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## Antitumour antibiotic containing regimens for metastatic breast cancer (Review)

Lord SJ, Ghersi D, Gattellari M, Wortley S, Wilcken N, Thornton C, Simes J

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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](https://doi.org/10.1002/14651858.CD003367.pub2).

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[Intervention Review]

# Antitumour antibiotic containing regimens for metastatic breast cancer

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## ABSTRACT

### Background

Antitumour antibiotics are used in the management of metastatic breast cancer. Some of these agents have demonstrated higher tumour response rates than non-antitumour antibiotic regimens, however a survival benefit has not been established in this setting.

### Objectives

To review the randomised evidence comparing antitumour antibiotic containing chemotherapy regimens with regimens not containing an antitumour antibiotic in the management of women with metastatic breast cancer.

### Search methods

The Specialised Register maintained by the Cochrane Breast Cancer Group was searched on 3rd October, 2006 using the codes for 'advanced breast cancer' and 'chemotherapy'. Details of the search strategy and coding applied by the Group to create the register are described in the Group's module on The Cochrane Library.

### Selection criteria

Randomised trials comparing antitumour antibiotic containing regimens with regimens not containing antitumour antibiotics in women with metastatic breast cancer.

### Data collection and analysis

Data were collected from published trials. Studies were assessed for eligibility and quality, and data were extracted by two independent reviewers. Hazard Ratios (HRs) were derived from time-to-event outcomes where possible, and a fixed effect model was used for meta-analysis. Response rates were analysed as dichotomous variables. Quality of life and toxicity data were extracted where present. A primary analysis was conducted for all trials and by class of antitumour antibiotic.

### Main results

Thirty-four trials reporting on 46 treatment comparisons were identified. All trials published results for tumour response and 27 trials published time-to-event data for overall survival. The observed 4244 deaths in 5605 randomised women did not demonstrate a statistically significant difference in survival between regimens that contained antitumour antibiotics and those that did not (HR 0.96, 95% CI 0.90 to 1.02,  $P = 0.22$ ) and no significant heterogeneity. Antitumour antibiotic regimens were favourably associated with time-to-progression

(HR 0.84, 95% CI 0.77 to 0.91) and tumour response rates (odds ratio (OR) 1.33, 95% CI 1.21 to 1.48) although statistically significant heterogeneity was observed for these outcomes. These associations were consistent when the analysis was restricted to the 30 trials that reported on anthracyclines. Patients receiving anthracycline containing regimens were also more likely to experience toxic events compared to patients receiving non-antitumour antibiotic regimens. No statistically significant difference was observed in any outcome between mitoxantrone containing and non-antitumour antibiotic-containing regimens.

### Authors' conclusions

Compared to regimens without antitumour antibiotics, regimens that contained these agents showed a statistically significant advantage for tumour response and time to progression in women with metastatic breast cancer but were not associated with an improvement in overall survival. The favourable effect on tumour response and time to progression observed in anthracycline containing regimens was also associated with greater toxicity.

## PLAIN LANGUAGE SUMMARY

### Antitumour antibiotic containing regimens for metastatic breast cancer

Advanced (metastatic) breast cancer is cancer that has spread beyond the breast. Treatment for metastatic disease usually involves some type of chemotherapy (anti-cancer drugs) to try to reduce the cancer. Chemotherapy drugs can either be given as a single agent or in combination with other chemotherapy drugs. This is done according to a plan or a course of the drug referred to as a regimen. There are many types of chemotherapy drugs which work in various ways. Antitumour antibiotics work by damaging the cancer cells thereby preventing those cells from multiplying. Chemotherapy in general produces a range of side effects or adverse events related to the treatment. The known side effects of antitumour antibiotics include nausea, vomiting, a reduction in the number of white blood cells (known as leukopenia), and in some cases a toxic reaction which alters the working of the heart (called cardiotoxicity).

This review sought to identify and review the randomised evidence comparing courses of chemotherapy containing antitumour antibiotics against courses not containing antitumour antibiotics. This review identified 34 eligible trials involving 5605 women. This review found that for women with advanced breast cancer, taking antitumour antibiotics did not result in better survival than women who took other types of chemotherapy drugs. Despite the lack of evidence of survival benefit, this review demonstrated that women taking these drugs had an advantage in time to progression (the length of time it takes for the cancer to progress after taking the drug) and tumour response (shrinking of the tumour) compared to women who did not take the antitumour antibiotic drugs. In addition however, the risks of side effects including cardiotoxicity, leukopenia and nausea/vomiting were all significantly increased in the women taking the antitumour antibiotics. Given that this review failed to show a benefit in survival for women taking this group of drugs but a higher rate of side effects, the use of these drugs in the management of metastatic breast cancer must be carefully weighed against the risk of these side effects.

## BACKGROUND

Breast cancer is the most common type of cancer in women and the most common cause of cancer death in that group. In 2002, there were over 1 million new cases and approximately 410,000 deaths from breast cancer worldwide; an age standardised death rate (ASR) of 13.2 (per 100,000). ASRs of 25 or greater were recorded that same year by Barbados (25.5), Belgium (27.7), Botswana (25.0), Cyprus (29.6), Denmark (27.8), Georgia (25.1), Ireland (25.7), Malta (29.6), The Netherlands (27.5) and The Philippines (27.1). (Ferlay 2002).

The stage of breast cancer at the time of diagnosis is an important indicator of prognosis. Median survival in women with metastatic breast cancer (MBC) is around 18 to 24 months although this could range from a few weeks to several years (Stockler 2000). Although there is no randomised evidence comparing chemotherapy with observation in women with metastatic breast cancer, it is widely accepted that women with metastatic disease should receive some form of systemic therapy at some time during the course of their disease. Chemotherapy is considered by many to be the appropriate first treatment option for women with multiple sites of recurrence or where visceral disease is not easily treated by local modalities (Hayes 1995). Chemotherapy is also considered to be useful in women whose cancer is hormone refractory or expected to be hormone resistant (Hortobagyi 1996).

As a class, antitumour antibiotics are agents that have been isolated, or synthetically derived, from a variety of fungal organisms for their cytotoxic properties. They damage the DNA template by a variety of mechanisms including intercalation into DNA and RNA, alkylation of DNA and the generation of oxygen free radicals to produce single- and double-strand DNA breaks (Perry 1997). Antitumour antibiotics include the anthracyclines (for example doxorubicin and epirubicin); anthracenediones (mitoxantrone/mitozantrone); and mitomycin-C.

This class of drugs, in particular anthracycline-based FAC (cyclophosphamide, 5-fluorouracil and doxorubicin) and FEC (cyclophosphamide, 5-fluorouracil and epirubicin) regimens, have been used in chemotherapy for the management of metastatic breast cancer for the last three decades (Hortobagyi 2003). Several large randomised trials have supported their use over standard CMF (cyclophosphamide, 5-fluorouracil, methotrexate) regimens but despite yielding higher response rates, the evidence for survival benefit has not been conclusive (Fossati 1998). Common side effects of these agents are nausea, vomiting, hair loss and leucopenia. Rarely, anthracyclines may cause cardiomyopathy and these agents should be used with care in patients with known cardiac disease.

## OBJECTIVES

The objective of this review was to compare antitumour antibiotic containing chemotherapy regimens with regimens not containing antitumour antibiotics in the management of women with MBC.

Antitumour antibiotics were classified as anthracyclines, anthracenediones or other antitumour antibiotics for the purposes of this review. Pre-specified subquestions within the review for each of these classes were:

- a) regimen A plus antitumour antibiotic versus regimen A;
- b) regimen A plus antitumour antibiotic versus regimen B;
- c) single agent antitumour antibiotic versus regimen C.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Properly randomised controlled clinical trials.

#### Types of participants

1. Women diagnosed with advanced breast cancer
  - a. advanced breast cancer was defined as metastatic disease;
  - b. women with locoregional disease only were excluded\*;
  - c. both newly diagnosed and recurrent cases were included.
2. Women randomised to receive chemotherapy for advanced disease as first line treatment (ie. no previous chemotherapy given except as adjuvant therapy)\*\*
3. No age restrictions were applied

\*Trials which included both women with metastatic disease and women with locoregionally recurrent disease only were included if women with locoregional recurrence were less than 20% of the total group.

\*\*Trials reporting on antitumour antibiotics for advanced disease were excluded if more than 50% of participants had received prior cytotoxic chemotherapy for MBC.

#### Types of interventions

Intervention group: any chemotherapy regimen containing an antitumour antibiotic.

Comparator: any chemotherapy regimen not containing an antitumour antibiotic.

See Table 1 for classification of chemotherapeutic agents;

Table 2 for classification of antitumour agents (Perry 1997).

Endocrine therapy may also have been given to both treatment groups.

Trials may or may not specify recommended treatment upon disease progression or initial treatment failure. Trials where patients crossed over to the other treatment arm at the time of progression or received other treatment off-study were included in this review and analysed according to the treatment they were originally randomised to receive. Sequential trials where patients were allocated to receive a set number of cycles of one treatment and then crossed over to the other treatment arm (not at the time of progression but upon completion of the first treatment) were excluded from this review.

#### Types of outcome measures

1. Overall survival
2. Time to progression (or progression-free survival)
3. Response
4. Quality of life measures (trial-specific instruments)
5. Toxicity

For the purpose of this review, the following outcome definitions applied:

1. Overall survival (OS): time from date randomised to date of death (any cause);
2. Time to progression (TTP): time from date randomised to date of progression or death (any cause);
3. Response rate (RR): the proportion of patients with a complete or partial response as defined by the National Cancer Institute's Response Evaluation Criteria in Solid Tumors (NCI 2002).

This review also attempted to investigate treatment-related death which, for the purpose of this review, was defined as death due to the toxicity of the drug and not to disease progression. If an individual trial did not include the definition used by that trial but used the terms 'toxic death' or 'lethal toxicity', or indicated that death was due to treatment, then the information was included in the review.

Time-to-treatment failure was a planned outcome for this review and was defined as time from date randomised to date of progression, death (any cause), withdrawal due to adverse event, patient refusal or further anti-cancer therapy for documented progression. Eight trials reported data on time to treatment failure, however, not all these trials used definitions in alignment with our pre-specified definition and this outcome was not included in this review.

### Search methods for identification of studies

The specialised register maintained by the Secretariat of the Cochrane Breast Cancer Group (CBCG) was searched (3rd October 2006). Details of the search strategy applied by the Group to create the register, and the procedure used to code references, are described in the Group's module on *The Cochrane Library*. The register includes both published and unpublished (including ongoing) trials identified from searches of electronic databases including MEDLINE, EMBASE and the Cochrane Controlled Trials Register, and handsearching of journals and conference proceedings. All references that had been assigned the CBCG codes 'advanced' and 'chemotherapy' as applied to the specialised register and the abstracts were screened in an attempt to determine if the reference pertained to a randomised trial in women with metastatic breast cancer comparing one chemotherapy combination with another. The complete article was obtained for references that were definitely eligible, or where it was not possible to determine eligibility based only on information in the abstract.

The reference lists of other related literature reviews were also searched. The reviews searched included [Fossati 1998](#) and [Stockler 2000](#) as well as review articles identified by the search strategy.

### Data collection and analysis

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 hazard ratio (HR) and associated variances for overall survival and time to progression were extracted directly from the trial publication/s. If not reported, this data was obtained indirectly using the methods described by [Parmar 1998](#) et al using either other available summary statistics or from data extracted from published Kaplan-Meier curves. To allow for immature follow up, the numbers at risk were adjusted based on estimated minimum and maximum follow-up times. If these were not reported in any of the reports available, minimum follow up was estimated 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. These follow-up estimates are recorded in the Characteristics of Included Studies table under 'Notes'.

A pooled HR was obtained from the derived observed (O) less 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 containing antitumour antibiotics versus those not containing antitumour antibiotics.

All outcomes available from the individual studies were included in the meta-analysis with heterogeneity reported using chi-square tests (see the Cochrane Reviewers' Handbook).

Ratios of treatment effects for time-to-event outcomes were reported so that HRs less than 1.0 favour regimens containing antitumour antibiotics and values greater than 1.0 favour regimens that do not contain antitumour antibiotics. The plots for overall survival and progression-free survival are hazard ratio (HR) plots, although they are labelled as odds ratio (OR) plots in the default mode of meta-view.

Response rates were analysed as dichotomous variables (complete or partial response versus stable disease or no response) and a pooled odds ratio was derived. Response has been reported based on assessable (not randomised) patients as most of the trials included in this review only reported response in this way. Ratios of treatment effects for response were reported so that ORs less than 1.0 favour regimens containing antitumour antibiotics and values greater than 1.00 favour regimens that do not contain antitumour antibiotics.

If all arms in a multi-arm trial were included in the meta-analysis and one treatment arm was included in more than one of the treatment comparisons then the number of events and the number of participants in that arm were divided by the number of treatment comparisons made. This method was used to avoid the multiple use of participants in the pooled estimate of treatment effect while retaining information from each arm of the trial and is likely to compromise the precision of the pooled estimate slightly.

Quality of life data were collected using a variety of instruments across trials. These data were not statistically synthesised but were summarised and evaluated qualitatively.

Toxicity data was extracted for Grade III or Grade IV events of leukopenia, nausea or vomiting, alopecia and cardiotoxicity. This data was not consistently reported across the included trials and the analysis was limited to the calculation a single odds ratio (with 95% confidence intervals) using the total number events and number at risk added up across trials.

As specified in the protocol, each of these outcomes was reported, where available, for all trials combined and by class of antitumour antibiotic (primary analyses). Two secondary analyses were also performed as pre-specified: 1. analysis by type of antitumour antibiotic-containing regimen (single, additional or replacement agent to comparator regimen); and 2. sensitivity analysis using studies with adequate concealment clearly stated. Planned subgroup analysis by menopausal status, hormone receptor status and stage of disease was not undertaken due to the lack of data available in the included trials for these subgroups.

Post-hoc subgroup analyses were conducted for the subclass of anthracycline containing antitumour antibiotic regimens by type of comparator regimen. These analyses were planned after identification of the eligible trials, and prior to the pooling of results. Comparator regimens used in each trial were classified into

four subgroups to allow analyses of antitumour antibiotic efficacy by comparator class. These subgroups were selected on the basis that they each represented classes of agents of similar activity:

1. CMF;
2. CMF based, with addition of other cytotoxics for example Vincristine;
3. other C- or CF-based (no methotrexate);
4. taxanes.

Chlorambucil was considered equivalent to cyclophosphamide and regimens that included prednisone were considered equivalent to those that did not for the purpose of this classification.

Overall this review tested 40 comparisons for each of the six outcome variables.

## RESULTS

### Description of studies

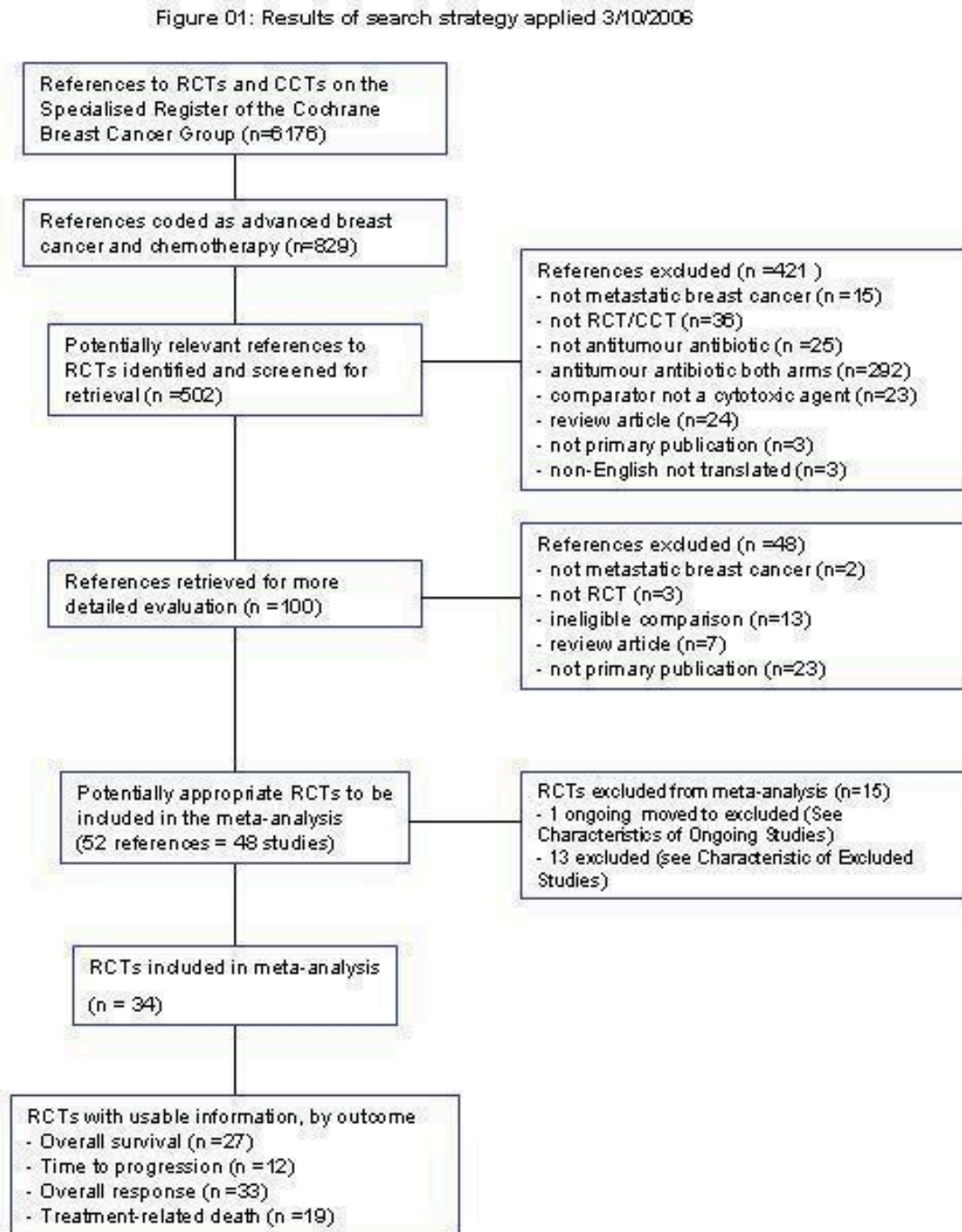
On the 3rd October 2006, the Cochrane Breast Cancer Group Specialised Register contained 6,176 references of which 829 were

coded as references to studies of chemotherapy and advanced breast cancer (see [Figure 1](#) for the quorum flow chart). Of these, 502 were references that reported the comparison of two different chemotherapy combinations in metastatic breast cancer, of which 421 were not eligible based on information in the abstract. The complete paper was obtained for 100 references leading to the exclusion of a further 48 references. The remaining 52 references reported the results of 48 randomised trials, 15 of which were excluded from the meta-analysis: 15 were not considered to be eligible for the review (see Characteristics of excluded studies).

The 34 eligible trials reported on 46 treatment comparisons: 42 comparisons of anthracyclines, and four comparisons of mitoxantrone with non-antitumour antibiotic containing regimens. The regimens used in each trial are summarised in [Figure 2](#) and [Figure 3](#). Where a trial included more than one comparison these were labelled alphabetically (a, b, c). The trials included in the forest plots were labelled by trial name or primary author and date of publication.



Figure 1.



**Figure 2. Summary of regimens included in the analyses a) Treatment arm = Anthracycline containing regimens**

Trial ID	Treatment (containing antitumour antibiotic)	Control (non-antitumour antibiotic)	Anti-tumour Antibiotic naive	Accrual
Ahmann 1974 (a) (b)	A A	CFP CFVP	Y	48
Ahmann 1991	CAP	CFP	Y	94
ANZBCTG Coates (a) (b)	CA - continuous therapy - intermittent therapy	CMFP - continuous therapy - intermittent therapy	Y	308
B122	CAF	CMF	Y	92
Brambilla 1976	A + V <sup>1</sup>	CMF	Y	110
CALGB Aisner 1987 (a) (b) (c) (d)	CAF CAFVP CAF + MER CAFVP + MER	CMF CMF CMF + MER CMF + MER	Y	432
CALGB Tormey (a) (b)	CAFVP	CMFVP - C CMFVP - I	Y	396
Carmo-Pereira 1981	C + A + V <sup>1</sup>	CMFP	Y	51
Chauvergne 1978	A + M + V <sup>1</sup>	CFV <sup>1</sup>	Y	70
Creagan 1984	C + A + CDDP	CFP	Y	88
Creech 1979	CAMF	CMF	Y	78
DBC 1999	CAF + TAM	CMF + TAM	Y	415
ECOG Cummings 1985	CAF	CMFP	Y	177
ECOG E1193 (a) (b)	A A + PACL	PACL PACL	Y	739
ECOG EST 2173 (a) (b)	A + V <sup>1</sup> A + V <sup>1</sup>	CMF CMFP	Y	404
EORTC 10923	A	PACL	?	331
Fountzilas 2004	E + PACL	PACL + CARB	Y	327
Fraser 1993	E	CMF	Y	40
HEPI 013 Study	FEC	CMF	Y	460
Hoogstraten 1976 (a) (b)	A A	- CMFVP-I - CMFVP-W	Y	297
Kolaric 1977	CAMFP	CMFVP	Y	74
Kolaric 1985	C + A + CDDP	CMFVP	Y	128
Muss 1978	CAFVP	CMFVP	Y	175
Muss 1982	C + A + V <sup>1</sup>	CMF	Y	100
Nemoto 1978	A	CFP	Y	94
Nemoto 1982 (a) (b) (c)	CFP-CA CAF CA	CFP CFP CFP	Y	126
Pannuti 1984	CA + M + V1 + V2	CMF	?	46
Rosner 1989 (a) (b)	CA CA	CFP CMFVP	Y	182
SAKK 1983 (a)	CDDP + A + M + F +	CDDP + M + F + P		

**Figure 2. (Continued)**

SAKK 1983 (a) (b)	CDDP + A + M + F + P CDDP + A + M + F + P	CDDP + M + F + P CDDP + M + F + V <sup>1</sup> + P	Y	230
SECSG 1983	CAF	CMFVP	Y	362

**Figure 3.**

Trial ID	Treatment (containing antitumour antibiotic)	Control (non-antitumour antibiotic)	Antitumour Antibiotic naive	Accrual
ANZ BCTG 8614	MZA	CMFP	?	391
Hainsworth 1997	MZA + LEUC + F	CMF	Y	126
Harper-Wynne 1999	MZA + M	CMF	?	116
Lorusso 1993	C + MZA + F	CMF	Y	128

Key to summary of regimens in the analyses  
 A – doxorubicine; C – cyclophosphamide; CARB – carboplatin; CDDP – cisplatin; CLB – chlorambucil;  
 CMF – cyclophosphamide, methotrexate, fluoracil; CMFP – cyclophosphamide, methotrexate, fluoracil, prednisone; CMFVP – cyclophosphamide, methotrexate, fluoracil, vincristine, prednisone; CMFVP-C – continuous; CMFVP-1 – intermittent; CMFVP-W – weekly; E – epirubicin; F – fluoracil; FEC – epirubicin, fluoracil, cyclophosphamide; LEUC – leucovorin; M – methotrexate; MER – methanol-extracted residue of bacillus Calmette-Guerin; MMC – mitomycin; MPA – medroxyprogesterone acetate; MZA – mitoxantrone; P – prednisone/prednisolone; PACL – paclitaxel; TAM – tamoxifen; TXT – docetaxel; V<sup>1</sup> – vincristine; V<sup>2</sup> – vinblastine; V<sup>3</sup> – vinorelbine; V<sup>4</sup> – vindesine.

**Risk of bias in included studies**

Each study was reviewed, according to its design and by how the study was conducted, to assess the potential for bias. Trial quality was assessed based on:

- quality of randomisation;
- comparability between groups (treatment arms) at the baseline;
- inclusion of all randomised participants in the analysis.

The quality of randomisation was assessed based on generation and concealment of the allocation sequence. This was graded as A - clearly adequate, B - possibly adequate, C - clearly inadequate (see Characteristics of Included Studies). It was not possible to accurately assess the quality of randomisation used in most studies due to lack of information in the published articles. The following sensitivity analyses were conducted.

**Sensitivity analysis A**

Trials graded as having clearly adequate allocation concealment (grade A). In this review these trials were:

- ANZ BCTG 8614B122;
- CALGB Aisner;
- Coates 1987;
- EORTC 10923;
- HEPI;
- SECSG.

**Sensitivity analysis B**

Trials graded as having possibly adequate allocation concealment and having good comparability of baseline characteristics and adequate reporting of outcomes.

In this review, eligible trials that did not meet the quality criterion (A) satisfied quality criterion (B).

#### Sensitivity analysis C

Trials graded as having inadequate allocation concealment, for example the use of alternation, case record numbers or other open lists of random numbers. No studies included in this review were graded at this level.

Trials were considered to have adequate reporting of time-to-event outcomes if: i) they included all patients in the analysis; or ii) patients were excluded from analysis and reasons were given for excluding patients, and the exclusions were not of a number that could lead to a misleading conclusion. See the Characteristics of Included Studies table for details.

### Effects of interventions

The 34 trials (46 treatment comparisons) included in this review randomised 7237 women; of these, 6474 (89%) were randomised to 30 trials (42 treatment comparisons) comparing anthracycline based therapies to non-antitumour antibiotic based regimens, and 763 were randomised to four trials (four treatment comparisons) comparing mitoxantrone containing regimens with non-antitumour antibiotic based regimens. Time-to-event data was extractable for overall survival from 27 trials (35 treatment comparisons, 76% of all patients randomised) and progression-free survival from 12 trials (treatment comparisons, 36% of all patients randomised). Tumour response rates based on assessable patients were available for all trials and treatment comparisons.

The observed 4244 deaths in 5605 randomised women did not demonstrate a statistically significant difference in survival

between regimens that contained antitumour antibiotics and those that did not contain these agents, with an overall HR of 0.96 (95% CI 0.90 to 1.02,  $P = 0.22$ ) and no statistically significant heterogeneity (Forest plot 1.1). Antitumour antibiotic containing regimens were favourably associated with time-to-progression (HR 0.84, 95% CI 0.77 to 0.91) and tumour response rates (OR 1.33, 95% CI 1.21 to 1.48) although statistically significant heterogeneity was observed for these outcomes across the trials (Forest plots 1.2, 1.3). Treatment related deaths were reported in 2% of participants across the 19 trials (treatment comparisons) reporting on this outcome. Of the 81 treatment related deaths reported, 46 occurred in the antitumour antibiotic arm compared to 35 in the non-antitumour antibiotic arm (OR 1.18, 95% CI 0.77 to 1.83).

