Cochrane Library

Cochrane Database of Systematic Reviews

Addition of drug/s to a chemotherapy regimen for metastatic breast cancer (Review)

Butters DJ, Ghersi D, Wilcken N, Kirk SJ, Mallon PT

Butters DJ, Ghersi D, Wilcken N, Kirk SJ, Mallon PT.
Addition of drug/s to a chemotherapy regimen for metastatic breast cancer.
Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003368.
DOI: 10.1002/14651858.CD003368.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Addition of drug/s to a chemotherapy regimen for metastatic breast cancer

Daria J Butters[1], Davina Ghersi[2], Nicholas Wilcken[3], Steven J Kirk[4], Peter T Mallon[5]

[1]Footscray, Australia. [2]Research Policy and Translation, National Health and Medical Research Council, Canberra, Australia. [3]Medical Oncology, Crown Princess Mary Cancer Centre, Westmead, Australia. [4]Ulster Hospital, Belfast, UK. [5]Department of Surgery, Institute of Clinical Science, Belfast, UK

Contact: Peter T Mallon, petermallon@hotmail.com.

Editorial group: Cochrane Breast Cancer Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 5, 2021.

Citation: Butters DJ, Ghersi D, Wilcken N, Kirk SJ, Mallon PT. Addition of drug/s to a chemotherapy regimen for metastatic breast cancer. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No.: CD003368. DOI: 10.1002/14651858.CD003368.pub3.

ABSTRACT

Background

The addition of a chemotherapy drug or drugs to an established regimen is one method used to increase the dose and intensity of treatment for metastatic breast cancer.

Objectives

To assess the effects of adding one or more chemotherapy drugs to an established regimen in women with metastatic breast cancer.

Search methods

We searched the Cochrane Breast Cancer Group's Specialised Register (to August 2009) using the codes for "advanced breast cancer" and "chemotherapy". This review is an update of the original Cochrane Review (Issue 3, 2006).

Selection criteria

Randomised trials with a first line regimen of at least two chemotherapy drugs compared to the same regimen plus the addition of one or more chemotherapy drugs in women with metastatic breast cancer.

Data collection and analysis

Two authors extracted data independently from published trials. We derived hazard ratios (HR) from time-to-event outcomes where possible, and used a fixed-effect model for meta-analysis. We analysed response rates as dichotomous variables and extracted toxicity data where available.

Main results

We identified 17 trials reporting on 22 treatment comparisons (2674 patients randomised). Fifteen trials (20 treatment comparisons) reported results for tumour response and 11 trials (14 treatment comparisons) published time-to-event data for overall survival. There were 1532 deaths in 2116 women randomised to trials of the addition of a drug to the regimen and control (the regimen alone). There was no detectable difference in overall survival between these patients, with an overall HR of 0.96 (95% confidence interval (CI) 0.87 to 1.07, P = 0.47) and no significant heterogeneity. We found no difference in time to progression between these regimens, with an overall HR of 0.93 (95% CI 0.81 to 1.07, P = 0.31) and no significant heterogeneity. Addition of a drug to the regimen was favourably associated with overall tumour response rates (odds ratio 1.21, 95% CI 1.01 to 1.44, P = 0.04) although we observed significant heterogeneity for this outcome across the trials. Where measured, acute toxicities such as alopecia, nausea and vomiting and leucopenia were more common with the addition of a drug.

Authors' conclusions

The addition of one or more drugs to the regimen shows a statistically significant advantage for tumour response in women with metastatic breast cancer but the results suggest no difference in survival time or time to progression. The positive effect on tumour response was also associated with increased toxicity.

PLAIN LANGUAGE SUMMARY

Addition of drugs to a chemotherapy regimen for metastatic breast cancer

Advanced breast cancer is treatable but not curable. Women with advanced breast cancer have an average survival of about 2 years, although some women may live for many years beyond this. Therefore, it is important to investigate different chemotherapy treatment options. Chemotherapy can improve survival for women with metastatic breast cancer, but it can also cause toxic side effects. Of interest is whether there is any benefit by adding additional chemotherapy drugs, particularly given the potential harm caused by more dose-intensive treatment. This review investigated the value of adding one or more chemotherapy drugs to a chemotherapy regimen. We found that the addition of chemotherapy drug/s to a regimen caused greater shrinkage of the tumour seen with imaging but increased toxicity. There is insufficient evidence to determine if there is an impact on time to disease progression and overall survival.

BACKGROUND

Description of the condition

Breast cancer is the most common type of cancer in women, and the most common cause of cancer-related death in women. In 2002, there were 1.15 million new cases of breast cancer reported worldwide. In the same year, there were approximately 410,712 deaths as a result of breast cancer; with an age-standardised death rate (ASR) of 13.2 (per 100,000). ASRs of 25 or greater were recorded in 2002 by Barbados (25.53), Belgium (27.7), Botswana (25), Cyprus (29.6), Denmark (27.8), Ireland (25.5), Malta (29.6), Philippines (27.1) and the Netherlands (27.5) (Ferlay 2004).

While treatable, metastatic breast cancer is rarely curable at present. Some women with metastatic breast cancer live for many years; however, the median survival ranges from 18 to 24 months (Stockler 2000). Chemotherapy is considered by many to be the appropriate first treatment option for women with multiple sites of recurrence, or in women whose cancer is hormone refractory, or expected to be hormone resistant (Esteva 2001). See Table 1 for a list of chemotherapeutic agents and their site of action.

Description of the intervention

Most chemotherapeutic agents used in the treatment of cancer show a steep dose-response curve. This has led to the conclusion that increasing the intensity of treatment will result in an increase in the rate and duration of response, and hence to improvements in survival (Hryniuk 1987). One widely accepted theory is that combining chemotherapy agents will produce regimens that are more active, thereby improving tumour response and overall survival.

How the intervention might work

The concurrent addition of a drug to a chemotherapy regimen is one method used to increase the dose and intensity of treatment. In the management of metastatic disease, it is important to understand if combination therapy offers a survival advantage over other treatment options (Hamilton 2005). Of interest is whether there is any benefit to increasing the dose intensity of a regimen, particularly given the potential harm caused by more dose-intensive treatment. If palliation is the primary goal of treatment, and anticipated survival is limited, then toxicity and quality of life become important factors when deciding on a treatment regimen.

Why it is important to do this review

This review expands further on the potential benefit, or lack thereof, of the addition of a drug to a regimen containing two or more drugs in women with metastatic breast cancer. Single agent versus combination chemotherapy for metastatic breast cancer (Carrick 2005) is one such review in this series and this review of the addition of a drug to a regimen further complements these results. Compared with single-chemotherapy agents, combination regimens show a statistically significant advantage for tumour response and time to progression in women with metastatic breast cancer, a modest improvement in overall survival and significantly worse toxicities (Carrick 2005). This updated review examines the potential benefit, or lack thereof, of the addition of a drug to a regimen, by comparing regimens that contain at least two chemotherapy drugs, in comparison to that same regimen with the concurrent addition of one or more chemotherapy drugs in women with metastatic breast cancer. We considered all chemotherapy agents regardless of their mechanism of action including antimetabolites, spindle poisons and agents that damage the DNA template.

There is a clear need to summarise the current research and to determine if the addition of one or more drugs to the regimen provides a survival benefit to aid decision making when choice of chemotherapy regimen is being considered for a woman with metastatic breast cancer.

OBJECTIVES

To assess the value of adding a drug (or drugs) to the regimen of at least two chemotherapy drugs in the management of women with metastatic breast cancer. Throughout this review, this addition of a drug arm is defined as 'Regimen A + $drug_n$' and the regimen alone defined as 'Regimen A'.

METHODS

Criteria for considering studies for this review

Types of studies

Properly randomised controlled clinical trials (see 'Methodological quality of included studies').

Types of participants

1. Women diagnosed with advanced breast cancer in accordance with the following criteria:
   a. advanced breast cancer was defined as metastatic disease;
   b. women with loco-regional disease only were excluded*.
2. Women randomised to receive chemotherapy for advanced disease as first line treatment (i.e. no previous chemotherapy given except as adjuvant therapy).

We applied no age restrictions.

*We included trials which randomised both women with metastatic disease and women with loco-regionally recurrent disease but only if women with isolated loco-regional recurrence comprised less than 20% of the total group, or the trials stratified by stage so that metastatic disease data could be extracted.

Types of interventions

Intervention group:

(Regimen A + drug) A chemotherapy regimen of at least two cytotoxic drugs (Regimen A) plus the addition of one or more cytotoxic drugs (drug).

Comparator:

(Regimen A) Any chemotherapy regimen containing at least 2 cytotoxic drugs.

Following publication of the protocol, but prior to assessing trial eligibility, we decided to exclude sequential or alternating regimens which were defined as adding a drug to a regimen with a delay of more than five weeks (see table Characteristics of excluded studies: Aisner 1995 Cocconi 1999; Costanza 1999 Creagan 1984).

We included studies using endocrine therapy if both treatment groups received it.

Trials could specify or not specify recommended treatment upon disease progression/initial treatment failure.

Types of outcome measures

1. Overall survival.
2. Quality of life measures (trial specific instruments).
3. Progression-free survival (time to disease progression, death or both).
4. Tumour response (World Health Organization [WHO], Response Evaluation Criteria In Solid Tumours [RECIST] or individual protocol criteria).
5. Toxicity (WHO criteria or individual protocol based definition).
6. Time to treatment failure (treatment stopped due to progressive disease, toxicity or death).

Primary outcomes

1. Overall survival.

Secondary outcomes

1. Quality of life measures.
2. Progression-free survival.
3. Tumour response.
4. Toxicity.
5. Time to treatment failure.

Search methods for identification of studies

See: Breast Cancer Group methods used in reviews.

There will be no language restrictions on included studies and we will arrange to translate any potentially eligible studies if required.

Electronic searches

We will search the following databases:

(a) The Cochrane Breast Cancer Group's (CBCG's) Specialised Register and identify studies and code references as outlined in the CBCG's module (www.mrw.interscience.wiley.com/cochrane/clabout/articles/BREASTCA/frame.html). Trials coded with the key words 'advanced' and 'chemotherapy ' will be extracted and considered for inclusion in the review.

(b) EMBASE (via Embase.com) (2002 - August 2009).

(c) Pubmed (January 1966 - August 2009).

(d) 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 1 for details).

(e) Health on the Net Northern Ireland (HONNI) (January 1966 - August 2009) which is an Internet based search engine for worldwide journal articles provided by Queen's University Belfast.

We obtained a copy of the full article for each reference reporting a potentially eligible trial.

Searching other resources

(a) Bibliography Searching

We will try to identify further studies from reference lists of identified relevant trials, reviews and other related literature reviews (such as those by Fossati et al (Fossati 1998), and Stockler et al (Stockler 2000)). A copy of the full article for each reference reporting a potentially eligible trial will be obtained, where possible. Where this is not possible, attempts will be made to contact authors to provide additional information.

(b) Handsearching of Journals

We will search for abstracts published in scientific meetings relevant to metastatic breast cancer such as Proceedings of the American Assoication for Cancer Research and Symposium for Breast Cancer Research.

Data collection and analysis

We performed the analysis in accordance with the guidelines published in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 (Higgins 2008).

Selection of studies

At least two individuals applied the selection criteria (including the quality of randomisation) to each reference identified by the search strategy, masked to the study results. A third reviewer resolved any discrepancies regarding eligibility or quality. The types of studies selected were randomised controlled clinical trials. At least two groups needed to be included in the trial, one group needed a chemotherapy regimen of at least two cytotoxic drugs (Regimen A), the other group needed Regimen A with the addition of at least one new cytotoxic drug. Other criteria for selection required at least 80% of the study group to have metastatic breast cancer and the chemotherapy regimens needed to be first line.

Data extraction and management

Data were extracted directly from the trial publications by two individuals and entered into results tables using Review Manager 5.

We extracted the hazard ratio (HR) and associated variances directly from the trial publication/s. If not reported, we obtained these data indirectly using the methods described by Parmar 1998 et al, either using other available summary statistics or from data extracted from published Kaplan-Meier curves.

The pooled HR from the derived observed (O)-expected (E) number of events and the variance for each trial using the fixed-effect model (Yusuf 1985). The pooled HR represents the overall risk of an event on chemotherapy regimens with the addition of a drug versus control regimens (non-addition of a drug). We used Chi^2 tests to test for heterogeneity of trials (see the Cochrane Handbook for Systematic Reviews of Interventions Higgins 2008).

We analysed response rates as dichotomous variables (complete or partial versus stable disease or no response) and derived a pooled relative risk. As trialists generally report response for both randomised and assessable patients, we have done the same in this review.

We extracted toxicity data and added up the total number of WHO grade III or IV events and number at risk across trials. We

used these data to calculate a crude odds ratio (OR) (with 95% confidence intervals). Five trials did not utilise the WHO toxicity criteria, defining toxicity only as 'severe'. We decided to assume that trials which used the definition 'severe' assessed toxicity in the same manner as trials with toxicity WHO grade III or IV. We have, therefore, reported these toxicity data for WHO grade III and IV alone, and toxicity defined as 'severe' alone, and then all together as combined results. Following publication of the protocol and prior to data extraction, we decided to extract the total number of toxic events for leukopenia, nausea or vomiting and alopecia (hair loss) (see Table 2).

None of the studies included in this review reported quality of life data.

Assessment of risk of bias in included studies

We assessed risk of bias using the Cochrane Colloboration assessment tool (Table 8.5a, *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2008). The quality of six domains of risk of bias was assessed in each publication by two individuals. The domains were:

1. sequence generation;
2. allocation concealment;
3. blinding of participants, personnel and outcome assessors;
4. incomplete outcome data;
5. selective outcome reporting; and
6. other sources of bias such as comparability between groups.

We graded the quality of each domain as A - clearly adequate, B - possibly adequate, C - clearly inadequate (see table Characteristics of included studies). It was not possible to accurately assess all domains in most studies due to the lack of information in the published articles.

Measures of treatment effect

Treatment effect was measured by overall survival, percentage of patients achieving tumour response (partial or complete), incidence of toxicity and the mean time to treatment failure or tumour progression.

Unit of analysis issues

There were no issues regarding unit of analysis in most studies, however, Creech 1979 was a cross-over trial (cyclophosphamide, methotrexate, fluorouracil (CMF) patients crossed over to doxorubicin on progression).

Dealing with missing data

We used statistical models to allow for missing data, either using other available summary statistics or by extracting data from published Kaplan-Meier curves, as described by Parmar 1998. To allow for immature follow-up, we adjusted the numbers at risk based upon estimated minimum and maximum follow-up times. If these were not reported in any of the reports available, we estimated minimum follow-up using the estimated time taken to complete treatment, and maximum follow-up was estimated using the last event reported in the relevant time-to-event curve. We have recorded these follow-up estimates in the table Characteristics of included studies under "Notes". No attempt was made to contact trial investigators for additional information.

Assessment of heterogeneity

Heterogeneity was assessed formally using the Chi^2 test. There was significant heterogeneity for overall response of all trials (P heterogeneity = 0.03, I^2 = 42.1%). There was also observed significant heterogeneity in other overall response subgroups, however, no heterogeneity was observed in any time-to-event and toxic related death data.

Assessment of reporting biases

Reporting bias was assessed using the Cochrane Colloboration assessment tool (Table 8.5a, *Cochrane Handbook for Systematic Reviews of Interventions* Higgins 2008).

Data synthesis

We used a fixed-effect model for meta-analysis. Response rates were analysed as dichotomous variables and derived a pooled relative risk.

Subgroup analysis and investigation of heterogeneity

As outlined in the protocol, we extracted all of these outcomes, where available, from all trial publications. We completed pre-specified subgroup analysis for: (a) first line trials, (b) dose adjustment in addition of a drug arm, and (c) addition of a drug now considered less active (vincristine, dibromodulcitol and ICRF-159) compared to the addition of drugs considered more active (e.g. doxorubicin, cyclophosphamide and 5-fluorouracil). We did not carry out planned subgroup analysis by menopausal status, hormone receptor status and stage of disease, due to the lack of data available in the included trials for these subgroups.

We conducted the following post hoc subgroup analyses: addition of an anthracycline; and addition of one, or two or more, drugs to a regimen. We planned these analyses, prior to pooling of results, with one of the authors who is a medical oncologist (NW) who was blinded to results of individual studies and was not involved in eligibility assessment and data extraction. We provided NW with details of the drugs, dosages and schedules compared in each trial to determine a meaningful way to group the studies. We applied Chi^2 tests for interaction to these subgroup analyses.
No attempt was made to contact trial investigators for additional information.

Sensitivity analysis

All of the trials designated as eligible trials comprised women randomised to receive chemotherapy for metastatic disease as first line treatment. We conducted a sensitivity analysis for trials in which the line of treatment was not entirely clear (see table Characteristics of included studies). The sensitivity analysis demonstrated comparable results to those found in the primary analysis so we decided to include all trials in the primary analysis.

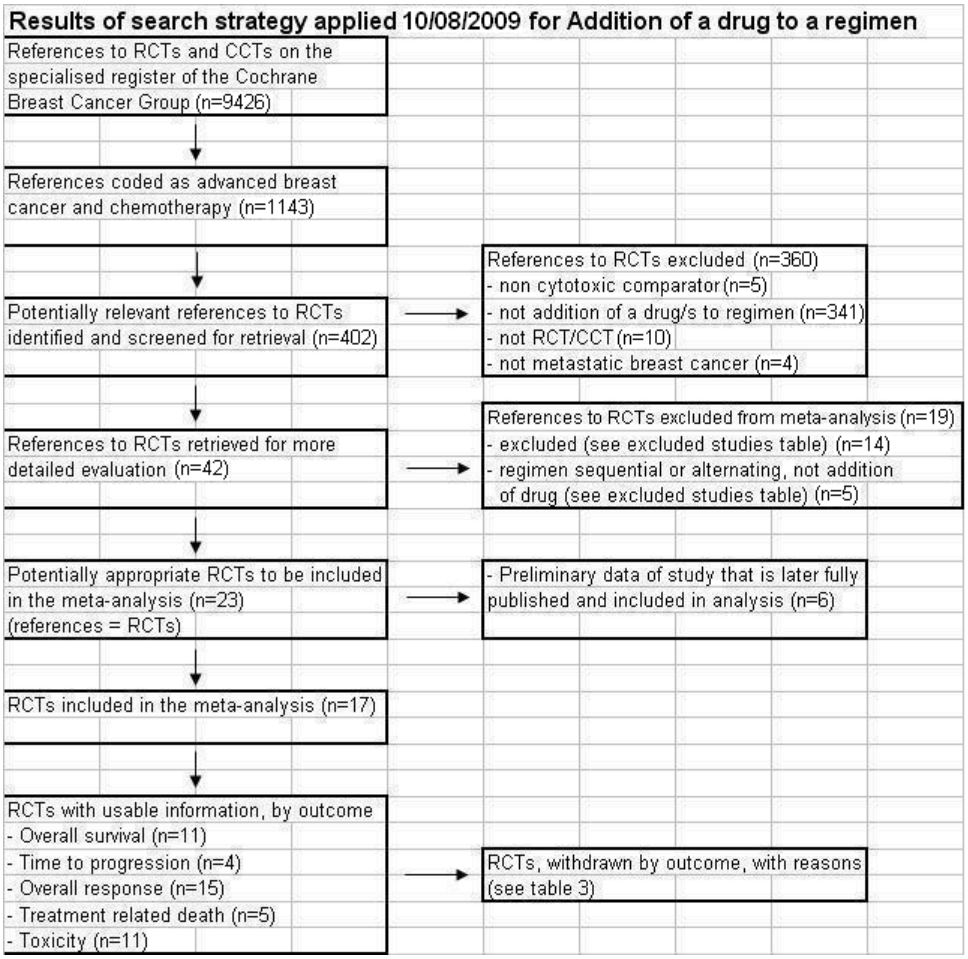
RESULTS

Description of studies

We searched the specialised register of the Cochrane Breast Cancer Group on 16 March 2009, with an updated search on 10 August 2009. Of the 9426 references included in the register, 1143 were coded as references to studies of chemotherapy and advanced breast cancer (Figure 1). Of these, 402 were references that reported the comparison of two different chemotherapy combinations in

metastatic breast cancer, of which 360 were not eligible for this review based on information in the abstract. We obtained the complete paper for 42 references; this led to the exclusion of a further 19 references, which we considered ineligible for the review (see table Characteristics of included studies). The remaining 23 references reported the results of 17 randomised trials; six of these references were the preliminary data of a trial that was later fully published and included in this review. The 17 eligible trials reported on 22 treatment comparisons summarised in Table 3. The trials included in the forest plots were labelled by primary author and date of publication.

