cancer\$.tw,sh.
19	metastatic breast carcinoma\$.tw,sh.
20	metastatic breast neoplasm\$.tw,sh.
21	metastatic breast tumour\$.tw,sh.
22	metastatic breast tumor\$.tw,sh.
23	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24	11 and 23
25	exp Cisplatin/
26	exp Carboplatin/
27	cisplatinum.tw.
28	carboplatinum.tw.
29	exp Platinum/
30	platinum compound*.tw.
31	platinum containing regime*.tw.
32	platin*.tw.
33	platinum diamminedichloroplatinum.tw.
34	cis-diamminedichloroplatinum.tw.
35	cis-dichlorodiammineoplatinum.tw.
36	biocisplatinum.tw.
37	dichlorodiammineplatinum.tw.
38	nsc-119875.tw.
39	platidiam.tw.
40	platino.tw.
41	platinol.tw.
42	paraplatin.tw.
43	cis-diamminedichloroplatinum.tw.
44	cis-platinum.tw.
45	cyclobutanedicarboxylato.tw.

(Continued)

46	jm-8.tw.
47	cbdca.tw.
48	nsc-241240.tw.
49	or/25-48
50	11 and 23 and 49
51	Animals/
52	Humans/
53	51 not 52
54	50 not 53

Appendix 3. Embase (via Embase.com)

1. **random*** OR **factorial*** OR **crossover*** OR **cross** NEXT/1 **over*** OR **placebo*** OR (**doubl*** AND **blind***) OR (**singl*** AND **blind***) OR **assign***OR **allocat*** OR **volunteer*** OR **'crossover procedure'/exp** OR **'crossover procedure'** OR **'double blind procedure'/exp** OR **'double blind procedure'** OR **'randomized controlled trial'/exp** OR **'randomized controlled trial'** OR **'single blind procedure'/exp** OR **'single blind procedure'**
2. **'advanced breast cancer'/exp** OR **'advanced breast cancer'**
3. **'advanced breast carcinoma'**
4. **'advanced breast neoplasm'**
5. **'advanced breast tumour'**
6. **'advanced breast tumor'**
7. **'metastatic breast cancer'/exp** OR **'metastatic breast cancer'**
8. **'metastatic breast carcinoma'**
9. **'metastatic breast neoplasm'**
10. **'metastatic breast tumour'**
11. **'metastatic breast tumor'**
12. **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10** OR **#11**
13. **'breast cancer'/exp** OR **'breast cancer'**
14. **#12** AND **#13**
15. **'cisplatin'/exp** OR **cisplatin**
16. **'cisplatin'/exp** OR **cisplatin**
17. **'cisplatinum'/exp** OR **cisplatinum**
18. **carboplatinum**
19. **'platinum'/exp** OR **platinum**
20. **'platinum containing regime'**
21. **platin***
22. **'platinum diamminedichloroplatinum'**
23. **'cis diamminedichloroplatinum'**
24. **'cis dichlorodiammineplatinum'/exp** OR **'cis dichlorodiammineplatinum'**
25. **'biocisplatinum'/exp** OR **biocisplatinum**
26. **'dichlorodiammineplatinum'/exp** OR **'dichlorodiammineplatinum'**
27. **'nsc 119875'/exp** OR **'nsc 119875'**
28. **'platidiam'/exp** OR **platidiam**
29. **'platinol'/exp** OR **platinol**

30. 'paraplatin'/exp OR paraplatin
31. 'cis diamminedichloroplatinum'/exp OR 'cis diamminedichloroplatinum'
32. 'cis platinum'/exp OR 'cis platinum'
33. cyclobutanedicarboxylato
34. 'cbdca'/exp OR cbdca
35. 'jm 8'/exp OR 'jm 8'
36. 'nsc 241240'/exp OR 'nsc 241240'
37. #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36
38. #1 AND #14 AND #37
39. #1 AND #14 AND #37

Appendix 4. WHO ICTRP Search Portal

Basic Searches:

1. Platinum-containing regimens for metastatic breast cancer
2. Metastatic breast cancer AND platinum
3. Advanced breast cancer AND platinum

Advanced Searches:

1. Title: Platinum-containing regimens for metastatic breast cancer
Recruitment Status: ALL
2. Condition: metastatic breast cancer
Intervention: platinum-containing regime% OR platinum compound% OR platinum% OR cisplatin OR carboplatin OR platin% OR cisplatinum OR carboplatinum OR platinum diamminodichloride OR cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR biocisplatinum OR dichlorodiammineplatinum OR nsc-119875 OR platidiam OR platino OR platinol OR paraplatin OR cis-diamminedichloroplatinum OR cis-platinum OR cyclobutanedicarboxylato OR cbdca OR jn-8 OR nsc-241240
Recruitment Status: ALL
3. Condition: advanced breast cancer
Intervention: platinum-containing regime% OR platinum compound% OR platinum% OR cisplatin OR carboplatin OR platin% OR cisplatinum OR carboplatinum OR platinum diamminodichloride OR cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR biocisplatinum OR dichlorodiammineplatinum OR nsc-119875 OR platidiam OR platino OR platinol OR paraplatin OR cis-diamminedichloroplatinum OR cis-platinum OR cyclobutanedicarboxylato OR cbdca OR jn-8 OR nsc-241240
Recruitment Status: ALL
4. Condition: advanced breast cancer OR metastatic breast cancer
Intervention: platinum-containing chemotherapy regimen% OR platinum-containing chemotherapy regimen%
Recruitment Status: ALL
5. Condition: advanced breast cancer OR metastatic breast cancer
Intervention: platinum AND chemotherapy%
Recruitment Status: ALL