The results for the analyses by class of antitumour antibiotic (anthracycline containing or mitoxantrone containing) are presented below.

#### 1. Anthracycline-containing regimens versus non-antitumour antibiotic regimens

Twenty-seven trials (39 treatment comparisons) reported on doxorubicin and three trials (three treatment comparisons) reported on epirubicin (HEPI 013 2001; Fraser 1993; Fountzilas 2004). The majority of comparator regimens were CMF (14 trials, 18 treatment comparisons), CMFVP (eight trials, ten treatment comparisons) or other CF-based regimens (seven trials, ten treatment comparisons). Two trials (three treatment comparisons) compared doxorubicin or a doxorubicin/paclitaxel combination regimen with single agent paclitaxel (ECOG E1193a; ECOG E1193b; EORTC 10923). Figure 4 and Figure 5 lists the outcomes extracted from each trial.

**Figure 4. Summary of outcomes included in the analyses a) Treatment arm = Anthracycline containing regimen**

Trial ID	Survival curve HR	TTP curve	Overall response	Grade III-IV Toxicity*	Treatment-related deaths	Accrual
Ahmann 1974	Y		Y	a, c	Y	48
Ahmann 1991	Y	Y	Y	l, a, c		94
ANZBCTG Coates	Y		Y	l, a	Y	308
B122	Y	Y	Y	l, v, c		92
Brambilla 1976	Y		Y	a, c	Y	110
CALGB Aisner 1987			Y	c	Y	432
CALGB Tormey	Y		Y	l, v, c		396
Carmo-Pereira 1981	Y		Y	l, a, c	Y	51
Chauvergne 1978			Y	l, v, a, c	Y	70
Creagan 1984	Y	Y	Y	l, a		88
Creech 1979	Y		Y	l, a, c		78
DBCG 1999	Y	Y	Y	v, a, c	Y	415
ECOG Cummings 1985	Y		Y	l, c		177
ECOG E1193	Y		Y	l, v, c	Y	739
ECOG EST 2173	Y		Y	l, v, a, c	Y	404
EORTC 10923	Y	Y	Y	l, v, c	Y	331
Fountzilias 2004	Y	Y	Y	l, v, a, c	Y	327
Fraser 1993	Y		Y	-		40
HEPI 013 Study	Y	Y	Y	l, v, a, c	Y	460
Hoogstraten 1976			Y	l, a, c		297
Kolaric 1977			Y	l, v, a		74
Kolaric 1985			Y	l, a, c		128
Muss 1978			Y	l, c	Y	175
Muss 1982	Y		Y	l, v, c	Y	100
Nemoto 1978	Y		Y	a, c	Y	94
Nemoto 1982	Y	Y	Y	l, v, a, c		126
Pannuti 1984	Y		Y	l, a		46
Rosner 1989	Y		Y	a, c	Y	182
SAKK 1983	Y		Y	-		230
SECSG 1983	Y	Y	Y	l, v, c	Y	362

\* WHO criteria for Grade III – IV toxicity: l = leukopenia, a = alopecia, v = nausea & vomiting, c = cardiotoxicity

**Figure 5.**

Summary of outcomes included in the analyses  
b) Treatment arm = antitumour antibiotic containing regimen (non- anthracyclines).

Trial ID	Survival curve HR	TTP curve	Overall response	Grade III-IV Toxicity	Treatment-related deaths	Accrual
ANZ BCTG 8614	Y	Y	Y	l, v, a		391
Hainsworth 1997	Y		Y	l, v, a, c	Y	128
Harper-Wynne 1999	Y	Y	Y	l, v, a		116
Lorusso 1993	Y	Y	Y	l, a, c	Y	128

\* WHO criteria for Grade III – IV toxicity: l = leukopenia, a = alopecia, v = nausea & vomiting, c = cardiotoxicity

**Overall survival**

Sufficient data was available for 23 of the 30 eligible trials (31 treatment comparisons) to calculate an HR for overall survival (Forest plot 2.1). No survival advantage was observed for anthracycline containing regimens, with an HR of 0.97 (95% CI 0.91 to 1.04). A null effect was also observed within each of the three subquestions where anthracyclines were used as an additional agent (question a: three trials, four treatment comparisons); replacement agent in combination therapy (question b: 18 trials, 22 treatment comparisons); or single agent (question c: five trials, five treatment comparisons). Heterogeneity of survival effect across the 31 treatment comparisons was not statistically significant (heterogeneity chi-square 34.12, df = 30, P = 0.28).

A statistically significant survival advantage for anthracycline containing regimens was observed when a sensitivity analysis was undertaken (Forest plot 3.1). Four trials (five treatment comparisons) addressing Question (b) reported randomisation methods of high quality (B122; Coates 1987a; Coates 1987b; HEPI 013 2001; SECSG 1983). Each of these studies suggested a survival advantage for regimens where an anthracycline was used to replace methotrexate, or methotrexate in combination with fluorouracil or vincristine (comparator CMF or CMFVP), with an overall HR of 0.86 (95% CI 0.75 to 0.98). One other study reported clearly adequate allocation concealment (EORTC 10923). This trial addressed question (c) and compared doxorubicin with paclitaxel

as single agent therapy. No statistically significant difference in survival was observed between these two single agents (HR 0.93, 95% CI 0.73 to 1.19).

**Time to progression**

Data on time to progression was available from ten trials reporting on 12 treatment comparisons (Forest plot 2.2). There was a statistically significant difference in favour of anthracycline containing regimens for time to progression, with an HR of 0.76 (95% CI 0.69 to 0.83).

This beneficial effect was consistently observed in each of the three categories of anthracycline regimens. Nine trials (nine treatment comparisons) compared anthracycline containing regimens with alternate non-anthracycline combination therapies (question b), with an HR of 0.82 (95% CI 0.74 to 0.91) for time to progression. One of these trials also reported on the addition of an anthracycline to a regimen (Nemoto 1982a; Nemoto 1982b), which also showed a favourable effect but this did not reach statistical significance (HR 0.67, 95% CI 0.37 to 1.24). Another trial investigating the use of anthracyclines as a single agent (EORTC 10923) reported that anthracycline was favoured over paclitaxel in time to progression, with an HR of 0.55 (95% CI 0.44 to 0.68). Heterogeneity across the 12 treatment comparisons was statistically significant (heterogeneity chi-square 22.73, df = 11, P = 0.02) but not within each of the three subquestions.

## Overall response

All of the 30 eligible trials (42 treatment comparisons) reporting on anthracycline containing regimens versus non-antitumour antibiotic containing regimens provided information about response rates based on assessable patients (Forest plot 02.3). The odds ratio for overall response showed a statistically significant difference in favour of anthracycline containing regimens, with an OR of 1.40 (95% CI 1.26 to 1.56).

Four trials (5 treatment comparisons) addressed question (a), the addition of an anthracycline to a regimen, to demonstrate a benefit in favour of anthracyclines, with an OR of 1.90 (95% CI 1.33 to 2.72). Each of the five comparisons favoured the addition of an anthracycline and a test for heterogeneity was not statistically significant (heterogeneity chi-square 2.08,  $df = 4$ ,  $P = 0.72$ ).

Twenty three trials (29 treatment comparisons) addressed question (b), the replacement of a non-antitumour antibiotic with an anthracycline in a combination therapy, demonstrating a statistically significant difference in overall response in favour of anthracycline containing regimens, with an OR of 1.44 (95% CI 1.27 to 1.63). Heterogeneity of effect was statistically significant across these treatment comparisons (heterogeneity chi-square 49.49  $df = 28$ ,  $P = 0.007$ ).

Five trials (eight treatment comparisons) addressed question (c), the use of anthracyclines as a single agent versus non-anthracycline containing regimens. Overall, no statistically significant difference in response rates was observed (OR 1.09, 95% CI 0.85 to 1.41), although there was significant heterogeneity across treatment comparisons (heterogeneity chi-square 16.41,  $df = 7$ ,  $P = 0.02$ ).

## Toxicity

Leukopenia (white blood cell count (WCC) less than 2000 x 10<sup>9</sup>/litre) was the commonest Grade III to IV toxic event in both anthracycline and comparator arms (Table 3). Twenty-two trials reported 1540 events in 4425 participants, with an OR of 1.25 (95% CI 1.10 to 1.41), to show a significantly increased risk for anthracycline containing regimens. Twenty-three trials provided data on Grade III to IV cardiotoxicity, with 110 events in 4777 participants for an OR of 5.17 (95% CI 3.16 to 8.48) in patients receiving anthracyclines. Patients receiving anthracycline based regimens also were more likely to experience moderate to severe nausea/vomiting (OR 1.98, 95% CI 1.62 to 2.41) and alopecia (OR 3.87, 95% CI 3.31 to 4.52) compared to patients receiving non-antitumour antibiotic regimens.

Seventeen anthracycline trials provided information about treatment related deaths (Forest plot 2.4). Overall, there was no statistically significant difference in risk of treatment related deaths (OR 1.16, 95% CI 0.74 to 1.82).

## Quality of life

Information about quality of life (QoL) was only available from two trials comparing anthracycline containing regimens with non-antitumour antibiotic (Fraser 1993; EORTC 10923). No difference in global QoL scores were reported between the two treatment groups in these two trials (Table 4).

## Subgroup analyses

Anthracycline containing regimens demonstrated a statistically significant difference in survival compared to CMFVP (four trials,

five treatment comparisons; HR 0.84, 95% CI 0.72 to 0.99). This benefit was not observed in the 11 trials (13 treatment comparisons) using CMF as the comparator (HR 0.95, 95% CI 0.86 to 1.05) nor in the other comparator subclasses (Forest plot 4.1). Anthracycline containing regimens showed a statistically significant advantage in time to progression compared to CMF regimens (four trials, four treatment comparisons; HR 0.82, 95% CI 0.72 to 0.93) and CMFVP regimens (one treatment comparison; HR 0.72, 95% CI 0.57 to 0.90) (Forest plot 4.2).

Anthracycline containing regimens demonstrated a statistically significant increase in tumour response compared to CMF regimens (14 trials, 18 comparisons; OR 1.41, 95% CI 1.20 to 1.66), CMFVP regimens (eight trials, nine treatment comparisons; OR 1.42, 95% CI 1.13 to 1.78), taxanes (two trials, three treatment comparisons; OR 1.57, 95% CI 1.20 to 2.06). No difference was observed in comparison with regimens based on cyclophosphamide and 5-fluorouracil that did not include methotrexate for example CFP, CFVP (seven trials, ten comparisons; OR 1.23, 95% CI 0.87 to 1.76) (Forest plot 4.3).

## 2. Mitoxantrone-containing regimens versus non-antitumour antibiotic regimens

Four trials reported on four treatment comparisons of mitoxantrone containing regimens versus CMF regimens as first line chemotherapy for metastatic breast cancer (Forest plot 5). No statistically significant difference in overall survival (HR 0.95, 95% CI 0.81 to 1.12) or response (HR 0.88, 95% CI 0.64 to 1.19) was observed and heterogeneity was statistically significant for response (heterogeneity chi-square 17.06,  $df = 3$ ,  $P = 0.0007$ ). A statistically significant benefit for time to progression was observed in one of these trials (ANZ BCTG 8614) comparing single agent mitoxantrone to CMFP (HR 0.79, 95% CI 0.65 to 0.94); but response favoured the comparator regimen with an OR of 0.56 (95% CI 0.36 to 0.86). The three other trials did not show a statistically significant difference in response for regimens containing mitoxantrone versus non-antitumour antibiotic containing regimens.

There was no statistically significant association between the use of mitoxantrone and toxic events or treatment related deaths compared to the comparator regimens (treatment-related deaths: OR 1.58, 95% CI 0.26 to 9.44). Of the two trials reporting treatment related deaths, both addressing Question (b), one trial reported a toxic death in the control group; the other trial reported two toxic deaths in the mitoxantrone group. Two trials reported on QoL and demonstrated no difference in global QoL scores between the treatment groups (Table 4) (ANZ BCTG 8614; Harper-Wynne 1999).

## DISCUSSION

This review did not identify a statistically significant benefit in overall survival for antitumour antibiotic containing regimens over non-antitumour antibiotic containing regimens in the first line management of metastatic breast cancer. Despite the lack of evidence of survival benefit, this review demonstrated that anthracycline containing regimens provided a statistically significant advantage in time to progression and tumour response compared to non-antitumour antibiotic containing regimens. Only ten anthracycline trials provided data on time to progression (2226 randomised patients; HR 0.76, 95% CI 0.69 to 0.83). All eligible anthracycline trials provided response data for 6,538 assessable patients, for an OR of 1.33 (95% CI 1.21 to 1.48). The favourable effect on time to progression and response was consistent and

statistically significant in regimens where an anthracycline was used as a replacement agent (29 treatment comparisons; 4439 patients). Fewer trials reported on comparisons between an anthracycline as an additional agent (five treatment comparisons; 604 patients) or an anthracycline as a single agent (eight treatment comparisons; 1104 patients). In these trials we observed a response benefit for regimens that included an anthracycline as an additional agent (OR 1.90, 95% CI 1.33 to 2.72), but not for regimens that included anthracyclines as a single agent (OR 1.09, 95% CI 0.85 to 1.41).

An exploratory subgroup analysis by class of comparator demonstrated that anthracycline containing regimens were statistically significantly associated with improved tumour response compared to CMF, CMFVP and taxane regimens and showed no difference to other cyclophosphamide based regimens. We also observed a statistically significant survival benefit for anthracycline containing regimens compared to CMFVP regimens (HR 0.84, 95% CI 0.72 to 0.99,  $P = 0.04$ ). It is unclear why anthracycline containing regimens would be more effective compared to CMFVP regimens and not regimens containing CMF alone. One possible explanation is that the dose or scheduling of CMF varied between these regimens or that patients allocated to CMF regimens received the potential benefit of anthracyclines as second line therapy earlier or more frequently than those allocated CMFVP regimens. Further investigation of the type of regimens and protocols used in the individual trials is required to address this question. It is also possible that this modest finding represents a type I error, and we note that this finding is not statistically significant after correction for the multiple comparisons performed. A pre-specified sensitivity analysis of the four anthracycline trials that reported clearly adequate methods of allocation concealment also indicated a modest survival benefit for anthracycline containing regimens (HR 0.86, 95% CI 0.75 to 0.98) compared to CMF (two trials) or CMFVP regimens (two trials) to suggest that anthracyclines dominated CMF regimens, however as one of multiple comparisons performed in this review this result must also be interpreted with caution.

This review did not demonstrate a difference in overall survival or tumour response for mitoxantrone containing regimens versus non-antitumour antibiotic regimens, although a benefit was observed for time to progression (HR 0.84, 95% CI 0.72 to 0.98). Statistically significant heterogeneity was observed for tumour response ( $P$  heterogeneity = 0.0007). Similarly, there was statistically significant heterogeneity of effect across the anthracycline trials for response ( $P$  heterogeneity = 0.0009). In contrast, no significant heterogeneity was observed in the survival estimates for trials within each class of antitumour antibiotic trials (anthracyclines and mitoxantrone). The heterogeneity in the response estimates most likely reflects the different activity of the wide range of different regimens and protocols represented in the included trials, however, specific factors have not been explored in this review.

The interpretation of treatment effect on response is also problematic in this review due to the lack of information provided in some of the trials about the reasons for excluding patients from

the analysis of response rates and it is possible that the definition of 'assessable' varied across the trials.

Given the lack of survival benefit, the use of anthracyclines in the management of metastatic breast cancer must be carefully weighed against the risk of toxicities associated with these agents. The risks of cardiotoxicity, leukopenia and nausea/vomiting were all significantly increased in anthracycline containing regimens (cardiac toxicity OR 5.91, 95% CI 3.56 to 9.80; leukopenia OR 1.25, 95% CI 1.11 to 1.41; nausea/vomiting OR 1.71, 95% CI 1.42 to 2.06).

Our results are consistent with an earlier review of 30 trials (5241 patients) of first and second line therapy for metastatic breast cancer, which found no overall survival benefit for combination therapies that included anthracyclines compared to those that did not (Fossati 1998). A recent large trial comparing the efficacy of doxorubicin and paclitaxel as single and combined agents has recently reported similar findings that antitumour response activity did not confer an advantage in overall survival (Sledge 2003).

The tumour response associated with these agents appeared to offer a poor surrogate for overall survival gain, however, some correlation between these outcomes cannot be ruled out. One possible explanation is that while anthracyclines provide a highly active initial anti-tumour response, 'catch-up' occurs after tumour progression when a subsequent and less active regimen is used as salvage therapy. Conversely, the initial use of less active combinations may be rectified with the subsequent use of anthracyclines.

## AUTHORS' CONCLUSIONS

### Implications for practice

Regimens that contain antitumour antibiotics do not offer any additional benefit in overall survival over regimens that do not contain these agents in the first line management of metastatic breast cancer. Anthracycline containing regimens do provide advantages in tumour response and time to progression over standard non-antitumour antibiotic containing regimens but these benefits need to be weighed against the increased risk of toxicity before consideration as palliative therapy. There is insufficient evidence to determine the relative efficacy of other non-anthracycline antitumour antibiotic regimens compared to non-antitumour antibiotics.

### Implications for research

A review of trials comparing overall survival, quality of life and toxicity for anthracyclines as a first line agents in regimens of sequential therapy is warranted to further investigate the optimal use of these agents.

## 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 also acknowledge the contribution made to the original concept for this review by I. Craig Henderson, Kathleen Pritchard, Martin Tattersall, Martin Stockler, Christine Brunswick, Roldano Fossati and Alessandro Liberati.



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## CHARACTERISTICS OF STUDIES

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

#### Ahmann 1974a

##### Study characteristics

Methods	Single centre randomised controlled trial. 3 arm trial. Method of randomisation and allocation concealment not reported. Stratification by disease free interval, time since menopause and dominant site of metastases. Other baseline comparability not reported.
Participants	48 pts. Women with metastatic breast cancer. No prior cytotoxic chemotherapy.
Interventions	Comparison 1: A vs CFP  Arm A: A doxorubicin 60mg/m <sup>2</sup> iv day 1 and repeated 3-4 weeks Maximum cumulative dose of doxorubicin = 550mg/m <sup>2</sup>  Arm B: CFP cyclophosphamide 150mg/m <sup>2</sup> iv day 1-5; 5-fluorouracil 300mg/m <sup>2</sup> day 1-5; and prednisone po at a dose level of 30mg/d for 2 wks, 20mg/day for 1 week and a maintenance dose of 10mg/d. 4 week cycle  Arm C: CVFP

**Ahmann 1974a** (Continued)

cyclophosphamide 150mg/m<sup>2</sup> iv day 1-5; 5-fluorouracil 300mg/m<sup>2</sup> day 1-5; vincristine was given 1.4mg/m<sup>2</sup> on days 1 and 5 and prednisone was given orally at a dose level of 30mg/d for 2 wks, 20mg/day for 1 week and a maintenance dose of 10mg/d;

Outcomes	Response Overall survival Toxicity
Notes	ITT analysis. 47/48 pt followed up until death. Est min f/up 2 months (2 x 4 week cycles), est max 102 months (from OS curve). Overall survival for doxorubicin vs polychemotherapy regimens extracted for meta-analysis from follow-up publication (Ahmann, 1987) Cross over to alternate regimen on disease progression. 1 possible treatment-related death due to cardiac failure in a pt on Doxorubicin. Another pt withdrawn from doxorubicin arm due to early cardiac failure.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Ahmann 1974b**

**Study characteristics**

Methods		
Participants		
Interventions	Comparison 2: A vs CVFP  Arm A: A doxorubicin 60mg/m <sup>2</sup> iv day 1 and repeated 3-4 weeks Maximum culmulative dose of doxorubicin = 550mg/m <sup>2</sup>  Arm C: CVFP cyclophosphamide 150mg/m <sup>2</sup> iv day 1-5; 5-fluorouracil 300mg/m <sup>2</sup> day 1-5; vincristine was given 1.4mg/m <sup>2</sup> on days 1 and 5 and prednisone was given po at a dose level of 30mg/d for 2 wks, 20mg/day for 1 week and a maintenance dose of 10mg/d;	
Outcomes		
Notes		
<b>Risk of bias</b>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Ahmann 1991**
**Study characteristics**

Methods	<p>Single centre randomised controlled trial.</p> <p>Pts were stratified by menopausal age, ECOG performance score, hormonal treatment and dominant disease status.</p> <p>Patients randomised according to a dynamic allocation scheme. Method of allocation concealment not reported.</p> <p>Dates of accrual not reported.</p> <p>Baseline comparability achieved.</p>
Participants	<p>94pts (93 eligible)</p> <p>Women with histologically confirmed BC, and progressive metastatic disease not amenable to standard surgical or radiotherapeutic techniques.</p> <p>No patients had prior treatment with the chemotherapy agents used in this study.</p> <p>Age range: 36-75 yrs in CAP arm; 33-78 yrs in CFP arm.</p> <p>Median age 58 yrs in CAP arm, 56 years in CFP arm</p>
Interventions	<p>CAP vs CFP</p> <p>Arm A: CAP                      cyclophosphamide 400mg/m<sup>2</sup> iv over 30min; doxorubicin 40mg/m<sup>2</sup> by iv push every 4 weeks in stable or responding patients; prednisone 30mg po on days 2-14, 20mg orally on days 15-21 and 10mg orally thereafter</p> <p>Arm B: CFP                      cyclophosphamide 150mg/m<sup>2</sup> iv by push over 30min on each of 5 successive days every 5 weeks if stable or responding, 5-fluorouracil 300mg/m<sup>2</sup> by iv push every 30mins on each 5 successive days every 5 weeks, prednisone 30mg po on days 2-14, 20mg orally on days 15-21 and 10mg po thereafter.</p> <p>Regimens continued until objective evidence of progressive disease                      - or a maximum cumulative dose of doxorubicin was 450mg/m<sup>2</sup> was reached- then pts just received CP</p>
Outcomes	<p>Response</p> <p>Overall Survival</p> <p>Time to progression</p> <p>Toxicity</p>
Notes	<p>One pt was ineligible due to heart disease, 93 eligible pts were included in the analyses.</p> <p>Follow-up details not reported. Estimated min = 5.5 months (median time to progression, averaged over both arms), est. max OS = 66 months (from curve), est max PFS = 34.5 months (from curve). Toxic deaths not reported. Cardiac toxicity was observed in 4 pts on the CAP arm but it was not clinically severe.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**ANZ BCTG 8614**
**Study characteristics**

Methods	<p>Multi-centre international randomised controlled trial.</p> <p>Accrual January 1988 to June 1993.</p> <p>Pts stratified by performance status, metastatic site &amp; institution.</p>
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**ANZ BCTG 8614** (Continued)

Randomisation via centralised office.  
Baseline comparisons of pt characteristics not available

Participants	391 pts Advanced/metastatic breast cancer No prior chemotherapy for metastatic disease
Interventions	MZA vs CMFP  Arm A: MZA mitoxantrone 14mg/m <sup>2</sup> iv. day 1 of 21 day cycle  Arm B: CMFP cyclophosphamide 100mg/m <sup>2</sup> po. day 1-14; methotrexate 40mg/m <sup>2</sup> iv day 1, 8; 5-fluorouracil 600mg/m <sup>2</sup> i.v. day 1, 8 prednisone 40mg/m <sup>2</sup> p.o. day 1-14. 28 day cycle.
Outcomes	Response Overall survival Time to Treatment failure Time to first disease progression. Toxicity Quality of Life (self-assessment, spitzer QL index)
Notes	Analysis by ITT. 9 pts excluded: ineligible, reasons given (8); did not receive protocol treatment (1) Min reported follow-up 9 months, max reported follow-up 74 months. Toxic deaths not reported.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**B122**

**Study characteristics**

Methods	Multi-centre randomised controlled trial Pts were stratified according to menstrual status, disease free survival, number of disease sites, and dominant disease sites. Centralised randomisation used for 3 hospitals (Pocock method), randomisation using sealed envelopes used for 1 hospital. Dates of accrual not reported. Pre-treatment pt characteristics balanced across the 2 treatment arms.
Participants	92 pts (78 evaluable) Women with evidence of metastatic disease, no prior chemotherapy. 56% of pts were age 50yrs or older.
Interventions	CAF vs CMF  Arm A: CAF cyclophosphamide 100mg/m <sup>2</sup> po as a single daily dose on days 1-14; doxorubicin 30mg/m <sup>2</sup> iv days 1, 8; 5-fluorouracil 500mg/m <sup>2</sup> iv 1, 8.  Arm B: CMF cyclophosphamide 100mg/m <sup>2</sup> po on days 1-14; methotrexate 40mg/m <sup>2</sup> iv day 1 and 8 each cycle; 5-fluorouracil 600mg/m <sup>2</sup> i. days 1, 8

**B122** (Continued)

Both regimens were given at 4 week cycles with 2 weeks on drug and 2 weeks off therapy until evidence of disease progression  
- or a maximum culminative dose of doxorubicin was 450mg/m<sup>2</sup> was reached- then pts received CMF

Outcomes	Overall Survival Progression free survival Reponse Toxicity
Notes	Did not report as ITT. 92 pts were enrolled, 78 pts were evaluable. Of the 14pts excluded from the analysis 10pts did not meet eligibility criteria (reasons stated), 3pts refused therapy after randomisation, one pt refused further therapy after day 1 of cycle. Follow-up time not reported. Est min follow-up =2 months (minimum 2 cycles followed to assess response), est max f/up from curve 29 months (OS), 23 months (PFS). Treatment-related deaths not reported. No cardiovascular toxicity observed in any pt.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**Brambilla 1976**

**Study characteristics**

Methods	Randomised controlled trial. Accrual dates: March 1973 to June 1974 Before randomisation pts were stratified according to menopausal status, disease free interval and site of dominant lesion. Method of randomisation and allocation concealment not stated. Baseline comparability in pt age, prior therapy and disseminated osseous metastases noted between each arm.
Participants	110 pts (105 evaluable) Advanced/metastatic breast cancer. Excluded if the only manifestation of disease was either pleural effusion, osteoblastic or mixed osteoblastic-osteolytic lesions, or a previously irradiated lesion of the breast. No pts had received prior chemotherapy. Age range: 25 -69 yrs in AV arm; 29-70 yrs in CMF arm. Median age: 49 yrs in AV arm; 54 yrs in CMF arm.
Interventions	AV vs CMF  Arm A: AV doxorubicin 75mg/m <sup>2</sup> iv every three weeks; vincristine 1.4mg/m <sup>2</sup> iv days 1, 8. x 8 cycles  Arm B: CMF cyclophosphamide 100mg/m <sup>2</sup> po days 1-14; methotrexate 40mg/m <sup>2</sup> iv days 1, 8; 5-fluorouracil 600mg/m <sup>2</sup> iv days 1 and 8. x 8 cycles
Outcomes	Response Overall Survival Toxicity

**Brambilla 1976** (Continued)

Notes

ITT not followed. 110 pts randomised, 5 pts were not considered evaluable as lost to follow-up (1), or died early of progressive disease after the first cycle of treatment (4). Efficacy analyses conducted using 105 evaluable pts.