Figure 1.

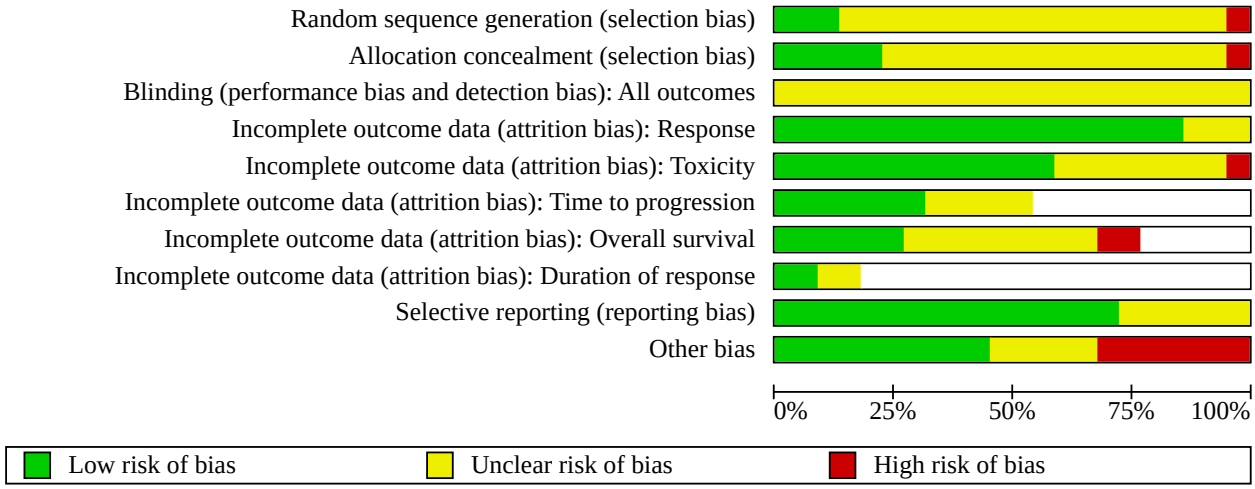


Where a trial included more than one comparison we labelled these alphabetically (a, b, c). Five of the included studies (Ahmann 1976a; Ahmann 1976b; Aisner 1987a; Aisner 1987b; Cavalli 1983a; Cavalli 1983b; Cummings 1981a; Cummings 1981b; Nemoto 1982a; Nemoto 1982b) published two or more comparisons that were included in this review (3-arm trials). In 3-arm trials (e.g. drugs CMFD versus CMF versus CMFV), comparisons of interest were arm 1 versus arm 2 for addition of drug D and arm 2 versus arm 3 for addition of drug V. To avoid double counting of patients in arm 2, the number of included patients in that arm was halved and the proportion with the outcome of interest was assumed to be the same in each half as that observed in the whole group. The exception to this method was for the Ahmann 1976a; Ahmann 1976b paper. The number of included patients in the arm to be halved was an odd number (N = 23), in this case the number of patients was rounded up (Ahmann 1976a, N = 12; Ahmann 1976b, N = 12 Forest plots 3.1 to 3.6).

Risk of bias in included studies

The 'Risk of bias' tables for each study are given in the table Characteristics of included studies. Figure 2 shows a summary of methodological quality as judged by the authors.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

Sequence generation was clearly reported in two trials (Aisner 1987a; Aisner 1987b; Marschke 1989), unclear in 14 trials (Ahmann 1976a; Ahmann 1976b; Cavalli 1983a Cavalli 1983b Chlebowski 1983 Creech 1979; Cummings 1981a; Cummings 1981b; Inoue 1984; Lokich 1977; Nemoto 1982a Nemoto 1982b Pannuti 1984 Rosner 1989 Segaloff 1985 Stein 1992 Tranum 1982 Vogel 1984 and inadequately generated in one trial (Kennealey 1978).

In this review, we graded one trial as having clearly adequate allocation concealment (grade A; Aisner 1987a; Aisner 1987b). We graded 15 trials as having possibly adequate allocation concealment and having good comparability of baseline characteristics and adequate reporting of outcomes (grade B; Ahmann 1976a; Ahmann 1976b Cavalli 1983a Cavalli 1983b Chlebowski 1983 Creech 1979 Cummings 1981a Cummings 1981b Inoue 1984 Lokich 1977 Marschke 1989 Nemoto 1982a; Nemoto 1982b; Pannuti 1984; Rosner 1989; Segaloff 1985; Stein 1992; Tranum 1982; Vogel 1984). One trial (Kennealey 1978) reported on randomised patients and non-randomised patient data. The data for both were pooled and it was not possible to distinguish between randomised and non-randomised patients for inclusion in this review (Table 4).

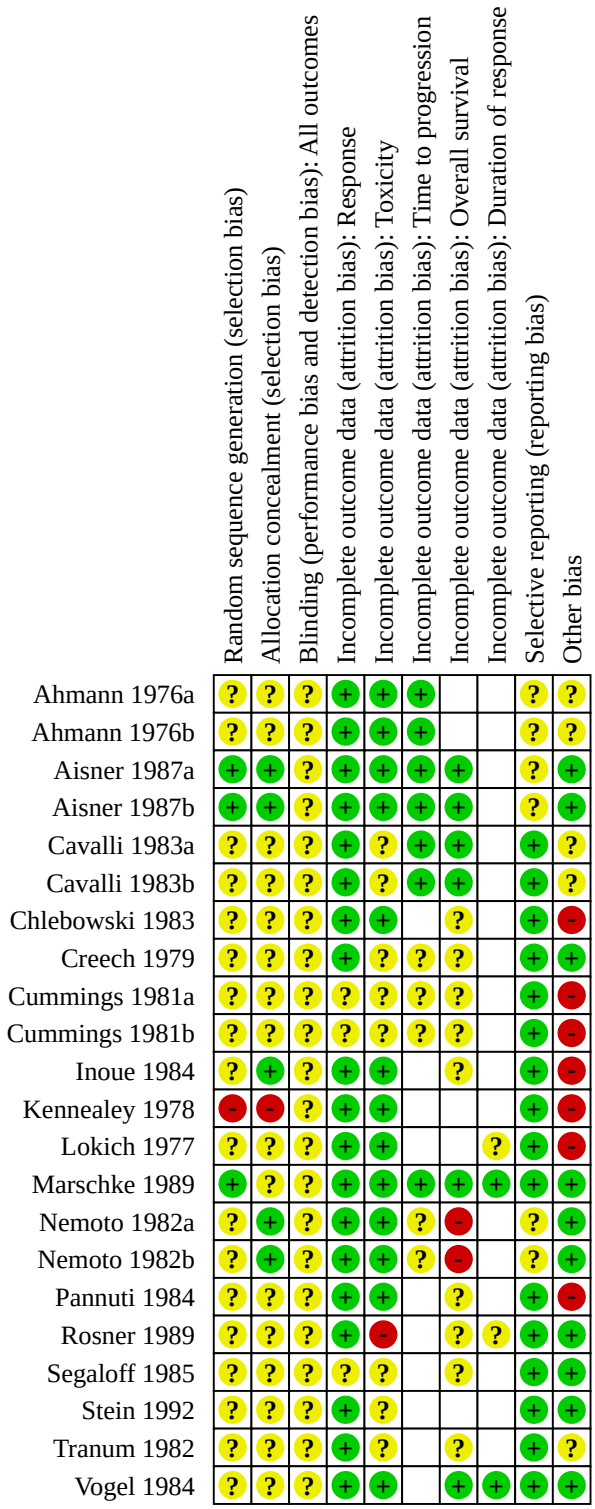
Blinding

For all trials, it was unclear as to whether there was blinding of study participants or outcome assessors.

Incomplete outcome data

Five trials displayed adequate completeness of all outcome data (Ahmann 1976a; Ahmann 1976b Aisner 1987a Aisner 1987b Kennealey 1978 Marschke 1989; Vogel 1984), however, in two trials it was unclear for all outcome data (Cummings 1981a Cummings 1981b Segaloff 1985). In the remaining trials the majority of outcomes had adequate completeness although there was at least one outcome in which it was unclear (Figure 3). One trial was inadequate for completeness of one outcome (Nemoto 1982a Nemoto 1982b): there was conflicting information in the paper clearly stating that all 126 patients had been included in analysis whereas the survival graph displayed 120 patients.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Selective reporting

In three trials (Ahmann 1976a; Ahmann 1976b Aisner 1987a Aisner 1987b Nemoto 1982a Nemoto 1982b) there was uncertainty regarding selective outcome reporting whereas the other 14 trials showed no evidence. Some trials had other sources of bias such as group variations in menopausal status (Chlebowski 1983 Cummings 1981b) and severity of metastatic disease (Inoue 1984 Lokich 1977).

Other potential sources of bias

All of the trials designated as eligible trials comprised women randomised to receive chemotherapy for metastatic disease as first line treatment. We conducted a sensitivity analysis for trials in which the line of treatment was not entirely clear (see table Characteristics of included studies). The sensitivity analysis demonstrated comparable results to those found in the primary analysis so we decided to include all trials in the primary analysis.

Effects of interventions

NOTE: ratios of treatment effects for time-to-event outcomes are reported so that hazard ratios (HRs) less than 1.0 favour the addition of one or more drugs to the regimen and values greater than 1.0 favour the control group (that is, the regimen alone). We have reported ratios of treatment effects for response so that odds ratio (OR) greater than 1.00 favour addition of one or more drugs to the regimen.

We have detailed results for the pooled data from all trials (with extractable data) first, followed by the four subgroup analyses. When interpreting the plots for all trials, readers may want to refer to the analyses plots 1.1, 2.1, 3.1 and 4.1, and plots 1.2 to 1.6, 2.2 to 2.6 and so on for the subgroup analyses.

Addition of one or more drugs to a regimen - all trials

The 17 trials (22 treatment comparisons) included in this review randomised 2674 women. Time-to-event data were extractable for overall survival from 11 trials (14 treatment comparisons, 79% of all patients randomised) and progression-free survival from four trials (six treatment comparisons, 34% of all patients randomised). Readers should interpret the results of the meta-analysis with this information in mind. Tumour response rates based on assessable patients were available for 15 trials (20 treatment comparisons, 82% of all patients randomised).

Overall survival - all trials

There were 1532 deaths in 2116* randomised women, we found no detectable difference in overall survival between the addition of one or more drugs to the regimen and control (the regimen alone). The overall HR was 0.96 (95% CI 0.87 to 1.07, P = 0.47) and we found no statistically significant heterogeneity (P heterogeneity = 0.89, I^2 = 0%) (Forest plot 1.1).

**There is conflicting information in Nemoto 1982, it is clearly stated that all 126 patients have been included in survival analysis, however, the graph displays N = 120. For the purposes of this review, N = 120 has been used for survival statistics from Nemoto 1982*

Time to progression - all trials

We found no difference in time to progression between these regimens, with an overall HR of 0.93 (95% CI 0.81 to 1.07, P = 0.31) and no statistically significant heterogeneity (P heterogeneity = 0.83, I^2 = 0%) (Forest plot 2.1).

Overall tumour response - all trials

Addition of one or more drugs to the regimen was favourably associated with overall tumour response rates in comparison to the control (OR 1.21, 95% CI 1.01 to 1.44, P = 0.04) although we observed statistically significant heterogeneity for this outcome across the trials (P heterogeneity = 0.04, I^2 = 40%) (Forest plot 3.1).

Toxicity - all trials

Treatment-related deaths were reported in three per cent of participants across the four trials (five treatment comparisons reporting on this outcome) (Forest plot 4.1). Of the 27 treatment-related deaths reported, eight occurred in the addition of a drug arm and eight occurred in the control arm, (OR 1.03, 95% CI 0.39 to 2.69, P = 0.96). It was not possible to identify the treatment arm for an additional 11 toxicity-related deaths.

Toxicity data were not reported consistently across the included trials. Of the 17 eligible trials, 10 provided extractable data on grade III or IV toxicity. Of these (Table 2), seven trials reported on leucopenia (1011 patients), four on hair loss (340 patients) and eight on nausea and vomiting (1119 patients). Overall, addition of a drug to a regimen appeared to be associated with increased likelihood of leucopenia (white blood cell count less than 2000 x 10^9/litre) (OR 1.51, 95% CI 1.17 to 1.95), severe nausea and vomiting (OR 1.76, 95% CI 1.25 to 2.46) and hair loss (OR 2.85, 95% CI 1.83 to 4.44) in assessable patients.

Quality of life data were not reported in any of the included studies in this review.

We completed funnel plots for all treatment comparisons. These plots did not demonstrate any obvious asymmetry, suggesting it is unlikely that publication bias is an issue in this review.

Sensitivity analysis: First line trials Thirteen trials (17 treatment comparisons) were clearly first line treatment for metastatic breast cancer, with seven of these reporting on time-to-event outcomes. We excluded four trials (Chlebowski 1983; Cummings 1981a; Cummings 1981b; Segaloff 1985; Vogel 1984) from this sensitivity analysis because it was not entirely clear that these were trials of first line treatment (reported in the table Characteristics of included studies). However, because of this uncertainty, it was not clear that these trials were definitely second line either; therefore, we have not excluded them from the overall analysis.

Overall survival - first line trials First line trials documented 840 deaths in 1229 randomised women. A statistically significant difference in survival was not evident between addition of one or more drugs to the regimen and control, with an overall HR of 0.95 (95% CI 0.82 to 1.09, P = 0.46) and no statistically significant heterogeneity (P heterogeneity = 0.69, I^2 = 0%) (Forest plot 1.2).

Time to progression - first line trials

We found no detectable difference in time to progression between these regimens (three comparisons, 465 patients), with an overall HR of 0.90 (95% CI 0.74 to 1.09, P = 0.29) and no statistically significant heterogeneity (P heterogeneity = 0.76, I^2 = 0%) (Forest plot 2.2).

Overall tumour response - first line trials

Addition of one or more drugs to the regimen had a significantly positive effect on overall tumour response (OR 1.38, 95% CI 1.14 to 1.68, P = 0.001) and no statistically significant heterogeneity was observed for this outcome across the trials (P heterogeneity = 0.21, I^2 = 22%) (Forest plot 3.2).

Toxicity - first line trials
There were three trials (four treatment comparisons) that reported treatment-related deaths. Of the 14 treatment-related deaths reported, seven occurred in the addition of a drug arm and seven occurred in the control arm, (OR 0.99, 95% CI 0.35 to 2.75, P = 0.98) (Forest plot 4.2).

The sensitivity analysis revealed that the results are consistent, both for all trials and for the sensitivity analysis which looks at first line trials only. Therefore, the analyses by subgroup is based on all included trials (17 trials; 22 treatment comparisons; 2674 randomised women).

Addition of a 'less active' versus 'more active' drug
We conducted this pre-specified subgroup analysis to investigate the treatment effect with the addition of a drug/s now considered less active (vincristine, dibromodulcitol and ICRF-159) compared to the addition of drug/s considered more active (e.g. doxorubicin, cyclophosphamide and 5-fluorouracil). The addition of less active drug/s was investigated in five trials (seven treatment comparisons, 1086 patients), four of which reported survival outcomes. The addition of more active drug/s was considered in 12 trials (14 treatment comparisons, 1524 patients).

Overall survival - 'less active' versus 'more active'
There were 653 deaths observed in 837 women randomised to trials where the additional drug to a regimen was a less active drug and time-to-event outcomes were reported. There was no detectable difference in overall survival between addition of a less active drug regimen and control, with a HR of 0.94 (95% CI 0.81 to 1.10, P = 0.47) and no statistically significant heterogeneity (P heterogeneity = 0.55, I^2 = 0%) (Forest plot 1.3).

Data from the eight trials (nine treatment comparisons) where the additional drug was more active, and where time-to-event outcomes were reported, revealed no detectable difference in overall survival (HR 0.98, 95% CI 0.85 to 1.12, P = 0.75) and no significant heterogeneity (P heterogeneity = 0.85, I^2 = 0%) (Forest plot 1.3).

A test for interaction between the two groups for overall survival revealed no significant interaction (P = 0.73).

Overall tumour response - 'less active' versus 'more active'
Addition of a less active drug to the regimen did not have a significant effect on overall tumour response in comparison to control (OR 1.03, 95% CI 0.74 to 1.43, P = 0.86), with no statistically significant heterogeneity (P heterogeneity = 0.11, I^2 = 44%) (Forest plot 3.3).

In comparison, the addition of a more active agent provided a significantly positive effect on overall tumour response (OR 1.34, 95% CI 1.09 to 1.65, P = 0.006). Heterogeneity was statistically significant for this outcome across the trials (P heterogeneity = 0.05, I^2 = 43%) (Forest plot 3.3).

A test for interaction between the two groups for overall response revealed no significant interaction (P = 0.21).

Due to the small number of trials that reported time to progression and toxicity data in this subgroup, we did not complete this analysis.

Dose adjustment present in the addition of a drug arm versus no dose adjustment
This pre-specified subgroup analysis investigated Regimen A versus Regimen A (same dose) plus additional cytotoxic drug/s, and also Regimen A versus Regimen A (lesser dose) plus addition cytotoxic drug/s. Dose adjustment in the addition of a drug arm occurred in nine trials (12 treatment comparisons, 1483 patients), seven of which (nine treatment comparisons) reported survival outcomes.

Overall survival - dose adjustment versus no dose adjustment
There were 982 deaths observed in 1401 randomised women in trials with adjustment of dose in the addition of a drug arm. No detectable difference in survival was observed in these patients, with an overall HR of 0.94 (95% CI 0.83 to 1.07, P = 0.36) and no statistically significant heterogeneity (P heterogeneity = 0.86, I^2 = 0%) (Forest plot 1.4).

There were 550 deaths in 715 women randomised in trials which did not adjust the dose of the agents in the addition of a drug arm. Similarly, no detectable difference in survival was observed in these patients in comparison to control (HR 1.00, 95% CI 0.84 to 1.18, P = 1.00) with no statistically significant heterogeneity (P heterogeneity = 0.56, I^2 = 0%) (Forest plot 1.4).

A test for interaction between the two groups for overall survival revealed no significant interaction (P = 0.58).

Overall tumour response - dose adjustment versus no dose adjustment
When the dose of a regimen was adjusted with the addition of a cytotoxic drug/s, a conventionally significant effect on overall tumour response was demonstrated (OR 1.27, 95% CI 1.01 to 1.58, P = 0.04), with no significant heterogeneity observed (P heterogeneity = 0.13, I^2 = 33%) (Forest plot 3.4).

In comparison, when no dose adjustment was present, no detectable effect on overall tumour response was observed (OR 1.10, 95% CI 0.81 to 1.50, P = 0.54), however, significant heterogeneity was observed for this outcome across the trials (P heterogeneity = 0.05, I^2 = 50%) (Forest plot 3.4).

A test for interaction between the two groups for overall response revealed no significant interaction (P = 0.46).

Toxicity and time to progression analysis was not appropriate due to the small number of trials that reported these outcomes in this subgroup.

Addition of an anthracycline versus addition of a non-anthracycline
We conducted post hoc subgroup analyses to investigate the treatment effect with the addition of an anthracycline. The addition of an anthracycline was investigated in five trials (352 patients), three of which reported survival outcomes.