Appendix 5. ClinicalTrials.gov

Basic Searches:

1. Platinum-containing regimens for metastatic breast cancer
2. Metastatic breast cancer AND platinum
3. Advanced breast cancer AND platinum

Advanced Searches:

1. Title: Platinum-containing regimens for metastatic breast cancer
Recruitment: All studies
Study Results: All studies
Study Type: All studies
Gender: All studies

2. Condition: metastatic breast cancer OR advanced breast cancer

Platinum-containing regimens for metastatic breast cancer (Review)

Intervention: platinum-containing regime OR platinum compound OR platinum OR cisplatin OR carboplatin OR platin OR cisplatinum OR carboplatinum OR platinum diamminodichloride OR cis-diamminedichloroplatinum OR cis-dichlorodiammineplatinum OR biocisplatinum OR dichlorodiammineplatinum OR nsc-119875 OR platidiam OR platino OR platinol OR paraplatin OR cis-diamminedichloroplatinum OR cis-platinum OR cyclobutanedicarboxylato OR cbdca OR jn-8 OR nsc-241240

Recruitment: All studies

Study Results: All studies

Study Type: All studies

Gender: All studies

3. **Condition:** advanced breast cancer OR metastatic breast cancer

Intervention: platinum-containing chemotherapy regimen% OR platinum-containing chemotherapy regimen

Recruitment: All studies

Study Results: All studies

Study Type: All studies

Gender: All studies

4. **Condition:** advanced breast cancer OR metastatic breast cancer

Intervention: platinum AND chemotherapy

Recruitment: All studies

Study Results: All studies

Study Type: All studies

Gender: All studies

WHAT'S NEW

Date	Event	Description
23 August 2017	Review declared as stable	The effect of platinum-containing regimens for women with metastatic breast cancer is generally well established. The results in the 2016 review update are consistent with findings of the previous review, mainly in women without triple-negative breast cancer. In the future, however, the scope of this review topic will be modified and likely involve an assessment of platinum-containing regimens in women with a specific subtype of breast cancer (that is, triple-negative breast cancer or BRCA mutation and metastatic breast cancer). Such a topic will be classified as a new review in the Cochrane Library.

HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 2, 2004

Date	Event	Description
28 May 2015	New citation required and conclusions have changed	Conclusions are largely unchanged although there is now preliminary, low-quality evidence of a survival benefit from platinum-containing chemotherapy regimens compared to non-platinum regimens for women with metastatic triple negative breast cancer
28 May 2015	New search has been performed	Performed searches for new studies on 28 May 2015. Twelve new studies with 15 new treatment-comparisons were included in this review update, adding 2327 (analysed) participants since the original 2004 version of this review. Risk of bias was assessed for all domains. New subgroup analyses have been added to this review update in response to new hypotheses and available sub-

Date	Event	Description
		groups. The measure of effect for proportion (dichotomous) outcomes has been changed from odds ratio to risk ratio for ease of interpretation
19 April 2012	Amended	Additional table linked to text.
4 August 2008	Amended	Converted to new review format.
25 February 2004	New citation required and conclusions have changed	First review publication

CONTRIBUTIONS OF AUTHORS

Original review

DG designed the review and wrote the protocol. JS and NW provided clinical input and commented on the drafts of the review. SC undertook the review including assessing trial eligibility, data extraction, analyses and writing the review. All other authors commented on the draft review.

2016 review update

SE, NW, MW, JM and HW assessed trial eligibility. SE, MW, JM and HW performed data extraction and 'risk of bias' assessments. SE, JM and HW entered the data. SE performed the statistical analysis and wrote the update. NW provided clinical input. All authors commented on and contributed to the writing of the update.

DECLARATIONS OF INTEREST

SE: none; MW: none; JM: none; HW: none; DO'C: none; SC: none; DG: none; NW: none.

SOURCES OF SUPPORT

Internal sources

- NHMRC Clinical Trials Centre, Australia.

External sources

- U.S. Army Medical Research Acquisition Activity, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The protocol for this review proposed that trials would be included if study participants were to receive first-line treatment. As few trials assessing first-line treatment were identified for inclusion in the original version of this review, those meeting the remaining eligibility criteria but which involved participants who were not first-line naive were included. This modification of the inclusion criteria was maintained for this review update with subgroup analysis by treatment line being performed (treatment-comparisons with first-line therapy for > 80% of participants vs second- or third-line therapy for ≥ 20% of participants).
- Six of the seven subgroup analyses in this review were not prespecified in the review protocol and were added to the review in response to new hypotheses and available subgroups. Three of the six 'post hoc' subgroup analyses were added in this review update and the other three were included in the original version of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Alopecia [chemically induced] [epidemiology]; Anemia [chemically induced]; Antineoplastic Combined Chemotherapy Protocols [adverse effects] [*therapeutic use]; Breast Neoplasms [*drug therapy] [mortality] [pathology]; Carboplatin [administration & dosage] [adverse effects]; Cisplatin [administration & dosage] [adverse effects]; Disease-Free Survival; Leukopenia [chemically induced] [epidemiology]; Nausea [chemically induced]; Organoplatinum Compounds [administration & dosage] [adverse effects]; Pyridines [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Survival Rate; Triple Negative Breast Neoplasms [drug therapy] [mortality] [pathology]; Vomiting [chemically induced] [epidemiology]

MeSH check words

Female; Humans