Pts cross-over on disease progression. Pts with complete or partial remission after 8 cycles AV crossed over to CMF for the next 8 cycles to avoid cardiotoxicity.

Pts over 60 or with widespread metastases had an initial dose reduction.

Follow-up time not reported. Est min=5 months (8 cycles x 2-3 weeks), est max=32 months (from survival curve)

The dominant site of disease was in the soft tissues (breast, skin, lymph nodes) in 56%, in viscera in 22% and in bones in 22% in AV Arm and 51%, 24% and 24% respectively in the CMF arm. Response reported overall and by site of metastases. One treatment-related death reported due to cardiac toxicity in a pt who had completed 8 full cycles of doxorubicin (total 600mg/m<sup>2</sup>).

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**CALGB Aisner 1987a**

**Study characteristics**

Methods	<p>Multi-centre national randomised controlled trial. 6 arm trial</p> <p>Pts were stratified by disease free interval &amp; dominant site of disease.</p> <p>Dates of accrual: 11 October, 1976 to 1 February, 1980.</p> <p>Randomisation was by sealed envelope using a Latin square design balancing across and within institutions.</p> <p>Baseline comparability between chemo-immunotherapy and chemotherapy trials and between intervention arms achieved.</p>
Participants	<p>432 pts (395 evaluable).</p> <p>Women with recurrent, progressive or metastatic disease. Over 80% of patients has visceral or osseous metastatic disease.</p> <p>No pts had been treated with cytotoxic chemotherapy.</p> <p>Median age: 57 yrs in CAF arm; 55 yrs in CAFVP arm and CMF arm</p> <p>Median age across chemo-immunotherapy arms: 56 yrs.</p>
Interventions	<p>Comparison 1: CAF vs CMF</p> <p>Arm A: CAF cyclophosphamide 100mg/m<sup>2</sup>/d po, days 1-14; doxorubicin 25mg/m<sup>2</sup> iv, days 1, 8 (after total dose of 450mg/m<sup>2</sup> replaced with methotrexate 40mg/m<sup>2</sup> iv, days 1 &amp; 8); 5-fluorouracil 500mg/m<sup>2</sup> iv, days 1 &amp; 8. 28 day cycle.</p> <p>Arm B: CMF cyclophosphamide 100mg/m<sup>2</sup>/d po days 1-14; methotrexate 40mg/m<sup>2</sup> iv days 1, 8; 5-fluorouracil 500mg/m<sup>2</sup> iv days 1, 8. 28 day cycle.</p>
Outcomes	<p>Response</p> <p>Overall survival (from the date of initiating therapy)</p> <p>Time to treatment failure</p> <p>Toxicity</p>
Notes	<p>6 arm trial. 4 comparisons used for this meta-analysis. Randomisation to chemoimmunotherapy ceased after an interim evaluation showed no benefit &amp; increased toxicity. 432 pts were enrolled. 37</p>

**CALGB Aisner 1987a** (Continued)

pts were unevaluable: ineligible (20), protocol violations, early deaths (4), inadequate records (2), improper randomisation(1). Analyses 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 meta-analysis as unable to do so accurately to replicate reported study findings. Overall survival benefit reported for the CAF arm versus the CMF arm (p=0.04). A three way comparison between time to progression in the 3 chemotherapy arms showed a statistically significant difference (p=0.01) favouring the CAF arm. No statistically significant differences in survival or time to progression reported between the 3 chemoimmunotherapy arms. Follow-up times not reported. Estimated min = 2 months (2 cycles), est. max = 36 months (from survival curve). 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.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**CALGB Aisner 1987b**
**Study characteristics**

Methods

Participants

Interventions

Comparison 2: CAFVP vs CMF

Arm C: CAFVP

cyclophosphamide 100mg/m<sup>2</sup>/d po, days 1-14; doxorubicin 25mg/m<sup>2</sup> iv, days 1, 8 (after total dose 450mg/m<sup>2</sup> replaced with methotrexate 40mg/m<sup>2</sup> iv, days 1 & 8); vincristine 1.0mg/m<sup>2</sup> iv, days 1, 8; prednisone 40mg/m<sup>2</sup>/d po, days 1-14. 28 day cycle

Arm A: CMF

cyclophosphamide 100mg/m<sup>2</sup>/d po days 1-14; methotrexate 40mg/m<sup>2</sup> iv days 1, 8; 5-fluorouracil 500mg/m<sup>2</sup> iv days 1, 8. 28 day cycle

Outcomes

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**CALGB Aisner 1987c**
**Study characteristics**

Methods

**CALGB Aisner 1987c** (Continued)

## Participants

## Interventions

Comparison 3: CAF + MER vs CMF + MER

Arm A: CAF + MER

 cyclophosphamide 100mg/m<sup>2</sup>/d po, days 1-14; doxorubicin 25mg/m<sup>2</sup> iv, days 1, 8 (after total dose of 450mg/m<sup>2</sup> replaced with methotrexate 40mg/m<sup>2</sup> iv, days 1, 8); 5-fluorouracil 500mg/m<sup>2</sup> iv, days 1, 8. 28 day cycle

Arm B: CMF + MER

 cyclophosphamide 100mg/m<sup>2</sup>/d po days 1-14; methotrexate 40mg/m<sup>2</sup> iv days 1, 8; 5-fluorouracil 500mg/m<sup>2</sup> iv days 1, 8. 28 day cycle

MER 200µg days 1 &amp; 8.

## Outcomes

## Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**CALGB Aisner 1987d**
**Study characteristics**

## Methods

## Participants

## Interventions

Comparison 4: CAFVP + MER vs CMF + MER

Arm C: CAFVP + MER

 cyclophosphamide 100mg/m<sup>2</sup>/d po, days 1-14; doxorubicin 25mg/m<sup>2</sup> iv, days 1, 8 (after total dose 450mg/m<sup>2</sup> replaced with methotrexate 40mg/m<sup>2</sup> iv, days 1, 8); vincristine 1.0mg/m<sup>2</sup> iv, days 1, 8; prednisone 40mg/m<sup>2</sup>/d po, days 1-14. 28 day cycle

Arm A: CMF + MER

 cyclophosphamide 100mg/m<sup>2</sup>/d po days 1-14; methotrexate 40mg/m<sup>2</sup> iv days 1, 8; 5-fluorouracil 500mg/m<sup>2</sup> iv days 1, 8. 28 day cycle

MER 200µg days 1 &amp; 8.

## Outcomes

## Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**CALGB Tormey 1984a**
**Study characteristics**

Methods	Multi-centre international randomised controlled trial. 3 arm trial. Method of randomisation and allocation concealment not reported. Accrual commenced in 1974. Baseline comparability achieved.
Participants	396 randomised (302 evaluable). Women with progressive metastatic breast carcinoma. No prior chemotherapy Median age of entry 54-57 yrs across each arm.
Interventions	Comparison 1: CAFVP vs CMFVP-Continuous  Arm A: CAFVP cyclophosphamide 80mg/m <sup>2</sup> po q day, adriamycin 25mg/m <sup>2</sup> iv q week, 5-fluorouracil 500mg/m <sup>2</sup> i.v. q week, vincristine 1.0mg/m <sup>2</sup> iv q week, prednisone 40mg/m <sup>2</sup> po day 1-14. 28 day cycles. After 6 cycles of CAFVP, cross-over to CMFVP-I.  Arm B: CMFVP-C cyclophosphamide 80mg/m <sup>2</sup> po.daily, methotrexate 40mg/m <sup>2</sup> iv weekly, 5-fluorouracil 500mg/m <sup>2</sup> iv weekly, vincristine 1.0mg/m <sup>2</sup> iv weekly, prednisone 30mg/m <sup>2</sup> days 1-21 then tapering to zero over 7 days. 12 weeks of therapy then a 2 week break followed by maintenance therapy with cyclophosphamide 80mg/m <sup>2</sup> po daily, methotrexate 40mg/m <sup>2</sup> i. q 3weeks, 5-fluorouracil 500mg/m <sup>2</sup> iv q 3weeks, vincristine 1.0mg/m <sup>2</sup> iv q6weeks, and from week 18 additional prednisone 30mg/m <sup>2</sup> po days 1-7
Outcomes	Response Overall survival Time to treatment failure Toxicity
Notes	3 arm trial. 2 comparisons used in this meta-analysis: CAFVP vs CMFVP-C, CAFVP vs CMFVP-I. ITT analysis not followed. Time to event data based on 302/396 patients. Follow-up time not reported. Est min f/up =9.3 months (median time to treat failure, average over 3 arms), est max f/up = 48 months (from survival curve). The median time for overall survival was 19 months for CAFVP compared to 13 months for CMFVP-I (p=0.01) and 16 months for CMFVP-I (p=0.24). The time to treatment failure for CAFVP was also statistically significantly longer than CMFVP-I (p=0.01) but not CMFVP-C (p=0.09). The CR+PR median remission duration was 14 months for CAFVP compared to 7 months for CMFVP-I (p<0.01) and 9 months for CMFVP-C (p=0.07). Using reported table percentages, 10% of deaths associated with toxicities in CAFVP arm (cardiac toxicity 1%, sepsis 4%, leukopenia 3%, thrombocytopenia 1%, GI toxicity 1%); 10% in the CMFVP-C arm (cardiac toxicity 1%, sepsis 5%, leukopenia 3%, thrombocytopenia 1%); and 18% in the CMFVP-I arm (cardiac toxicity 1%, sepsis 8%, leukopenia 7%, thrombocytopenia 1%, GI toxicity 1%). Total number of treatment-related deaths not estimable from table. One death associated with cardiac toxicity in each arm, and 2 additional pts with severe non-fatal cardiac toxicity and 4 pts with mild CHF observed in CAFVP arm.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**CALGB Tormey 1984b**
**Study characteristics**

Methods

Participants

Interventions

Comparison 2: CAFVP vs CMFVP-Intermittent

Arm A: CAFVP

 cyclophosphamide 80mg/m<sup>2</sup> po q day, adriamycin 25mg/m<sup>2</sup> iv q week, 5-fluorouracil 500mg/m<sup>2</sup> iv q week, vincristine 1.0mg/m<sup>2</sup> iv q week, prednisone 40mg/m<sup>2</sup>. 28 day cycles.

Arm C: CMFVP -I

 cyclophosphamide 100mg/m<sup>2</sup> po days 1-4, methotrexate 40mg/m<sup>2</sup> iv days 1 and 8, 5-fluorouracil 500mg/m<sup>2</sup> iv days 1 and 8, vincristine 1.0mg/m<sup>2</sup> iv days 1 and 8, prednisone 40mg/m<sup>2</sup> days 1-14. 28 day cycles

After 6 cycles of CAFVP, cross-over to CMFVP-I.

Outcomes

Notes

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

 Allocation concealment  
 (selection bias)

Unclear risk

B - Unclear

**Carmo-Pereira 1981**
**Study characteristics**

Methods

Randomised controlled trial

Pts stratified by disease-free interval, menopausal status, site of dominant lesion

Method of randomisation and allocation concealment not reported.

Dates of accrual: March 1976 to June 1979

Baseline comparability achieved.

Participants

51 pts.

Women with progressive, histologically proven metastatic breast cancer, refractory to endocrine therapy and irradiation

No pt had prior cytotoxic chemotherapy

Age range: 29-64 yrs in VAC arm; 28-62 yrs in CMFP arm.

Median age: 49 yrs in VAC arm; 50.5yrs in CMFP arm.

Interventions

VAC vs CMFP

Arm A: VAC

 vincristine 1.4mg/m<sup>2</sup> iv on days 1, 8; doxorubicin 40mg/m<sup>2</sup> iv on day 1; cyclophosphamide 500mg/m<sup>2</sup> iv on day 1 with the cycle repeated every 21 days

Arm B: CMFP

 cyclophosphamide 100mg/m<sup>2</sup> p.o. day 1-15; methotrexate 20mg/m<sup>2</sup> iv; 5-fluorouracil 500mg/m<sup>2</sup> iv weekly for 20 weeks; prednisone 20mg/m<sup>2</sup> po daily with diminishing doses.

**Carmo-Pereira 1981** (Continued)

Maintenance regimen: cyclophosphamide 100mg/m<sup>2</sup> po day 1-15; methotrexate 20mg/m<sup>2</sup> iv on days 1,8 and 15; 5-fluorouracil 500mg/m<sup>2</sup> iv on days 1,8 and 15; prednisone 20mg/m<sup>2</sup> po daily on days 1-15 with a 3 week rest period between the courses.

Outcomes	Response (UICC) Overall survival (lifetable method) Toxicity
Notes	ITT analysis followed. CMFP regime had a maintenance phase Pts crossed-over on progression. There was no statistically significant difference in median duration of response (12 months for each arm) or median survival between the VAC (median = 22.4 months) and CMFP (median=18 months) arms. Minimum follow-up of 6 months reported. Estimated maximum follow-up of 48 months (from lifetable plot of survival). 1 treatment-related death in VAC arm due to sepsis. Cardiac toxicity was observed in 1 pt in VAC arm (symptomatic CHF).

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Chauvergne 1978**

**Study characteristics**

Methods	Multi-centre randomised controlled trial Method of randomisation and allocation concealment not stated. Dates of accrual: October 1975 to April 1976 Baseline comparability achieved.
Participants	70pts All pts had advanced breast cancer. 69/70 patients had metastatic disease. All patients had no prior cytotoxic chemotherapy. Age range: 24-71 yrs in DVM arm; 31-85 yrs in VCF arm Median age reported: 58-62 yrs in DVM arm; 60-64 yrs in VCF arm.
Interventions	AMV vs CVF  Arm A: AMV doxorubicin 50mg/m <sup>2</sup> iv day 1; vincristine 1mg/m <sup>2</sup> iv day 2; methotrexate 6mg/m <sup>2</sup> day 3,4,5. 20 day cycle  Arm B: CVF cyclophosphamide 300mg/m <sup>2</sup> iv days 3,4,5,6; 5-fluorouracil 500mg/m <sup>2</sup> iv 3,4,5; vincristine 0.6mg/m <sup>2</sup> iv day 1,2. 31 day cycle.
Outcomes	Response Toxicity
Notes	ITT analysis not followed, some pts not considered evaluable due to discontinuation of treatments. 61/70 patients completed at least 2 cycles and were included in evaluation of efficacy. Overall survival not reported. 1 treatment -related death reported in the DVM arm (leukothrombocytopenia) and nil in the VCF arm.



**Chauvergne 1978** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Coates 1987a**
**Study characteristics**

Methods	<p>Multi-centre randomised controlled trial, two-by-two factorial design. 4 arm trial.</p> <p>Accrual: June 1982 - June 1985</p> <p>Pts were stratified by institution, performance score and history of adjuvant chemotherapy.</p> <p>Randomisation was conducted through a central telephone centre</p> <p>Baseline comparability achieved.</p>
Participants	<p>308 Pts (305 evaluable). 154 evaluable pts allocated to the 2 continuous therapy arms.</p> <p>307 women and 1 man with histologically confirmed breast cancer and recurrent or metastatic disease.</p> <p>No prior use of cytotoxic agents. The majority of pts had received endocrine therapy for metastatic disease.</p> <p>69% of pts were aged 50 yrs of age or over</p>
Interventions	<p>Comparison 1: DC vs CMFP - Continuous therapy</p> <p>Arm A: DC - Continuous therapy doxorubicin 50mg/m<sup>2</sup>; cyclophosphamide 750mg/m<sup>2</sup> iv each for 21 days</p> <p>Arm B: CMFP - Continuous therapy cyclophosphamide 100mg/m<sup>2</sup> orally daily for 14 days; methotrexate 40mg/m<sup>2</sup> iv; 5-fluorouracil on days 1, 8; prednisone 40mg/m<sup>2</sup> daily for 14 days.</p> <p>28-day cycles.</p> <p>In each arm 3 cycles repeated continuously until disease progression occurred.</p>
Outcomes	<p>Response (WHO)</p> <p>Survival</p> <p>Time to Progression</p> <p>Quality of life</p>
Notes	<p>4 arm trial with 2 comparisons, both DC vs CMFP. Comparison 1= Continuous therapy: 3 cycles given and repeated until evidence of disease progression occurred. Comparison 2 = Intermittent therapy: 3 cycles given and repeated until there was evidence of disease progression. 308 subjects randomized, 2 subjects ineligible and one patient lost to follow-up. Time-to-event analyses were performed on the 305 remaining patients. Pts in whom disease progressed during treatment or within six weeks of the last day of therapy were withdrawn from the study and followed only for survival. Minimum reported follow-up=12 months, max reported f/up=48 months. Overall, 6 treatment related deaths in the CMFP arm and 2 in the DC arm.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**Coates 1987b**
**Study characteristics**

Methods

Participants

Interventions	<p>Comparison 2: DC vs CMFP - Intermittent therapy</p> <p>Arm A: DC - Intermittent therapy doxorubicin 50mg/m<sup>2</sup>; cyclophosphamide 750mg/m<sup>2</sup> iv each for 21 days. 3 cycles</p> <p>Arm B: CMFP - Intermittent therapy cyclophosphamide 100mg/m<sup>2</sup> orally daily for 14 days; methotrexate 40mg/m<sup>2</sup> iv, 5-fluorouracil on days 1, 8; prednisone 40mg/m<sup>2</sup> daily for 14 days. 28-day cycles, 3 cycles</p> <p>In each arm the 3 cycles were repeated when evidence of disease progression</p>
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Outcomes

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

**Creagan 1984**
**Study characteristics**

Methods	<p>Randomised controlled trial. Treatments assigned according to a dynamic allocation scheme. Method of allocation concealment not reported. Stratification by ECOG performance score, yrs since menopause, site of dominant metastases and prior chemotherapy used. Baseline comparability achieved.</p>
Participants	<p>88 pts (86 eligible) Histologically confirmed, progressive metastatic breast cancer unable to be managed by standard surgical or therapeutic techniques. No prior use of the chemotherapeutic agents used in this study. Median age: 58 yrs in both arms</p>
Interventions	<p>CA + CDDP vs CFP</p> <p>Arm A: CA + CDDP Single-day i.v. infusion of cyclophosphamide 400mg/m<sup>2</sup> and doxorubicin 40mg/m<sup>2</sup>, cisplatin 40mg/m<sup>2</sup> was delivered over one-hour. Repeated every 4 weeks. cross-over to CFP after 4 cycles</p> <p>Arm B: CFP</p>

**Creagan 1984** (Continued)

cyclophosphamide 150mg/m<sup>2</sup> and 5-fluorouracil 300mg/m<sup>2</sup> administered by iv on days 1- 4; prednisone po 30mg/d days 1 through to 14, 20mg/d during days 15 to 21. Repeated every 5 weeks until progression.

Outcomes	Response Overall survival Time to progression Toxicity
Notes	86/88 pts included in the efficacy analyses. 1 pt was ineligible due to prior treatment, 1 pt was ineligible due to concurrent treatment for CNS metastases. Fixed cross-over from CAP to CFP after 4 treatment cycles. Patients failing CAP early entered a pilot study using 5-FU, dibromodulcitol and prednisone. Follow-up times not reported. Estimated minimum = 7.5 months (average median time to progression over both arms), est. max = 55 months (OS) and 44 months (PFS). Treatment related deaths and cardiotoxicity not reported.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Creech 1979**
**Study characteristics**

Methods	Randomised controlled trial. No information on randomisation provided. Pts were stratified according to 'poor' or 'good' risk Baseline comparability achieved.
Participants	78 pts. Women with visceral metastatic breast cancer. No prior cytotoxic chemotherapy Age range: 34-79 yrs in CAMF arm; 32-87 yrs in CMF arm. Median age: 56 yrs both arms
Interventions	CAMF vs CMF  Arm A: CAMF cyclophosphamide 50mg/m <sup>2</sup> po, days 1-14; doxorubicin 20mg/m <sup>2</sup> iv, days 1, 8; methotrexate 20mg/m <sup>2</sup> iv, days 1, 8; 5-fluorouracil 300mg/m <sup>2</sup> iv, days 1, 8. 28 day cycle.  Arm B: CMF cyclophosphamide 50mg/m <sup>2</sup> po, days 1-14; methotrexate 20mg/m <sup>2</sup> iv, days 1, 8; 5-fluorouracil 300mg/m <sup>2</sup> iv, days 1, 8. 28 day cycle.  Cycles continued until progression. CMF arm received doxorubicin 20mg/m <sup>2</sup> , iv days 1,8 after progression. Doxorubicin ceased after a maximum cumulative dose of 550 mg/m <sup>2</sup> reached.
Outcomes	Response (ECOG) Survival (reported by response status) Progression-free survival (reported by response status) Toxicity

**Creech 1979** (Continued)

Notes Randomised controlled trial of 2 low dose regimens. CMF pts crossed over to low dose Doxorubicin on progression. ITT analysis followed. Estimated min f/up = Estimated min f/up = 5months (median time to progression), max follow-up = 39 months (from survival curve). Overall survival and time to progression were reported for subsets of pts by response status and not extracted for meta-analysis. No statistically significant differences between CAMF and CMF were reported for time to event data. Median survival for PR/CR pts was 20 months in CAMF arm vs 19 months in CMF arm. Treatment related deaths were not reported. No cardiotoxicity was observed in either arm.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**DBCG 1999**
**Study characteristics**

Methods	Multi-centre national randomised controlled trial Randomisation occurred within department by a sealed envelope system Dates of accrual: April 1980- August 1984 Pre-treatment characteristics of eligible pts balanced across treatment arms.
Participants	415 pts (341 eligible) Postmenopausal women with locally advanced (9%) or metastatic (91%) histologically confirmed breast cancer. Age range: 45-65yrs in CAF arm; 43-65 yrs in CMF arm. Median age: 58 yrs in both arms No prior cytotoxic therapy for recurrent disease. Prior adjuvant treatment with tamoxifen if over one year ago since completion.
Interventions	CAF + tamoxifen vs CMF + tamoxifen  Arm A: CAF + Tamoxifen cyclophosphamide 400mg/m <sup>2</sup> , doxorubicin 25mg/m <sup>2</sup> and 500mg/m <sup>2</sup> 5-fluorouracil iv days 1, 8. Repeated every 4 weeks. + tamoxifen 30mg p.o. daily doxorubicin was replaced by methotrexate at a cumulative dose of 550mg/m <sup>2</sup> .  Arm B: CMF + Tamoxifen cyclophosphamide 400mg/m <sup>2</sup> , and 40mg/m <sup>2</sup> methotrexate; 500mg/m <sup>2</sup> 5-fluorouracil iv days 1, 8. Repeated every 4 weeks + tamoxifen 30mg po daily
Outcomes	Response (WHO) Survival Time to Progression Toxicity
Notes	74/415 women were ineligible (reasons provided). Distribution of ineligible pts not equal across treatment arms (p=0.008). 6 pts in each arm not evaluable (protocol violation, missing data, lost to follow-up). Time-to-event analysis used 341 eligible pts. Minimum follow-up reported: 48 months (PFS), 132 months (OS). Maximum f/up reported: 108 months (PFS), 180 months (OS). There were no treatment-related deaths. 1 pt in CAF arm developed CHF at a cumulative dose of Doxorubicin of 346mg/m <sup>2</sup> and treatment was stopped.