Overall survival - addition of an anthracycline
There were 144 deaths observed in 193 women randomised to 3 of the 5 trials where the addition of a drug/s included an anthracycline and time-to-event outcomes were reported. There was no detectable difference in overall survival between anthracycline-containing regimens and control (HR 0.87, 95% CI 0.61 to 1.24, P = 0.44) and no statistically significant heterogeneity (P heterogeneity = 0.63, I^2 = 0%) (Forest plot 1.5).

Data from the 10 trials (11 treatment comparisons) where the drug added was a non-anthracycline and where time-to-event data was reported, revealed no detectable difference in overall survival (HR 0.97, 95% CI 0.87 to 1.08, P = 0.60) and no statistically significant heterogeneity (P heterogeneity = 0.82, I^2 = 0%) (Forest plot 1.5).

A test for interaction between the two groups for overall survival revealed no significant interaction (P = 0.55).

Overall tumour response - addition of an anthracycline

Addition of an anthracycline drug to a regimen had a significantly positive effect on overall tumour response in comparison to control (OR 1.87, 95% CI 1.22 to 2.86, P = 0.004). There was no statistically significant heterogeneity (P heterogeneity = 0.15, I^2 = 41.0% (Forest plot 3.5).

In comparison, the addition of a non-anthracycline did not have a statistically significant effect on overall tumour response (OR 1.13, 95% CI 0.94 to 1.37, P = 0.20) with no significant heterogeneity observed for this outcome across the trials (P heterogeneity = 0.06, I^2 = 39%) (Forest plot 3.5).

A test for interaction for overall tumour response reveals significant interaction (P = 0.04). This suggests that the addition of an anthracycline has a greater effect on tumour response in those trials randomising patients to addition of an anthracycline to the regimen, in comparison to randomising patients to the addition of a non-anthracycline.

Toxicity and time to progression analysis was not appropriate due to the small number of trials that reported these outcomes in this subgroup.

Addition of one drug versus the addition of two or more drugs

We conducted post hoc subgroup analyses to investigate the treatment effect with the addition of one drug in comparison to the addition of two or more drugs. The addition of only one drug was investigated in 13 trials (17 treatment comparisons, 2301 patients), of which eight reported survival outcomes.

Overall survival - addition of one drug versus the addition of two or more drugs

There were 1754 women randomised to the addition of one drug to the regimen trials, 1269 deaths were observed in this group with no detectable difference in overall survival observed (HR 0.95, 95% CI 0.85 to 1.06, P = 0.35) and no statistically significant heterogeneity (P heterogeneity = 0.73, I^2 = 0%) (Forest plot 1.6).

There were 263 deaths in 362 women randomised to trials of the addition of two or more drugs to the regimen, with an overall HR of 1.05 (95% CI 0.81 to 1.35, P = 0.73) and no statistically significant heterogeneity (P heterogeneity = 0.88, I^2 = 0%) (Forest plot 1.6).

A test for interaction between the two groups for overall survival reveals no significant interaction (P = 0.49).

Overall tumour response - addition of one drug versus the addition of two or more drugs

The addition of one drug to the regimen in comparison to the regimen alone, had a significant impact on overall tumour response (OR 1.22, 95% CI 1.01 to 1.48, P = 0.04), with no significant heterogeneity observed (P heterogeneity = 0.17, I^2 = 25%). (Forest plot 3.6).

In comparison, the addition of two or more drugs to the regimen (in comparison to the regimen alone) did not have a significant effect on tumour response (OR 1.12, 95% CI 0.70 to 1.81, P = 0.64), and statistically significant heterogeneity was observed (P heterogeneity = 0.01, I^2 = 73%). (Forest plot 3.6).

A test for interaction between the two groups for overall response reveals no significant interaction (P = 0.69).

Due to the small number of trials that reported time to progression and toxicity in this subgroup, we did not complete this analysis.

DISCUSSION

This review did not find a statistically significant benefit in overall survival or time to progression for the addition of one or more drugs to the regimen over control (that is, the regimen alone) in the first line treatment of metastatic breast cancer.

Despite the lack of evidence of a survival or time to progression benefit, this review demonstrated that addition of one or more drugs to the regimen provided a statistically significant advantage in tumour response compared to control. All eligible trials provided response data for 2101 assessable patients, for an OR of 1.21 (95% CI 1.01 to 1.44, P = 0.04). The favourable effect on response was consistent and statistically significant in regimens where an anthracycline was used as an additional agent (five treatment comparisons; 352 patients) which is consistent with an earlier review of 33 trials (5284 patients) (Lord 2004). This favourable effect on response was also observed in exploratory subgroup analysis with addition of a drug considered 'more active' (such as 5-fluorouracil and anthracyclines) (14 treatment comparisons; 1518 patients), dose adjustment in the addition of a drug arm (12 treatment comparisons, 1483 patients) and in trials that added just one agent to a regimen (16 comparisons, 1772 patients).

Such a benefit in response rate, however, comes at the cost of toxicity. Where measured, acute toxicities such as alopecia, nausea and vomiting and leucopenia were more common with the addition of a drug.

This review includes 22 clinically diverse regimens, which differ in dose, activity and potency (e.g. the addition of vincristine versus the addition of doxorubicin). Despite this diversity, there is a significant benefit in overall response rates with the addition of drug/s to the regimen. We observed statistically significant heterogeneity for overall response of all trials (P heterogeneity = 0.04, I^2 = 40%). We also observed significant heterogeneity in other overall response subgroups; however, no heterogeneity was observed in any time-to-event and toxic related death data.

It must be noted that many of the trials included in this review are not recent, and, therefore, new drug groups such as the addition of a taxane to a regimen have not been explored in this review. We found no recent research matching the eligibility study criteria for this review. Such research has been considered, and the addition of a taxane to a single agent regimen was examined in Ghersi 2004 et al.

The subgroup analyses lead to speculation about what type of drug may be beneficial in the addition of a drug regimen. The results of subgroup analysis suggest that adding a drug or drugs to a regimen produces a positive impact on tumour response. This may, in fact,

be primarily due to the addition of an anthracycline, the addition of a more active drug and the addition of one drug only.

Addition of one or more drugs to a regimen does not have a positive impact on survival or time to response. If the addition of drugs to the regimen (such as those added) does not appear to benefit overall survival, the same clinical effect may potentially be achieved by administering three drugs all at once (A+B+C), as by administering them over time (A, then over time B, then over time C). The results of this review, however, do not answer this question with confidence. Furthermore, there is a lack of papers with quality of life and toxicity data. The results and limitations of this review demonstrate the necessity for further research in this field. This review will be updated as and when trials using current therapies are completed, at this stage the authors are not aware of such trials being conducted. More research is required in this area to fully understand the benefit, or lack thereof, of the addition of drugs to the regimen in order to understand the overall question of chemotherapy intensity for the treatment of metastatic breast cancer.

AUTHORS' CONCLUSIONS

Implications for practice

Addition of one or more drugs to the regimen does not provide a survival benefit compared to control (the regimen alone), nor does addition of one or more drugs to the regimen have a positive impact on time to progression. The addition of a drug/s to the regimen does produce a benefit in overall response in comparison to control (the regimen alone), but this benefit needs to be considered against the increased risk of toxicity.

Implications for research

We did not examine sequential therapy and alternating therapy in this review. A review of trials which examine the addition of a drug in a sequential or alternating regimen in the treatment of metastatic breast cancer may provide further information as to the benefit of addition of one or more drugs to the regimen.

ACKNOWLEDGEMENTS

We would like to thank Nicole Holcroft for her work in the identification of studies through the Cochrane Breast Cancer Group's specialised register. We would also like to thank Sharon Parker for her work editing and revising this review. We also acknowledge the initial contribution made to the original concept for this review by Craig Henderson, Kathleen Pritchard, Martin Tattersall, Martin Stockler, Christine Brunswick, Roldano Fossati, Russell Basser, Franco Nole and Alessandro Liberati. We would also like to thank Stephane Heritier for providing statistical guidance.

REFERENCES

References to studies included in this review

Ahmann 1976a *{published data only}*

* Ahmann DL, O'Connell MJ, Bisel HF. An evaluation of Cytoxan/Adriamycin (CA) vs. Cytoxan/Adriamycin/5-Fluorouracil (CAF) vs. Cytoxan/5-Fluorouracil/Prednisone (CFP) in advanced breast cancer. In: Proceedings of the American Association for Cancer Research. Vol. 17. 1976:278.

Ahmann 1976b *{published data only}*

* Ahmann DL, O'Connell MJ, Bisel HF. An evaluation of Cytoxan/Adriamycin (CA) vs. Cytoxan/Adriamycin/5-Fluorouracil (CAF) vs. Cytoxan/5-Fluorouracil/Prednisone (CFP) in advanced breast cancer. In: Proceedings of the American Association for Cancer Research. Vol. 17. 1976:278.

Aisner 1987a *{published data only}*

* Aisner J, Weinberg V, Perloff M, Weiss R, Perry M, Korzun A, et al. Chemotherapy versus chemoimmunotherapy (CAF v CAFVP v CMF each +/- MER) for metastatic carcinoma of the breast: a CALGB study. Cancer and Leukemia Group B. *Journal of Clinical Oncology* 1987;**5**(10):1523-33.

Aisner 1987b *{published data only}*

* Aisner J, Weinberg V, Perloff M, Weiss R, Perry M, Korzun A, et al. Chemotherapy versus chemoimmunotherapy (CAF v CAFVP v CMF each +/- MER) for metastatic carcinoma of the breast: a CALGB study. Cancer and Leukemia Group B. *Journal of Clinical Oncology* 1987;**5**(10):1523-33.

Cavalli 1983a *{published data only}*

Cavalli F, Pedrazzini A, Martz G, Jungi WF, Brunner KW, Goldhirsch A, et al. Randomized trial of 3 different regimens of combination chemotherapy in patients receiving simultaneously a hormonal treatment for advanced breast cancer. *European Journal of Cancer and Clinical Oncology* 1983;**19**(11):1615-24.

Cavalli 1983b *{published data only}*

Cavalli F, Pedrazzini A, Martz G, Jungi WF, Brunner KW, Goldhirsch A, et al. Randomized trial of 3 different regimens of combination chemotherapy in patients receiving simultaneously a hormonal treatment for advanced breast cancer. *European Journal of Cancer and Clinical Oncology* 1983;**19**(11):1615-24.

Chlebowski 1983 *{published data only}*

* Chlebowski RT, Pugh R, Weiner JM, Block JB, Bateman JR. Doxorubicin and CCNU with or without vincristine in patients with advanced refractory breast cancer. A randomized trial. *Cancer* 1983;**52**(4):606-9.

Chlebowski RT, Pugh R, Weiner JM, Block JB, Bateman JR. Influence of vincristine on survival in advanced refractory breast cancer. *Breast Cancer Research and Treatment* 1981;**1**(1):171.

Creech 1979 *{published data only}*

Creech R, Harris D, Grotzinger P, Engstrom P. Low dose therapy of metastatic breast cancer with CAMF vs. sequential CMF and adriamycin. Proceedings of the American Association for Cancer Research 1977;**Mar 16-17**:300.

Creech R, Holroyde C, Catalano R, Koons L, Miller D, Engstrom P. Low dose CMF vs. CAMF treatment for metastatic breast cancer. Proceedings of the American Association for Cancer Research 1976;**17**:259.

* Creech RH, Catalano RB, Harris DT, Engstrom PF, Grotzinger PJ. Low dose chemotherapy of metastatic breast cancer with cyclophosphamide, adriamycin, methotrexate, 5-fluorouracil (CAMF) versus sequential cyclophosphamide, methotrexate, 5-fluorouracil (CMF) and adriamycin. *Cancer* 1979;**43**:51-9.

Cummings 1981a *{published data only}*

Cummings FJ, Gelman R, Tormey DC, DeWys W, Glick J. Adriamycin plus vincristine alone or with dibromodulcitol or ICRF-159 in metastatic breast cancer. *Cancer Clinical Trials* 1981;**4**:253-60.

Cummings 1981b *{published data only}*

Cummings FJ, Gelman R, Tormey DC, DeWys W, Glick J. Adriamycin plus vincristine alone or with dibromodulcitol or ICRF-159 in metastatic breast cancer. *Cancer Clinical Trials* 1981;**4**:253-60.

Inoue 1984 *{published data only}*

Inoue K, Ogawa M, Inagaki J, Horikoshi N, Miyamoto H, Ikeda K, et al. A randomized trial of adriamycin, cyclophosphamide, ftorafur (ACF) and adriamycin, cyclophosphamide, ftorafur, methotrexate (ACFM) in patients with advanced breast cancer. *Cancer Chemotherapy and Pharmacology* 1984;**13**:95-9.

Kennealey 1978 *{published data only}*

Kennealey GT, Boston B, Mitchell MS, Knobf MK, Bobrow SN, Pezzimenti JF, et al. Combination chemotherapy for advanced breast cancer: two regimens containing adriamycin. *Cancer* 1978;**42**(1):27-33.

Lokich 1977 *{published data only}*

Lokich JJ, Skarin AT, Mayer RJ, Henderson IC, Blum RH, Frei E. Adriamycin plus alkylating agents in the treatment of metastatic breast cancer. *Cancer* 1977;**40**(6):2801-5.

Marschke 1989 *{published data only}*

Marschke RF Jr, Ingle JN, Schaid DJ, Krook JE, Mailliard JA, Cullinan SA, et al. Randomized clinical trial of CFP versus CMFP in women with metastatic breast cancer. *Cancer* 1989;**63**(10):1931-7.

Nemoto 1982a *{published data only}*

Horton J, Dao T, Cunningham T, Nemoto T, Sponzo R, Rosner D, et al. Alternating combination therapy for metastatic breast cancer. Proceedings of the American Association for Cancer Research 1976;**17**:247.

* Nemoto T, Horton J, Simon R, Dao TL, Rosner D, Cunningham T, et al. Comparison of four-combination chemotherapy programs in metastatic breast cancer:

comparison of multiple drug therapy with cytoxan, 5-FU and prednisone versus cytoxan and adriamycin, versus cytoxan, 5-FU and adriamycin, versus cytoxan, 5-FU and prednisone alternating with cytoxan and adriamycin. *Cancer* 1982;**49**(10):1988-93.

Nemoto 1982b *{published data only}*

Nemoto T, Horton J, Simon R, Dao TL, Rosner D, Cunningham T, et al. Comparison of four-combination chemotherapy programs in metastatic breast cancer: comparison of multiple drug therapy with cytoxan, 5-FU and prednisone versus cytoxan and adriamycin, versus cytoxan, 5-FU and adriamycin, versus cytoxan, 5-FU and prednisone alternating with cytoxan and adriamycin. *Cancer* 1982;**49**(10):1988-93.

Pannuti 1984 *{published data only}*

Pannuti F, Iafelice G, Martoni A, Fruet F, Angelelli B, Casadei M. A new six-drug antiblastic regimen (R 14) at low doses (micropolychemotherapy) compared to CMF in the treatment of metastatic breast cancer: phase III study. *Chemioterapia* 1984;**3**(4):216-9.

Rosner 1989 *{published data only}*

* Rosner D, Lane WW, Nemoto T. Differential response to chemotherapy in metastatic breast cancer in relation to estrogen receptor level. Results of a prospective randomized study. *Cancer* 1989;**64**(1):6-15.

Rosner D, Nemoto T, Lane WW. A randomized study of intensive versus moderate chemotherapy programs in metastatic breast cancer. *Cancer* 1987;**59**(5):874-83.

Segaloff 1985 *{published data only}*

Segaloff A, Hankey BF, Carter AC, Escher GC, Ansfield FJ, Talley RW. An evaluation of the effect of vincristine added to cyclophosphamide, 5-fluorouracil, methotrexate, and prednisone in advanced breast cancer. *Breast Cancer Research and Treatment* 1985;**5**(3):311-9.

Stein 1992 *{published data only}*

Stein RC, Bower M, Law M, Bliss JM, Barton C, Gazet JC, et al. Mitozantrone and methotrexate chemotherapy with and without mitomycin C in the treatment of advanced breast cancer: a randomised clinical trial. *European Journal of Cancer* 1992;**28A**(12):1963-5.

Tranum 1982 *{published data only}*

Tranum B. Treatment of advanced breast cancer: A 3-arm prospective study. Proceedings of the American Association for Cancer Research 1977;**Mar 16-17**:274.

* Tranum BL, McDonald B, Thigpen T, Vaughn C, Wilson H, Maloney T, et al. Adriamycin combinations in advanced breast cancer. A Southwest Oncology Group Study. *Cancer* 1982;**49**(5):835-9.

Vogel 1984 *{published data only}*

Vogel CL, Smalley RV, Raney M, Krauss S, Carpenter J, Velez Garcia E, et al. Randomized trial of cyclophosphamide, doxorubicin, and 5- fluorouracil alone or alternating with a "cycle active" non-cross-resistant combination in women with visceral metastatic breast cancer: a Southeastern Cancer Study Group project. *Journal of Clinical Oncology* 1984;**2**:643-51.

References to studies excluded from this review

Ahmann 1974a *{published data only}*

Ahmann DL, Bisel HF, Hahn RG. Phase II clinical trial of isophosphamide (NSC-109724) in patients with advanced breast cancer. *Cancer Chemotherapy Reports - Part 1* 1974;**58**(6):861-5.

Ahmann 1974b *{published data only}*

Ahmann DL, Bisel HF, Eagan RT, Edmonson JH, Hahn RG. Controlled evaluation of adriamycin (NSC-123127) in patients with disseminated breast cancer. *Cancer Chemotherapy Reports* 1974;**58**(6):877-82.

Ahmann 1975 *{published data only}*

Ahmann DL, Bisel HF, Hahn RG, Eagan RT, Edmonson JH, Steinfeld JL, et al. An analysis of a multiple-drug program in the treatment of patients with advanced breast cancer utilizing 5-fluorouracil, cyclophosphamide, and prednisone with or without vincristine. *Cancer* 1975;**36**(6):1925-35.

Aisner 1981 *{published data only}*

Aisner J, Weinberg V, Perloff M, Weiss R, Raich P, Perry M, et al. Chemoimmunotherapy for advanced breast cancer: A randomized comparison of 6 combinations (CMF, CAF vs CAFVP) each with or without MER immunotherapy. A CALGB study. In: Proceedings of the American Association of Cancer Research. 1981:C-433.

Aisner 1995 *{published data only}*

Aisner J, Cirricione C, Perloff M, Perry M, Budman D, Abrams J, et al. Combination chemotherapy for metastatic or recurrent carcinoma of the breast - A randomised phase III trial comparing CAF versus VATH versus VATH alternating with CMFVP: Cancer and Leukemia Group B study 8281. *Journal of Clinical Oncology* 1995;**13**(6):1443-52.

Brown 1976 *{published data only}*

Brown I, Ward HW. Doxorubicin in the treatment of advanced breast cancer; comparative studies of three combination chemotherapy regimes. *Clinical Oncology* 1976;**2**(2):105-11.

Brown 1977 *{published data only}*

Brown I, Arthur K, Banks AJ, Bond WH, Chowdhury MS, Freeman WE, et al. The polychemotherapeutic treatment of advanced breast cancer. *Clinical Oncology* 1977;**3**(2):183-9.

Cocconi 1990 *{published data only}*

Cocconi G, Bisagni G, Bacchi M, Buzzi F, Canaletti R, Carpi A, et al. A comparison of continuation versus late intensification followed by discontinuation of chemotherapy in advanced breast cancer. A prospective randomized trial of the Italian Oncology Group for Clinical Research (G.O.I.R.C.). *Annals of Oncology* 1990;**1**(1):36-44.

Cocconi 1999 *{published data only}*

Cocconi G, Bisagni G, Bella M, Acito L, Anastasi P, Carpi A, et al. Comparison of CMF (cyclophosphamide, methotrexate and 5-fluorouracil) with a rotational crossing and a sequential

intensification regimen in advanced breast cancer. A prospective randomised study. *American Journal of Clinical Oncology* 1999;**22**(6):593-600.

Costanza 1999 *{published data only}*

Costanza ME, Korzun AH, Norton L, Rice MA, Wood WC. A fair trial for trimetrexate (TMTX) in advanced breast cancer. In: Breast cancer research and treatment. Vol. 12. 1988:125.

* Costanza ME, Weiss RB, Henderson C, Norton L, Berry DA, Cirricione C, et al. Safety and efficacy of using a single agent or a phase II agent before instituting standard combination chemotherapy in previously untreated metastatic breast cancer patients: report of a randomised study - Cancer and Leukemia Group B 8642. *Journal of Clinical Oncology* 1999;**17**(5):1397-1406.

Creagan 1984 *{published data only}*

Creagan ET, Green SJ, Ahmann DL, Ingle JN, Edmonson JH, Marschke RF. A phase III clinical trial comparing the combination cyclophosphamide, adriamycin, cisplatin with cyclophosphamide, 5-fluorouracil, prednisone in patients with advanced breast cancer. *Journal of Clinical Oncology* 1984;**2**(11):1260-5.

Horton 1975 *{published data only}*

Horton J, Dao T, Cunningham T, Nemoto T, Sponzo R, Rosner D. A comparison of 4 combination chemotherapies for metastatic breast cancer. Proceedings of the American Association for Cancer Research 1975;**16**:240.

Milano 1985 *{published data only}*

Milano G, Thyss A, Caldani C, Renée N, Buray L, Lesbats G, et al. Treatment of human carcinoma by alpha-difluoromethylornithine: Effect on polyamine levels. *Journal of Experimental and Clinical Cancer Research* 1985;**4**:25-30.

Mukaiyama 1989 *{published data only}*

Mukaiyama T, Ogawa M, Horikoshi N, Inoue K, Tada A, Ueno K, et al. [A randomized trial comparing ACF (adriamycin, cyclophosphamide, ftorafur) and ACF/MVMF (mitomycin C, vincristine, methotrexate, ftorafur)--a non-cross-resistant alternating chemotherapy of recurrent and advanced breast cancer]. [Japanese]. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]* 1989;**16**(3 Pt 1):327-32.

Priestman 1975 *{published data only}*

Priestman TJ. Results of a prospective clinical trial comparing two cytotoxic regimes containing adriamycin in women with advanced breast cancer. *Clinical Oncology* 1975;**1**(3):207-11.

Saeki 2007 *{published data only}*

Saeki T, Nomizu T, Toi M, Ito M, Noguchi S, Kobayashi T, et al. Dofequidar fumarate (MS-209) in combination with cyclophosphamide, doxorubicin, and fluorouracil for patients with advanced recurrent breast cancer. *Journal of Clinical Oncology* 2007;**25**(4):411-7.

Venturino 2000 *{published data only}*

Venturino A, Comandini D, Simoni C, Merlini L, Naso C, Palumbo R, et al. Is salvage chemotherapy for metastatic breast cancer always effective and well tolerated? A phase II randomized trial of vinorelbine versus 5-fluorouracil plus leucovorin versus combination of mitoxantrone, 5-fluorouracil plus leucovorin. *Breast Cancer Research and Treatment* 2000;**60**(3):195-200.

Von Minckwitz 2005 *{published data only}*

Von Minckwitz G, Chernozemsky I, Sirakova L, Chilingirov P, Souchon R, Marschner N, et al. Bendamustine prolongs progression-free survival in metastatic breast cancer (MBC): a phase III prospective, randomized, multicentre trial of bendamustine hydrochloride, methotrexate and 5-fluorouracil (BMF) versus cyclophosphamide, methotrexate and 5-fluorouracil (CMF) as first-line treatment of MBC. *Anti-Cancer Drugs* 2005;**16**(8):871-7.

Zhao 1986 *{published data only}*

Zhao TP, Ding GX, Gao HY, Shen ZZ, Li KY. A clinical trial of homoharringtonine in the treatment of advanced breast cancer. *Tumori* 1986;**72**:395-8.

Additional references

Carrick 2005

Carrick S, Parker S, Wilcken N, Ghersi D, Marzo M, Simes J. Single agent versus combination chemotherapy for metastatic breast cancer. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No: CD003372. [DOI: 10.1002/14651858.CD003372.pub2]

Esteva 2001

Esteva FJ, Valero V, Pusztai L, Boehnke-Michaud L, Buzdar AU, Hortobagyi GN. Chemotherapy of metastatic breast cancer: What to expect in 2001 and beyond. *The Oncologist* 2001;**6**(2):133-46.

Ferlay 2004

Ferlay J, Bray F, Pisani P, Parkin DM. Cancer incidence, mortality and prevalence worldwide. GLOBOCAN, version 2.0;**IARC CancerBase No. 5. Lyon, IARCPress, 2004: http://www-dep.iarc.fr/globocan/globocan.html**.

Fossati 1998

Fossati R, Confalonierir C, Torri V, Ghislandi E, Penna A, Pistotti V, et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. *Journal of Clinical Oncology* 1998;**16**(10):3439-60.

Ghersi 2004

Ghersi D, Wilcken N, Simes J, Donoghue E. Taxane containing regimens for metastatic breast cancer. *Cochrane Database of Systematic Reviews* 2004, Issue 3. Art. No: CD003366. [DOI: 10.1002/14651858.CD003366.pub2]

Hamilton 2005

Hamilton A, Hortobagyi G. Chemotherapy: What progress in the last 5 years? *Journal of Clinical Oncology* 2005;**23**(8):1760-75.

Higgins 2008

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Chichester: John Wiley & Sons, 2008.

Hryniuk 1987

Hryniuk WA, Figueredo A, Goodyear M. Applications of dose intensity to problems in chemotherapy of breast and colorectal cancer. *Seminars in Oncology* 1987;**11**(Suppl 4):3-11.

Lord 2004

Lord S, Ghersi D, Gattellari M, Wortley S, Wilcken N, Simes J. Antitumour antibiotic containing regimens for metastatic breast cancer. *Cochrane Database of Systematic Reviews* 2004, Issue 4. Art. No: CD003367. [DOI: 10.1002/14651858.CD003367.pub2]

Parmar 1998

Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**:2815-34.

Stockler 2000

Stockler M, Wilcken NRC, Ghersi D, Simes RJ. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treatment Reviews* 2000;**26**:151-68.

Yusuf 1985

Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction: an overview of the randomized trials. In: Progress in Cardiovascular Diseases. Vol. 27. 1985:335-71.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ahmann 1976a

Study characteristics	
Methods	Accrual dates: not reported Sample size: 68 USA Randomisation method: not reported Baseline comparability: not reported
Participants	Female % first line not reported unclear % metastatic breast cancer (MBC) (72% had visceral dominant disease) Age and ethnicity not stated
Interventions	AC vs CFP vs CAF (+/- calusterone) Arm 1: (AC) doxorubicin + cyclophosphamide Arm 2: (CFP) cyclophosphamide + 5-fluorouracil + prednisone Arm 3: (CAF) cyclophosphamide + doxorubicin + 5-fluorouracil Ahmann 1976a = AC vs CAF
Outcomes	Regression (defined as ≥ 50% reduction in tumour mass) Mean response duration Toxicity
Notes	Abstract only available Reports on 68/68 randomised patients Toxicity related death not reported Doses of the same chemotherapy agent are reduced in the addition of a drug arm

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear

Ahmann 1976a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Time to progression	Low risk	A - Adequate
Selective reporting (reporting bias)	Unclear risk	B - Unclear
Other bias	Unclear risk	B - Unclear

Ahmann 1976b

Study characteristics		
Methods	As for Ahmann 1976a	
Participants	As for Ahmann 1976a	
Interventions	Ahmann 1976b = CF (with Prednisone) vs CAF	
Outcomes	As for Ahmann 1976a	
Notes	As for Ahmann 1976a	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate

Ahmann 1976b *(Continued)*

Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Time to progression	Low risk	A - Adequate
Selective reporting (reporting bias)	Unclear risk	B - Unclear
Other bias	Unclear risk	B - Unclear

Aisner 1987a

Study characteristics	
Methods	Accrual dates October 1976 to February 1980 Multicentre national trial (USA) Sample size: 432 Randomisation by sealed envelope using a Latin square design balancing across and within institutions. Baseline comparability: No significant imbalance apparent or reported
Participants	Female Over 80% had visceral or osseous metastatic disease 100% first line Median age: 57 (CAF), 55 (CAFVP)
Interventions	CAF vs CMF vs CAFVP vs CAF+MER vs CMF+MER vs CAFVP+MER Arm I: (CAF) cyclophosphamide + doxorubicin + 5-fluorouracil Arm II: (CAFVP) cyclophosphamide + doxorubicin + fluorouracil + vincristine + prednisone Arm III: (CMF) cyclophosphamide + 5-fluorouracil + methotrexate Arm IV, V, VI as above each with the addition of MER Aisner 1987a: CAF vs CAFVP
Outcomes	Overall survival Time to treatment failure Response Toxicity
Notes	395/432 evaluable. 37 patients were unevaluable: ineligible (20), protocol violations (10), early deaths (4), inadequate records (2), improper randomisation(1) 6 arm trial. Randomisation to chemoimmunotherapy ceased after an interim evaluation showed no benefit & increased toxicity. Analysis was conducted using 395 evaluable patients (260/283 patients randomised to chemotherapy, 135/149 patients randomised to chemoimmunotherapy). Time-to-event data not extracted from published curves for inclusion in this review as unable to do so accurately to replicate reported study findings. Follow-up details not reported. Estimated minimum follow-up = 2 months. Estimated maximum follow-up = 36 months. 8 treatment-related deaths: 5 due to infection in arms CAF+MER, CAFVP+MER, CAF, CAFVP (2); 2 due to haemorrhage in arms CAF+MER, CMF; 1 due to cardiac toxicity in CAF arm.

Aisner 1987a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A - Adequate, Latin square design
Allocation concealment (selection bias)	Low risk	A - Adequate, closed envelope
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Time to progression	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Low risk	A - Adequate
Selective reporting (reporting bias)	Unclear risk	B - Unclear, time to treatment failure results not included
Other bias	Low risk	A - Other sources of bias not identified in methods

Aisner 1987b

Study characteristics	
Methods	As for Aisner 1987a
Participants	As for Aisner 1987a
Interventions	Aisner 1987b: CAF+MER vs CAFVP+MER
Outcomes	As for Aisner 1987a
Notes	As for Aisner 1987a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A - Adequate, Latin square design

Aisner 1987b *(Continued)*

Allocation concealment (selection bias)	Low risk	A - Adequate, closed envelope
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Time to progression	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Low risk	A - Adequate
Selective reporting (reporting bias)	Unclear risk	B - Unclear, time to treatment failure results not included
Other bias	Low risk	A -Adequate, other sources of bias not identified in methods

Cavalli 1983a

Study characteristics	
Methods	Multicentre national Accrual: September 1975 - December 1980 Sample size: 230 Randomisation method not defined Baseline comparability: no significant difference apparent or reported
Participants	Female 100% MBC 100% first line Median age: 57.2-57.9 years
Interventions	CLB+AMFP vs CLB+MFP vs CLB+MFVP Arm I: (CLB+AMFP) chlorambucil, methotrexate, 5-fluorouracil, prednisone, doxorubicin Arm II: (CLB+MFP) chlorambucil, methotrexate, 5-fluorouracil plus prednisone Arm III: (CLB+MFVP) chlorambucil plus methotrexate plus prednisone plus 5-fluorouracil plus vincristine Cavalli 1983a = CLB+AMFP vs CLB+MFP
Outcomes	Survival Time to progression

Cavalli 1983a *(Continued)*

	Response (defined as ≥ 50% reduction in tumour size) Toxicity
Notes	464 patients entered in study and randomised to receive tamoxifen/oophorectomy or tamoxifen/oophorectomy plus concurrent chemotherapy. The 230 patients assigned to the chemotherapy arm were further randomised to 3 different chemotherapy regimens. 216/230 patients evaluable: excluded for major protocol violations (10), poorly evaluable tumour parameters (2) and early death (2). Minimum reported follow-up= 17 months Maximum reported follow-up = 80 months Time-to-event analyses calculated from entrance in to the study. Time-to-event data extracted directly from time-to-event curve. Toxicity related deaths were not reported. Doses of the same chemotherapy agent are increased in the addition of a drug arm, however, cycles are less frequent.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Time to progression	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Low risk	A - Adequate
Selective reporting (reporting bias)	Low risk	A - Adequate, all outcomes reported
Other bias	Unclear risk	B - Unclear, mean age of pre- and post-menopausal groups not mentioned in each treatment group

Cavalli 1983b

Study characteristics

Methods	As for Cavalli 1983a

Cavalli 1983b *(Continued)*

Participants	As for Cavalli 1983a
Interventions	Cavalli 1983b = CLB+MFVP vs CLB+MFP
Outcomes	As for Cavalli 1983a
Notes	As for Cavalli 1983a except doses of the same chemotherapy agent are increased in the addition of a drug arm (cycles remain the same between treatment arms)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Time to progression	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Low risk	A - Adequate
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	Unclear risk	B - Unclear, mean age of pre- and post-menopausal groups not mentioned in each treatment group

Chlebowski 1983

Study characteristics

Methods	Accrual dates: not reported (accepted for publication May 1982) Sample size: 35 Number of centres: unknown (USA) Randomisation method: not reported Baseline comparability: no significant imbalance apparent or reported
Participants	Female

Chlebowski 1983 *(Continued)*

	100% MBC Unclear if this is a first line trial for MBC: 'patients admitted to study if they had failed an initial combination chemotherapy program' 'all patients received prior chemotherapy with at least cyclophosphamide and 5-FU'. However, patients typically received prior chemotherapy of CMF or CMFP which are typically adjuvant regimens. Age range 24-74 years Median 50 (both groups)
Interventions	A-CCNU vs A-CCNU-V Arm I: (A-CCNU) Doxorubicin + CCNU (lomustine) Arm II: (A-CCNU-V) Doxorubicin + CCNU (lomustine) + vincristine
Outcomes	Overall survival (not defined) Response (objective response, defined as ≥ 50% reduction in tumour size) Toxicity
Notes	35/35 evaluable for toxicity and response. Follow-up details not reported. - estimated minimum 30 months - estimated maximum 30 months Presents survival as life tables not Kaplan-Meier curves. Time-to-event data extracted directly from time-to-event curve. Toxicity related deaths not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	High risk	C - difference between groups in proportion of pre/post menopausal patients

Creech 1979

Study characteristics	
Methods	Accrual dates: not reported (Accepted for publication March 1978) Sample size: 78 Number of centres: Unknown (USA) Randomisation method not reported Patients were stratified according to poor or good risk Baseline comparability: no significant imbalance apparent or reported
Participants	100% women with visceral MBC Age range: 34-79 years CAMF arm; 32-87 years CMF arm Median age: 56 both arms
Interventions	CMF vs CAMF Arm I: (CMF) cyclophosphamide + methotrexate + 5-fluorouracil Arm II: (CAMF) as arm I plus doxorubicin
Outcomes	Response (defined as ≥ 50% reduction in tumour size) Survival (reported by response status) Progression-free survival (reported by response status) Toxicity
Notes	78/78 evaluable. ITT analysis. CMF patients crossed over to doxorubicin on progression. - estimated minimum follow-up = 5 months - estimated maximum follow-up = 39 months Overall survival and time to progression were reported for subsets of patients by response status and not extracted for this review. No statistically significant difference between CAMF and CMF were reported for time-to-event data. Median survival for PR/CR patients was 20 months in CAMF arm vs 19 months in CMF arm. Treatment related deaths were not reported.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Time to progression	Unclear risk	B - Unclear

Creech 1979 *(Continued)*

Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	Low risk	A -Adequate, other sources of bias not identified in methods

Cummings 1981a

Study characteristics	
Methods	Accrual dates: not reported (before 1981) Sample size: 268 Number of centres: unknown (USA) Randomisation method: 'randomly allocated' but method not described Baseline comparability: no significant imbalance apparent or reported other than AVI group with higher percentage postmenopausal women and diagnosis more than 5 years before entry
Participants	Female Age range: under 70 82% dominant metastatic site visceral or bone 100% had prior chemotherapy but unclear if adjuvant or for MBC
Interventions	AV vs AVD vs AVI Arm I: (AV) doxorubicin + vincristine Arm II: (AVD) doxorubicin + vincristine + dibromodulcitol Arm III: (AVI) doxorubicin + vincristine + ICRF-159 Cummings 1981a = AV vs AVD
Outcomes	Overall survival Time to treatment failure (TTF) (date entry to date progression or death from breast cancer within 6 weeks of ceasing therapy) Response (defined as ≥ 50% reduction in tumour size) Toxicity
Notes	230/268 evaluable: patient withdrew from study or died without objective progression within 8 weeks (26), reason for drop out not reported (12). Follow up details not reported. Based on median TTF: - estimated minimum 3.5 months - estimated maximum 24 months Time-to-event data extracted directly from time-to-event curve.Toxicity related deaths not reported. Doses of the same chemotherapy agent are reduced in the addition of a drug arm.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Cummings 1981a *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Time to progression	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, all outcomes reported
Other bias	High risk	C - Higher proportion of premenopausal patients in AV group

Cummings 1981b

Study characteristics		
Methods	As for Cummings 1981a	
Participants	As for Cummings 1981a	
Interventions	Cummings 1981b = AV vs AVI	
Outcomes	As for Cummings 1981a	
Notes	As for Cummings 1981a	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias)	Unclear risk	B - Unclear

Cummings 1981b *(Continued)*

Response		
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Time to progression	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, all outcomes reported
Other bias	High risk	C - Higher proportion of premenopausal patients in AV group

Inoue 1984

Study characteristics	
Methods	Accrual dates: 01/03/1979 to not reported (date closed to accrual not reported, study closed 30/04/1983 and date submitted for publication 25/11/1983) Unknown (Japan) Sample size:58 Randomisation method: Envelope system Baseline comparability: no significant imbalance apparent or reported
Participants	Female 100% MBC 100% first line Age range: 31-69 years Median age Arm I: 55 years, arm II: 49 years Anthracycline naive
Interventions	ACF vs ACFM Arm I: ACF doxorubicin + cyclophosphamide + ftorafur Arm II ACFM: arm I + methotrexate
Outcomes	Overall survival Response (defined as ≥ 50% reduction in tumour size) Toxicity
Notes	58/60 evaluable. 2 patients excluded (ACF arm) due to protocol violation. Survival measured from start of chemotherapy. Follow-up details not reported. Based on accrual and date of submission: - estimated minimum follow-up 1 month - estimated maximum follow-up 51 months Time-to-event data extracted directly from time-to-event curve. Toxicity related deaths not reported.