**DBCG 1999** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**ECOG Cummings 1985**
**Study characteristics**

Methods	Randomised controlled trial. Method of randomisation not reported. Pts stratified by performance status and site of metastases. Dates of accrual: May 1978 to November 1979. Baseline imbalance in disease free interval (DFI). 41% of pts had a DFI <1month in CAF arm vs 29% in CMFP arm. 10% of pts had a DFI of 5+ yrs in CAF arm, 20% in CMFP arm.
Participants	177 pts (155 evaluable for CAF vs CMFP comparison arms) Women with histologically documented recurrent or metastatic breast cancer aged 65 yrs or younger. Age distribution: 84% aged 50+ yrs in CAF arm; 75% aged 50+ yrs in CMFP arm. No prior cytotoxic chemotherapy.
Interventions	CAF vs CMFP  Arm A: CAF cyclophosphamide 100mg/m <sup>2</sup> /d orally on days 1, 14; adriamycin 30mg/m <sup>2</sup> and 5-fluorouracil 500mg/m <sup>2</sup> given iv on days 1, 8. 4 week cycles x 8 cycles  Arm B: CMFP cyclophosphamide 100mg/m <sup>2</sup> orally on days 1 -14; methotrexate 40mg/m <sup>2</sup> iv on days 1 and 8; 5-fluorouracil 600mg/m <sup>2</sup> iv. on days 1, 8; prednisone 40mg/m <sup>2</sup> orally on days 1- 14. 4 week cycles x 6 cycles.
Outcomes	Response Overall survival Time to treatment failure Toxicity
Notes	177 women randomised to CAF (82) CMFP (83) or CAF + Cp immunotherapy (12). CAF+Cp arm dropped at 6 months due to poor accrual and not included in this analysis. 10 pts not evaluated: ineligibility (6), transferred hospitals (1), pt refusal(1), reason not reported (2). 155 evaluable pts included in efficacy analysis. Min follow-up = 30 months, Max f/up=48 months. There was no statistically significant difference between median response duration, times to treatment failure and survival times between the 2 arms. Treatment-related deaths were not reported. 1 case of severe cardiotoxicity was reported in a pt in the CAF+Cp arm.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**ECOG E1193a**
**Study characteristics**

Methods	Multi-centre randomised controlled trial. 3 arm trial. Accrual dates: Feb 1993 - Sept 1995. Pts stratified by institution. Randomisation method not described. Baseline comparability of pt pre-treatment characteristics achieved..
Participants	739 pts (683 evaluable) Women with histologically confirmed breast adenocarcinoma with progressing regional (13-19%) or metastatic disease No prior cytotoxic chemotherapy for metastatic disease. Prior adjuvant chemotherapy eligible if ceased $\geq$ 6 months prior and the regimen did not include anthracyclines or taxanes. Age range: 25-79 yrs in doxorubicin arm; 27-78yrs in combined agent arm; 27-76 yrs in paclitaxel arm. Median age: 58 yrs in doxorubicin arm; 56 yrs in paclitaxel and combined agent arms.
Interventions	Comparison 1: A vs T  Arm A: A doxorubicin 60mg/m <sup>2</sup> iv day 1. 3 week cycle x 8.  Arm B: T paclitaxel 175mg/m <sup>2</sup> iv day 1. 3 week cycle until disease progression.
Outcomes	Response Survival Time to treatment failure Toxicity QoL
Notes	Pts on single agent arms were crossed over to the alternate single agent at progression. ITT not followed, data on 683 pts included in time-to-event analyses. 41 pts cancelled or excluded from analysis due to ineligibility (reasons stated), additional 15 pts excluded with reasons not given. Estimated min follow-up = 6 months (3 week cycle x 8), estimated max f/up = 75 months from curve. Treatment-related deaths were reported in 2.5% of pts assigned to doxorubicin and 1.6% of pts assigned to the other 2 arms. Moderate-severe cardiac complications were reported in 8.6-8.7% of pts assigned to the 2 doxorubicin-containing arms and 3.7% of pts assigned to paclitaxel.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**ECOG E1193b**
**Study characteristics**

Methods	
Participants	
Interventions	Comparison 2: A T vs T.  Arm C: AT doxorubicin 50mg/m <sup>2</sup> iv day 1; paclitaxel 150mg/m <sup>2</sup> iv, day 1. 3 week cycle x 8

**ECOG E1193b** (Continued)

Arm B: T  
paclitaxel 175mg/m<sup>2</sup> iv day 1. 3 week cycle until disease progression.

Outcomes

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**ECOG EST 2173a**

**Study characteristics**

Methods	Multi-centre national randomised controlled trial. 3 arm trial. Pts stratified by performance status, disease-free interval and dominant metastatic site. Method of randomisation and allocation concealment not reported Dates of accrual: October 1973 - April 1974
Participants	404 pts (331 evaluable) Women had recurrent or metastatic breast cancer. No prior cytotoxic chemotherapy. Age distribution: 61% aged 50-65, 39% <50yrs.
Interventions	Comparison 1: AV vs CMF  Arm A: AV adriamycin 60mg/m <sup>2</sup> iv and vincristine 1.2 mg/m <sup>2</sup> iv (maximum dose of 2mg) day 1 of each 21 day cycle. 8 cycles.  Arm B: CMF cyclophosphamide 100mg/m <sup>2</sup> po. days 1-14; methotrexate 40mg/m <sup>2</sup> iv days 1-8 and 5-FU 600mg/m <sup>2</sup> iv days 1, 8 of each 28 day cycle. 6 cycles.  Responding patients were subsequently randomised to a maintenance program.
Outcomes	Response Survival Time to treatment failure Toxicity
Notes	19 pts cancelled prior to treatment, 53 pts ineligible (reasons not stated), 1 pt lost to follow-up, 331 evaluable pts included in efficacy analysis. Cross-over to alternate arm if disease progression. Responders were randomised to CMF or CMF + fluoxymesterone maintenance therapy after completing 6 month AV/CMF induction phase. Estimated minimum f/up = 6 months (time for completion of induction), est. max f/up = 48 months (from survival curve). Median time to treatment failure: AV = 5.7 months, CMF = 5.3 months, CMFP = 9.1 months (p=0.04). Median survival: AV = 13.7 months, CMF = 14.5 months, CMFP = 16.4 months (p=0.03). x treatment-related deaths. AV arm: leukopenia (1%), infection(2%), cardiotoxicity (1%). CMF arm: infection (1%). CMFP arm: leukopenia (4%), infection (2%), other (1%). Mod-severe, non-fatal cardiotoxicity observed in 1% of pts in each arm.

**Risk of bias**

**ECOG EST 2173a** (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**ECOG EST 2173b**
**Study characteristics**

Methods

Participants

Interventions

Comparison 2: AV vs CMFP

Arm A: AV

 adriamycin 60mg/m<sup>2</sup> iv and vincristine 1.2 mg/m<sup>2</sup> iv (maximum dose of 2mg) day 1 of each 21 day cycle. 8 cycles.

Arm C: CMFP

 cyclophosphamide 100mg/m<sup>2</sup> po days 1-14; methotrexate 40mg/m<sup>2</sup> iv days 1-8 and 5-FU 600mg/m<sup>2</sup> iv days 1 and 8 of each 28 day cycle, Prednisone 40mg/m<sup>2</sup> orally days 1-14 of each 28 day cycle. 6 cycles.

Responding patients were subsequently randomised to a maintenance program.

Outcomes

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**EORTC 10923**
**Study characteristics**

Methods

International, multi-centre randomised trial.

Opened to accrual Aug 1993 and closed May 1996.

Pts were stratified according to institution and prior adjuvant CT and randomised using centralised randomisation centre.

Participants

331 pts.

Women with histologically proven metastatic breast cancer.

No prior cytotoxic chemotherapy for advanced BC.

Age range: 26-75yrs.

Median age: 54-55 yrs.

Interventions

Arm A: A

 doxorubicin 75mg/m<sup>2</sup> iv every 3 weeks.



**EORTC 10923** (Continued)

Arm B: T  
paclitaxel 200mg/m<sup>2</sup> iv every 3 weeks.

Outcomes  
Survival  
Progression-free survival  
Response  
Toxicity  
QoL.

Notes  
331 pts randomised, 4 pts never started treatment. If pts progressed within first 7 cycles they were crossed over to the alternate therapy.  
F/up details not reported - est min = 5 months, est max = 46 months.  
All randomized patients included in time to event analyses.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
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Allocation concealment (selection bias)	Low risk	A - Adequate
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**Fountzilias 2004**

**Study characteristics**

Methods  
Multi centre national, randomised Phase III trial

Participants  
327 histologically proven ABC

Interventions  
Arm A:  
epirubicin 80mg/m<sup>2</sup> iv followed by paclitaxel 175mg/m<sup>2</sup> iv every 3 weeks  
  
Arm B: T  
paclitaxel 175mg/m<sup>2</sup> iv followed by carboplatin 180mg for 6 cycles

Outcomes  
Overall response  
Survival  
Time to treatment failure  
Toxicity

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
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Allocation concealment (selection bias)	Unclear risk	B - Unclear
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**Fraser 1993**

**Study characteristics**

Methods  
Single centre randomised controlled trial.

**Fraser 1993** (Continued)

Method of randomisation and allocation concealment not stated.  
 Dates of accrual: October 1988 and March 1990.  
 11 year difference in median age between the 2 arms (not statistically significant). Menopausal status and site of disease balanced across the 2 arms.

Participants	40pts Pts with locally advanced or metastatic breast cancer. Failure to respond to hormone therapy. No prior use of non-adjuvant cytotoxic chemotherapy. Age range: 26-80 yrs in Epirubicin arm; 39-84 yrs in CMF arm. Median age: 52yrs in Epirubicin arm; 63 yrs in CMF arm.
Interventions	Epirubicin vs CMF  Arm A: epirubicin 20mg iv every 7 days for 6 months or until disease progression.  Arm B: CMF cyclophosphamide 100mg/m <sup>2</sup> po on days 1-14; methotrexate 35mg/m <sup>2</sup> iv on days 1 and 8; 5-fluorouracil 600mg/m <sup>2</sup> iv on days 1, 8 on a 28 day cycle for 6 months or until disease progression.
Outcomes	Reponse (UICC) Survival Time to treatment failure Toxicity (WHO) Quality of Life (NHP, LASA)
Notes	ITT analysis. Different number of pts evaluable for different QoL instruments. 3 pt did not receive treatment and were not assessed for QoL. 1 pt did not complete the LASA correctly. Estimated minimum follow-up time = 6 months (completion of course), est max f/u = 26 months (from survival curve). No treatment-related deaths were observed. Cardiotoxicity was not reported.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Hainsworth 1997**
**Study characteristics**

Methods	Multi-centre phase 2 randomised controlled trial. Pts stratified by age & site of metastases. Randomisation by a random card system, method of allocation concealment not stated. Accrual dates: July 1991 - Nov 1994. Baseline comparability reported.  128 pts entered, 126 were evaluable for response (1 death, 1 PE). All evaluable for survival & toxicity.
Participants	128 pts Biopsy proved metastatic BC No prior cytotoxic chemotherapy for metastatic disease. Age range: 34-81 yrs in NFL arm; 35-78yrs in CMF arm. Median age: 57 yrs in NFL arm; 59 yrs in CMF arm.
Interventions	MZA + FL vs CMF

**Hainsworth 1997** (Continued)

Arm A: MZA + FL  
 mitoxantrone 12mg/m<sup>2</sup> iv, day 1; 5-fluorouracil 350mg/m<sup>2</sup> iv bolus, days 1-3; leucovorin 300mg iv, days 1-3. 21 day cycle x 8 cycles

Arm B: CMF  
 cyclophosphamide 600mg/m<sup>2</sup> iv, day 1; methotrexate 40mg/m<sup>2</sup> iv, day 1; 5-fluorouracil 600mg/m<sup>2</sup> iv, day 1. 21 day cycle x 8 cycles

Outcomes	Response Survival Toxicity
Notes	ITT followed for time-to-event analysis. 2 patients in CMF arm unevaluable for response (reasons stated). Estimated minimum follow-up time = 6 months (21 day cycles x 8), estimated max f/up = 45 months (from survival curve). 1 treatment-related death reported in CMF arm (neutropenic sepsis). No clinically significant cardiotoxicity observed. Pts with bone metastases who had only abnormal bone scans were included but stratified and analysed separately.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Harper-Wynne 1999**
**Study characteristics**

Methods	Single-centre randomised controlled trial. Method of randomisation and allocation concealment not reported. Dates of accrual: January 1992 and December 1996 Baseline comparability achieved.
Participants	116 pts Locally advanced or metastatic disease Age range: 28-84yrs in MM arm; 28-84 yrs in CMF arm. Median age: 61 yrs in MM arm; 58 yrs in CMF arm 1 (2%) pt in each arm had prior chemotherapy for advanced disease. 10% of all pts had prior adjuvant chemotherapy.
Interventions	MZA + MX vs CMF  Arm A: MZA + MX methotrexate 30mg/m <sup>2</sup> , mitoxantrone 6.5mg/m <sup>2</sup> iv day 1. 3 week cycles x 8.  Arm B: CMF cyclophosphamide 600mg/m <sup>2</sup> day 1 and 8 iv; methotrexate 40mg/m <sup>2</sup> day 1 and 8 iv monthly; 5-fluorouracil 600mg/m <sup>2</sup> day 1, 8 iv. 4 week cycle x 6 cycles.
Outcomes	Response (UICC criteria) Time to progressive disease Toxicity (WHO criteria) Quality of Life (HADS, RSCL)
Notes	ITT followed for time-to-event analyses. 21 pts (18%) not evaluable for response assessment (ineligible, unevaluable, or protocol deviations - reasons stated). Estimated min f/up = 6 months (completion of

**Antitumour antibiotic containing regimens for metastatic breast cancer (Review)**

**Harper-Wynne 1999** (Continued)

regimen), est. max f/up for overall survival = 24 months (from OS curve). Treatment-related deaths not reported.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**HEPI 013 2001**
**Study characteristics**

Methods	Multi-centre, international randomised controlled trial Dates of accrual: September 1990 and November 1992. Pts were stratified and a separate randomisation code was computer generated and centrally assigned for each stratum. Baseline comparability achieved.
Participants	460 pts (454 eligible) Women with histologically proven breast cancer metastatic progression No prior cytotoxic chemotherapy for metastatic BC. No prior anthracyclines. Age range: 22-71 yrs in CEF arm; 26-71 yrs in CMF arm Median age: 56 yrs in CEF arm; 55 yrs in CMF arm
Interventions	FEC vs CMF  Arm A: FEC cyclophosphamide 400mg/m <sup>2</sup> iv; epirubicin 50mg/m <sup>2</sup> iv and 5-fluorouracil 600mg/m <sup>2</sup> on days 1, 8. 3-4 week cycles x 6-9 (according to response)  Arm B: CMF cyclophosphamide 400mg/m <sup>2</sup> iv; methotrexate 40mg/m <sup>2</sup> iv and 5-fluorouracil 600mg/m <sup>2</sup> on days 1, 8. 3-4 week cycles x 6-9 (according to response)
Outcomes	Response (UICC criteria) Survival Time to progression Time to treatment failure Toxicity
Notes	ITT analysis for all efficacy analyses. Tumour response measured for randomised (460) and assessable pt (389). F/up time not reported. Est min = 5 months (6 cycles of 3-4weeks), est max for OS = 72 months (from curve). Treatment -related deaths: CEF (7) vs CMF (9). 3 pts in CEF arm developed congestive heart failure due to cardiotoxicity (no deaths).

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

## Hoogstraten 1976a

### Study characteristics

Methods	Multi-centre randomised controlled trial. 3 arm trial. Initial randomisation into three treatment groups with non compulsory 'crossover' following relapse or failure to respond Accrual dates: Jan 1972 - Feb 1974
Participants	297 pt (283 evaluable) Women with measurable metastatic BC No prior chemotherapy (except for hormones)  Randomised no's - Not provided  Of remaining 283 evaluable pts, 97 were crossed over to phase 11 Evaluable numbers Phase 1 1) n = 79 2) n = 98 3) n = 106
Interventions	Comparison 1: A vs CMFVP-Intermittent  1) doxorubicin 60 mg/m <sup>2</sup> iv, 3 week cycle 2) Intermittent - vincristine 0.625 mg/m <sup>2</sup> / iv days 1 and 5 + methotrexate 4 mg/m <sup>2</sup> / iv dx5 + 5-fluorouracil 180 mg/m <sup>2</sup> / iv dx5 + cyclophosphamide 120 mg/m <sup>2</sup> iv dx5 + prednisone 40 mg/m <sup>2</sup> /day X 5 28 day cycle then crossover
Outcomes	Response (Phase 1) Toxicity
Notes	ITT not followed. 14 were invaluable and not analysed due to protocol violations and lack of adequate data. Duration of follow-up not reported. Treatment-related deaths were reported in the CMFVP arms due to sepsis (4), haemorrhage (2) and pulmonary embolism with associated thrombocytopenia (1). No treatment-related deaths were reported in the doxorubicin arm, 1 patient in this arm was reported to have grade III cardiotoxicity.

### Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

## Hoogstraten 1976b

### Study characteristics

Methods	As above
Participants	As above
Interventions	Comparison 2: A vs CMFVP- weekly  1) doxorubicin 60 mg/m <sup>2</sup> iv, 3 week cycle

**Hoogstraten 1976b** (Continued)

3) Weekly vincristine 0.625 mg/m<sup>2</sup>/week iv + methotrexate 15 mg/m<sup>2</sup>/wk iv + 5-fluorouracil 300 mg/m<sup>2</sup>/wk iv + cyclophosphamide 60 mg/m<sup>2</sup>/day po + prednisone 30 mg/m<sup>2</sup>/day X 14, 20 mg/m<sup>2</sup>/day X 14, 10 mg/m<sup>2</sup>/day then crossover

Outcomes	As above - All outcomes documented in (A)
Notes	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Kolaric 1977**
**Study characteristics**

Methods	Randomised controlled trial Method of randomisation and allocation concealment not reported. Age distribution and prior treatment were similar in both arms, bone metastases more common in CM-FAP (63%) vs CMFVP (50%)
Participants	74pts All metastatic breast cancer No prior cytotoxic chemotherapy. Age range: 28-70 yrs (average 48 yrs)
Interventions	CAMFP vs CMFVP  Arm A: CAMFP cyclophosphamide 5mg/kg iv 1-5 day; 5-fluorouracil 8mg/kg iv day 1,3,5; methotrexate 0.4mg/k iv days 2-4; doxorubicin 40mg/m <sup>2</sup> iv 1 day; prednisolone 40mg po daily 1-5 days  Arm B: CMFVP cyclophosphamide 5mg/kg iv days 1-5; 5-fluorouracil 8mg/kg iv 1, 3,5; methotrexate 0.4mg/kg iv 2,4 days; vincristine 0.025mg/kg iv 1-5 days; prednisolone 40mg po daily 1-5 day
Outcomes	Response Toxicity
Notes	Response and toxicity data reported for 74 pts. There was no signif difference between the overall response rate or average remission duration in both arms. Treatment-related deaths not reported.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Kolaric 1985**
**Study characteristics**

Methods	Randomised controlled trial Method of randomisation and allocation concealment not reported. Stratification by dominant metastatic site. Slight imbalance with 56% of postmenopausal women in CMFVP arm vs 44% in CAP arm.
Participants	128 pts (123 evaluable) Metastatic breast cancer. No prior cytotoxic chemotherapy. Age range was 30-70 yrs.
Interventions	CA + CDDP vs CMFVP  Arm A: CA + CDDP cisplatin, 30mg/m <sup>2</sup> daily as an iv days 1, 3, 5; doxorubicin 40mg/m <sup>2</sup> on day 1; cyclophosphamide 200mg/m <sup>2</sup> iv daily on days 1, 3, 5. 3-4 week cycles x 10 cycles  Arm B: CMFVP cyclophosphamide 200mg/m <sup>2</sup> iv daily 1,2,3,4 and 4; methotrexate 20mg/m <sup>2</sup> iv days 2, 4; 5-fluorouracil 500mg/m <sup>2</sup> iv daily days 1, 3, 5, vincristine 1mg/m <sup>2</sup> iv days 1 and 5 and prednisolone 40mg po daily days 1, 2, 3, 4, 5. 3-4 week cycles x 10 cycles.
Outcomes	Response Progression Toxicity (WHO/UICC)
Notes	123/128 pts considered to be evaluable (received more than 2 chemotherapy cycles. Minimum reported f/up = 6 months, maximum reported f/up=33 months. Overall response and complete remission rate favoured the CAP regimen (p<0.01) All pts who had no response with CAP underwent treatment with FIVB + P

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Lorusso 1993**
**Study characteristics**

Methods	A multicentre randomised controlled trial. Method of randomisation and allocation concealment not reported. Dates of accrual: April 1988 to December 1990 Pretreatment characteristics showed some imbalance of metastatic site by treatment arm. Visceral metastases CNF = 53% vs CMF = 38%. Soft tissue metastases: CNF = 19% vs CMF = 31%.
Participants	128 pts (119 considered evaluated) Locally advanced or metastatic breast cancer No prior chemotherapy for metastatic disease, no anthracycline-containing adjuvant chemotherapy. Age range: 37-67yrs in CNF arm; 34-71 yrs in CMF arm Median age: 56 yrs in CNF arm; 57 yrs in CMF arm
Interventions	C+ MZA + F vs CMF

**Lorusso 1993** (Continued)

Arm A: C + MZA + F

 5-fluorouracil 600mg/m<sup>2</sup> iv, cyclophosphamide 600mg/m<sup>2</sup> iv and mitoxantrone 10mg/m<sup>2</sup> iv. 3 week cycle x 8 cycles

Arm B: CMF

 5-fluorouracil 600mg/m<sup>2</sup> iv, cyclophosphamide 600mg/m<sup>2</sup> iv and methotrexate 40mg/m<sup>2</sup> iv. 3 week cycle x 8 cycles

Outcomes	Response Overall survival Progression free survival Toxicity
Notes	ITT not followed. 119/128 pts completed a minimum of 2 cycles and included in the efficacy analysis (3 pt refused treatment, 6 pt lost to follow-up). Estimated minimum follow-up = 1.5 months (2 cycles), est max f/up = 21 months (from survival curve). Non-responding pts were treated with an anthracycline every 3 weeks. 1 treatment-related death reported in the CNF arm (sepsis). 2 pts ceased treatment in the CNF arm due to MUGA scan signs of cardiotoxicity, but did not demonstrate clinical or ECG signs of heart failure.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Muss 1978**
**Study characteristics**

Methods	Randomised controlled trial Method of randomisation and allocation concealment not stated Dates of accrual: May 1975 - August 1976. No imbalance in the pre-treatment characteristics in each arm.
Participants	175 pts (148 evaluable) All pts had a histologically confirmed diagnosis of breast cancer and metastatic disease. 148/175 evaluable pts. 27 pts were cancelled due to protocol violations. Mean age of 55yrs in each arm 93% of evaluable pt had not received prior chemotherapy. 8% of pt in CVFP + ADR arm and 6% of pt in CFVP + MTX arm had received prior single agent chemotherapy (not doxorubicin or methotrexate).
Interventions	CAFVP vs CMFVP  Arm A: CAFVP cyclophosphamide 2mg/kg/po day 1-14 then 100mg daily; vincristine 25 mcg/kg/iv day 1, then Q2 wk X 3, then Q4 wk; fluorouracil, 12 mg/kg/iv, day 1-3, Q2 wk; prednisone 0.75 mg/kg/po day 1-14, then 10mg daily; doxorubicin 20mg/m <sup>2</sup> /iv day 1 then Q2 wk  Arm B: CMFVP cyclophosphamide 2mg/kg/po day 1-14 then 100mg daily; vincristine 25 mcg/kg/iv day 1, then Q2 wk X 3, then Q4 wk; fluorouracil, 12 mg/kg/iv, day 1-3, Q2 wk; prednisone 0.75 mg/kg/po day 1-14, then 10mg daily; methotrexate 0.2mg/kg/iv day 1 then Q2 wk  Phase 1 intervention: induction and maintenance cycles, 30 weeks for completion Phase 2 intervention: maintenance cycles of doxorubicin (Arm A) or methotrexate (Arm B) every for weeks for a minimum of 40 wks.



**Muss 1978** (Continued)

After completion of Phase 2, pts crossed over to alternate arm of Phase 2 maintenance.  
Maximum cumulative dose of doxorubicin was 500mg/m<sup>2</sup>, after which it was discontinued.

Outcomes	Response Overall Survival (for complete and partial responders) Toxicity
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Notes	ITT not followed. 175 subjects randomized, 13 pts were ineligible. Another 14 pts were cancelled due to other protocol violations (reasons stated). Analyses used 148 evaluable pts: Arm A: 76/92 pts Arm B: 72/83 pts. Duration of f/up not reported. Survival for each treatment arm only reported for partial and complete responders. Cross-over design was used after maintenance phase 2 (at 70 weeks). The median survival for CR and PR patients with CMFVP was 20.2 months compared to 33 month for CAFVP (p=0.07). No treatment-related deaths reported. 1 pt with prior atherosclerotic heart disease developed congestive heart failure after receiving 200mg/m <sup>2</sup> of Doxorubicin.
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**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Muss 1982**

**Study characteristics**

Methods	Randomised controlled trial Pts stratified according to estrogen receptor status. Method of randomisation and allocation concealment not reported. Baseline imbalance in dominant site of metastatic disease: CMF 52% visceral, 34% bone; VAC 24% visceral, 58% bone Dates of accrual: June 1979-March 1981
Participants	100pts (89 evaluable). Advanced breast cancer, recurrent or metastatic disease. No prior use of chemotherapeutic agents used in study protocol.
Interventions	VAC vs CMF  Arm A: VAC vincristine 1mg/m <sup>2</sup> day 1 iv; doxorubicin 40mg/m <sup>2</sup> day 1 iv; cyclophosphamide 200mg/m <sup>2</sup> day 3-6 po. 3 week cycle  When cumulative maximum dose of doxorubicin = 450 mg/m <sup>2</sup> reached, maintenance regimen CVMF.  Arm B: CMF cyclophosphamide 350mg/m <sup>2</sup> ; methotrexate 20mg/m <sup>2</sup> ; fluorouracil 350mg/m <sup>2</sup> iv. 3 week cycle for 1 year then 4 week cycle.
Outcomes	Response (IUCC) CR, PR Survival Toxicity
Notes	ITT not followed. 11 eligible pts not considered evaluable (reasons stated) and not included in analyses. Estimated minimum follow-up = 6 months (from last accrual to publication acceptance), estimated maximum follow-up = 13 months (from survival curve). 3 pts on VAC arm developed symptomatic cardiotoxicity. Treatment-related deaths not reported.

**Muss 1982** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Nemoto 1978**
**Study characteristics**

Methods	<p>Multi-centre national randomised controlled trial.</p> <p>Pts stratified according to dominant site of metastasis, disease free interval &amp; menopausal status. Description of randomisation not given.</p> <p>Dates of accrual: Nov 1972 - May 1974.</p> <p>Baseline comparability achieved</p>
Participants	<p>94 pts.</p> <p>Postmenopausal women with metastatic BC</p> <p>No prior cytotoxic or hormonal agents.</p> <p>Median age: 57 yrs in Adriamycin arm; 56 years in CFP arm.</p>
Interventions	<p>A vs CFP</p> <p>Arm A: A doxorubicin 40mg/m<sup>2</sup> iv; 4 week cycles. cumulative maximum dose of doxorubicin = 500mg/m<sup>2</sup>.</p> <p>Arm B: CFP cyclophosphamide 150mg/m<sup>2</sup> iv, days 1-5; 5-fluorouracil 300mg/m<sup>2</sup> iv, days 1-5; prednisone 40 to 10mg po, daily. 5 week cycle.</p>
Outcomes	<p>Survival</p> <p>Response</p> <p>Toxicity</p>
Notes	<p>ITT analysis. Cross-over to alternate regimen on disease progression. Three sequences were: 1)ADX, CFP, ADR 2)CFP, ADR, ADX 3)ADR, ADX, CFP.</p> <p>Time-to-event data extracted for pts initially allocated to Adriamycin and CFP arms for meta-analysis. Minimum reported f/up = 18 months, max estimated f/up = 36 months (from OS curve). 2 treatment-related deaths within one month of CFP combination therapy observed. 3 treatment-related death in Adriamycin arm due to hepatic failure (1) and delayed cardiac toxicity (2).</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Nemoto 1982a**
**Study characteristics**
**Antitumour antibiotic containing regimens for metastatic breast cancer (Review)**

### Nemoto 1982a (Continued)

Methods	Multi-centre national randomised controlled trial. Dates of accrual; July 1974 - Oct 1975. 4 arm study Randomisation by closed-envelope at one institution. Pts stratified by menopausal status, DFI and dominant site of metastasis. Baseline comparability achieved.
Participants	126 pts. Postmenopausal women with metastatic breast cancer. No prior cytotoxic chemotherapy. Age distribution: 80% pts 50yrs +
Interventions	Comparison 1: CFP-CA vs CFP  Arm A: CFP-CA alternating regimens: Cyclophosphamide 150mg/m <sup>2</sup> iv, days 1-5; 5-fluorouracil 300mg/m <sup>2</sup> iv, days 1-5; prednisone 30mg/d po for 1 week, then 10mg/d po. 5 week cycle then cyclophosphamide 500mg/m <sup>2</sup> iv and doxorubicin 40mg/m <sup>2</sup> iv every nine weeks.  Arm B: CFP cyclophosphamide 150mg/m <sup>2</sup> iv, days 1-5; 5-fluorouracil 300mg/m <sup>2</sup> iv, days 1-5; prednisone 30mg/d po for 1 week, then 10mg/d po. 5 week cycles.
Outcomes	Survival Response Toxicity
Notes	ITT analysis. 9 pts were nonevaluable due to early deaths or withdrawal from study. Cumulative dose of adriamycin did not exceed 500mg/m <sup>2</sup> . Pts rerandomised to tamoxifen or adrenalectomy at progression. One pt on CA arm developed moderate cardiotoxicity. Treatment-related deaths not reported.

#### Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

### Nemoto 1982b

#### Study characteristics

Methods	
Participants	
Interventions	Comparison 2: CAF vs CFP  Arm C: CAF cyclophosphamide 400mg/m <sup>2</sup> iv, day 1; 5-fluorouracil 200mg/m <sup>2</sup> iv, days 1-3; doxorubicin 40mg/m <sup>2</sup> iv, day 1.  Arm B: CFP cyclophosphamide 150mg/m <sup>2</sup> iv, days 1-5; 5-fluorouracil 300mg/m <sup>2</sup> iv, days 1-5; prednisone 30mg/d po for 1 week, then 10mg/d po
Outcomes	

**Nemoto 1982b** (Continued)

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Nemoto 1982c**
**Study characteristics**

Methods

Participants

Interventions	Comparison 3: CA vs CFP  Arm D: CA cyclophosphamide 500mg/m <sup>2</sup> iv, day 1; doxorubicin 40mg/m <sup>2</sup> iv, day 1  Arm B: CFP cyclophosphamide 150mg/m <sup>2</sup> iv, days 1-5; 5-fluorouracil 300mg/m <sup>2</sup> iv, days 1-5; prednisone 30mg/d po for 1 week, then 10mg/d po
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Outcomes

Notes

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Pannuti 1984**
**Study characteristics**

Methods	Randomised controlled trial Method of randomisation and allocation concealment not reported. Baseline comparability achieved.
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Participants	46pts Advanced breast cancer (87% with metastatic disease of viscera or bone). 17% pts had prior hormone and cytotoxic chemotherapy. Age range: 37-74yrs R14; 36-74yrs CMF. Median age: 55yrs both arms
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Interventions	R14 vs CMF  Arm A: R14
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**Pannuti 1984** (Continued)

cyclophosphamide 2mg/kg iv vincristine 0.01mg/kg iv, vinblastine 0.1mg/kg iv Day 1 and methotrexate 0.7mg/kg iv, doxorubicin 0.5mg/kg iv Day 2. 21 day cycle.

Arm B: CMF

cyclophosphamide 100mg/m<sup>2</sup> days 1-14; methotrexate 40mg/m<sup>2</sup> day 1, 8; 5-fluorouracil 600mg/m<sup>2</sup> day 1, 8. 28 day cycle.

Outcomes	Response (CR, PR, P, NC) Survival Toxicity
Notes	46 pts included in all analyses. Estimated min f/up = 5.5 months (median time to progression), estimated max f/up = 45 months (from survival curve). treatment-related deaths not reported.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Rosner 1989a**

**Study characteristics**

Methods	Randomised controlled trial. 3 arm trial. Method of randomisation and allocation concealment not reported. Stratification by receptor status & dominant site of disease before randomisation. Estrogen receptor-positive or receptor-unknown pts received hormone therapy and randomised on disease progression. Estrogen receptor-negative pts were randomised at enrolment. Baseline comparability achieved. Dates of accrual: Sept 1981 - Dec 1987
Participants	182 pts Progressive, metastatic breast cancer No prior chemotherapy. Age range (first 141 pts): 26-71 yrs in CA arm; 34-73 yrs in CFP arm; 32-72 yrs in CFPMV arm. Median age (first 141 pts): 54 yrs in CA arm; 57 yrs in CFP arm; 56 yrs in CFPMV arm.
Interventions	Comparison 1: CA vs CFP  Arm A: CA doxorubicin 40mg/m <sup>2</sup> iv; cyclophosphamide 400mg/m <sup>2</sup> iv. 4 week cycles. cumulative maximum dose of doxorubicin = 500mg/m <sup>2</sup> .  Arm B: CFP cyclophosphamide 150mg/m <sup>2</sup> iv, days 1-5; 5-fluorouracil 300mg/m <sup>2</sup> iv, days 1-5; prednisone 40 to 10mg po, daily. 5 week cycle.
Outcomes	Response Overall survival (from date of first chemotherapy) Toxicity
Notes	Randomised trial of sequential CT. 108/182 pts were ER-positive and received hormone therapy prior to randomisation. Pts were crossed over upon disease progression. ITT analysis. Reported minimum follow-up = 6 months, maximum f/up = 81 months. 6 treatment-related deaths reported in the preliminary report of 141/182 pts. 3 deaths in the CFPMV arm (GI bleed and bronchopneumonia(1), pulmonary

**Rosner 1989a** (Continued)

embolism (2)) and 3 deaths in the CA arm reported due to cardiotoxicity. 3 additional pts in the CA arm were also reported with non-fatal CHF.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**Rosner 1989b**

**Study characteristics**

Methods	
Participants	
Interventions	<p>Comparison 2: CA vs CFPMV</p> <p>Arm A: CA doxorubicin 40mg/m<sup>2</sup> iv; cyclophosphamide 400mg/m<sup>2</sup> iv. 4 week cycles. culmulative maximum dose of doxorubicin = 500mg/m<sup>2</sup>.</p> <p>Arm B CFPMV cyclophosphamide 50mg po twice daily; 5-fluorouracil 500mg iv, weekly; methotrexate 25mg iv, weekly; vincristine 1mg iv, weekly; prednisone 40 to 10mg po, daily. 5 week cycles.</p>
Outcomes	
Notes	

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**SAKK 1983a**

**Study characteristics**

Methods	<p>Multi-centre national randomised controlled trial. 3 arm trial. Pts were stratified according to menopausal status and risk group. Method of randomisation and allocation concealment not described. Dates of accrual: Sept 1975 - Dec 1980. Baseline comparability reported for evaluable pts.</p>
Participants	<p>230 pts randomised (216 evaluable). Women with measurable metastatic breast cancer. No prior cytotoxic chemotherapy or hormonotherapy. Median age: 57.2 -57.9 yrs in each arm</p>

**SAKK 1983a** (Continued)

Interventions	<p>Comparison 1: CLB + AMFP vs CLB + MFP</p> <p>Arm A: CLB + AMFP chlorambucil 5/mg/m2/d po, days 1-14; methotrexate 40mg/m2/w iv, days 1, 8; 5-fluorouracil 600mg/m2/w iv, days 1, 8; prednisone 30mg/m2/d, days 1-14 (then decreasing); doxorubicin 60mg/m2, day 28. 8 week cycles for 6 months maximum culmulative dose of doxorubicin = 450mg/m2.</p> <p>Arm B: CLB + MFP chlorambucil 5mg/m2/d po, days 1-14; methotrexate 10mg/m2/w po, days 1 &amp; 8; 5-fluorouracil 500mg/m2/w po, days 1 &amp; 8; prednisone 30mg/m2/d, days 1-14 (then decreasing). 4 week cycles for 6 months</p>
Outcomes	<p>Response (UICC) Survival Time to progression (median) Toxicity</p>
Notes	<p>464 pts were entered in study and randomised to receive tamoxifen/oophorectomy or tamoxifen/oophorectomy with concurrent chemotherapy. The 230 pts assigned to the chemotherapy arm were further randomised to 3 different chemotherapy regimens. 216/230 pts were reported as evaluable: 14 were excluded from analysis due to major protocol violations (10 pts), 2 poorly evaluable tumour parameters &amp; 2 early deaths. Minimum reported follow-up = 17 months, maximum reported follow-up = 80 months. Median time to progression was 19.5 months (Adrimaycin arm) vs 20.5 months (CLB, Mtx, 5-FU, Pred) and 19.5 months (CLB, Mtx, 5-FU, Vcr, Pred). Treatment-related deaths not reported.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**SAKK 1983b**

**Study characteristics**

Methods	
Participants	
Interventions	<p>Comparison 2: CLB + AMFP vs CLB + MFVP</p> <p>Arm A: CLB + AMFP chlorambucil 5/mg/m2/d po, days 1-14; methotrexate 40mg/m2/w iv, days 1, 8; 5-fluorouracil 600mg/m2/w iv, days 1, 8; prednisone 30mg/m2/d, days 1-14 (then decreasing); doxorubicin 60mg/m2, day 28. 8 week cycles for 6 months maximum culmulative dose of doxorubicin = 450mg/m2.</p> <p>Arm C: CLB + MFVP chlorambucil 5/mg/m2/d po, days 1-14; methotrexate 15mg/m2/w po, days 1-3 &amp; 8-10; prednisone 30mg/m2/d, days 1-14; 5-fluorouracil 500mg/m2/w iv, days 15 &amp; 22; vincristine 1.2mg/m2/w iv, days 15 &amp; 22; prednisone 30mg/m2/d days 5-28 (then decreasing). 4 week continuous cycle for 6 months.</p>
Outcomes	
Notes	

**SAKK 1983b** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

**SECSG 1983**
**Study characteristics**

Methods	Multi-centre randomised trial. Randomised by telephone without stratification Accrual dates: April 1974 - July 1977 Baseline comparability of number of metastatic sites and prior use of hormone therapy achieved.
Participants	362 pts (265 pts were considered evaluable) Pts with metastatic or recurrent breast carcinoma. No prior cytotoxic chemotherapy. No age restrictions or age ranges reported.
Interventions	CAF vs CMFVP  Arm A: CAF cyclophosphamide 500mg/m <sup>2</sup> , doxorubicin 50mg/m <sup>2</sup> ; 5-fluorouracil 500mg/m <sup>2</sup> iv. 3 week cycle, 9-10 cycles. to a maximum dose of 500mg/m <sup>2</sup> doxorubicin.  Arm B: CMFVP cyclophosphamide 400mg/m <sup>2</sup> iv. day 1, methotrexate 30mg/m <sup>2</sup> iv. day 1, 8, 5-fluorouracil 400mg/m <sup>2</sup> iv. days 1, 8; vincristine 1mg days 1 and 8 iv.; prednisone 20mg days 1-7 po. 28 day cycle X 6.
Outcomes	Response (SECSG) Survival Progression free survival Toxicity
Notes	During the last six months of accrual eligibility was limited to patients with visceral metastases. ITT not followed. 265/362 patients were considered evaluable due to: ineligibility (41); protocol violations (25); or incomplete data (31). Estimated minimum follow-up time = 7 months (from protocol), est max f/up = 60 months (from survival curve). No treatment-related deaths observed. Cardiotoxicity observed in one pt who received the maximum dose of 500mg/m <sup>2</sup> of doxorubicin ( CHF responsive to treatment).

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

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



Study	Reason for exclusion
303 Study Group	2nd line chemotherapy trial. All pts had received previous alkylating agent chemotherapy eg. CMF or variants for adjuvant (47%) and/or advanced disease (53%).
304 Study Group	2nd line chemotherapy trial. 81% pts had previous anthracycline chemotherapy for advanced disease or disease progression within 12 months of anthracycline based adjuvant therapy.
Ahmann 1978	Subjects were re-randomized after 2 cycles (10 weeks) if stable disease or regression. Complete time-to-event data on subsets of subjects not available.
Bezwoda 1979	15 (12%) of patients failing treatment prior to 3 month evaluation not included in efficacy analyses. Admission of scientific fraud by principal investigator noted in a later trial.
Dieras 1995	2nd line chemotherapy trial. All pts had prior metastatic or adjuvant chemotherapy, 98% had prior anthracycline treatment.
Erkisi 1997	2nd line chemotherapy trial. All pts had prior CMF chemotherapy, 52% for advanced disease.
Falkson 1988	2nd line chemotherapy trial. 85% of pts had prior chemotherapy.
GOIRC 1990	2nd line chemotherapy trial. 198 pts underwent 6 cycles of CMF, 96pts showed no progression and were randomised to continuation of CMF or AV with CF, CM or MF 'intensification-discontinuation' arm. 96 pts were not randomised due to progression within first 6 cycles.
Hori 2001	Patients were found not to have ABC following randomisation.
Legha 1979	30 patients received combination of hexamethylamine, vincristine, mitomycin C (HOM) V 23 patients received hexamethylamine(HMM). The HMM arm was closed early. Therefore, it is unclear whether patients were automatically allocated to HOM after the closure of the HMM arm compromising randomisation.
Leiden Uni Centre	This trial was previously listed as "Ongoing". Clarification was sought from authors regarding status of trial. Trial is closed. No further information available.
Porzsolt 1990	99 subjects entered the trial and received 2 cycles of anthracycline. 66 Subjects who remained stable or responded were eligible for randomisation to one of the 2 regimens.
SWG Gottlieb 1974	Not properly randomised trial, patients with prior doxorubicin or nitrosurea use assigned to alternate arm.
Venturino 2000	2nd line chemotherapy trial. Pts had received one course of prior chemotherapy for metastatic disease (including CMF, CEF).
Zekan 1984	Of the 51 patients recruited into the study, 24 had been allocated to treatment arms using an 'alternating sequence' recorded on unsealed cards. The remaining 27 were allocated according to a random number sequence generated by random number tables recorded on sealed cards. Results are presented on entire sample of 51 patients and hence we could not identify results attributable to those 27 patients appropriately randomised.

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

#### Butler 2004

Study name	A study of docetaxel monotherapy or DOXIL/CAELYX and doxetaxel in patients with advanced breast cancer
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**Butler 2004** (Continued)

Methods

Participants

Interventions

Outcomes

Starting date

Contact information

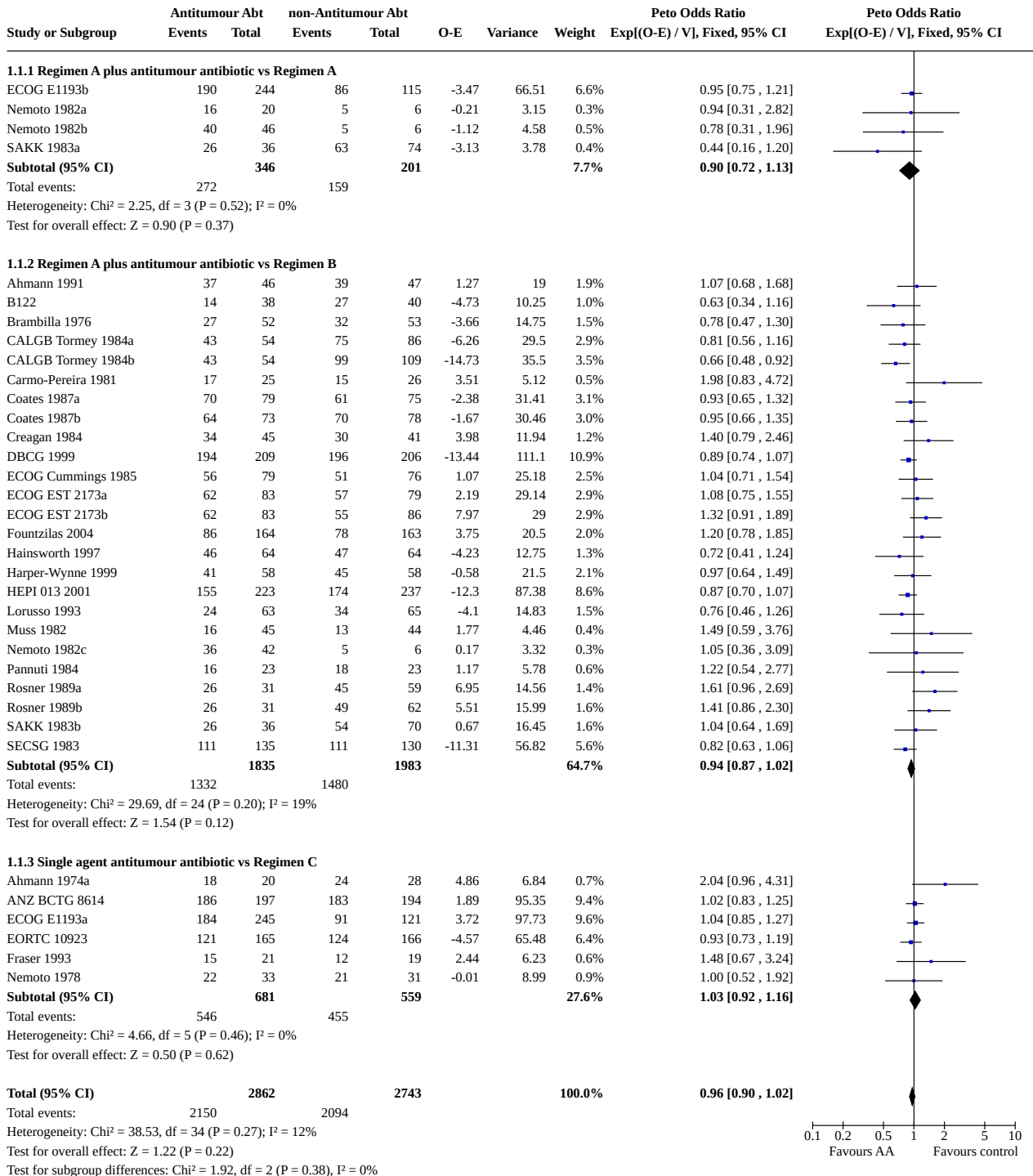
Notes

**DATA AND ANALYSES**
**Comparison 1. Antitumour antibiotic containing regimens vs not: all trials**

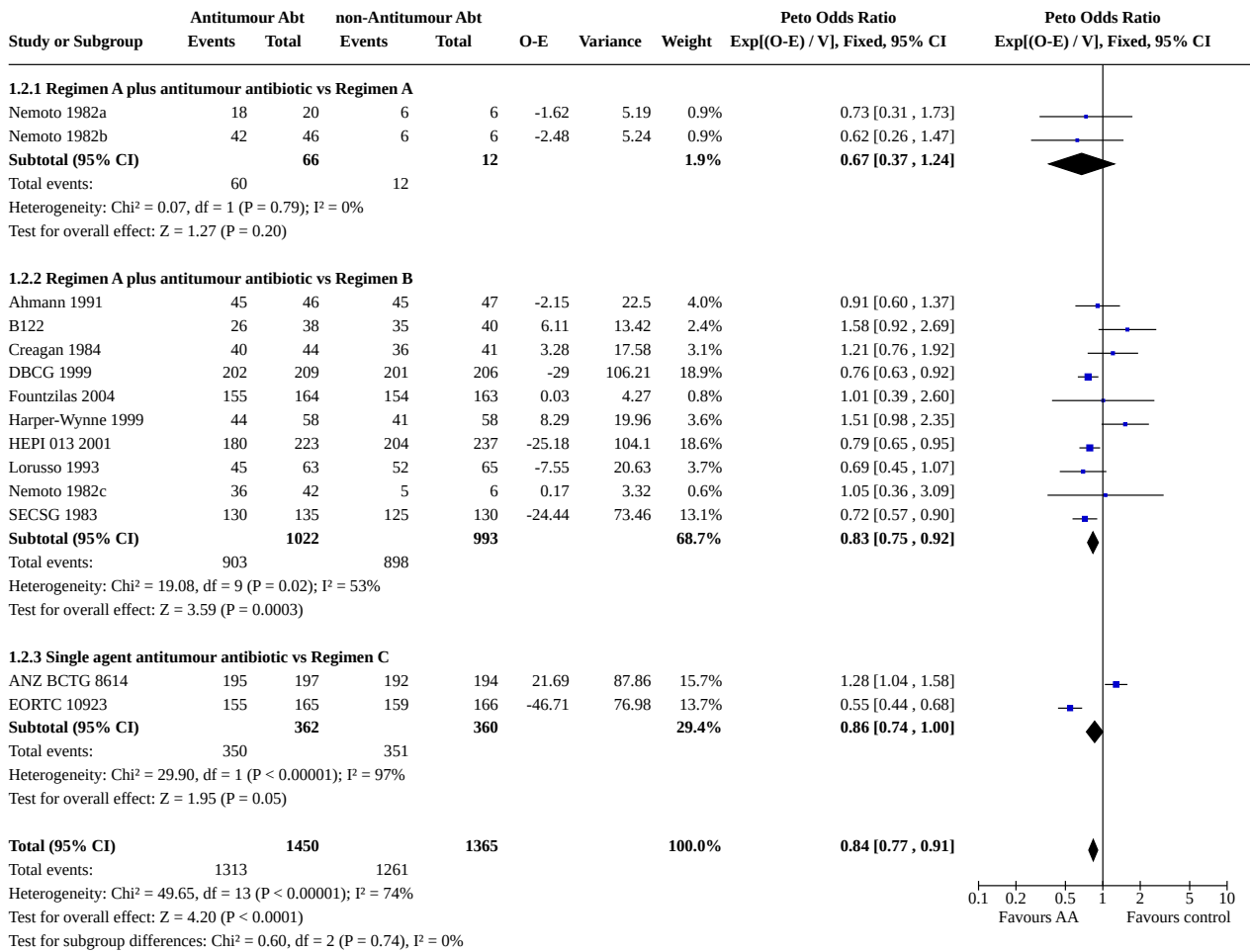
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>1.1 Overall survival</b>	35	5605	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.96 [0.90, 1.02]
1.1.1 Regimen A plus antitumour antibiotic vs Regimen A	4	547	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.90 [0.72, 1.13]
1.1.2 Regimen A plus antitumour antibiotic vs Regimen B	25	3818	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.94 [0.87, 1.02]
1.1.3 Single agent antitumour antibiotic vs Regimen C	6	1240	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.03 [0.92, 1.16]
<b>1.2 Time to progression</b>	14	2815	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.84 [0.77, 0.91]
1.2.1 Regimen A plus antitumour antibiotic vs Regimen A	2	78	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.67 [0.37, 1.24]
1.2.2 Regimen A plus antitumour antibiotic vs Regimen B	10	2015	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.83 [0.75, 0.92]
1.2.3 Single agent antitumour antibiotic vs Regimen C	2	722	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.86 [0.74, 1.00]
<b>1.3 Overall response (assessable patients)</b>	45	6538	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [1.21, 1.48]
1.3.1 Regimen A plus antitumour antibiotic vs Regimen A (assessable patients)	5	604	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.33, 2.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3.2 Regimen A plus antitumour antibiotic vs Regimen B (assessable patients)	32	4439	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [1.27, 1.62]
1.3.3 Single agent antitumour antibiotic vs Regimen C (assessable patients)	9	1495	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.74, 1.15]
<b>1.4 Treatment-related death</b>	<b>20</b>	<b>4364</b>	<b>Odds Ratio (M-H, Fixed, 95% CI)</b>	<b>1.18 [0.77, 1.83]</b>
1.4.1 Regimen A plus antitumour antibiotic vs Regimen A	1	345	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.18, 5.54]
1.4.2 Regimen A plus antitumour antibiotic vs Regimen B	15	3242	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.61, 1.67]
1.4.3 Single agent antitumour antibiotic vs Regimen C	4	777	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.80, 6.41]

**Analysis 1.1. Comparison 1: Antitumour antibiotic containing regimens vs not: all trials, Outcome 1: Overall survival**



**Analysis 1.2. Comparison 1: Antitumour antibiotic containing regimens vs not: all trials, Outcome 2: Time to progression**



**Analysis 1.3. Comparison 1: Antitumour antibiotic containing regimens vs not: all trials, Outcome 3: Overall response (assessable patients)**