Inoue 1984 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Low risk	A - Adequate, envelope
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	High risk	C - 37% ACFM group had ≥3 organs involved compared to 14% in ACF group

Kennealey 1978

Study characteristics	
Methods	Accrual dates: September 1974 to July 1976 Sample size: 42 randomised (+15 on pilot) Number of centres: unknown (USA) Randomisation method: not reported Baseline comparability: more patients in AC group had prior chemotherapy and endocrine therapy, although this is based on all patients not just randomised patients
Participants	Female Age range: median 58 (AC) and 54 (ACMF) 100% MBC 100% not first line
Interventions	AC vs ACMF Arm I: (AC) doxorubicin + cyclophosphamide Arm II: (ACMF) doxorubicin + cyclophosphamide + methotrexate + 5-fluorouracil
Outcomes	Response Toxicity

Kennealey 1978 *(Continued)*

Notes	Not possible to distinguish between randomised and non-randomised patients (on pilot) therefore study outcomes not included in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	C - Inadequate, 15 patients not randomised
Allocation concealment (selection bias)	High risk	C - Inadequate
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	High risk	C - 15/48 patients were not randomised, more patients in AC group (21/26) had prior hormonal therapy compared to ACMF (13/22)

Lokich 1977

Study characteristics

Methods	Accrual dates: April 1975 to March 1976 Sample size: 43 Number of centres: unknown (USA) Randomisation method: not reported Baseline comparability: imbalance reported with more patients in MA group having skin metastases (15 vs 10), longer disease-free interval (27 (range 0-72) vs 8 (range 0-48) months) and duration of metastases
Participants	Female Age range 39-78 years (median 53 (MA) and 59 (MAC)) 100% MBC 100% first line unclear: 9/43 had received prior chemotherapy but unclear if this was for metastatic disease
Interventions	MA vs MAC Arm I: (MA) melphalan + doxorubicin Arm II: (MAC) melphalan + doxorubicin + cyclophosphamide
Outcomes	Response (defined as ≥ 50% reduction in tumour size) Duration of response

Lokich 1977 *(Continued)*

	Toxicity
Notes	40/43 evaluable: reason for exclusion, early death at 3 weeks (1), low dosage of drug therapy with death at 6 weeks (1), absence of measurable disease at 7 weeks (1). 1 treatment related death: severe sepsis (MAC arm) Doses of the same chemotherapy agent are reduced in the addition of a drug arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Duration of response	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	High risk	C - Inadequate, MA group had longer disease free interval and more skin metastases compared to MAC group.

Marschke 1989

Study characteristics

Methods	Accrual dates: June 1982 to December 1987 Sample size: 345 Multicentre: USA and Canada
Participants	Female Age range: 22-82 years (median 59-60) 100% MBC 100% first line
Interventions	CFP vs CMFP Arm I: (CFP) cyclophosphamide + 5-fluorouracil + prednisone Arm II: (CMFP) cyclophosphamide + methotrexate + 5-fluorouracil + prednisone

Marschke 1989 *(Continued)*

Outcomes	Overall survival Time to progression Response (defined as ≥ 50% reduction in tumour size) Duration of response Toxicity
Notes	Follow-up details not reported. Based on length of chemotherapy: - estimated minimum 5 months - estimated maximum 48 months 345 randomised: 9 ineligible (5 CFP, 4 CMFP). Time to progression defined as date randomised to date of progression. Time-to-event data estimated from statistics presented in trial publication. 6 toxic related deaths: severe myelosuppression (3 from each treatment arm) Doses of the same chemotherapy agent are reduced (C) or increased (5-FU) in the addition of a drug arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A - Pocock-Simon procedure
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Time to progression	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Duration of response	Low risk	A - Adequate
Selective reporting (reporting bias)	Low risk	A - Adequate
Other bias	Low risk	A - Adequate

Nemoto 1982a

Study characteristics	
Methods	Accrual dates: July 1974 to October 1975 Sample size: 126 Multicentre: 2 sites in USA Randomisation method: 'closed envelopes' kept at one of the centres (unclear how randomisation was achieved) Baseline comparability: no imbalance apparent or reported
Participants	Female Age range not reported (> 50 to < 70 years) 100% MBC 100% first-line
Interventions	AC vs CFP vs CAF vs CFP-CA Arm I: (AC) cyclophosphamide + doxorubicin Arm II: (CFP) cyclophosphamide + 5-fluorouracil + prednisone Arm III: (CAF) cyclophosphamide + doxorubicin + 5-fluorouracil Arm IV: (CFP-CA) CFP as above, then cyclophosphamide + doxorubicin Nemoto 1982a = CFP vs CFP-CA
Outcomes	Overall survival Time to progression (TTP) Response (defined as ≥ 50% reduction in tumour size) Toxicity
Notes	117/126 evaluable: reason for exclusion, 9 withdrawn due to early death or withdrawal from study (no reason given). There is conflicting information in the paper, it is clearly stated that all 126 patients have been included in analysis, however, the graph displays N = 120 with the groups as follows CFP 18; CFP-CA 20; CAF 40; CA 42. The group numbers as detailed which total to 120 (CFP 18; CFP-CA 20; CAF 40; CA 42) have been used in this review. Follow-up details not reported. Based on median TTP: - estimated minimum 12 months - estimated maximum 54 months Time-to-event data extracted directly from time-to-event curve. Reported that no toxic deaths occurred.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Low risk	A - Adequate, closed envelope
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias)	Low risk	A - Adequate

Nemoto 1982a *(Continued)*

Toxicity		
Incomplete outcome data (attrition bias) Time to progression	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Overall survival	High risk	C - Inadequate
Selective reporting (reporting bias)	Unclear risk	B - Unclear
Other bias	Low risk	A - Adequate

Nemoto 1982b

Study characteristics		
Methods	As for Nemoto 1982a	
Participants	As for Nemoto 1982a	
Interventions	Nemoto 1982b = AC vs CAF	
Outcomes	As for Nemoto 1982a	
Notes	As for Nemoto 1982a except doses of the same chemotherapy agent are reduced in the addition of a drug arm	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Low risk	A - Adequate, closed envelope
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Time to progression	Unclear risk	B - Unclear

Nemoto 1982b *(Continued)*

Incomplete outcome data (attrition bias) Overall survival	High risk	C - Inadequate
Selective reporting (reporting bias)	Unclear risk	B - Unclear
Other bias	Low risk	A - Adequate

Pannuti 1984

Study characteristics	
Methods	Accrual dates: not reported Sample size: 46 Randomisation method not reported Baseline comparability: no significant imbalance apparent or reported
Participants	Female 100% MBC (87% with metastases of bone or viscera) Unclear if prior chemotherapy received by 17% was for MBC Age range: 36-74 years Median age: 55 (both arms)
Interventions	CMF vs R14 Arm I: (CMF) cyclophosphamide + methotrexate + 5-fluorouracil Arm II: (R14) arm I + vincristine + vinblastine + doxorubicin
Outcomes	Overall survival Response (defined as ≥ 50% reduction in tumour size) Toxicity
Notes	46/46 included in analysis Follow-up details not reported: -estimated minimum follow-up 5.5 months -estimated maximum follow-up 45 months (from survival curve) Time-to-event data extracted directly from time-to-event curve. Treatment related deaths not reported. Doses of the same chemotherapy agent are markedly different between treatment arms.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear

Pannuti 1984 *(Continued)*

Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	High risk	C - Inadequate, higher proportion of R14 group premenopausal, small study groups

Rosner 1989

Study characteristics	
Methods	Accrual dates: September 1981 to December 1987 Sample size: 182 Number of centres: unknown (USA) Randomisation method not reported Baseline comparability: no significant imbalance reported
Participants	Female Age range: mean 53 years 100% MBC 100% first line
Interventions	AC vs CFP vs CFPMV Arm I: (AC) doxorubicin + cyclophosphamide Arm II: (CFP) cyclophosphamide + 5-fluorouracil + prednisone Arm III: (CFPMV) cyclophosphamide + 5-fluorouracil + prednisone + methotrexate + vincristine Rosner 1989 = CFP vs CFPMV
Outcomes	Overall survival Response Remission duration Toxicity
Notes	Follow-up details not reported. Based on median time of remission: - estimated minimum 6 months - estimated maximum 36 months All patients included in time-to-event analyses. Time-to-event data extracted directly from time-to-event curve. Survival from start of chemotherapy Toxicity related deaths not reported Doses of the same chemotherapy agent are reduced (C) or increased (5-FU) in the addition of a drug arm
Risk of bias	

Rosner 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	High risk	C - Inadequate
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Duration of response	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	Low risk	A - Adequate

Segaloff 1985

Study characteristics	
Methods	Accrual dates: July 1971 to October 1976 Sample size: 427 Number of centres: 11(USA) Randomisation method: 'randomised from a central statistical office' Baseline comparability: no significant imbalance apparent or reported
Participants	Female Age range: > 40 to 65+ years 91% MBC, 9% locally advanced Unclear if a first line trial for MBC 'patients eligible if they had a trial with 1 or 2 single agents'
Interventions	CMFP vs CMFVP Arm I: (CMFP) Cyclophosphamide + methotrexate + 5-fluorouracil + prednisone Arm II: (CMFVP) arm I + vincristine
Outcomes	Overall survival Response

Segaloff 1985 *(Continued)*

	Toxicity
Notes	All randomised patients included in analyses. Mean follow-up times reported, 17 months CMFP arm and 19 months CMFVP arm. Survival curve calculated using life table methodology. Time-to-event data estimated from statistics presented in trial publication. Toxic related deaths not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear, patients less than 1 year postmenopausal were centrally randomised
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	Low risk	A - Adequate

Stein 1992

Study characteristics

Methods	Accrual dates: March 1987 to May 1990 Sample size: 114 Number of centres: unknown (UK) Randomisation method: not reported Baseline comparability: no significant imbalance apparent or reported
Participants	Female Age range: mean 61-62 years Unclear % MBC (advanced and progressive disease) Approx 90% first line for MBC
Interventions	2M vs 3M Arm I: (2M) mitozantrone + methotrexate

Stein 1992 *(Continued)*

	Arm II: (3M) mitozantrone + methotrexate + mitomycin-C
Outcomes	Response Toxicity
Notes	107/114 eligible: reason for exclusion, randomised in error (4), primary site of cancer in doubt (3). Toxic related deaths not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	Low risk	A - Adequate

Tranum 1982

Study characteristics

Methods	Accrual dates: not reported Sample size: 497 Multicentre, national (USA) Randomisation method not reported Baseline comparability: reported as balanced (no baseline data included in article)
Participants	Female Age range not reported (34% < 50 years) 100% MBC 100% first-line
Interventions	AC vs FAC vs A+CMFVP Arm I AC: doxorubicin plus cyclophosphamide Arm II FAC: 5-fluorouracil, doxorubicin plus cyclophosphamide Arm III A+CMFVP: doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil, vincristine plus prednisone

Tranum 1982 *(Continued)*

	Tranum 1982a = AC vs FAC
Outcomes	Overall survival Response Toxicity
Notes	448/497 evaluable: reasons given for exclusion, did not satisfy eligibility (13), major protocol violation or inadequate data or too recent entry onto study (36). Follow-up details not reported. Based on minimum length of response: - estimated minimum 7.25 months - estimated maximum 39 months Unclear if time-to-event analyses included all patients randomised. Time-to-event outcomes not defined. Time-to-event data extracted directly from time-to-event curve. 11 toxic related deaths reported, however, these could not be included in the review as it is unclear in which arm the treatment deaths occurred. Doses of the same chemotherapy agent are reduced in the addition of a drug arm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Overall survival	Unclear risk	B - Unclear
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	Unclear risk	B - Unclear, no details of baseline characteristics given (e.g. disease free interval, number metastatic sites, ER status)

Vogel 1984

Study characteristics

Methods	Accrual dates: not reported (submitted for publication August 1983, accepted for publication December 1983) Number of centres unknown (USA) Sample size: 187

Vogel 1984 *(Continued)*

	Randomisation method not defined. 'projected 2:1 randomisation in favour of CAF+CAMELEON arm Baseline comparability: 'no significant differences reported' - baseline characteristics not displayed
Participants	Female Age range: not reported 100% visceral MBC % first-line not reported. Unclear if this is a first-line trial for MBC 'prior chemotherapy with any of the study drugs rendered a patient ineligible'
Interventions	CAF vs CAF+CAMELEON Arm I CAF: cyclophosphamide + doxorubicin + 5-fluorouracil Arm II CAF+CAMELEON: arm I plus cytosine arabinoside + methotrexate + oncovin
Outcomes	Overall survival Response Toxicity Overall duration of disease control Remission duration
Notes	157/187 evaluable - 8 on CAF arm and 22 on CAF+CAMELEON arm inevaluable. Reasons for this include patient ineligibility (2 CAF, 6 CAF+CAMELEON), early removal from study (4 CAF, 5 CAF+CAMELEON), patient refusal (3 CAF +CAMELEON), insufficient data (1 CAF, 1 CAF+CAMELOEN), protocol violation (1 CAF, 6 CAF+CAMELEON), drug toxicity (1 CAF+CAMELEON). Follow-up details not reported. Evaluable patients only included in time-to-event analyses. Time-to-event calculated from date of entry into study. Time-to-event data estimated from statistics presented in trial publication. Follow-up details not reported. Overall duration of disease control will be interpreted as progression free survival. 2 toxic related deaths reported, 1 due to renal failure (CAF+CAMELEON arm) and 1 due to granulocytopenia and sepsis (CAF arm).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	B - Unclear
Allocation concealment (selection bias)	Unclear risk	B - Unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	B - Unclear
Incomplete outcome data (attrition bias) Response	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Toxicity	Low risk	A - Adequate
Incomplete outcome data (attrition bias) Overall survival	Low risk	A - Adequate

Vogel 1984 *(Continued)*

Incomplete outcome data (attrition bias) Duration of response	Low risk	A - Adequate
Selective reporting (reporting bias)	Low risk	A - Adequate, outcomes reported
Other bias	Low risk	A - Adequate

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

Study	Reason for exclusion
Ahmann 1974a	Unclear that subjects allocated to addition of a drug arm were correctly randomised - 'vincristine was administered by random distribution to half of the control group.'
Ahmann 1974b	Subjects allocated to addition of a drug arm were not randomised.
Ahmann 1975	Unclear that subjects allocated to addition of vincristine arm were correctly randomised - 'the other 50% of patients were treated on a random basis'.
Aisner 1981	Unclear how many subjects randomised to each study arm. In addition, unclear how many subjects dropped out from each study arm and reason for drop out.
Aisner 1995	The eligible arms are VATH versus VATH +CMFVP, but the CMFVP is not given on the third arm until the 3rd cycle (28 day cycles) and then cycles 5, 7, 9 etc. This delay of over 70 days of CMFVP treatment does not meet the definition of addition of a drug for this review.
Brown 1976	Unclear how many subjects properly randomised and how many automatically allocated favourable treatment. All subjects (both randomised and allocated) are included in results so not possible to distinguish how many randomised and how many not randomised.
Brown 1977	Not clear how many patients randomised to each arm ('patients assessed'). Unequal distribution between treatment arms are reported, however, the number of patient drop outs from each arm is not reported. No baseline data are reported. Over half the participants received prior chemotherapy but it is unclear if this was for MBC.
Cocconi 1990	Trial of delayed chemotherapy. All patients receive first line CMF for 6 cycles. Therefore, this is not a trial of first line treatment. At point of randomisation, only patients with stable disease were randomised, which raises the issue of generalisation.
Cocconi 1999	Trial of rotational cross-over and sequential intensification which does not meet the definition of addition of a drug to a regimen for this review.
Costanza 1999	The eligible arms in this study are CAF versus one of a number of single agents + CAF. In the addition of a drug arm, the single agent is given every 21 days for up to four cycles and then patients are given CAF. This delay of over 80 days for the single agent + CAF treatment does not meet the definition of addition of a drug for this review.
Creagan 1984	The eligible arms in this study are CFP versus CAP-CFP. In the addition of a drug arm, CFP is administered following four cycles (28 days cycles) of CAP. This delay of over 80 days of CFP treatment does not meet the definition of addition of a drug for this review.
Horton 1975	Preliminary data only reported. Not all randomised subjects evaluated for response at time of publication.

Study	Reason for exclusion
Milano 1985	Exploratory study, a subset of which have metastatic breast cancer. Only outcome reported is urinary polyamine levels.
Mukaiyama 1989	Quality and conduct of the study questionable. Difficult to ascertain results from study as survival curve suggests no events for at least four months, response is reported as % of induction therapy and there is a small number of patients randomised (total N = 47).
Priestman 1975	Exploratory study. Both loco-regional and metastatic breast cancer patients are included, unclear how many MBC patients in trial.
Saeki 2007	Dofequidar Fumarate not a chemotherapy agent.
Venturino 2000	2nd line chemotherapy trial. Patients had received one course of prior chemotherapy for metastatic disease (including CMF, CEF).
Von Minckwitz 2005	The treatment arm did not add another chemotherapy agent, cyclophosphamide in the first study arm was switched to bendamustine.
Zhao 1986	Overall quality of the trial is questionable. Unclear if first line trial, a large percentage of patients received prior chemotherapy, but unclear if for metastatic disease. 23% of patients lost to follow up and it is unclear why these patients dropped out of the study before the completion of two courses of the regimen. In addition, analysis was not by intention-to-treat.

DATA AND ANALYSES

Comparison 1. Overall survival

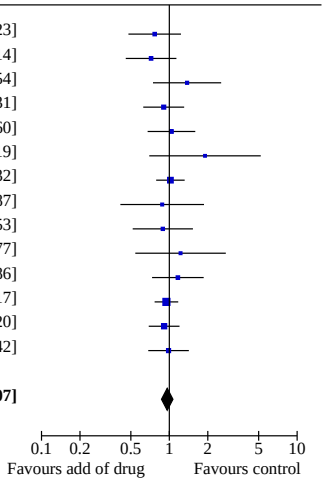
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival (all trials)	14	2116	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.96 [0.87, 1.07]
1.2 Overall survival (sensitivity analysis)	9	1229	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.82, 1.09]
1.3 Overall survival (addition of 'less active' drug vs addition of 'more active' drug)	14		Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Subtotals only
1.3.1 Addition of 'less active' drug	5	837	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.94 [0.81, 1.10]
1.3.2 Addition of 'more active' drug	9	1279	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.98 [0.85, 1.12]
1.4 Overall survival (adjusted dose in addition of drug arm vs no dose adjustment)	14		Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Subtotals only
1.4.1 Adjusted dose in addition of a drug arm	9	1401	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.94 [0.83, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.2 Dose not adjusted in addition of a drug arm	5	715	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.00 [0.84, 1.18]
1.5 Overall survival (addition of anthracycline vs addition of non-anthracycline)	14		Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Subtotals only
1.5.1 Addition of an anthracycline	3	193	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.87 [0.61, 1.24]
1.5.2 Addition of a non-anthracycline	11	1923	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.97 [0.87, 1.08]
1.6 Overall survival (addition of 1 agent vs addition of 2 or more agents)	14		Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Subtotals only
1.6.1 Addition of 1 agent	10	1754	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.85, 1.06]
1.6.2 Addition of 2 or more agents	4	362	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.05 [0.81, 1.35]

Analysis 1.1. Comparison 1: Overall survival, Outcome 1: Overall survival (all trials)

Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Cavalli 1983a	50	72	29	37	-4.52	17.16	4.7%	0.77 [0.48 , 1.23]
Cavalli 1983b	50	70	29	37	-6.06	18.44	5.1%	0.72 [0.46 , 1.14]
Chlebowski 1983	17	18	14	17	3.26	10.19	2.8%	1.38 [0.75 , 2.54]
Cummings 1981a	78	108	43	54	-2.86	28.29	7.8%	0.90 [0.63 , 1.31]
Cummings 1981b	39	52	43	54	0.8	20.85	5.7%	1.04 [0.68 , 1.60]
Inoue 1984	19	30	11	28	2.45	3.81	1.0%	1.90 [0.70 , 5.19]
Marschke 1989	113	174	115	171	1.15	58.31	16.0%	1.02 [0.79 , 1.32]
Nemoto 1982a	16	20	15	18	-0.87	6.77	1.9%	0.88 [0.41 , 1.87]
Nemoto 1982b	34	40	36	42	-1.53	13.05	3.6%	0.89 [0.52 , 1.53]
Pannuti 1984	16	23	18	23	1.17	5.78	1.6%	1.22 [0.54 , 2.77]
Rosner 1989	41	62	39	59	2.74	17.78	4.9%	1.17 [0.73 , 1.86]
Segaloff 1985	172	219	168	208	-4.44	84.94	23.3%	0.95 [0.77 , 1.17]
Tranum 1982	102	162	107	161	-4.68	49.98	13.7%	0.91 [0.69 , 1.20]
Vogel 1984	68	91	50	66	-0.4	28.75	7.9%	0.99 [0.68 , 1.42]
Total (95% CI)		**1141**		**975**			**100.0%**	**0.96 [0.87 , 1.07]**
Total events:	815		717					