Study or Subgroup	Antitumour Abt		non-Antitumour Abt		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
<b>1.3.1 Regimen A plus antitumour antibiotic vs Regimen A (assessable patients)</b>							
Creech 1979	24	39	19	39	1.1%	1.68 [0.68 , 4.14]	
ECOG E1193b	108	230	39	115	4.3%	1.73 [1.08 , 2.75]	
Nemoto 1982a	12	19	1	6	0.1%	8.57 [0.83 , 89.04]	
Nemoto 1982b	10	40	1	6	0.2%	1.67 [0.17 , 16.02]	
SAKK 1983a	19	36	24	74	1.1%	2.33 [1.03 , 5.26]	
<b>Subtotal (95% CI)</b>		<b>364</b>		<b>240</b>	<b>6.8%</b>	<b>1.90 [1.33 , 2.72]</b>	
Total events:	173		84				
Heterogeneity: Chi <sup>2</sup> = 2.08, df = 4 (P = 0.72); I <sup>2</sup> = 0%							
Test for overall effect: Z = 3.53 (P = 0.0004)							
<b>1.3.2 Regimen A plus antitumour antibiotic vs Regimen B (assessable patients)</b>							
Ahmann 1991	21	46	23	47	1.9%	0.88 [0.39 , 1.98]	
B122	31	38	24	40	0.7%	2.95 [1.05 , 8.32]	
Brambilla 1976	27	52	25	53	1.8%	1.21 [0.56 , 2.60]	
CALGB Aisner 1987a	45	82	19	50	1.6%	1.98 [0.97 , 4.07]	
CALGB Aisner 1987b	46	79	19	50	1.5%	2.27 [1.10 , 4.70]	
CALGB Aisner 1987c	20	49	10	23	1.2%	0.90 [0.33 , 2.44]	
CALGB Aisner 1987d	13	41	10	23	1.4%	0.60 [0.21 , 1.73]	
CALGB Tormey 1984a	38	54	43	86	1.5%	2.38 [1.15 , 4.88]	
CALGB Tormey 1984b	38	54	55	109	1.7%	2.33 [1.16 , 4.67]	
Carmo-Pereira 1981	14	25	17	26	1.1%	0.67 [0.22 , 2.09]	
Chauvergne 1978	19	35	10	35	0.7%	2.97 [1.10 , 7.99]	
Coates 1987a	39	79	36	75	2.9%	1.06 [0.56 , 1.99]	
Coates 1987b	24	73	25	78	2.5%	1.04 [0.53 , 2.05]	
Creagan 1984	22	45	19	41	1.6%	1.11 [0.47 , 2.59]	
DBC 1999	85	161	64	180	4.4%	2.03 [1.31 , 3.13]	
ECOG Cummings 1985	43	79	40	76	2.9%	1.07 [0.57 , 2.02]	
ECOG EST 2173a	93	166	99	165	6.7%	0.85 [0.55 , 1.31]	
Fountzilas 2004	70	149	59	144	4.9%	1.28 [0.80 , 2.03]	
Hainsworth 1997	29	64	16	62	1.4%	2.38 [1.12 , 5.05]	
Harper-Wynne 1999	9	58	17	58	2.2%	0.44 [0.18 , 1.10]	
HEPI 013 2001	125	189	104	200	5.3%	1.80 [1.20 , 2.72]	
Kolaric 1977	25	38	20	36	1.1%	1.54 [0.60 , 3.93]	
Kolaric 1985	43	61	26	62	1.2%	3.31 [1.57 , 6.98]	
Lorusso 1993	25	57	18	62	1.5%	1.91 [0.89 , 4.07]	
Muss 1978	44	76	41	72	2.7%	1.04 [0.54 , 2.00]	
Muss 1982	21	45	7	44	0.6%	4.63 [1.71 , 12.54]	
Nemoto 1982a	17	41	1	6	0.2%	3.54 [0.38 , 33.11]	
Pannuti 1984	9	23	8	23	0.8%	1.21 [0.36 , 4.00]	
Rosner 1989a	16	31	34	59	1.8%	0.78 [0.33 , 1.88]	
Rosner 1989b	16	31	42	62	2.1%	0.51 [0.21 , 1.23]	
SAKK 1983b	19	36	36	70	1.8%	1.06 [0.47 , 2.36]	
SECSG 1983	74	135	52	130	3.7%	1.82 [1.12 , 2.96]	
<b>Subtotal (95% CI)</b>		<b>2192</b>		<b>2247</b>	<b>67.3%</b>	<b>1.43 [1.27 , 1.62]</b>	
Total events:	1160		1019				
Heterogeneity: Chi <sup>2</sup> = 58.21, df = 31 (P = 0.002); I <sup>2</sup> = 47%							
Test for overall effect: Z = 5.82 (P < 0.00001)							
<b>1.3.3 Single agent antitumour antibiotic vs Regimen C (assessable patients)</b>							
Ahmann 1974a	5	10	8	16	0.5%	1.00 [0.21 , 4.86]	
Ahmann 1974b	5	10	5	12	0.4%	1.40 [0.26 , 7.58]	
ANZ BCTG 8614	47	197	70	194	8.3%	0.56 [0.36 , 0.86]	
ECOG E1193a	81	224	39	115	5.1%	1.10 [0.69 , 1.77]	
ECORTC 10022	67	165	47	166	3.8%	2.02 [1.26 , 3.22]	

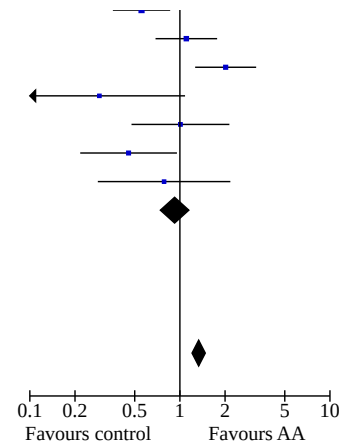
**Analysis 1.3. (Continued)**

Study	n	N	n	N	%	OR [95% CI]
ECOG E1193a	81	224	39	115	5.1%	1.10 [0.69, 1.77]
EORTC 10923	67	165	42	166	3.8%	2.02 [1.26, 3.22]
Fraser 1993	6	21	11	19	1.3%	0.29 [0.08, 1.08]
Hoogstraten 1976a	16	40	39	98	2.1%	1.01 [0.48, 2.14]
Hoogstraten 1976b	16	40	63	106	3.2%	0.46 [0.22, 0.96]
Nemoto 1978	12	32	13	30	1.3%	0.78 [0.28, 2.17]
<b>Subtotal (95% CI)</b>		<b>739</b>		<b>756</b>	<b>25.9%</b>	<b>0.92 [0.74, 1.15]</b>

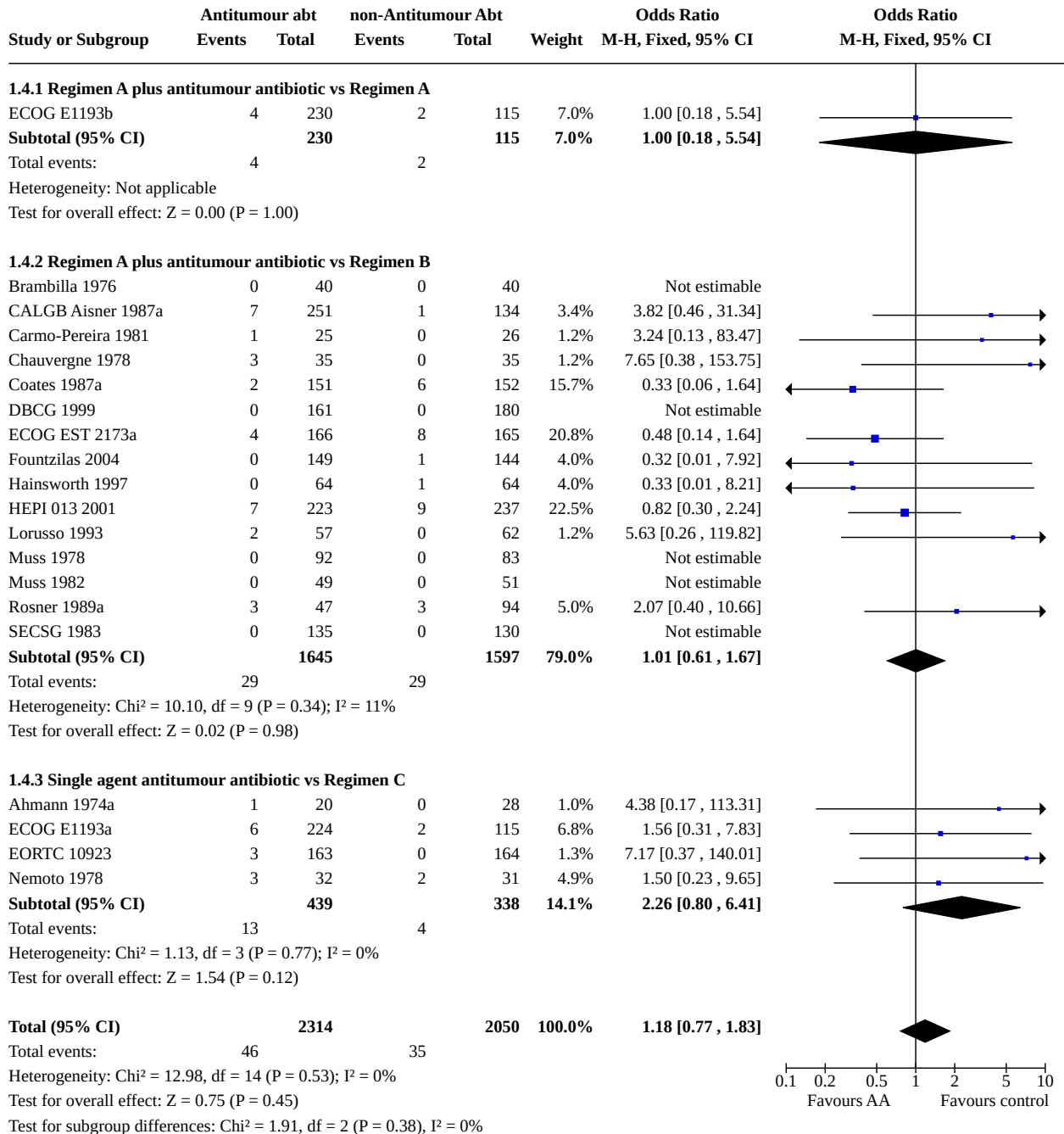
Total events: 255 290  
Heterogeneity: Chi<sup>2</sup> = 23.29, df = 8 (P = 0.003); I<sup>2</sup> = 66%  
Test for overall effect: Z = 0.73 (P = 0.47)

**Total (95% CI)** 3295 3243 **100.0%** **1.33 [1.21, 1.48]**

Total events: 1588 1393  
Heterogeneity: Chi<sup>2</sup> = 98.99, df = 45 (P < 0.00001); I<sup>2</sup> = 55%  
Test for overall effect: Z = 5.56 (P < 0.00001)  
Test for subgroup differences: Chi<sup>2</sup> = 16.16, df = 2 (P = 0.0003), I<sup>2</sup> = 87.6%



**Analysis 1.4. Comparison 1: Antitumour antibiotic containing regimens vs not: all trials, Outcome 4: Treatment-related death**



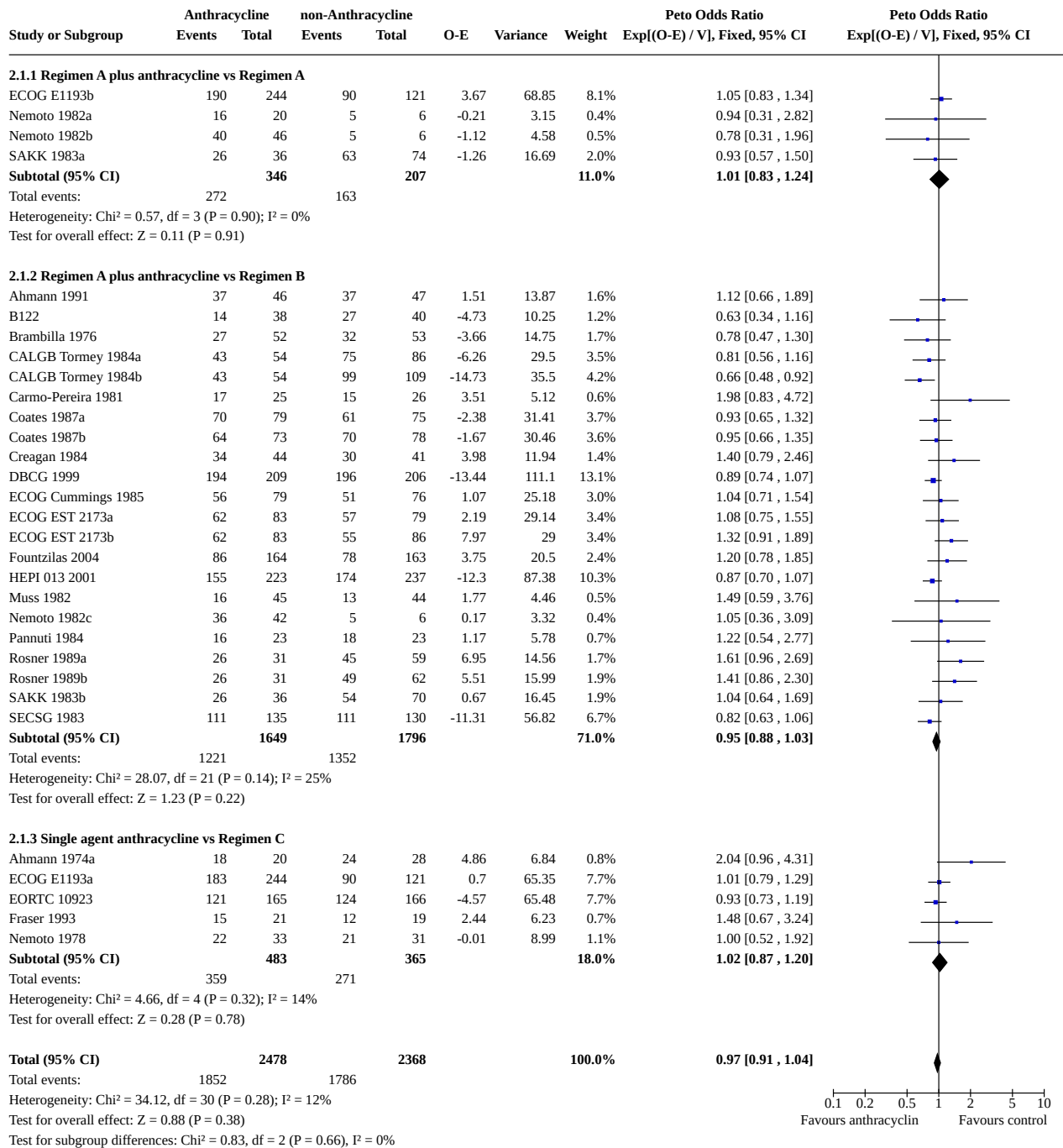
**Comparison 2. Antitumour antibiotic regimens containing anthracyclines vs non antitumour antibiotic containing regimens**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Overall survival	31	4846	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.97 [0.91, 1.04]

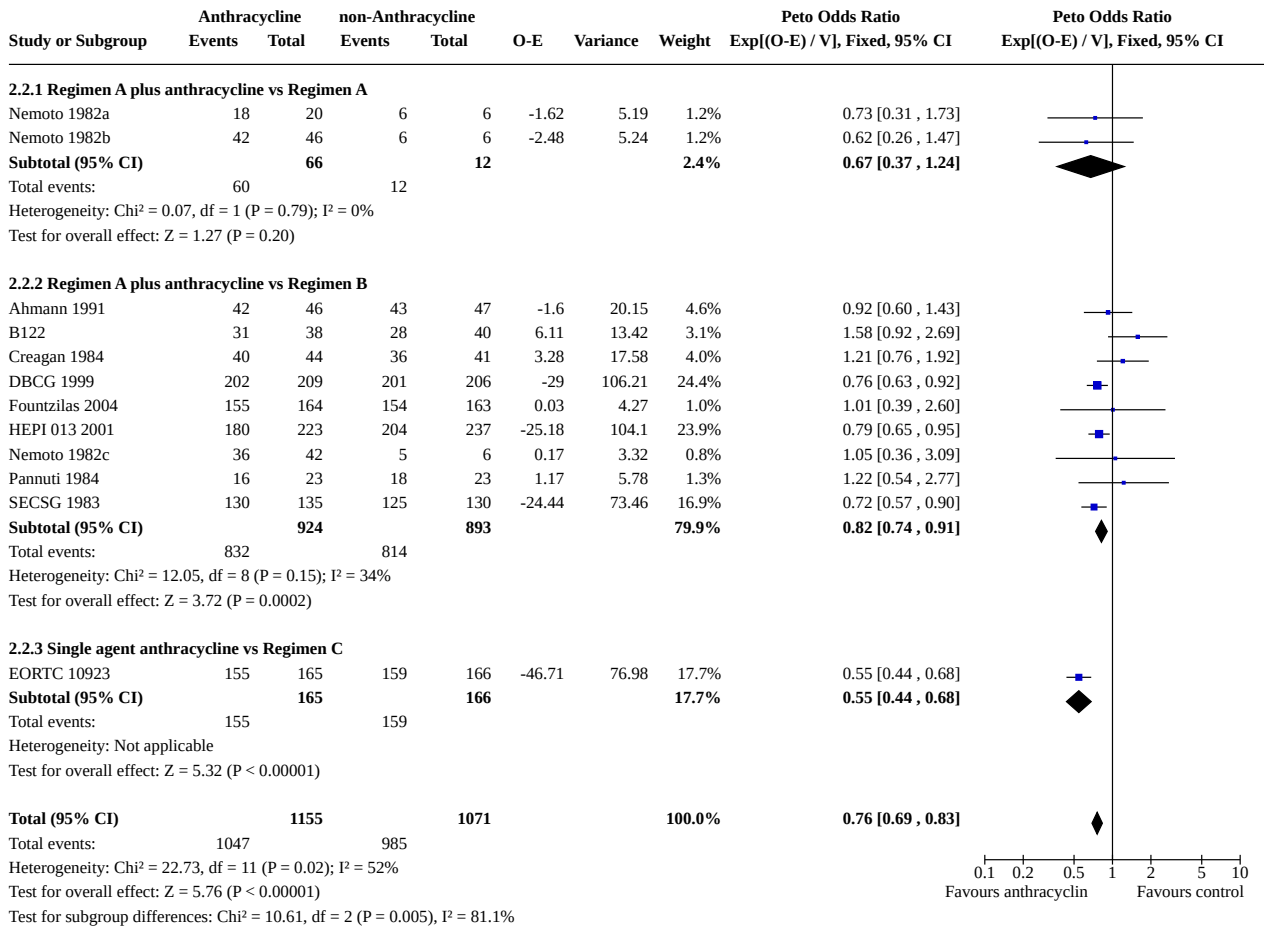


Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.1 Regimen A plus anthracycline vs Regimen A	4	553	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.01 [0.83, 1.24]
2.1.2 Regimen A plus anthracycline vs Regimen B	22	3445	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.88, 1.03]
2.1.3 Single agent anthracycline vs Regimen C	5	848	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.02 [0.87, 1.20]
<b>2.2 Time to progression</b>	<b>12</b>	<b>2226</b>	<b>Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)</b>	<b>0.76 [0.69, 0.83]</b>
2.2.1 Regimen A plus anthracycline vs Regimen A	2	78	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.67 [0.37, 1.24]
2.2.2 Regimen A plus anthracycline vs Regimen B	9	1817	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.82 [0.74, 0.91]
2.2.3 Single agent anthracycline vs Regimen C	1	331	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.55 [0.44, 0.68]
<b>2.3 Overall response (assessable patients)</b>	<b>42</b>	<b>5786</b>	<b>Odds Ratio (M-H, Fixed, 95% CI)</b>	<b>1.40 [1.26, 1.56]</b>
2.3.1 Regimen A plus anthracycline vs Regimen A (assessable patients)	5	604	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.33, 2.72]
2.3.2 Regimen A plus anthracycline vs Regimen B (assessable patients)	29	4078	Odds Ratio (M-H, Fixed, 95% CI)	1.44 [1.27, 1.63]
2.3.3 Single agent anthracycline vs Regimen C (assessable patients)	8	1104	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.41]
<b>2.4 Treatment-related death</b>	<b>18</b>	<b>4117</b>	<b>Odds Ratio (M-H, Fixed, 95% CI)</b>	<b>1.16 [0.74, 1.82]</b>
2.4.1 Regimen A plus anthracycline vs Regimen A	1	345	Odds Ratio (M-H, Fixed, 95% CI)	1.00 [0.18, 5.54]
2.4.2 Regimen A plus anthracycline vs Regimen B	13	2995	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.57, 1.64]
2.4.3 Single agent anthracycline vs Regimen C	4	777	Odds Ratio (M-H, Fixed, 95% CI)	2.26 [0.80, 6.41]

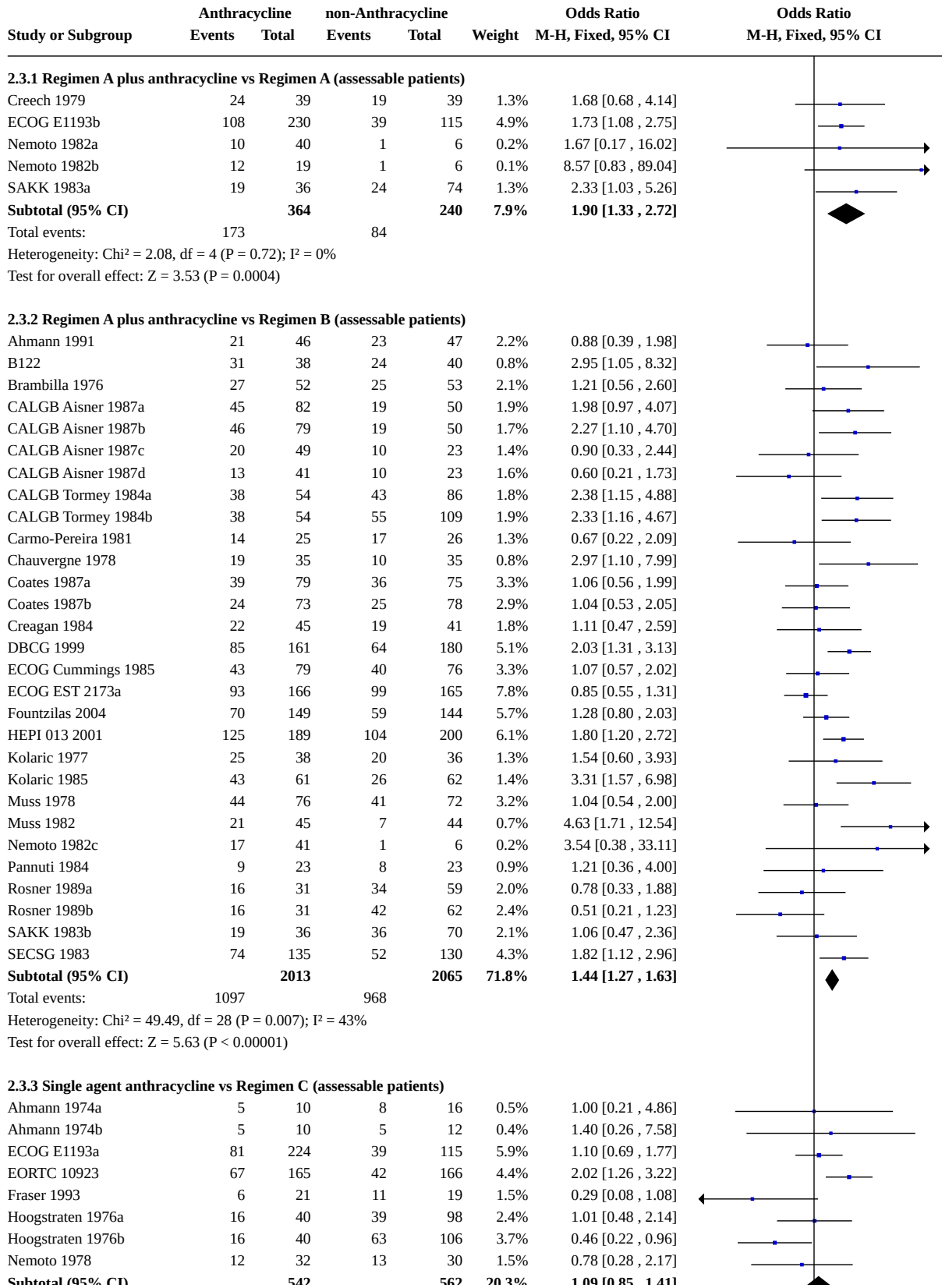
**Analysis 2.1. Comparison 2: Antitumour antibiotic regimens containing anthracyclines vs non antitumour antibiotic containing regimens, Outcome 1: Overall survival**



**Analysis 2.2. Comparison 2: Antitumour antibiotic regimens containing anthracyclines vs non antitumour antibiotic containing regimens, Outcome 2: Time to progression**

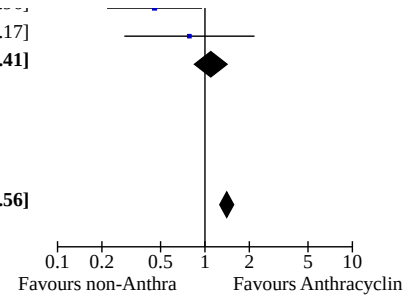


**Analysis 2.3. Comparison 2: Antitumour antibiotic regimens containing anthracyclines vs non antitumour antibiotic containing regimens, Outcome 3: Overall response (assessable patients)**

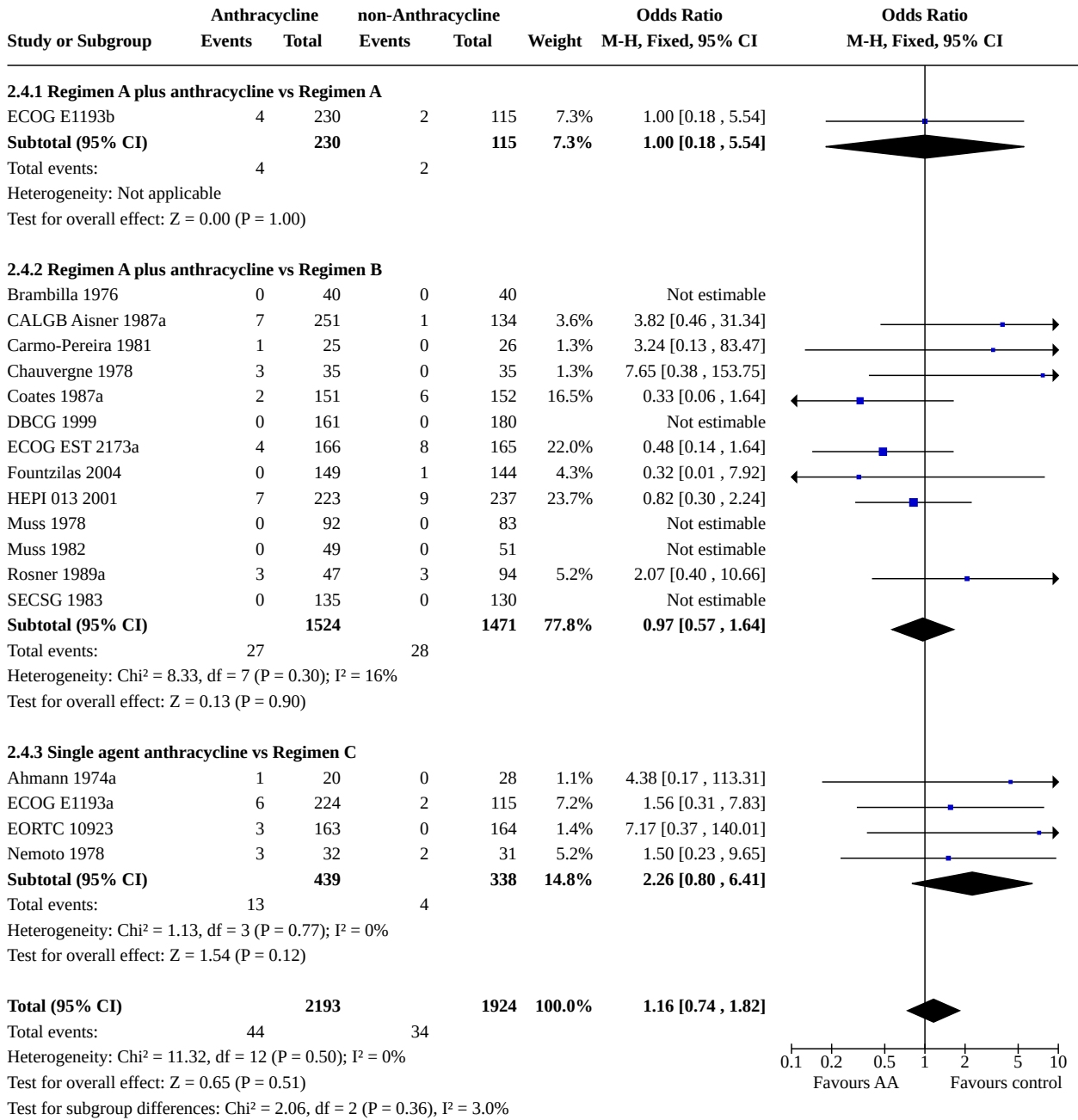


**Analysis 2.3. (Continued)**

Nemoto 1978	12	32	13	30	1.5%	0.78 [0.28 , 2.17]
<b>Subtotal (95% CI)</b>		<b>542</b>		<b>562</b>	<b>20.3%</b>	<b>1.09 [0.85 , 1.41]</b>
Total events:	208		220			
Heterogeneity: $\text{Chi}^2 = 16.41$ , $\text{df} = 7$ ( $P = 0.02$ ); $I^2 = 57\%$						
Test for overall effect: $Z = 0.70$ ( $P = 0.48$ )						
<b>Total (95% CI)</b>		<b>2919</b>		<b>2867</b>	<b>100.0%</b>	<b>1.40 [1.26 , 1.56]</b>
Total events:	1478		1272			
Heterogeneity: $\text{Chi}^2 = 74.14$ , $\text{df} = 41$ ( $P = 0.001$ ); $I^2 = 45\%$						
Test for overall effect: $Z = 6.18$ ( $P < 0.00001$ )						
Test for subgroup differences: $\text{Chi}^2 = 6.61$ , $\text{df} = 2$ ( $P = 0.04$ ), $I^2 = 69.7\%$						



**Analysis 2.4. Comparison 2: Antitumour antibiotic regimens containing anthracyclines vs non antitumour antibiotic containing regimens, Outcome 4: Treatment-related death**

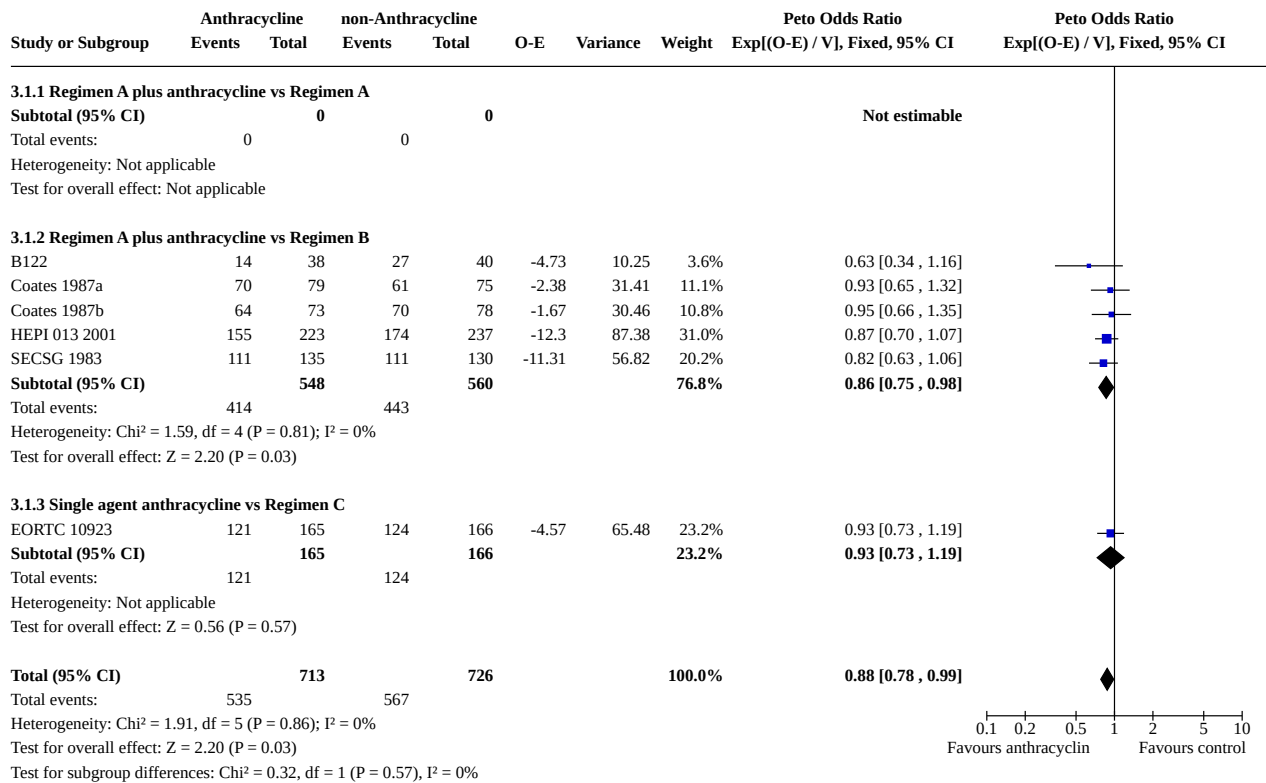


**Comparison 3. Sensitivity analysis: anthracyclines vs not, using studies with clearly described allocation concealment**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall survival	6	1439	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.88 [0.78, 0.99]

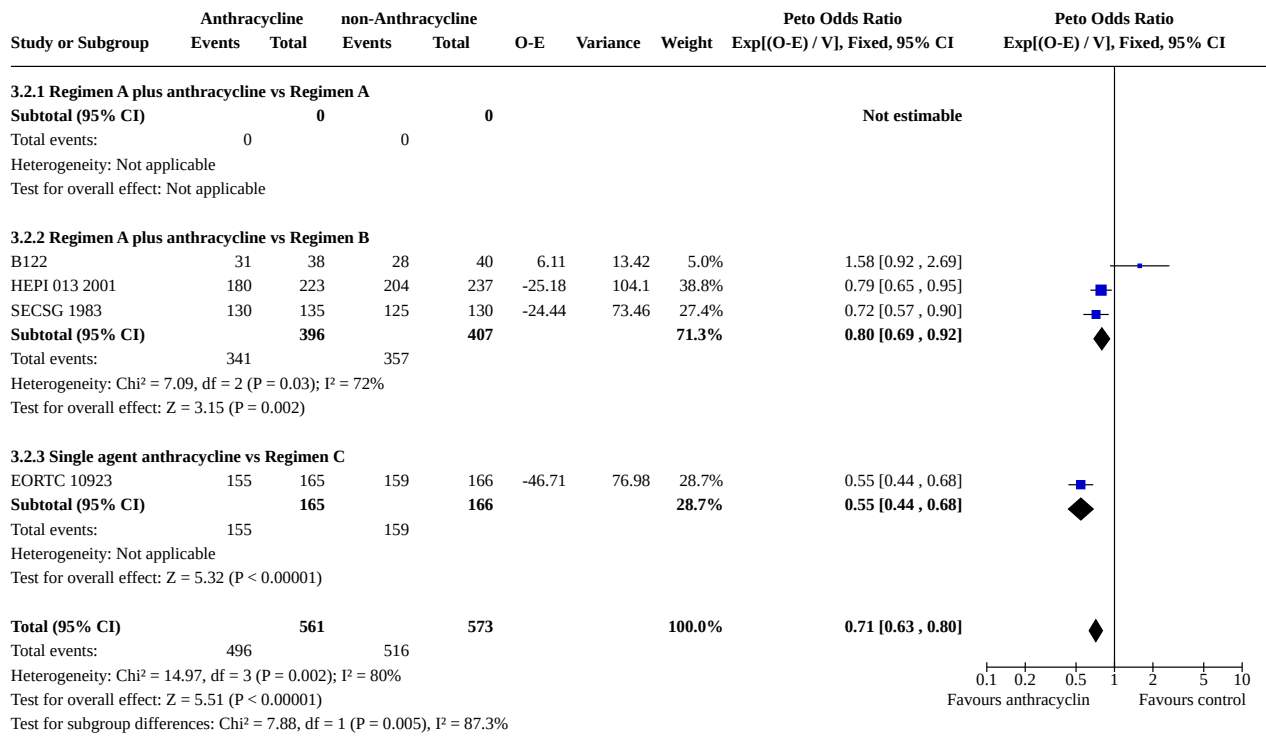
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.1 Regimen A plus anthracycline vs Regimen A	0	0	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Not estimable
3.1.2 Regimen A plus anthracycline vs Regimen B	5	1108	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.86 [0.75, 0.98]
3.1.3 Single agent anthracycline vs Regimen C	1	331	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.93 [0.73, 1.19]
<b>3.2 Time to progression</b>	<b>4</b>	<b>1134</b>	<b>Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)</b>	<b>0.71 [0.63, 0.80]</b>
3.2.1 Regimen A plus anthracycline vs Regimen A	0	0	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Not estimable
3.2.2 Regimen A plus anthracycline vs Regimen B	3	803	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.80 [0.69, 0.92]
3.2.3 Single agent anthracycline vs Regimen C	1	331	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.55 [0.44, 0.68]
<b>3.3 Overall response (assessable patients)</b>	<b>10</b>	<b>1765</b>	<b>Odds Ratio (M-H, Fixed, 95% CI)</b>	<b>1.63 [1.35, 1.98]</b>
3.3.1 Regimen A plus anthracycline vs Regimen A (assessable patients)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3.2 Regimen A plus anthracycline vs Regimen B (assessable patients)	9	1434	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [1.26, 1.94]
3.3.3 Single agent anthracycline vs Regimen C (assessable patients)	1	331	Odds Ratio (M-H, Fixed, 95% CI)	2.02 [1.26, 3.22]

**Analysis 3.1. Comparison 3: Sensitivity analysis: anthracyclines vs not, using studies with clearly described allocation concealment, Outcome 1: Overall survival**

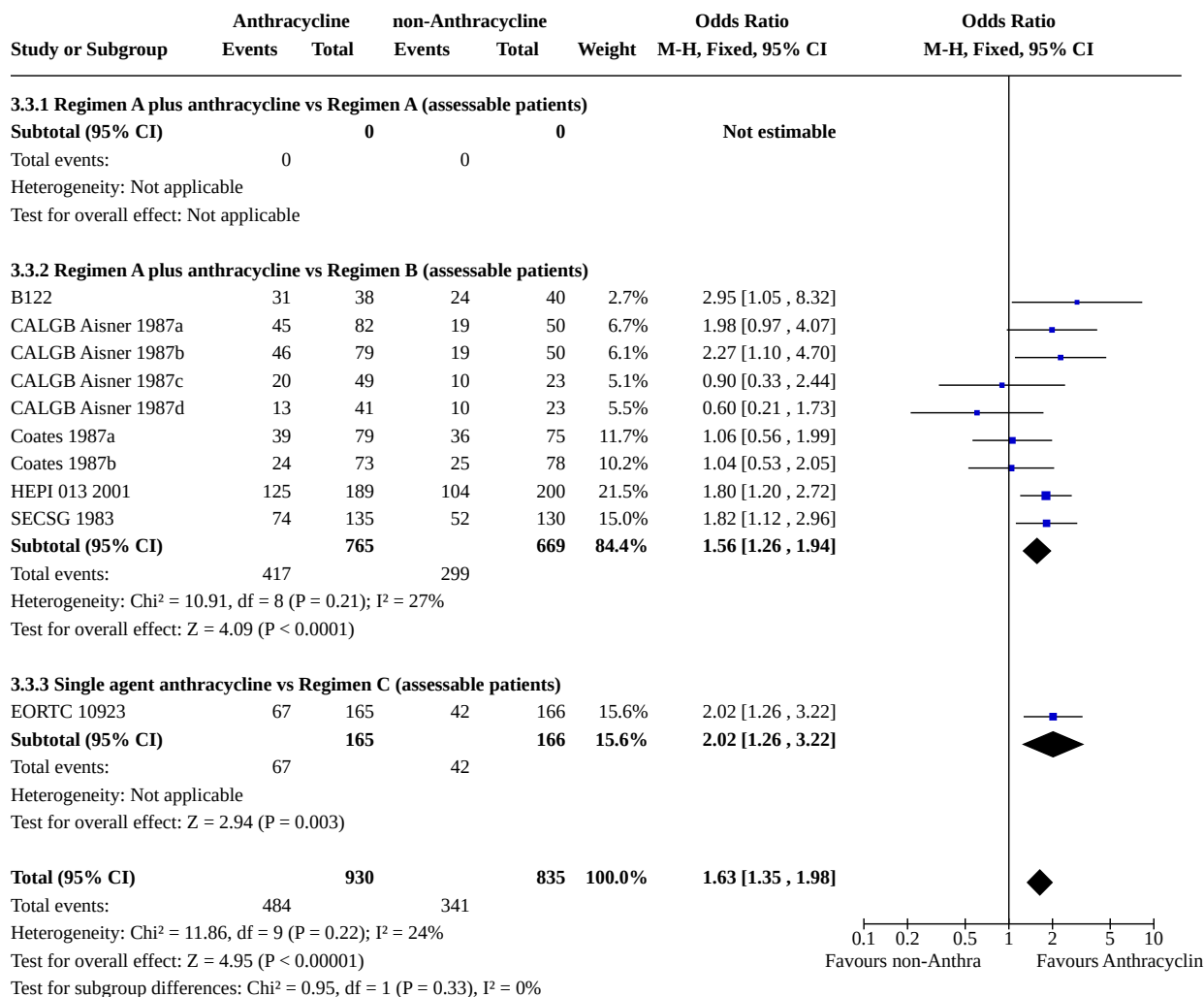




**Analysis 3.2. Comparison 3: Sensitivity analysis: anthracyclines vs not, using studies with clearly described allocation concealment, Outcome 2: Time to progression**



**Analysis 3.3. Comparison 3: Sensitivity analysis: anthracyclines vs not, using studies with clearly described allocation concealment, Outcome 3: Overall response (assessable patients)**

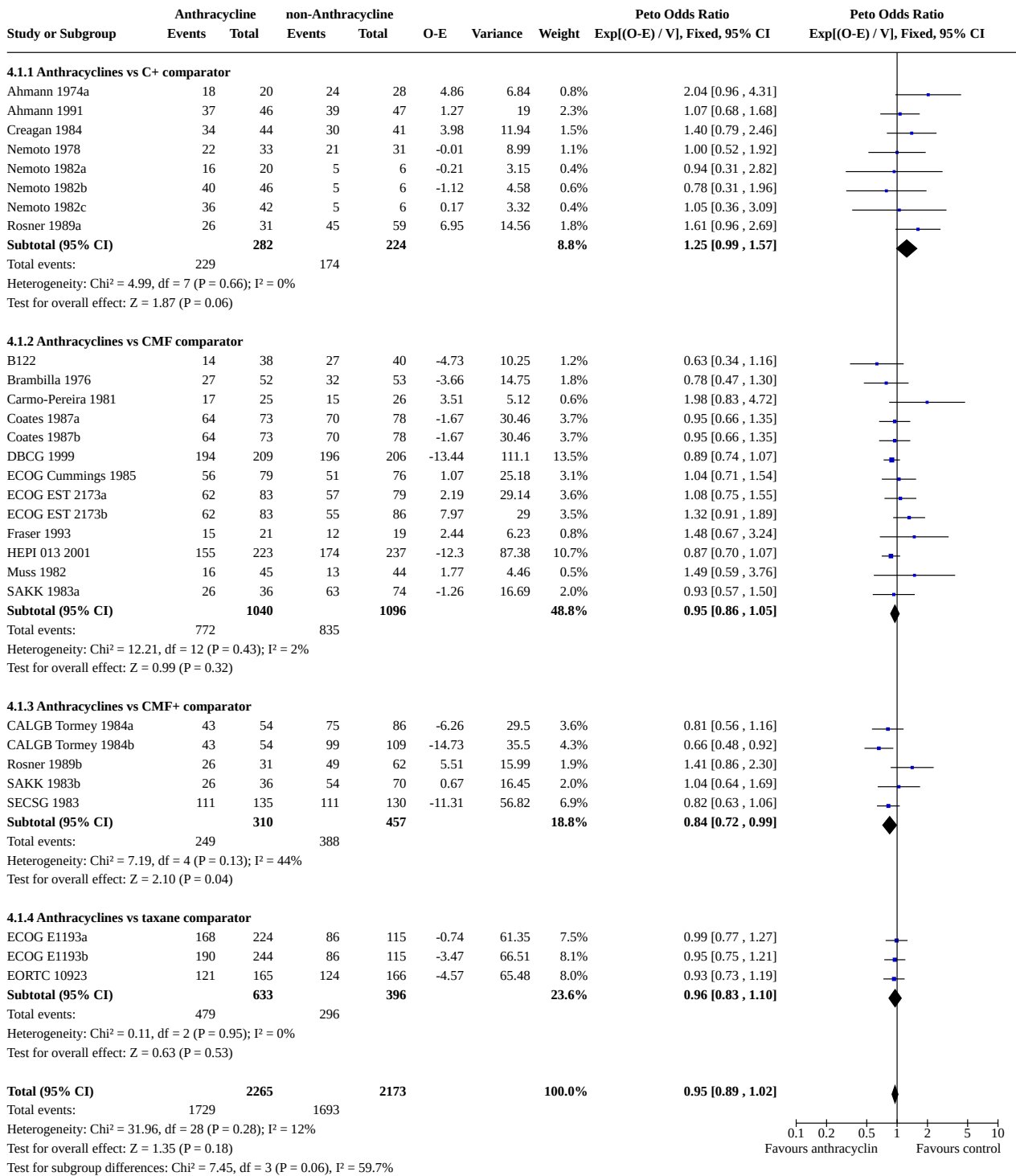


**Comparison 4. Subgroup analysis: anthracyclines vs not, by class of comparator**

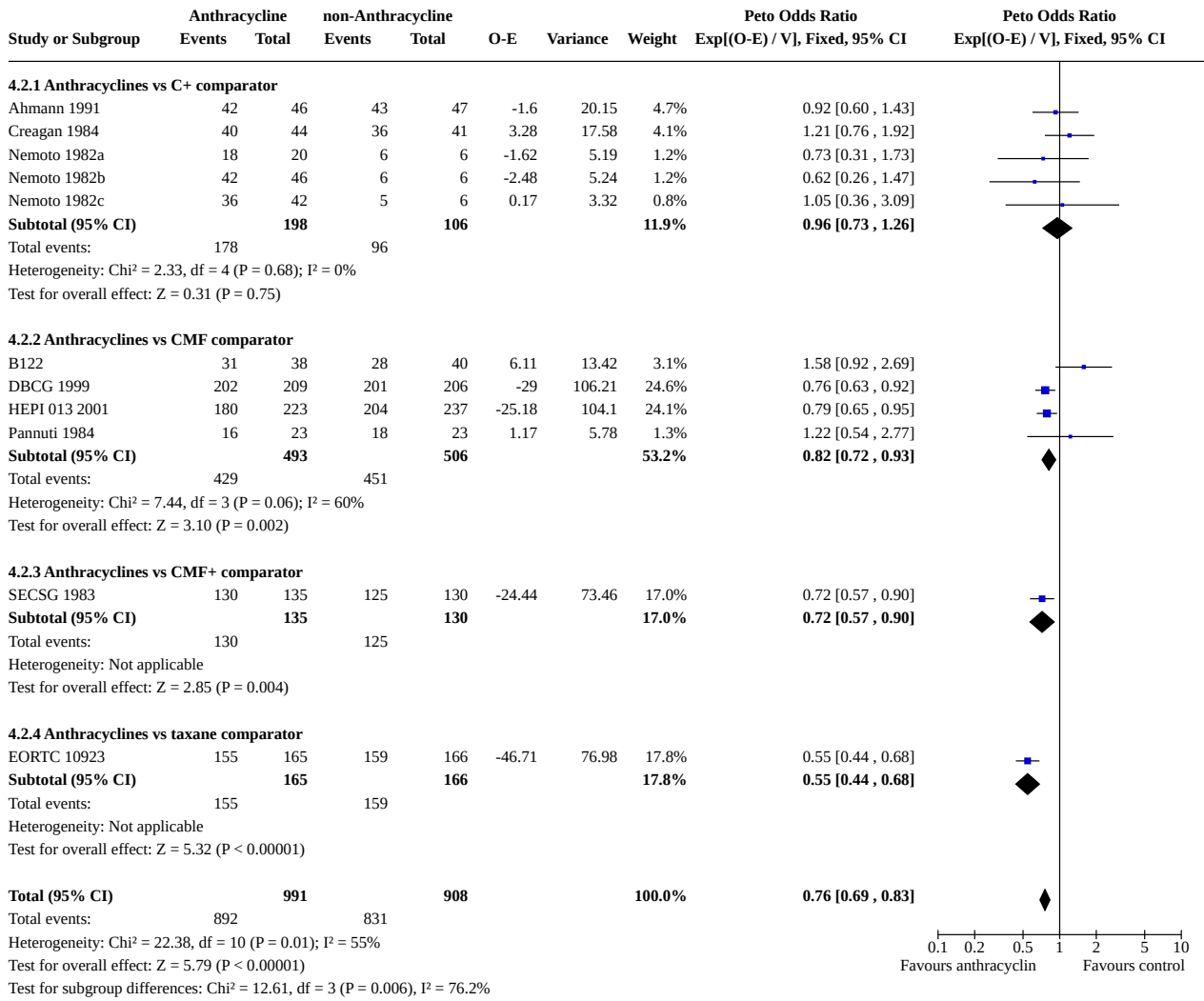
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Overall survival	29	4438	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.89, 1.02]
4.1.1 Anthracyclines vs C+ comparator	8	506	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.25 [0.99, 1.57]
4.1.2 Anthracyclines vs CMF comparator	13	2136	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.86, 1.05]
4.1.3 Anthracyclines vs CMF+ comparator	5	767	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.84 [0.72, 0.99]
4.1.4 Anthracyclines vs taxane comparator	3	1029	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.96 [0.83, 1.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">4.2 Time to progression</a>	11	1899	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.76 [0.69, 0.83]
4.2.1 Anthracyclines vs C+ comparator	5	304	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.96 [0.73, 1.26]
4.2.2 Anthracyclines vs CMF comparator	4	999	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.82 [0.72, 0.93]
4.2.3 Anthracyclines vs CMF+ comparator	1	265	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.72 [0.57, 0.90]
4.2.4 Anthracyclines vs taxane comparator	1	331	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.55 [0.44, 0.68]
<a href="#">4.3 Overall response (assessable patients)</a>	41	5493	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [1.26, 1.58]
4.3.1 Anthracyclines vs C+ comparator	10	567	Odds Ratio (M-H, Fixed, 95% CI)	1.23 [0.87, 1.76]
4.3.2 Anthracyclines vs CMF comparator	18	2515	Odds Ratio (M-H, Fixed, 95% CI)	1.41 [1.20, 1.66]
4.3.3 Anthracyclines vs CMFVP comparator	10	1396	Odds Ratio (M-H, Fixed, 95% CI)	1.38 [1.11, 1.72]
4.3.4 Anthracyclines vs taxane comparator	3	1015	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [1.20, 2.06]