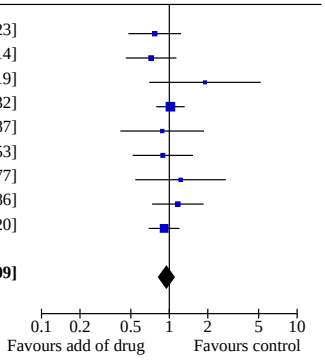
Heterogeneity: Chi² = 7.25, df = 13 (P = 0.89); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Overall survival, Outcome 2: Overall survival (sensitivity analysis)

Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Cavalli 1983a	50	72	29	37	-4.52	17.16	9.0%	0.77 [0.48 , 1.23]
Cavalli 1983b	50	70	29	37	-6.06	18.44	9.7%	0.72 [0.46 , 1.14]
Inoue 1984	19	30	11	28	2.45	3.81	2.0%	1.90 [0.70 , 5.19]
Marschke 1989	113	174	115	171	1.15	58.31	30.5%	1.02 [0.79 , 1.32]
Nemoto 1982a	16	20	15	18	-0.87	6.77	3.5%	0.88 [0.41 , 1.87]
Nemoto 1982b	34	40	36	42	-1.53	13.05	6.8%	0.89 [0.52 , 1.53]
Pannuti 1984	16	23	18	23	1.17	5.78	3.0%	1.22 [0.54 , 2.77]
Rosner 1989	41	62	39	59	2.74	17.78	9.3%	1.17 [0.73 , 1.86]
Tranum 1982	102	162	107	161	-4.68	49.98	26.2%	0.91 [0.69 , 1.20]
Total (95% CI)		**653**		**576**			**100.0%**	**0.95 [0.82 , 1.09]**
Total events:	441		399					

Heterogeneity: Chi² = 5.63, df = 8 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Overall survival, Outcome 3: Overall survival (addition of 'less active' drug vs addition of 'more active' drug)

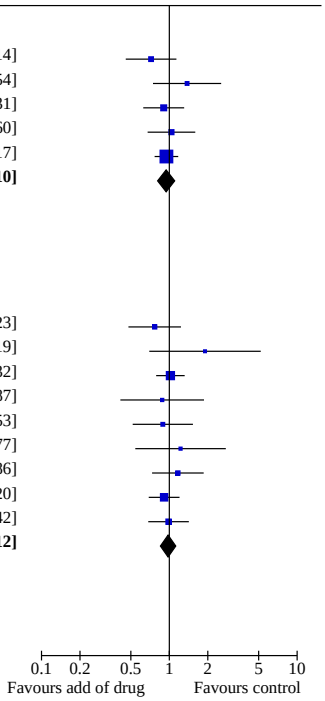
Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.3.1 Addition of 'less active' drug								
Cavalli 1983b	50	70	29	37	-6.06	18.44	11.3%	0.72 [0.46 , 1.14]
Chlebowski 1983	17	18	14	17	3.26	10.19	6.3%	1.38 [0.75 , 2.54]
Cummings 1981a	78	108	43	54	-2.86	28.29	17.4%	0.90 [0.63 , 1.31]
Cummings 1981b	39	52	43	54	0.8	20.85	12.8%	1.04 [0.68 , 1.60]
Segaloff 1985	172	219	168	208	-4.44	84.94	52.2%	0.95 [0.77 , 1.17]
Subtotal (95% CI)		**467**		**370**			**100.0%**	**0.94 [0.81 , 1.10]**
Total events:	356		297					

Heterogeneity: Chi² = 3.05, df = 4 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)

1.3.2 Addition of 'more active' drug								
Cavalli 1983a	50	72	29	37	-4.52	17.16	8.5%	0.77 [0.48 , 1.23]
Inoue 1984	19	30	11	28	2.45	3.81	1.9%	1.90 [0.70 , 5.19]
Marschke 1989	113	174	115	171	1.15	58.31	29.0%	1.02 [0.79 , 1.32]
Nemoto 1982a	16	20	15	18	-0.87	6.77	3.4%	0.88 [0.41 , 1.87]
Nemoto 1982b	34	40	36	42	-1.53	13.05	6.5%	0.89 [0.52 , 1.53]
Pannuti 1984	16	23	18	23	1.17	5.78	2.9%	1.22 [0.54 , 2.77]
Rosner 1989	41	62	39	59	2.74	17.78	8.8%	1.17 [0.73 , 1.86]
Tranum 1982	102	162	107	161	-4.68	49.98	24.8%	0.91 [0.69 , 1.20]
Vogel 1984	68	91	50	66	-0.4	28.75	14.3%	0.99 [0.68 , 1.42]
Subtotal (95% CI)		**674**		**605**			**100.0%**	**0.98 [0.85 , 1.12]**
Total events:	459		420					

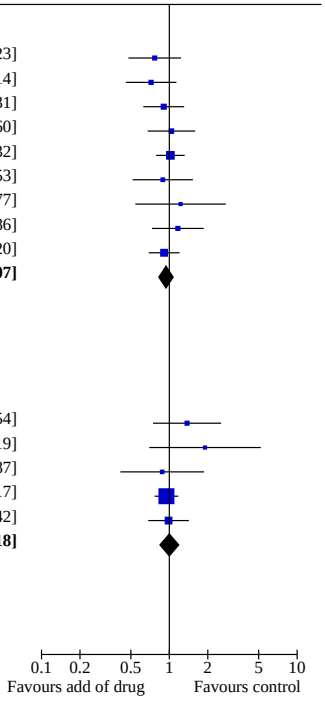
Heterogeneity: Chi² = 4.08, df = 8 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)

Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%



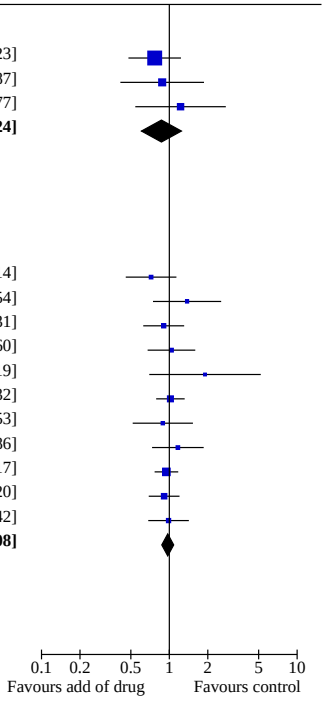
Analysis 1.4. Comparison 1: Overall survival, Outcome 4: Overall survival (adjusted dose in addition of drug arm vs no dose adjustment)

Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.4.1 Adjusted dose in addition of a drug arm								
Cavalli 1983a	50	72	29	37	-4.52	17.16	7.5%	0.77 [0.48 , 1.23]
Cavalli 1983b	50	70	29	37	-6.06	18.44	8.0%	0.72 [0.46 , 1.14]
Cummings 1981a	78	108	43	54	-2.86	28.29	12.3%	0.90 [0.63 , 1.31]
Cummings 1981b	39	52	43	54	0.8	20.85	9.1%	1.04 [0.68 , 1.60]
Marschke 1989	113	174	115	171	1.15	58.31	25.4%	1.02 [0.79 , 1.32]
Nemoto 1982b	34	40	36	42	-1.53	13.05	5.7%	0.89 [0.52 , 1.53]
Pannuti 1984	16	23	18	23	1.17	5.78	2.5%	1.22 [0.54 , 2.77]
Rosner 1989	41	62	39	59	2.74	17.78	7.7%	1.17 [0.73 , 1.86]
Tranum 1982	102	162	107	161	-4.68	49.98	21.8%	0.91 [0.69 , 1.20]
Subtotal (95% CI)		**763**		**638**			**100.0%**	**0.94 [0.83 , 1.07]**
Total events:	523		459					
Heterogeneity: Chi² = 3.97, df = 8 (P = 0.86); I² = 0%								
Test for overall effect: Z = 0.91 (P = 0.36)								
1.4.2 Dose not adjusted in addition of a drug arm								
Chlebowski 1983	17	18	14	17	3.26	10.19	7.6%	1.38 [0.75 , 2.54]
Inoue 1984	19	30	11	28	2.45	3.81	2.8%	1.90 [0.70 , 5.19]
Nemoto 1982a	16	20	15	18	-0.87	6.77	5.0%	0.88 [0.41 , 1.87]
Segaloff 1985	172	219	168	208	-4.44	84.94	63.2%	0.95 [0.77 , 1.17]
Vogel 1984	68	91	50	66	-0.4	28.75	21.4%	0.99 [0.68 , 1.42]
Subtotal (95% CI)		**378**		**337**			**100.0%**	**1.00 [0.84 , 1.18]**
Total events:	292		258					
Heterogeneity: Chi² = 2.97, df = 4 (P = 0.56); I² = 0%								
Test for overall effect: Z = 0.00 (P = 1.00)								
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%								



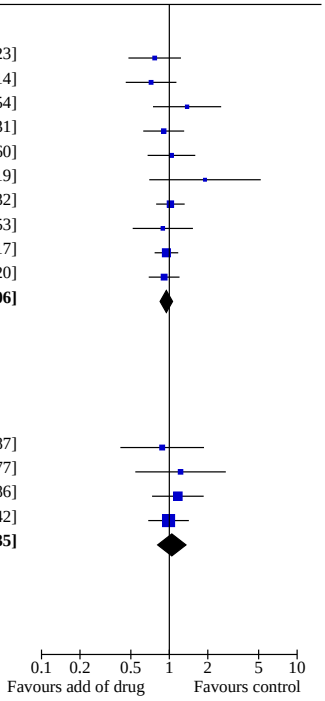
Analysis 1.5. Comparison 1: Overall survival, Outcome 5: Overall survival (addition of anthracycline vs addition of non-anthracycline)

Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.5.1 Addition of an anthracycline								
Cavalli 1983a	50	72	29	37	-4.52	17.16	57.8%	0.77 [0.48 , 1.23]
Nemoto 1982a	16	20	15	18	-0.87	6.77	22.8%	0.88 [0.41 , 1.87]
Pannuti 1984	16	23	18	23	1.17	5.78	19.5%	1.22 [0.54 , 2.77]
Subtotal (95% CI)		**115**		**78**			**100.0%**	**0.87 [0.61 , 1.24]**
Total events:	82		62					
Heterogeneity: Chi² = 0.94, df = 2 (P = 0.63); I² = 0%								
Test for overall effect: Z = 0.77 (P = 0.44)								
1.5.2 Addition of a non-anthracycline								
Cavalli 1983b	50	70	29	37	-6.06	18.44	5.5%	0.72 [0.46 , 1.14]
Chlebowski 1983	17	18	14	17	3.26	10.19	3.0%	1.38 [0.75 , 2.54]
Cummings 1981a	78	108	43	54	-2.86	28.29	8.5%	0.90 [0.63 , 1.31]
Cummings 1981b	39	52	43	54	0.8	20.85	6.2%	1.04 [0.68 , 1.60]
Inoue 1984	19	30	11	28	2.45	3.81	1.1%	1.90 [0.70 , 5.19]
Marschke 1989	113	174	115	171	1.15	58.31	17.4%	1.02 [0.79 , 1.32]
Nemoto 1982b	34	40	36	42	-1.53	13.05	3.9%	0.89 [0.52 , 1.53]
Rosner 1989	41	62	39	59	2.74	17.78	5.3%	1.17 [0.73 , 1.86]
Segaloff 1985	172	219	168	208	-4.44	84.94	25.4%	0.95 [0.77 , 1.17]
Tranum 1982	102	162	107	161	-4.68	49.98	14.9%	0.91 [0.69 , 1.20]
Vogel 1984	68	91	50	66	-0.4	28.75	8.6%	0.99 [0.68 , 1.42]
Subtotal (95% CI)		**1026**		**897**			**100.0%**	**0.97 [0.87 , 1.08]**
Total events:	733		655					
Heterogeneity: Chi² = 5.96, df = 10 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.52 (P = 0.60)								
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%								



Analysis 1.6. Comparison 1: Overall survival, Outcome 6: Overall survival (addition of 1 agent vs addition of 2 or more agents)

Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.6.1 Addition of 1 agent								
Cavalli 1983a	50	72	29	37	-4.52	17.16	5.6%	0.77 [0.48 , 1.23]
Cavalli 1983b	50	70	29	37	-6.06	18.44	6.0%	0.72 [0.46 , 1.14]
Chlebowski 1983	17	18	14	17	3.26	10.19	3.3%	1.38 [0.75 , 2.54]
Cummings 1981a	78	108	43	54	-2.86	28.29	9.3%	0.90 [0.63 , 1.31]
Cummings 1981b	39	52	43	54	0.8	20.85	6.8%	1.04 [0.68 , 1.60]
Inoue 1984	19	30	11	28	2.45	3.81	1.2%	1.90 [0.70 , 5.19]
Marschke 1989	113	174	115	171	1.15	58.31	19.1%	1.02 [0.79 , 1.32]
Nemoto 1982b	34	40	36	42	-1.53	13.05	4.3%	0.89 [0.52 , 1.53]
Segaloff 1985	172	219	168	208	-4.44	84.94	27.8%	0.95 [0.77 , 1.17]
Tranum 1982	102	162	107	161	-4.68	49.98	16.4%	0.91 [0.69 , 1.20]
Subtotal (95% CI)		**945**		**809**			**100.0%**	**0.95 [0.85 , 1.06]**
Total events:	674		595					
Heterogeneity: Chi² = 6.11, df = 9 (P = 0.73); I² = 0%								
Test for overall effect: Z = 0.94 (P = 0.35)								
1.6.2 Addition of 2 or more agents								
Nemoto 1982a	16	20	15	18	-0.87	6.77	11.5%	0.88 [0.41 , 1.87]
Pannuti 1984	16	23	18	23	1.17	5.78	9.8%	1.22 [0.54 , 2.77]
Rosner 1989	41	62	39	59	2.74	17.78	30.1%	1.17 [0.73 , 1.86]
Vogel 1984	68	91	50	66	-0.4	28.75	48.7%	0.99 [0.68 , 1.42]
Subtotal (95% CI)		**196**		**166**			**100.0%**	**1.05 [0.81 , 1.35]**
Total events:	141		122					
Heterogeneity: Chi² = 0.66, df = 3 (P = 0.88); I² = 0%								
Test for overall effect: Z = 0.34 (P = 0.73)								
Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%								

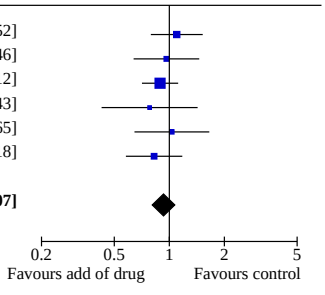


Comparison 2. Time to progression

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Time to progression (all trials)	6	890	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.93 [0.81, 1.07]
2.2 Time to progression (sensitivity analysis)	3	465	Hazard Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.90 [0.74, 1.09]

Analysis 2.1. Comparison 2: Time to progression, Outcome 1: Time to progression (all trials)

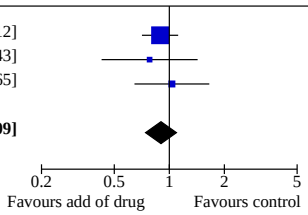
Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Cummings 1981a	95	108	46	54	3.38	36.01	18.9%	1.10 [0.79 , 1.52]
Cummings 1981b	41	52	46	54	-0.82	22.49	11.8%	0.96 [0.64 , 1.46]
Marschke 1989	149	174	149	171	-8.62	73.96	38.8%	0.89 [0.71 , 1.12]
Nemoto 1982a	18	20	17	18	-2.61	10.51	5.5%	0.78 [0.43 , 1.43]
Nemoto 1982b	38	40	41	42	0.56	17.31	9.1%	1.03 [0.64 , 1.65]
Vogel 1984	74	91	51	66	-5.84	30.46	16.0%	0.83 [0.58 , 1.18]
Total (95% CI)		**485**		**405**			**100.0%**	**0.93 [0.81 , 1.07]**
Total events:	415		350					
Heterogeneity: Chi² = 2.12, df = 5 (P = 0.83); I² = 0%								
Test for overall effect: Z = 1.01 (P = 0.31)								
Test for subgroup differences: Not applicable								



Analysis 2.2. Comparison 2: Time to progression, Outcome 2: Time to progression (sensitivity analysis)

Study or Subgroup	Addition of a drug Events	Total	Control Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Marschke 1989	149	174	149	171	-8.62	73.96	72.7%	0.89 [0.71 , 1.12]
Nemoto 1982a	18	20	17	18	-2.61	10.51	10.3%	0.78 [0.43 , 1.43]
Nemoto 1982b	38	40	41	42	0.56	17.31	17.0%	1.03 [0.64 , 1.65]
Total (95% CI)		**234**		**231**			**100.0%**	**0.90 [0.74 , 1.09]**
Total events:	205		207					

Heterogeneity: Chi² = 0.55, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.06 (P = 0.29)
Test for subgroup differences: Not applicable



Comparison 3. Overall response (assessable patients)

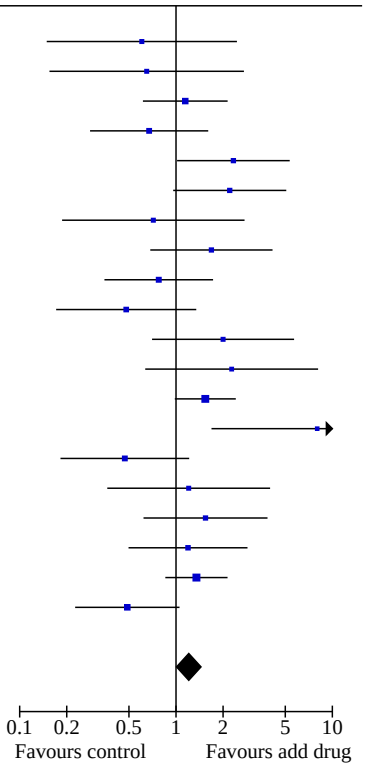
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall response (all trials)	20	2101	Odds Ratio (M-H, Fixed, 95% CI)	1.21 [1.01, 1.44]
3.2 Overall response (sensitivity analysis)	16	1682	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [1.14, 1.68]
3.3 Overall response (addition of 'less active' drug vs addition of 'more active' drug)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 Addition of 'less active' drug	6	659	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.43]
3.3.2 Addition of 'more active' drug	14	1518	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [1.09, 1.65]
3.4 Overall response (adjusted dose in addition of a drug arm vs no dose adjustment)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.4.1 Dose adjusted in addition of drug arm	12	1381	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [1.01, 1.58]
3.4.2 Dose not adjusted in addition of drug arm	8	722	Odds Ratio (M-H, Fixed, 95% CI)	1.10 [0.81, 1.50]
3.5 Overall response (addition of anthracycline vs addition of non-anthracycline)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.5.1 Addition of an anthracycline	5	352	Odds Ratio (M-H, Fixed, 95% CI)	1.87 [1.22, 2.86]
3.5.2 Addition of a non-anthracycline	15	1847	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.94, 1.37]
3.6 Overall response (addition of 1 agent vs addition of 2 or more agents)	20		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6.1 Addition of 1 agent	16	1772	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [1.01, 1.48]
3.6.2 Addition of 2 or more agents	4	331	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.70, 1.81]

Analysis 3.1. Comparison 3: Overall response (assessable patients), Outcome 1: Overall response (all trials)

Study or Subgroup	Addition of drug Events	Addition of drug Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ahmann 1976a	5	12	13	24	2.3%	0.60 [0.15 , 2.45]
Ahmann 1976b	5	12	11	21	2.2%	0.65 [0.16 , 2.72]
Aisner 1987a	46	79	45	82	8.5%	1.15 [0.61 , 2.14]
Aisner 1987b	13	41	20	49	5.8%	0.67 [0.28 , 1.61]
Cavalli 1983a	38	72	12	37	3.5%	2.33 [1.02 , 5.34]
Cavalli 1983b	36	70	12	37	3.5%	2.21 [0.96 , 5.07]
Chlebowski 1983	7	18	8	17	2.3%	0.72 [0.19 , 2.74]
Creech 1979	24	39	19	39	3.4%	1.68 [0.68 , 4.14]
Cummings 1981a	22	94	13	46	6.2%	0.78 [0.35 , 1.73]
Cummings 1981b	7	44	13	46	4.9%	0.48 [0.17 , 1.35]
Inoue 1984	18	30	12	28	2.3%	2.00 [0.70 , 5.69]
Lokich 1977	13	20	9	20	1.5%	2.27 [0.64 , 8.11]
Marschke 1989	83	156	65	153	14.2%	1.54 [0.98 , 2.41]
Nemoto 1982a	12	19	3	17	0.5%	8.00 [1.69 , 37.95]
Nemoto 1982b	10	40	17	41	5.8%	0.47 [0.18 , 1.21]
Pannuti 1984	9	23	8	23	2.3%	1.21 [0.36 , 4.00]
Rosner 1989	21	31	34	59	3.5%	1.54 [0.62 , 3.85]
Stein 1992	14	51	13	54	4.2%	1.19 [0.50 , 2.87]
Tranum 1982	77	160	57	140	14.6%	1.35 [0.85 , 2.14]
Vogel 1984	15	91	19	66	8.5%	0.49 [0.23 , 1.05]
Total (95% CI)		**1102**		**999**	**100.0%**	**1.21 [1.01 , 1.44]**
Total events:	475		403			

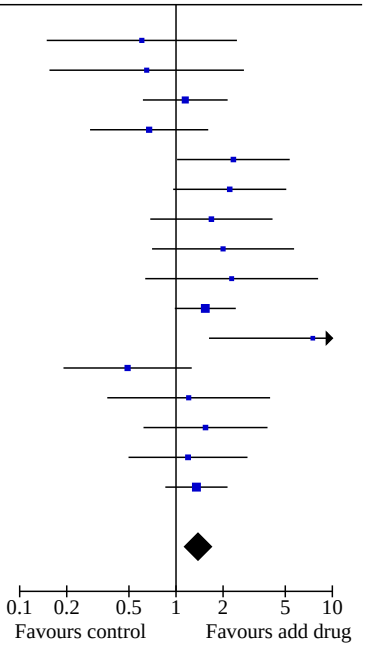
Heterogeneity: Chi² = 31.46, df = 19 (P = 0.04); I² = 40%
Test for overall effect: Z = 2.05 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Overall response (assessable patients), Outcome 2: Overall response (sensitivity analysis)

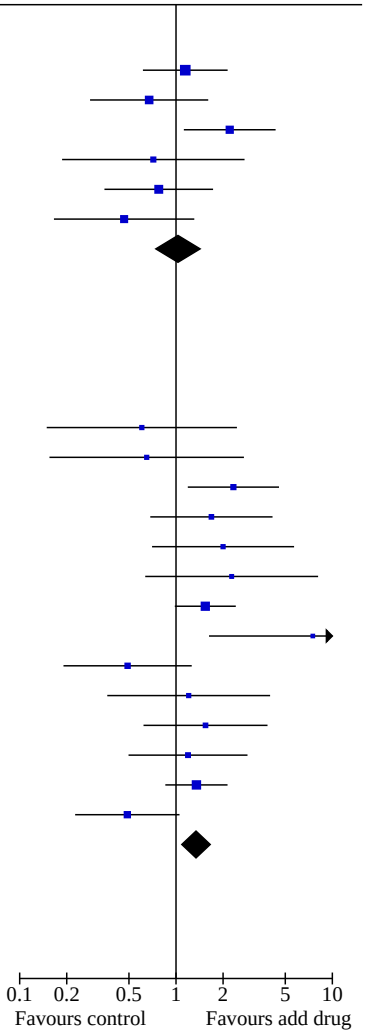
Study or Subgroup	Addition of drug Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ahmann 1976a	5	12	13	24	3.0%	0.60 [0.15 , 2.45]
Ahmann 1976b	5	12	11	21	2.8%	0.65 [0.16 , 2.72]
Aisner 1987a	46	79	45	82	10.9%	1.15 [0.61 , 2.14]
Aisner 1987b	13	41	20	49	7.4%	0.67 [0.28 , 1.61]
Cavalli 1983a	38	72	12	37	4.4%	2.33 [1.02 , 5.34]
Cavalli 1983b	36	70	12	37	4.5%	2.21 [0.96 , 5.07]
Creech 1979	24	39	19	39	4.3%	1.68 [0.68 , 4.14]
Inoue 1984	18	30	12	28	2.9%	2.00 [0.70 , 5.69]
Lokich 1977	13	20	9	20	1.9%	2.27 [0.64 , 8.11]
Marschke 1989	83	156	65	153	18.2%	1.54 [0.98 , 2.41]
Nemoto 1982a	12	20	3	18	0.7%	7.50 [1.63 , 34.59]
Nemoto 1982b	10	40	17	42	7.4%	0.49 [0.19 , 1.26]
Pannuti 1984	9	23	8	23	2.9%	1.21 [0.36 , 4.00]
Rosner 1989	21	31	34	59	4.5%	1.54 [0.62 , 3.85]
Stein 1992	14	51	13	54	5.4%	1.19 [0.50 , 2.87]
Tranum 1982	77	160	57	140	18.7%	1.35 [0.85 , 2.14]
Total (95% CI)		**856**		**826**	**100.0%**	**1.38 [1.14 , 1.68]**
Total events:	424		350			

Heterogeneity: Chi² = 19.13, df = 15 (P = 0.21); I² = 22%
Test for overall effect: Z = 3.22 (P = 0.001)
Test for subgroup differences: Not applicable



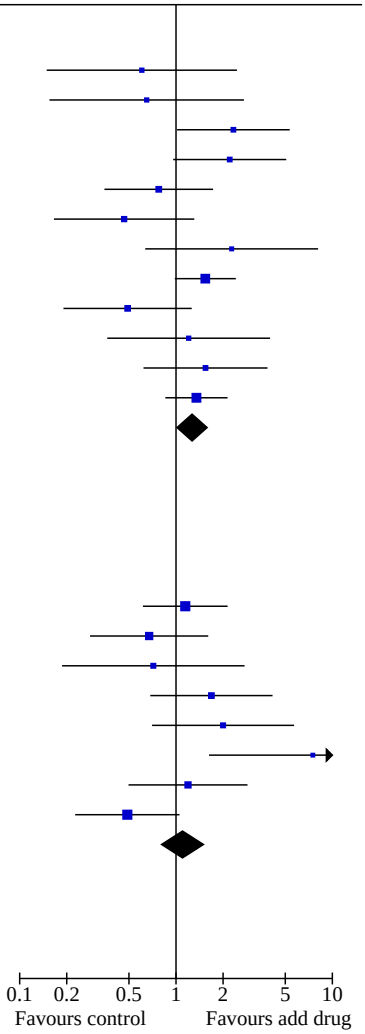
Analysis 3.3. Comparison 3: Overall response (assessable patients), Outcome 3: Overall response (addition of 'less active' drug vs addition of 'more active' drug)

Study or Subgroup	Addition of drug Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.1 Addition of 'less active' drug						
Aisner 1987a	46	79	45	82	25.8%	1.15 [0.61 , 2.14]
Aisner 1987b	13	41	20	49	17.4%	0.67 [0.28 , 1.61]
Cavalli 1983b	36	70	24	74	15.9%	2.21 [1.12 , 4.34]
Chlebowski 1983	7	18	8	17	7.0%	0.72 [0.19 , 2.74]
Cummings 1981a	22	94	13	46	18.7%	0.78 [0.35 , 1.73]
Cummings 1981b	7	44	13	45	15.1%	0.47 [0.17 , 1.31]
Subtotal (95% CI)		**346**		**313**	**100.0%**	**1.03 [0.74 , 1.43]**
Total events:	131		123			
Heterogeneity: Chi² = 8.94, df = 5 (P = 0.11); I² = 44%						
Test for overall effect: Z = 0.17 (P = 0.86)						
3.3.2 Addition of 'more active' drug						
Ahmann 1976a	5	12	13	24	3.3%	0.60 [0.15 , 2.45]
Ahmann 1976b	5	12	11	21	3.1%	0.65 [0.16 , 2.72]
Cavalli 1983a	38	72	24	74	7.3%	2.33 [1.19 , 4.56]
Creech 1979	24	39	19	39	4.8%	1.68 [0.68 , 4.14]
Inoue 1984	18	30	12	28	3.3%	2.00 [0.70 , 5.69]
Lokich 1977	13	20	9	20	2.1%	2.27 [0.64 , 8.11]
Marschke 1989	83	156	65	153	20.2%	1.54 [0.98 , 2.41]
Nemoto 1982a	12	20	3	18	0.8%	7.50 [1.63 , 34.59]
Nemoto 1982b	10	40	17	42	8.2%	0.49 [0.19 , 1.26]
Pannuti 1984	9	23	8	23	3.2%	1.21 [0.36 , 4.00]
Rosner 1989	21	31	34	59	5.0%	1.54 [0.62 , 3.85]
Stein 1992	14	51	13	54	6.0%	1.19 [0.50 , 2.87]
Tranum 1982	77	160	57	140	20.7%	1.35 [0.85 , 2.14]
Vogel 1984	15	91	19	66	12.1%	0.49 [0.23 , 1.05]
Subtotal (95% CI)		**757**		**761**	**100.0%**	**1.34 [1.09 , 1.65]**
Total events:	344		304			
Heterogeneity: Chi² = 22.71, df = 13 (P = 0.05); I² = 43%						
Test for overall effect: Z = 2.76 (P = 0.006)						



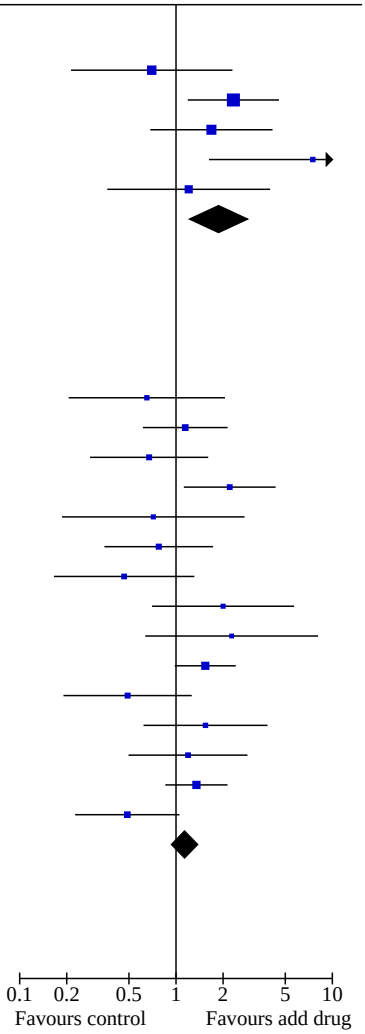
Analysis 3.4. Comparison 3: Overall response (assessable patients), Outcome 4: Overall response (adjusted dose in addition of a drug arm vs no dose adjustment)

Study or Subgroup	Addition of drug Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.4.1 Dose adjusted in addition of drug arm						
Ahmann 1976a	5	12	13	24	3.6%	0.60 [0.15 , 2.45]
Ahmann 1976b	5	12	11	21	3.4%	0.65 [0.16 , 2.72]
Cavalli 1983a	38	72	12	37	5.4%	2.33 [1.02 , 5.34]
Cavalli 1983b	36	70	12	37	5.5%	2.21 [0.96 , 5.07]
Cummings 1981a	22	94	13	46	9.6%	0.78 [0.35 , 1.73]
Cummings 1981b	7	44	13	45	7.8%	0.47 [0.17 , 1.31]
Lokich 1977	13	20	9	20	2.3%	2.27 [0.64 , 8.11]
Marschke 1989	83	156	65	153	22.1%	1.54 [0.98 , 2.41]
Nemoto 1982b	10	40	17	42	8.9%	0.49 [0.19 , 1.26]
Pannuti 1984	9	23	8	23	3.5%	1.21 [0.36 , 4.00]
Rosner 1989	21	31	34	59	5.4%	1.54 [0.62 , 3.85]
Tranum 1982	77	160	57	140	22.6%	1.35 [0.85 , 2.14]
Subtotal (95% CI)		**734**		**647**	**100.0%**	**1.27 [1.01 , 1.58]**
Total events:	326		264			
Heterogeneity: Chi² = 16.40, df = 11 (P = 0.13); I² = 33%						
Test for overall effect: Z = 2.09 (P = 0.04)						
3.4.2 Dose not adjusted in addition of drug arm						
Aisner 1987a	46	79	45	82	24.0%	1.15 [0.61 , 2.14]
Aisner 1987b	13	41	20	49	16.2%	0.67 [0.28 , 1.61]
Chlebowski 1983	7	18	8	17	6.5%	0.72 [0.19 , 2.74]
Creech 1979	24	39	19	39	9.5%	1.68 [0.68 , 4.14]
Inoue 1984	18	30	12	28	6.4%	2.00 [0.70 , 5.69]
Nemoto 1982a	12	20	3	18	1.6%	7.50 [1.63 , 34.59]
Stein 1992	14	51	13	54	11.9%	1.19 [0.50 , 2.87]
Vogel 1984	15	91	19	66	23.9%	0.49 [0.23 , 1.05]
Subtotal (95% CI)		**369**		**353**	**100.0%**	**1.10 [0.81 , 1.50]**
Total events:	149		139			
Heterogeneity: Chi² = 14.13, df = 7 (P = 0.05); I² = 50%						
Test for overall effect: Z = 0.61 (P = 0.54)						



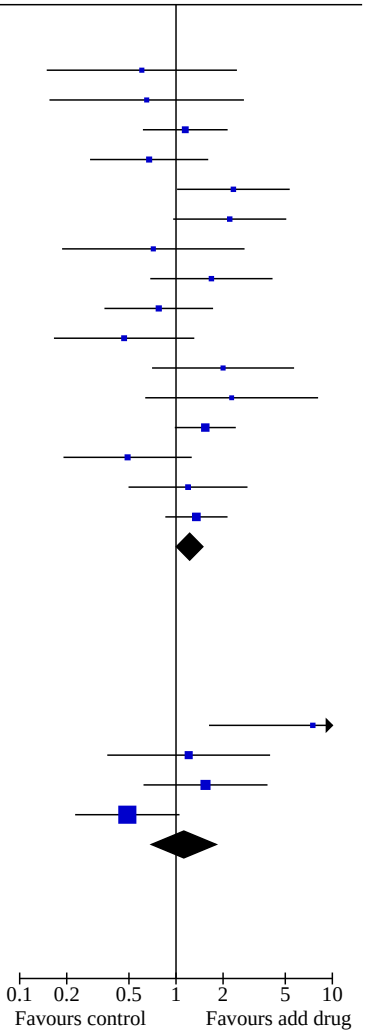
Analysis 3.5. Comparison 3: Overall response (assessable patients), Outcome 5: Overall response (addition of anthracycline vs addition of non-anthracycline)

Study or Subgroup	Addition of drug Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.5.1 Addition of an anthracycline						
Ahmann 1976b	10	23	11	21	20.9%	0.70 [0.21 , 2.30]
Cavalli 1983a	38	72	24	74	35.9%	2.33 [1.19 , 4.56]
Creech 1979	24	39	19	39	23.5%	1.68 [0.68 , 4.14]
Nemoto 1982a	12	20	3	18	4.1%	7.50 [1.63 , 34.59]
Pannuti 1984	9	23	8	23	15.6%	1.21 [0.36 , 4.00]
Subtotal (95% CI)		**177**		**175**	**100.0%**	**1.87 [1.22 , 2.86]**
Total events:	93		65			
Heterogeneity: Chi² = 6.78, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 2.89 (P = 0.004)						
3.5.2 Addition of a non-anthracycline						
Ahmann 1976a	10	23	13	24	3.7%	0.65 [0.21 , 2.06]
Aisner 1987a	46	79	45	82	9.4%	1.15 [0.61 , 2.14]
Aisner 1987b	13	41	20	49	6.3%	0.67 [0.28 , 1.61]
Cavalli 1983b	36	70	24	74	5.8%	2.21 [1.12 , 4.34]
Chlebowski 1983	7	18	8	17	2.6%	0.72 [0.19 , 2.74]
Cummings 1981a	22	94	13	46	6.8%	0.78 [0.35 , 1.73]
Cummings 1981b	7	44	13	45	5.5%	0.47 [0.17 , 1.31]
Inoue 1984	18	30	12	28	2.5%	2.00 [0.70 , 5.69]
Lokich 1977	13	20	9	20	1.6%	2.27 [0.64 , 8.11]
Marschke 1989	83	156	65	153	15.6%	1.54 [0.98 , 2.41]
Nemoto 1982b	10	40	17	42	6.3%	0.49 [0.19 , 1.26]
Rosner 1989	21	31	34	59	3.8%	1.54 [0.62 , 3.85]
Stein 1992	14	51	13	54	4.7%	1.19 [0.50 , 2.87]
Tranum 1982	77	160	57	140	16.0%	1.35 [0.85 , 2.14]
Vogel 1984	15	91	19	66	9.4%	0.49 [0.23 , 1.05]
Subtotal (95% CI)		**948**		**899**	**100.0%**	**1.13 [0.94 , 1.37]**
Total events:	392		362			
Heterogeneity: Chi² = 22.88, df = 14 (P = 0.06); I² = 39%						
Test for overall effect: Z = 1.28 (P = 0.20)						



Analysis 3.6. Comparison 3: Overall response (assessable patients), Outcome 6: Overall response (addition of 1 agent vs addition of 2 or more agents)

Study or Subgroup	Addition of drug Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.6.1 Addition of 1 agent						
Ahmann 1976a	5	12	13	24	2.7%	0.60 [0.15 , 2.45]
Ahmann 1976b	5	12	11	21	2.5%	0.65 [0.16 , 2.72]
Aisner 1987a	46	79	45	82	10.0%	1.15 [0.61 , 2.14]
Aisner 1987b	13	41	20	49	6.8%	0.67 [0.28 , 1.61]
Cavalli 1983a	38	72	12	37	4.1%	2.33 [1.02 , 5.34]
Cavalli 1983b	36	70	12	37	4.1%	2.21 [0.96 , 5.07]
Chlebowski 1983	7	18	8	17	2.7%	0.72 [0.19 , 2.74]
Creech 1979	24	39	19	39	4.0%	1.68 [0.68 , 4.14]
Cummings 1981a	22	94	13	46	7.3%	0.78 [0.35 , 1.73]
Cummings 1981b	7	44	13	45	5.9%	0.47 [0.17 , 1.31]
Inoue 1984	18	30	12	28	2.7%	2.00 [0.70 , 5.69]
Lokich 1977	13	20	9	20	1.7%	2.27 [0.64 , 8.11]
Marschke 1989	83	156	65	153	16.7%	1.54 [0.98 , 2.41]
Nemoto 1982b	10	40	17	42	6.8%	0.49 [0.19 , 1.26]
Stein 1992	14	51	13	54	5.0%	1.19 [0.50 , 2.87]
Tranum 1982	77	160	57	140	17.1%	1.35 [0.85 , 2.14]
Subtotal (95% CI)		**938**		**834**	**100.0%**	**1.22 [1.01 , 1.48]**
Total events:	418		339			
Heterogeneity: Chi² = 20.06, df = 15 (P = 0.17); I² = 25%						
Test for overall effect: Z = 2.02 (P = 0.04)						
3.6.2 Addition of 2 or more agents						
Nemoto 1982a	12	20	3	18	3.9%	7.50 [1.63 , 34.59]
Pannuti 1984	9	23	8	23	15.2%	1.21 [0.36 , 4.00]
Rosner 1989	21	31	34	59	23.5%	1.54 [0.62 , 3.85]
Vogel 1984	15	91	19	66	57.3%	0.49 [0.23 , 1.05]
Subtotal (95% CI)		**165**		**166**	**100.0%**	**1.12 [0.70 , 1.81]**
Total events:	57		64			
Heterogeneity: Chi² = 10.92, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 0.47 (P = 0.64)						