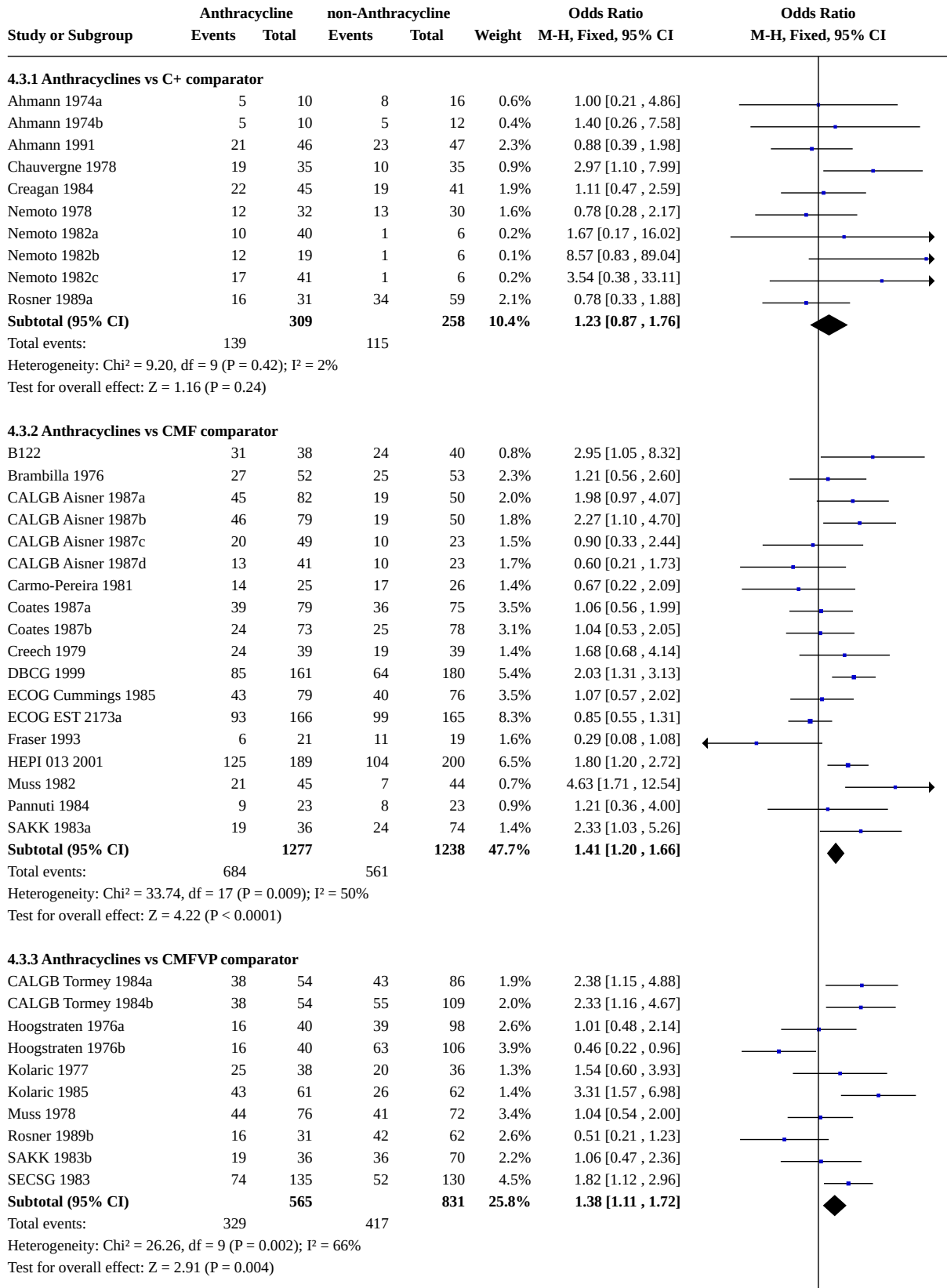
**Analysis 4.1. Comparison 4: Subgroup analysis: anthracyclines vs not, by class of comparator, Outcome 1: Overall survival**



**Analysis 4.2. Comparison 4: Subgroup analysis: anthracyclines vs not, by class of comparator, Outcome 2: Time to progression**



**Analysis 4.3. Comparison 4: Subgroup analysis: anthracyclines vs not, by class of comparator, Outcome 3: Overall response (assessable patients)**



**Analysis 4.3. (Continued)**

Test for overall effect:  $Z = 2.91$  ( $P = 0.004$ )

**4.3.4 Anthracyclines vs taxane comparator**

ECOG E1193a	81	224	39	115	6.2%	1.10 [0.69, 1.77]
ECOG E1193b	108	230	39	115	5.2%	1.73 [1.08, 2.75]
EORTC 10923	67	165	42	166	4.7%	2.02 [1.26, 3.22]
<b>Subtotal (95% CI)</b>		<b>619</b>		<b>396</b>	<b>16.1%</b>	<b>1.57 [1.20, 2.06]</b>

Total events: 256 120

Heterogeneity:  $\text{Chi}^2 = 3.40$ ,  $\text{df} = 2$  ( $P = 0.18$ );  $I^2 = 41\%$

Test for overall effect:  $Z = 3.28$  ( $P = 0.001$ )

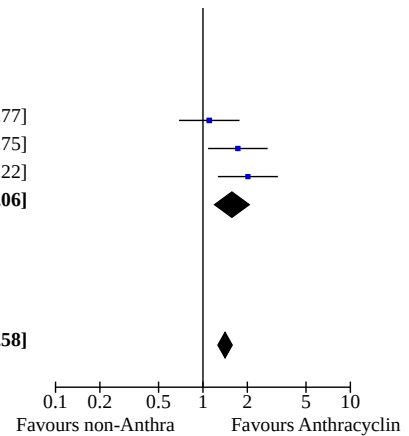
**Total (95% CI)** 2770 2723 **100.0%** **1.41 [1.26, 1.58]**

Total events: 1408 1213

Heterogeneity:  $\text{Chi}^2 = 73.98$ ,  $\text{df} = 40$  ( $P = 0.0009$ );  $I^2 = 46\%$

Test for overall effect:  $Z = 6.11$  ( $P < 0.00001$ )

Test for subgroup differences:  $\text{Chi}^2 = 1.18$ ,  $\text{df} = 3$  ( $P = 0.76$ ),  $I^2 = 0\%$

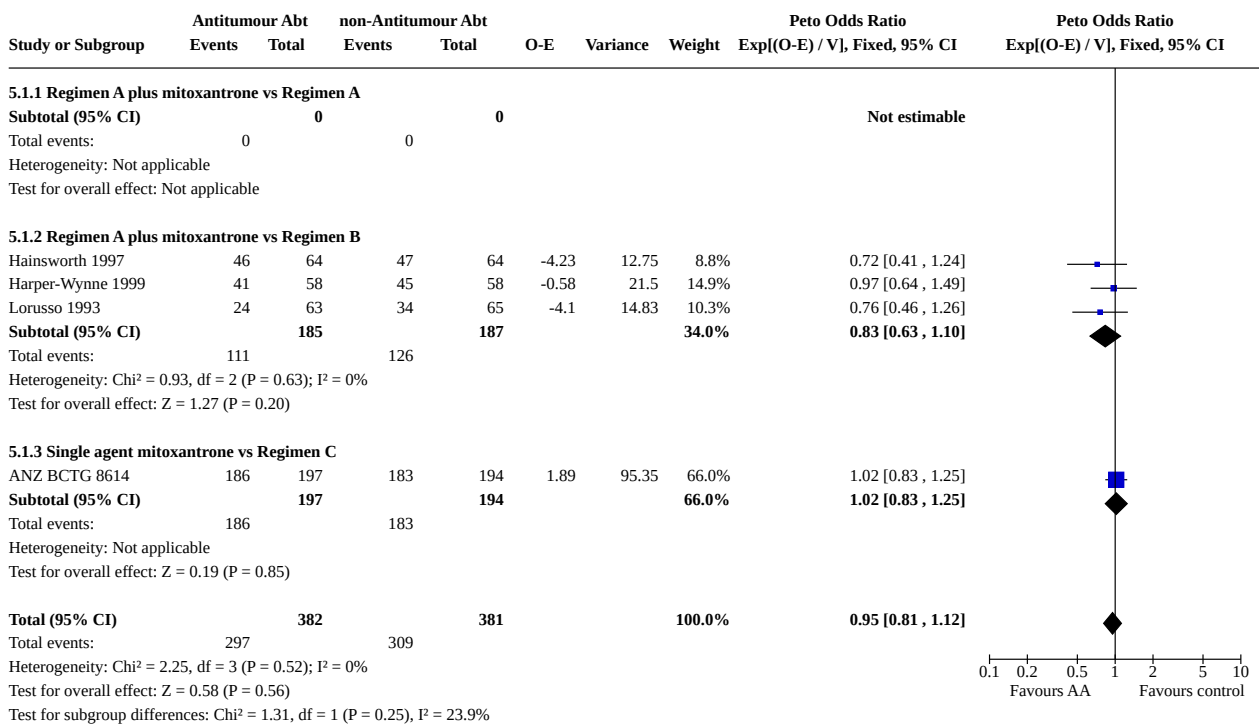


**Comparison 5. Mitoxantrone containing regimens vs non antitumour antibiotic containing regimens**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<b>5.1 Overall survival</b>	4	763	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.95 [0.81, 1.12]
5.1.1 Regimen A plus mitoxantrone vs Regimen A	0	0	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Not estimable
5.1.2 Regimen A plus mitoxantrone vs Regimen B	3	372	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.83 [0.63, 1.10]
5.1.3 Single agent mitoxantrone vs Regimen C	1	391	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.02 [0.83, 1.25]
<b>5.2 Time to progression</b>	3	635	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.84 [0.72, 0.98]
5.2.1 Regimen A plus mitoxantrone vs Regimen A	0	0	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	Not estimable
5.2.2 Regimen A plus mitoxantrone vs Regimen B	2	244	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	1.02 [0.75, 1.39]
5.2.3 Single agent mitoxantrone vs Regimen C	1	391	Peto Odds Ratio (Exp[(O-E) / V], Fixed, 95% CI)	0.79 [0.65, 0.94]
<b>5.3 Overall response (assessable patients)</b>	4	752	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.19]
5.3.1 Regimen A plus mitoxantrone vs Regimen A (assessable patients)	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3.2 Regimen A plus mitoxantrone vs Regimen B (assessable patients)	3	361	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.90, 2.18]

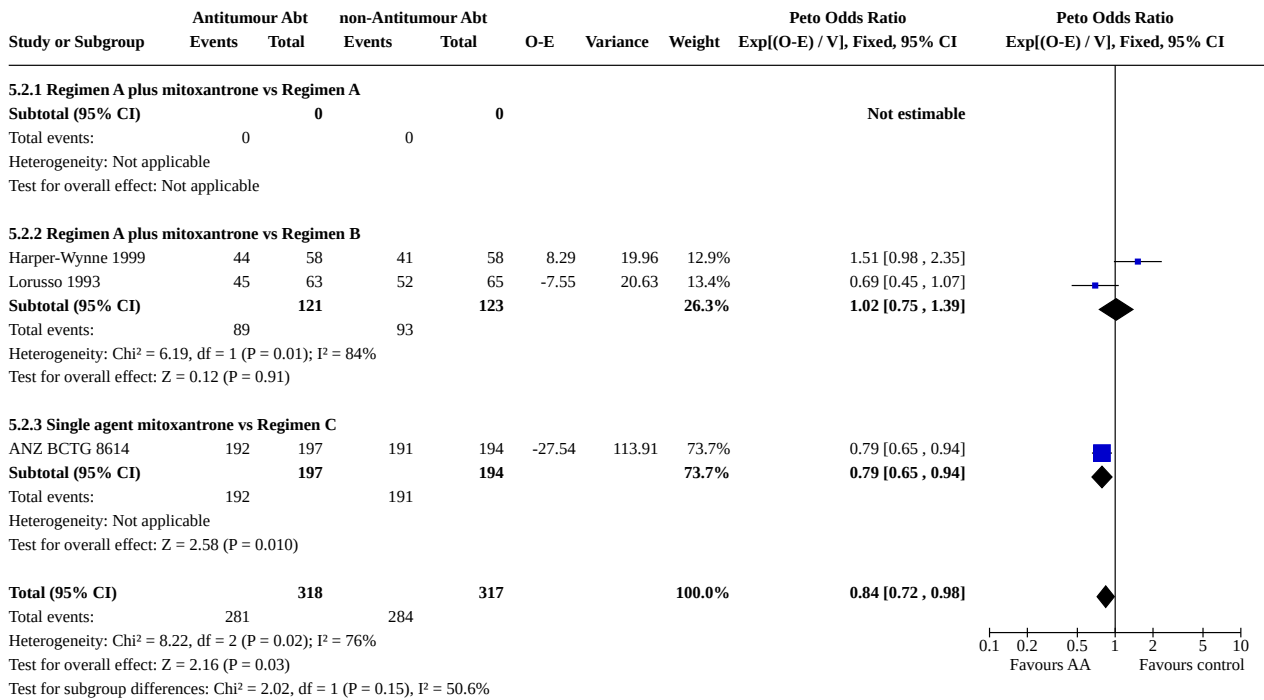
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3.3 Single agent mitoxantrone vs Regimen C (assessable patients)	1	391	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.36, 0.86]
5.4 Treatment-related death	2	247	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.26, 9.44]
5.4.1 Regimen A plus mitoxantrone vs Regimen A	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
5.4.2 Regimen A plus mitoxantrone vs Regimen B	2	247	Odds Ratio (M-H, Fixed, 95% CI)	1.58 [0.26, 9.44]
5.4.3 Single agent mitoxantrone vs Regimen C	0	0	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable

**Analysis 5.1. Comparison 5: Mitoxantrone containing regimens vs non antitumour antibiotic containing regimens, Outcome 1: Overall survival**

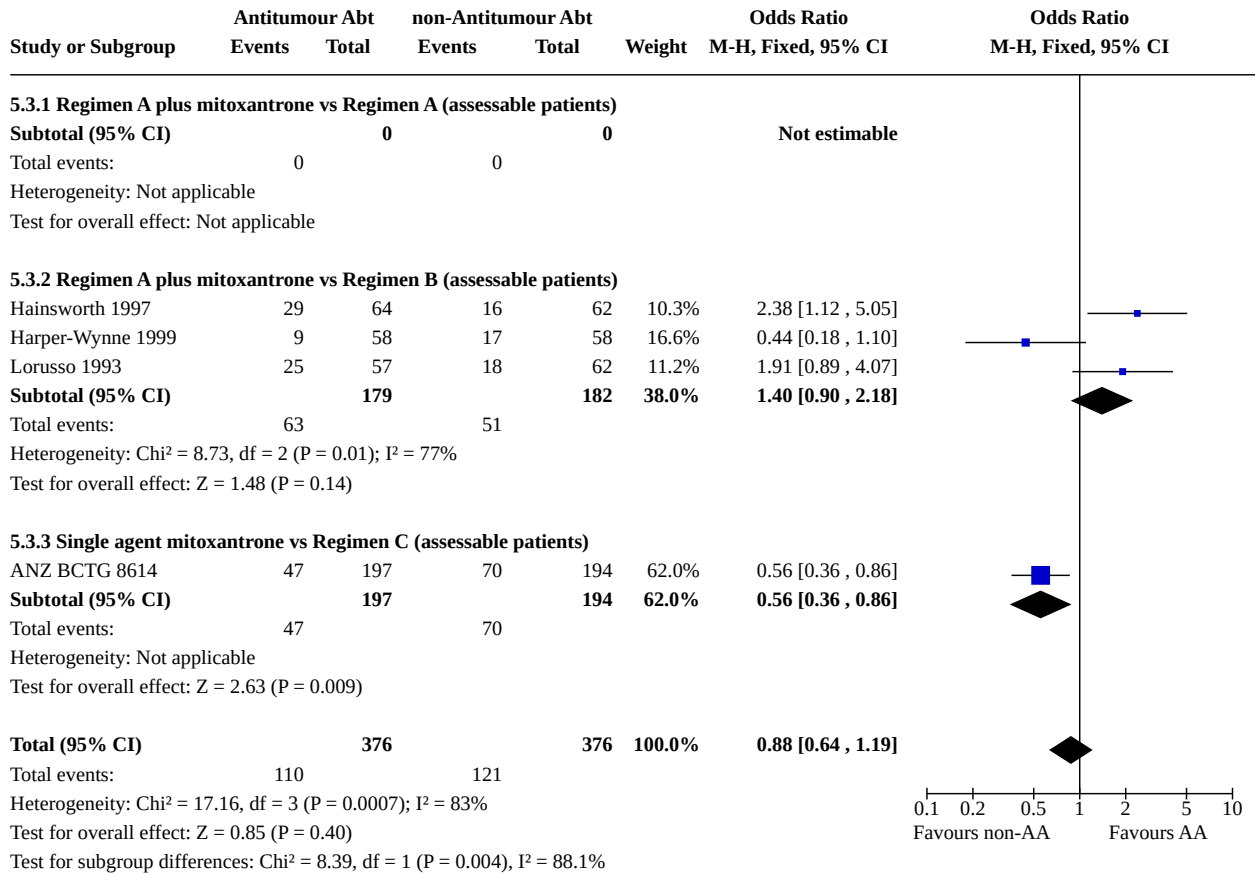




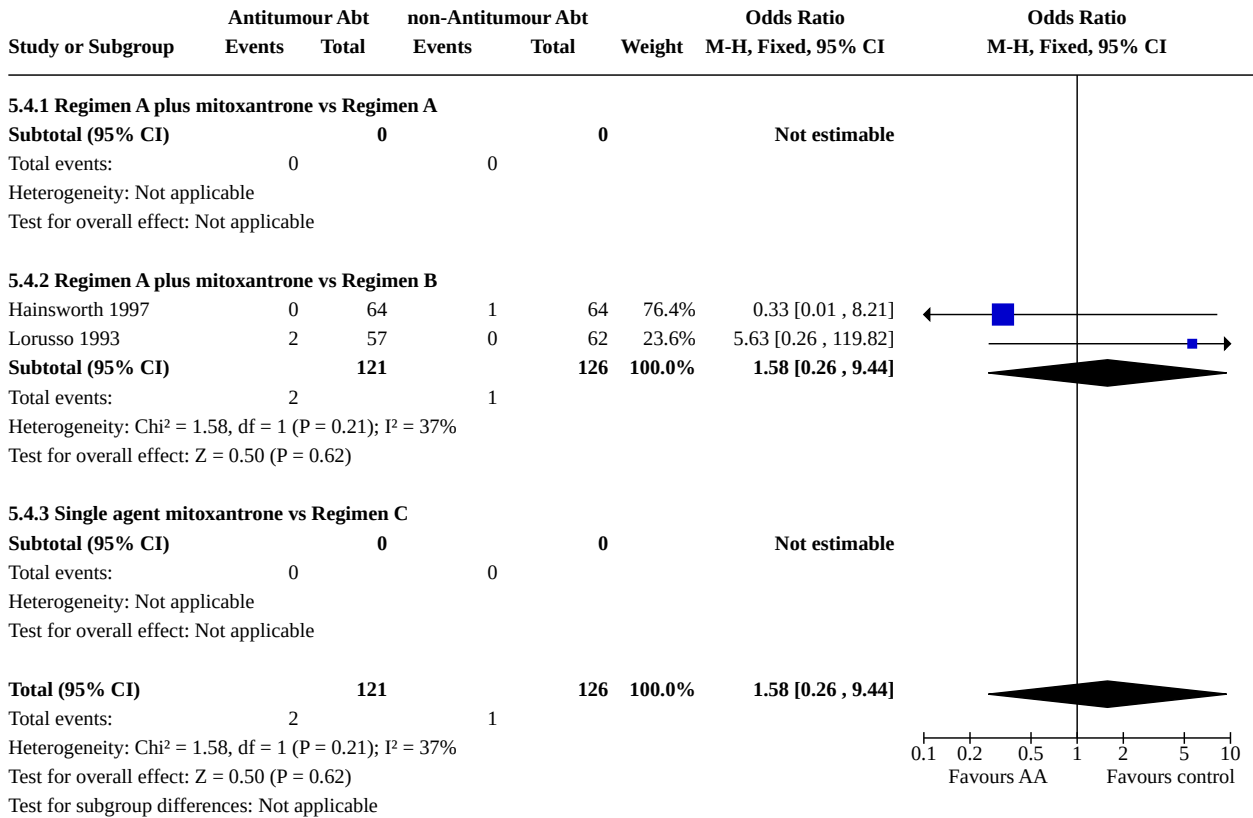
**Analysis 5.2. Comparison 5: Mitoxantrone containing regimens vs non antitumour antibiotic containing regimens, Outcome 2: Time to progression**



**Analysis 5.3. Comparison 5: Mitoxantrone containing regimens vs non antitumour antibiotic containing regimens, Outcome 3: Overall response (assessable patients)**



**Analysis 5.4. Comparison 5: Mitoxantrone containing regimens vs non antitumour antibiotic containing regimens, Outcome 4: Treatment-related death**



**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 alkylolation: nitrogen mustards	cyclophosphamide, melphalan, ifosfamide, chlorambucil
	by alkylolation: nitrosureas	carmustine (BCNU), lomustine (CCNU)
	by alkylolation: other agents	thiotepa, mitomycin C
	by platinum coordination cross-linking	cisplatin, carboplatin
	antibiotics	doxorubicin, daunorubicin, mitoxantrone, idarubicin, epirubicin, amsacrine
	podophyllotoxins	etoposide, teniposide
	by intercalation	dactinomycin, mithramycin
Spindle poisons	by uncertain mechanisms	bleomycin
	vinca alkaloids	vincristine, vinblastine, vendesine, vinorelbine

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

	taxanes	taxol, taxotere
Antimetabolites	thymidylate synthase	5-fluorouracil
	dihydrofolate reductase	methotrexate

**Table 2. Antitumour antibiotics**

Generic Name	Other names
doxorubicin hydrochloride	adriamycin, caelyx, doxorubicin, rubex
daunorubicin hydrochloride	cerubidine
dactinomycin	actinomycin D, cosmogen
mitomycin C	mitomycin, mitomycin C, mitomycin-C, mutamucin
mitozantrone	novantrone, mitoxantrone
epirubicin hydrochloride	ellence, epirubicin, pharmorubicin
plicamycin	mithramycin, mithracin
bleomycin sulfate	blenoxane

**Table 3. Acute toxicity Grade III-IV**

Site of toxicity	No. of trials	AA events (pts)/ n	Ctrl events (pts)/n	OR (95% CI)
ASSESSABLE PTS				
All Trials				
leukopenia*	26	931/2621	774/2527	1.25 (1.11-1.41)
nausea or vomiting**	17	341/2150	197/1945	1.71 (1.42-2.06)
alopecia	22	1177/1800	854/1934	2.36 (2.07-2.70)
cardiac toxicity	25	94/2572	18/2452	5.91 (3.56-9.80)
Anthracycline Trials				
leukopenia*	22	846/2265	694/2160	1.25 (1.10-1.41)
nausea or vomiting**	14	327/1852	170/1642	1.98 (1.62-2.41)
alopecia	18	1097/1447	705/1569	3.87 (3.31-4.52)

**Table 3. Acute toxicity Grade III-IV** (Continued)

cardiac toxicity	23	92/2451	18/2326	5.17 (3.16-8.48)
Anthracycline vs CMF based Trials				
leukopenia*	19	478/1622	531/1851	1.04 (0.90-1.20)
nausea or vomiting**	12	236/1359	180/1478	1.52 (1.23-1.87)
alopecia	16	847/1410	600/1585	2.47 (2.13-2.86)
cardiac toxicity	17	49/1565	7/1710	7.86 (3.55-17.41)
Mitoxantrone Trials				
leukopenia*	4	85/365	80/367	1.17 (0.84-1.63)
nausea or vomiting**	3	14/298	27/303	0.64 (0.34-1.18)
alopecia	4	100/353	149/365	0.66 (0.49-0.90)
cardiac toxicity	2	2/121	0/126	5.29 (0.25-111.39)
* data on grade II or IV neutropenia was included if data on leucopenia not reported				
** if data on nausea and vomiting was reported separately data on vomiting was included.				

**Table 4. Quality of life**

Trial ID	Instruments used	Summary of findings
ANZ BCTG 8614	Patients completed 14 linear analogue self-assessment scales. Clinicians used the Spitzer QL index.	Completion rates for each instrument are not available. No significant differences in patient or clinician rated overall QOL were reported between the treatment groups at 3 months. Patients on CMFP rated significantly higher for mood, pain, feeling sick, vomiting, appetite/taste and sexual interest, but worse for hair loss than patients on MTZ.
Harper Wynne 1999	HADS and RSCL (plus 3 satisfaction questions) pre-treatment and at weeks 12 and 24 (or on withdrawal)	Only 35 (30%) completed all 3 assessments. Reported no evidence of a difference between treatment groups.
IDBBC EORTC 10923	Patients completed EORTC QLQ-C30 and Rotterdam Symptom Checklist	64% of randomised patients completed baseline QLQ-C30 and 61% completed baseline RSCL. QOL comparisons were only performed for the first 3 cycles. Doxorubicin was associated with significantly more nausea/vomiting, loss of appetite and burden of disease and treatment, but less bone pain and rash.

**Table 4. Quality of life** (Continued)

Fraser 1993	Patients completed 3 quality of life instruments: 4 weekly Nottingham Health Profile (NHP - emotional state, energy, pain, physical mobility, sleep and social factors ) and Linear Analogue Self-Assessment (LASA) at the start of treatment and four weekly thereafter and the Qualitator daily dairy card throughout treatment which measured the domains of physical symptoms, social factors, emotional factors and physical performance.	Of the 40 patients randomised, compliance for the 29 who started the Qualitator, the 37 who started the NHP and 36 who started the LASA respectively were 88%, 89% and 92%. Quality of life measures only recorded a significant difference in energy and pain, influenced primarily by the non responders in each treatment group but with no difference in overall global scores. Scores for responders (58% for CMF, 29% for epirubicin $P>0.05$ ), irrespective of treatment were better to start with (LASA $P=0.001$ ); at 12 weeks, scores had improved (Qualitator $P<0.05$ ; NHP $P<0.05$ ) . Scores in non responders showed no change.
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## WHAT'S NEW

Date	Event	Description
6 February 2018	Review declared as stable	It is internationally accepted that anthracycline-containing regimens are part of standard clinical practice. Today, however, chemotherapy decisions are based on the specific molecular subtype of the breast cancer. As this Cochrane Review contains trials that are unselected for breast cancer subtype, it is no longer feasible to update this Review.

## HISTORY

Protocol first published: Issue 4, 2001

Review first published: Issue 4, 2004

Date	Event	Description
7 August 2008	Amended	Converted to new review format.

## CONTRIBUTIONS OF AUTHORS

DG designed the review and wrote the protocol. MG, JB, SW, CT, LB and SL collected the data for the review. SL and CT wrote the results and discussion for the review in collaboration with NW, DG and JS.

## DECLARATIONS OF INTEREST

None

## SOURCES OF SUPPORT

### Internal sources

- NHMRC Clinical Trials Centre, Australia

### External sources

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

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## NOTES

This review was updated for Issue 3, 2007. A new search was conducted October 2006. One new trial was added (Fountzilias 2004) to the meta-analysis, one new trial was excluded from the analysis (Hori 2001) and one ongoing trial was removed (Leiden Uni Centre) without results being available for inclusion.

This review was also copyedited and a plain language summary included to replace the previous synopsis.

There were no statistically significant changes resulting from the inclusion of Fountzilias 2004 and the recommendations of the authors remain unchanged.

## INDEX TERMS

### Medical Subject Headings (MeSH)

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

### MeSH check words

Female; Humans