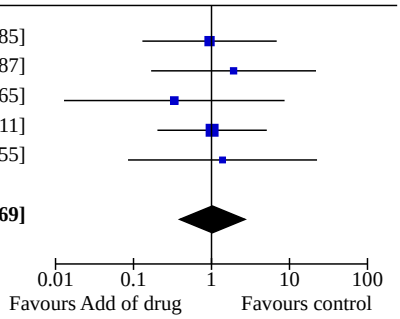
Comparison 4. Treatment-related deaths

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All trials	5	821	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.39, 2.69]
4.2 All trials (sensitivity analysis)	4	664	Odds Ratio (M-H, Fixed, 95% CI)	0.99 [0.35, 2.75]

Analysis 4.1. Comparison 4: Treatment-related deaths, Outcome 1: All trials

Study or Subgroup	Control Events	Control Total	Addition of a drug Events	Addition of a drug Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aisner 1987a	2	91	2	86	24.6%	0.94 [0.13 , 6.85]
Aisner 1987b	2	51	1	48	12.1%	1.92 [0.17 , 21.87]
Lokich 1977	0	21	1	22	17.5%	0.33 [0.01 , 8.65]
Marschke 1989	3	171	3	174	35.7%	1.02 [0.20 , 5.11]
Vogel 1984	1	66	1	91	10.1%	1.38 [0.09 , 22.55]
Total (95% CI)		**400**		**421**	**100.0%**	**1.03 [0.39 , 2.69]**
Total events:	8		8			

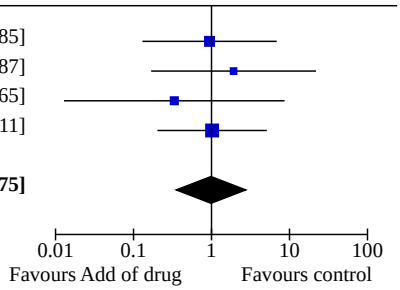
Heterogeneity: Chi² = 0.76, df = 4 (P = 0.94); I² = 0%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Treatment-related deaths, Outcome 2: All trials (sensitivity analysis)

Study or Subgroup	Control Events	Control Total	Addition of a drug Events	Addition of a drug Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Aisner 1987a	2	91	2	86	27.3%	0.94 [0.13 , 6.85]
Aisner 1987b	2	51	1	48	13.5%	1.92 [0.17 , 21.87]
Lokich 1977	0	21	1	22	19.5%	0.33 [0.01 , 8.65]
Marschke 1989	3	171	3	174	39.7%	1.02 [0.20 , 5.11]
Total (95% CI)		**334**		**330**	**100.0%**	**0.99 [0.35 , 2.75]**
Total events:	7		7			

Heterogeneity: Chi² = 0.72, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. 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	thitepa, mitomycin C
	by platinum coordination cross-linking	cisplatin, carboplatin
	by antibiotics	doxorubicin, daunorubicin, mitoxantrone, idarubicin, epirubicin, amsacrine
	by podophyllotoxins	etoposide, teniposide
	by intercalation	dactinomycin

Table 1. Chemotherapeutic Agents (adapted from Table 1.1 in The Chemotherapy Source Book) *(Continued)*

	by uncertain mechanisms	bleomycin
Spindle poisons	vinca alkaloids	vincristine, vinblastine, vendesine, vinorelbine
	taxanes	taxol, taxotere
Antimetabolites	thymidylate synthase	5-fluorouracil
	dihydrofolate reductase	methotrexate

Table 2. Acute Toxicity Grade III-IV

Site of toxicity	No. of trials	Add events (patients)/n	Control (patients)/n	OR (95% CI)
ASSESSABLE PATIENTS				
Trials with toxicity defined by WHO criteria Grade III and IV				
Alopecia	1	0/51	2/54	
Leucopenia*	7	224/517	166/494	1.51 (1.17-1.95)
Nausea/Vomiting**	4	53/282	23/271	2.50 (1.48-4.18)
Trials with criteria not defined. Trial grades the toxicity as 'severe'				
Alopecia	3	96/118	52/117	5.45 (3.02-9.84)
Leucopenia*	0	0	0	
Nausea/Vomiting**	4	52/286	40/280	1.33 (0.85-2.09)
If it is assumed that trials which defined toxicity as 'severe' have assessed toxicity the same as trials with toxicity WHO criteria grade III or IV, then these results can be combined (as below)				
All trials				
Alopecia	4	96/169	54/171	2.85 (1.83-4.44)
Leucopenia*	7	224/517	166/494	1.51 (1.17-1.95)
Nausea/Vomiting**	8	105/568	63/551	1.76 (1.25-2.46)

Table 2. Acute Toxicity Grade III-IV *(Continued)*

* data on grade III or IV neutropenia was included if data on leucopenia not reported
**data on vomiting included if nausea and vomiting reported separately

Table 3. Chemotherapy Details

Trial Name	Arm I	Arm II
Ahmann 1976a	Arm I: AC = doxorubicin 40 mg/m^2 and cyclophosphamide 500 mg/m^2 both day 1. Cycles repeated every 5 weeks. Number of cycles not reported.	Arm II: CAF = cyclophosphamide 400 mg/m^2 + doxorubicin 40 mg/m^2 (both day 1) + 5-fluorouracil 150 mg/m^2 (day 1-3). Cycles repeated every 5 weeks. Number of cycles not reported.
Ahmann 1976b	Arm I: CFP = cyclophosphamide 150 mg/m^2 + 5-fluorouracil 300 mg/m^2 both days 1 through 5 + prednisone. Cycles repeated every 5 weeks. Number of cycles not reported.	Arm II: CAF = cyclophosphamide 400 mg/m^2 + doxorubicin 40 mg/m^2 (both day 1) + 5-fluorouracil 150 mg/m^2 (day 1-3). Cycles repeated every 5 weeks. Number of cycles not reported.
Aisner 1987a	Arm I: CAF = cyclophosphamide 100 mg/m^2/day days 1-14 + doxorubicin 25 mg/m^2 days 1 & 8 (after total dose of 450 mg/m^2 replaced with methotrexate 40 mg/m^2 days 1 & 8)+ 5-fluorouracil 500 mg/m^2 days 1 & 8. 28 day cycle.	Arm II: CAFVP = cyclophosphamide 100 mg/m^2/day, days 1-14 + doxorubicin 25 mg/m^2 days 1 & 8 (after total dose 450 mg/m^2 replaced with methotrexate 40 mg/m^2 days 1 & 8) + 5-fluorouracil 500 mg/m^2 days 1 & 8 + vincristine 10 mg/m^2 days 1 & 8 + prednisone 40 mg/m^2/day days 1-14. 28 day cycle.
Aisner 1987b	Arm I: CAF+MER = cyclophosphamide 100 mg/m^2/day days 1-14 + doxorubicin 25 mg/m^2 days 1 & 8 (after total dose of 450 mg/m^2 replaced with methotrexate 40 mg/m^2 days 1 & 8) + 5-fluorouracil 500 mg/m^2 days 1 & 8 + MER 200 micrograms days 1 & 8. 28 day cycle.	Arm II: CAFVP+MER = cyclophosphamide 100 mg/m^2/day, days 1-14 + doxorubicin 25 mg/m^2 days 1 & 8 (after total dose 450 mg/m^2 replaced with methotrexate 40 mg/m^2 days 1 & 8) + 5-fluorouracil 500 mg/m^2 days 1 & 8 + vincristine 10 mg/m^2 days 1 & 8 + prednisone + MER 200 micrograms days 1 & 8. 28 day cycle.
Cavalli 1983a	Arm I: CLB+MFP = chlorambucil 5 mg/m^2/day days 1-14 + methotrexate 10 mg/m^2/wk days 1 & 8 + 5-fluorouracil 500 mg/m^2/wk days 1 & 8 + prednisone. 4 weeks cycles for 6 months.	Arm II: CLB+AMFP = chlorambucil 5 mg/m^2/day days 1-14 + methotrexate 40 mg/m^2/wk days 1 & 8 + 5-fluorouracil 600 mg/m^2/wk days 1 & 8 + prednisone 30 mg/m^2/day days 1-14 (then decreasing) + doxorubicin 60 mg/m^2 day 28. 8 week cycles for 6 months.
Cavalli 1983b	Arm I: CLB+MFP = chlorambucil 5 mg/m^2/day days 1-14 + methotrexate 10 mg/m^2/wk days 1 & 8 + 5-fluorouracil 500 mg/m^2/wk days 1 & 8 + prednisone. 4 weeks cycles for 6 months.	Arm II: CLB+MFVP = chlorambucil 5 mg/m^2/day days 1-14 + methotrexate 15 mg/m^2/wk days 1-3 & 8-10 + 5-fluorouracil 500 mg/m^2/wk days 15 & 22 + vincristine 1.2 mg/m^2/wk days 15 & 22 + prednisone. 4 week continuous cycle for 6 months.
Chlebowski 1983	Arm I: A-CCNU = doxorubicin (25-40 mg/m^2) every 3 weeks + CCNU (65-90 mg/m^2) every 6 weeks.	Arm II: A-CCNU-V = doxorubicin (25-40 mg/m^2) every 3 weeks + CCNU (65-90 mg/m^2) every 6 weeks + vincristine (1.4 mg/m^2 with individual dosage not exceeding 2 mg) every 3 weeks.

Table 3. Chemotherapy Details *(Continued)*

Creech 1979	Arm I: CMF = cyclophosphamide 50 mg/m^2 days 1-14 + methotrexate 20 mg/m^2 days 1 & 8 + 5-fluorouracil 300 mg/m^2 days 1 & 8. 28 day cycle.	Arm II: CAMF = cyclophosphamide 50 mg/m^2 days 1-14 + doxorubicin 20 mg/m^2 days 1 & 8 + methotrexate 20 mg/m^2 days 1 & 8 + 5-fluorouracil 300 mg/m^2 days 1 & 8. 28 day cycle.
Cummings 1981a	Arm I: AV = doxorubicin 60 mg/m^2 + vincristine 1.2 mg/m^2; Cycles repeated every 3 weeks until progressive disease	Arm II: AVD = doxorubicin 45 mg/m^2 + vincristine 1.2 mg/m^2 + dibromodulcitol 140 mg/m^2. Cycles repeated every 4 weeks (AVD) until progressive disease.
Cummings 1981b	Arm I: AV = doxorubicin 60 mg/m^2 + vincristine 1.2 mg/m^2; Cycles repeated every 3 weeks until progressive disease	Arm II: AVI = doxorubicin 45 mg/m^2 + vincristine 1.2 mg/m^2 + ICRF-159 250 mg/m^2. Cycles repeated every 4 weeks (AVI) until progressive disease.
Inoue 1984	Arm I: ACF = doxorubicin 40 mg/m^2 day 1 + cyclophosphamide 130 mg/m^2 day 1-5 + ftorafur 500 mg/m^2 daily, 21 day cycle.	Arm II: ACFM = doxorubicin 40 mg/m^2 day 1 + cyclophosphamide 130 mg/m^2 day 1-5 + ftorafur 500 mg/m^2 daily + methotrexate 10-15 mg/m^2 day 1 & 5, 21 day cycle.
Kennealey 1978	Arm I: AC = doxorubicin 40 mg/m^2 + cyclophosphamide 1.0 mg/m^2	Arm II: ACMF = doxorubicin 40 mg/m^2 + cyclophosphamide 1.0 mg/m^2 + methotrexate 30-40 mg/m^2 + 5-fluorouracil 400-600 mg/m^2.
Lokich 1977	Arm I: MA = melphalan 2.0 mg/m^2 + doxorubicin 50 mg/m^2.	Arm II: MAC = melphalan 1.0 mg/m^2 + doxorubicin 50 mg/m^2 + cyclophosphamide 250 mg/m^2 - to maximum dose doxorubicin 450 mg/m^2, then maintenance CMF every 4 weeks.
Marschke 1989	Arm I: CFP = cyclophosphamide 150 mg/m^2 + 5-fluorouracil 300 mg/m^2 + prednisone.	Arm II: CMFP = cyclophosphamide 100 mg/m^2 + methotrexate 40 mg/m^2 (< 65 yrs; 30 mg/m^2 if ≥ 65 yrs) + 5-fluorouracil 600 mg/m^2 (< 65 yrs; 400 mg/m^2 if ≥ 65 yrs) + prednisone.
Nemoto 1982a	Arm I: CFP = cyclophosphamide 150 mg/m^2 days 1-5 + 5-fluorouracil 300 mg/m^2 days 1-5 + prednisone. Number of cycles not specified.	Arm II: CFP-CA = Alternating regimens: cyclophosphamide 150 mg/m^2 days 1-5 + 5-flurouracil 300 mg/m^2 days 1-5 + prednisone. 5 week cycle then cyclophosphamide 500 mg/m^2 + doxorubicin 40 mg/m^2 every nine weeks. Maximum cumulative dose of Adriamycin 500 mg/m^2.
Nemoto 1982b	Arm I: AC = doxorubicin 40 mg/m^2 day 1 + cyclophosphamide 500 mg/m^2 day 1.	Arm II: CAF = cyclophosphamide 400 mg/m^2 day 1 + 5-fluorouracil 200 mg/m^2 days 1-3 + doxorubicin 40 mg/m^2 day 1.
Pannuti 1984	Arm I: CMF = cyclophosphamide 100 mg/m^2 days 1-14 + methotrexate 40 mg/m^2 day 1 & 8 + 5-fluorouracil 600 mg/m^2 day 1 & 8. 28 day cycle.	Arm II: R14 = cyclophosphamide 2 mg/kg + vincristine 0.01 mg/kg + vinblastine 0.1 mg/kg all on day 1 and then on day 2, 5-fluorouracil 5 mg/kg + methotrexate 0.7 mg/kg + doxorubicin 0.5 mg/kg. Cycle every 21 days.
Rosner 1989	Arm I: CFP = cyclophosphamide 150 mg/m^2 + 5-fluorouracil 300mg/m2 + prednisone every 5 weeks.	Arm II: CFPMV = 5-fluorouracil 500 mg + methotrexate 25 mg + vincristine 1 mg (all weekly) + cyclophosphamide 50 mg + prednisone.
Segaloff 1985	Arm I: CMFP = cyclophosphamide 100 mg/day + methotrexate 25 mg/week + 5-fluorouracil 500 mg/week + prednisone.	Arm II: CMFVP = cyclophosphamide 100 mg/day + methotrexate 25 mg/week + 5-fluorouracil 500 mg/week + vincristine 1 mg/week + prednisone.
Stein 1992	Arm I: 2M = mitozantrone 6.5 mg/m^2, methotrexate 30 mg/m^2 every 3 weeks.	Arm II: 3M = mitozantrone 6.5 mg/m^2, methotrexate 30 mg/m^2 every 3 weeks & mitomycin C 6.5 mg/m^2 every 6 weeks.
Tranum 1982	Arm I: AC = doxorubicin 40 mg/m^2 + cyclophosphamide 200 mg/m^2 (p.o) on day	Arm II: FAC = doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2 + 5-fluorouracil 500 mg/m^2 every 4 weeks

Table 3. Chemotherapy Details *(Continued)*

	3, 4, 5, 6 every 3 weeks for 3 courses, then ever 4 weeks. Number of cycles not reported	
Vogel 1984	Arm I: CAF = cyclophosphamide 500 mg/m^2 + doxorubicin 50 mg/m^2 + 5-fluorouracil 500 mg/m^2. 3 week cycle	Arm II: CAF+CAMELEON = CAF (as arm I) alternating cycle with CAMELEON at 3 weekly intervals. CAMELEON: vincristine 1.4 mg/m^2 + methotrexate 30 mg/m^2 (three additional doses of per os methotrexate given at 6 hourly intervals) + cytosine arabinoside 300 mg/m^2 + leucovorin 17.5 mg/m^2.

Table 4. Included RCTs withdrawn, by outcome, with reasons

Trial ID	Outcome	Reason not included
Ahman 1976	Toxicity	Does not report toxicity in sufficient detail to enable the data to be used in the review
Aisner 1987	Time-to-event data (survival and time to treatment failure)	Time-to-event data not extracted from published curves for inclusion in the review as unable to do so accurately to replicate reported study findings
Cavalli 1983	Toxicity	Does not report toxicity in sufficient detail to enable the data to be used in the review
Cummings 1981	Toxicity	Does not report toxicity in sufficient detail to enable the data to be used in the review
Inoue 1984	Toxicity	Does not report toxicity in sufficient detail to enable the data to be used in the review
Kennealey 1978	All outcomes	This paper included 42 randomised patients plus 15 non-randomised patients from a pilot study. The data for both was pooled and it was not possible to distinguish between randomised and non-randomised
Pannuti 1984	Toxicity	Does not report toxicity in sufficient detail to enable the data to be used in the review
Rosner 1989	Toxicity	Does not report toxicity in sufficient detail to enable the data to be used in the review
Segaloff 1985	Response, Toxicity	Does not report response and toxicity in sufficient detail to enable the data to be used in the review

APPENDICES

Appendix 1. WHO ICTRP Search Portal

Host: http://apps.who.it/trialsearch/
8 July 2010
Advanced search (with Recruitment set at ALL):

Search 1.
Condition field: metastatic breast cancer
Intervention field: addition of chemotherapy drug to a chemotherapy regimen OR addition of chemotherapy drugs to a chemotherapy regimen

Search 2.
Condition field: metastatic breast cancer
Intervention field: addition of cytotoxic drug to a chemotherapy regimen OR addition of cytotoxic drugs to a chemotherapy regimen

Search 3.
Condition field: metastatic breast cancer
Intervention field: chemotherapy

Search 4
Condition field: advance breast cancer
Intervention field: addition of chemotherapy drug to a chemotherapy regimen OR addition of chemotherapy drugs to a chemotherapy regimen

Search 5.
Condition field: advance breast cancer
Intervention field: addition of cytotoxic drug to a chemotherapy regimen OR addition of cytotoxic drugs to a chemotherapy regimen

Search 6.
Condition field: advance breast cancer
Intervention field: chemotherapy

WHAT'S NEW

Date	Event	Description
6 February 2018	Review declared as stable	This review question is broad and no longer reflects the clinical management of breast cancer. Today, chemotherapy decisions are based on the molecular subtype of the breast cancer. As the trials in this Review include women diagnosed with unselected metastatic breast cancer, this Review will no longer be updated.

HISTORY

Protocol first published: Issue 4, 2001
Review first published: Issue 3, 2006

Date	Event	Description
11 February 2011	Amended	Changed the address of the first author.
15 February 2010	New citation required but conclusions have not changed	No new studies included. New authors joined the author team.
9 September 2009	Amended	Converted to new review format.
10 August 2009	New search has been performed	Performed search for new studies on the 10th August 2009.

CONTRIBUTIONS OF AUTHORS

DG designed the review and wrote the protocol. D B, with input from DG, collected the data for the review. D B wrote the results and discussion for the review in collaboration with NW and DG.

SK and PT updated the review.

DECLARATIONS OF INTEREST

DB wrote the review published in May 2006 while u ndertaking her Masters course at The University of Sydney. Following its publication, DB was employed by the Clin ical Research Organisation Parexel (UK) from August 2006 until October 2009 and worked on a variety of oncology studies including breast cancer. DB was not involved in updating the review during 2009 and 2010 but it should be mentioned that DB wa s s till affiliated with Parexel in 2009.

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

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [adverse effects] [*therapeutic use]; Breast Neoplasms [*drug therapy] [mortality] [pathology]; Randomized Controlled Trials as Topic; Survival Analysis

MeSH check words

Female; Humans